

**OUTCOMES AND PHENOTYPE OF SUBJECTS WITH SCREEN-
DETECTED DIABETES AND NEW AND EMERGING THERAPIES
FOR TYPE 1 AND TYPE 2 DIABETES MELLITUS**

Dr Sudesna Chatterjee MBBS MRCP

2007

OUTCOMES AND PHENOTYPE OF SUBJECTS WITH SCREEN-DETECTED DIABETES AND NEW AND EMERGING THERAPIES FOR TYPE 1 AND TYPE 2 DIABETES MELLITUS

Abstract

Principal aims were to investigate long-term outcomes from T2DM and IGT screening, examine morphological and biochemical phenotypes of screened subjects, comparing White Europeans (WE) with South Asians (SA), and emerging therapies including basal insulin analogues in T1DM and meglitinides in T2DM and their place in management.

Following adjustment for age, sex and ethnicity, no significant difference in mortality, microvascular or macrovascular outcomes were detected between known and screened T2DM after ten years. Findings were limited by few events and relatively short follow-up. These data may be useful in power calculations for longer randomised controlled trials.

Body fat is higher in SA than WE for given BMI and increases with worsening glucose tolerance. Bioelectrical impedance analysis and skinfold thickness are less sensitive and specific with increasing body fat regardless of ethnicity and gender. Ethnicity and BMI, but not age, predict total and abdominal fat using DEXA scanning.

After adjustment for age, BMI, WHR, gender, smoking and drug history, no differences between SA and WE for adiponectin and resistin were detected. Leptin is predicted by age, gender and smoking in WE but only gender in SA. BMI predicts hsCRP in both groups while age and smoking predicts TNF α in SA. Longitudinal cohort studies are needed to determine impact of interventions on risk markers in different ethnic groups.

Insulin glargine results in a small but significant glycaemic improvement without significantly increased hypoglycaemia, weight gain or reduced patient satisfaction when used in a basal bolus regimen with aspart compared with NPH insulin in T1DM.

In a six-month randomised study, four different dual oral combinations including nateglinide, pioglitazone, metformin and gliclazide, in early T2DM result in significant glycaemic improvement without increasing hypoglycaemia or patient dissatisfaction with no significant differences between groups. Longer RCT are required to determine how duration of glycaemic improvement with each combination.

CONTENTS

	Page No.
CONTENTS	4
ACKNOWLEDGEMENTS	8
LIST OF TABLES	9
LIST OF ILLUSTRATIONS	12
ABBREVIATIONS	14
SUMMARY	15
CHAPTER ONE: INTRODUCTION	19
1:1 General Aims	20
1:2 South Asian Population in the United Kingdom	24
1:3 New and Emerging Therapies in Types 1 and 2 Diabetes	29
1:3:1 Glargine	29
1:3:2 Meglitinides	31
CHAPTER TWO: LONG TERM OUTCOMES OF SCREENING FOR DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE	33
2:1 Introduction	34
2:2 Key Research Questions	42
2:3 Patients and Methods	43
2:4 Statistical Analyses	46
2:5 Results	48
2:6 Discussion	53
2:7 Conclusion	57

**CHAPTER THREE: PHENOTYPE OF SUBJECTS WITH
SCREEN-DETECTED DIABETES**

Body Fat Composition	58
3:1 Introduction	59
3:2 Key Research Questions	66
3:3 Subjects and Methods	67
3:4 Statistical Analyses	69
3:5 Results	71
3:6 Discussion	82
3:7 Conclusion	86

**CHAPTER FOUR: PHENOTYPE OF SUBJECTS WITH
SCREEN-DETECTED DIABETES**

Circulating Risk Markers and Glucose Tolerance	87
4:1 Introduction	88
4:2 Key Research Questions	101
4:3 Subjects and Methods	102
4:4 Statistical Analyses	103
4:5 Results	104
4:6 Discussion	117
4:7 Conclusion	123

**CHAPTER FIVE: PHENOTYPE OF SUBJECTS WITH
SCREEN-DETECTED DIABETES**

Circulating Risk Markers and Metabolic Syndrome	124
5.1 Introduction	125
5.2 Key Research Questions	128
5.3 Subjects and Methods	129
5.4 Results	111
5.5 Discussion	136
5.6 Conclusion	139

CHAPTER SIX: EMERGING THERAPIES IN TYPE 1 AND TYPE 2 DIABETES	140
6:1 Glargine therapy in Type 1 Diabetes	141
6:2 Meglitinides in Type 2 Diabetes	148
CHAPTER SEVEN: GLARGINE VS INSULATARD: COMPARISON OF A BASAL BOLUS REGIMEN WITH MEAL-TIME ASPART IN TYPE 1 DIABETES (GLASS STUDY)	165
7.1 Introduction	166
7:2 Key Research Questions	168
7:3 Patients and Methods	169
7:4 Statistical Analysis	172
7:5 Results	174
7:6 Discussion	179
7:7 Conclusion	183
CHAPTER EIGHT:PIOGLITAZONE IN COMBINATION WITH NATEGLINIDE IN CARE OF TYPE 2 DIABETES (PICNIC STUDY)	188
8.1 Introduction	189
8:2 Key Research Questions	190
8:3 Patients and Methods	191
8:4 Statistical Analysis	196
8:5 Results	197
8:6 Discussion	210
8:7 Conclusion	212

CHAPTER NINE: DISCUSSION AND ISSUES FOR FUTURE RESEARCH	213
9.1 Introduction	214
9.2 Areas for Further Research	215
9.3 Final Conclusion	224
REFERENCES	225
PUBLICATIONS ARISING FROM THIS THESIS	255
APPENDICES	
i. Patient Satisfaction Questionnaires	
ii. Patient Information Leaflets	
iii. Consent Forms	
iv. Titration Algorithms	

ACKNOWLEDGEMENTS

This thesis incorporates a body of work I planned and conducted over four years. All the studies reported were fully under my supervision. However I would like to acknowledge the help and support of the following individuals.

The completion of this thesis would not have been possible without the invaluable support of my esteemed and learned supervisors Prof Melanie Davies and Prof Kamlesh Khunti. I shall always be grateful for their positive feedback and encouragement at all stages of the research process. I would also like to thank everyone in the Diabetes Research Team within the University Hospitals of Leicester for their constant hard work and unfailing enthusiasm. I am grateful for the statistical support provided by Dr Nick Taub of the Trent Institute and by Mrs Caroline Whatley-Smith. My fellow research colleagues, especially Dr Jennifer Tringham, played a major role in maintaining my morale throughout.

My research colleagues, in particular Dr Nancy Fernando Da Silva, at the Institute of Diabetes and Metabolism, Warwick Medical School, patiently taught me complex laboratory techniques for which I am very grateful. I would also like to acknowledge the help of Mr Neil Raymond and Dr Hanna Blackledge in the collection and analysis of the Long Term Outcomes data. I am grateful to Prof Ranjan Yajnik from Pune, India who along with his research team gave me advice and taught me methods of measuring body composition.

Finally I am indebted especially to all the patients who participated in the studies described in this thesis as without them this research would not have been possible.

LIST OF TABLES

	Page No.
TABLE 2:1 Baseline Characteristics of Study Population	50
TABLE 2:2 Outcome Events by Group	51
TABLE 2:3 Outcome Analyses for All Cause Mortality and Myocardial Infarction	52
TABLE 3:1 Baseline Characteristics of Study Population for Skinfold Measurements and Bioelectrical Impedance Analysis	75
TABLE 3:2 Baseline Characteristics of Diabetic Study Population undergoing DEXA Scanning	76
TABLE 3:3 Multiple Linear Regression of Total Body Fat Percentage using DEXA Scanning	77
TABLE 3:4 Multiple Linear Regression of Abdominal Fat Percentage using DEXA Scanning	77
TABLE 3:5 Correlation between Measurement Methods for Body Fat Composition in Male Subjects Screened for Diabetes	78
TABLE 3:6 Correlation between Measurement Methods for Body Fat Composition in Female Subjects Screened for Diabetes	79
TABLE 4:1 Key Associations of Risk Markers in South Asian Population in UK and Globally	100
TABLE 4:2 Baseline Characteristics of Male Subjects	106
TABLE 4:3 Baseline Characteristics of Female Subjects	107

TABLE 4:4	Concentrations of Circulating Risk Markers in Males	108
TABLE 4:5	Concentrations of Circulating Risk Markers in Females	109
TABLE 4:6	Multiple Linear Regression of Leptin	110
TABLE 4:7	Multiple Linear Regression of Adiponectin	111
TABLE 4:8	Multiple Linear Regression of Resistin	112
TABLE 4:9	Multiple Linear Regression of TNF α	113
TABLE 4:10	Multiple Linear Regression of HsCRP	114
TABLE 5:1	Major Definitions for Diagnosis of Metabolic Syndrome	127
TABLE 5:2	Baseline Characteristics of Subjects with and without Metabolic Syndrome using IDF Definition	131
TABLE 5:3	Baseline Characteristics of Subjects with and without Metabolic Syndrome using NCEP Definition	131
TABLE 5:4	Baseline Characteristics of Subjects with and without Metabolic Syndrome using WHO Definition	132
TABLE 5:5	Correlations of Markers with Different Definitions for Metabolic Syndrome	133
TABLE 5:6	Differences in Risk Markers between SA and WE with and without Metabolic Syndrome	135
TABLE 6:1	Association between Post-prandial Glucose Values and the Risk of Cardiovascular Heart Disease across the Spectrum of Glucose Tolerance	152
TABLE 7:1	Baseline Characteristics of GLASS Population	186

TABLE 7:2	Summary of Treatment Differences in GLASS	187
TABLE 8:1	PICNIC Study Visit Schedule	193
TABLE 8:2	Baseline Characteristics of PICNIC Study Population	200
TABLE 8:3	Change in HbA1c after Six Months’ Treatment with each Dual Combination of Oral Hypoglycaemic Agents	201
TABLE 8:4	Change in Weight during PICNIC Study	202
TABLE 8:5	Frequency of Hypoglycaemia with each Drug Combination During Study	204
TABLE 8:6	Patient Satisfaction using DTSQ	205
TABLE 8:7	Patient Satisfaction using ADDQoL Questionnaire	206

LIST OF ILLUSTRATIONS

	Page No.
FIGURE 2:1 Screening Outcomes from the Leicestershire Diabetes Screening Study	44
FIGURE 3:1 Body Fat Percentage in Subjects with Screen-detected T2DM using Three Different Methods of Measurement	80
FIGURE 3:2 Bland and Altman Plot of BF% Differences between DEXA and Bioelectrical Impedance Analysis	81
FIGURE 3:3 Bland and Altman Plot of BF% Differences between DEXA and Skinfolks	81
FIGURE 4:1 The Role of Activated Innate Immunity as the Antecedent of Type 2 Diabetes and Atherosclerosis	89
FIGURE 4:2 Proteins derived from Adipose Tissue	95
FIGURE 4:3 Concentrations of Resistin, Adiponectin and Leptin According to Glucose Tolerance and Ethnicity	115
FIGURE 4:4 Concentrations of hsCRP and TNF α according to Glucose Tolerance and Ethnicity	116
FIGURE 5:1 Prevalence of Metabolic Syndrome according to Definition in White European and South Asian Subjects	134
FIGURE 6:1 UKPDS Extrapolation of the Time of Deterioration of β Cell Dysfunction	149
FIGURE 7:1 Schematic Diagram of Study Design for GLASS	184
FIGURE 7:2 Change in HbA1c during Study	185

ABBREVIATIONS

T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
PDM	Pre-diabetes
IGT	Impaired glucose tolerance
IFG	Impaired fasting glucose
UKPDS	United Kingdom Prospective Diabetes Study
DCCT	Diabetes Control and Complications Trial
CVD	Cardiovascular disease
WHO	World Health Organisation
NCEP (ATPIII)	National Cholesterol Evaluation Program Adult Treatment Panel III
IDF	International Diabetes Federation
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes
OGTT	Oral glucose tolerance test
%BF	Body fat percentage
BIA	Bioelectrical impedance analysis
DEXA	Dual energy X-ray absorptiometry

SUMMARY

The principal aims of this thesis were to:-

- investigate long-term (ten year) outcomes from screening for T2DM and IGT
- examine morphological and biochemical phenotype of subjects with screen-detected diabetes, comparing White European (WE) and South Asian (SA) populations
- investigate efficacy of insulin glargine in a basal bolus regimen in T1DM
- investigate efficacy of different dual combinations of oral agents in early T2DM

The worldwide incidence and prevalence of T2DM continues to rise inexorably. Earlier identification and intensive management to avoid complications and mortality are necessary but data on the long-term impact of screening remain sparse. The second chapter of this thesis investigates long-term outcomes of screening from data collected approximately a decade earlier in Leicestershire.

Specific differences in morphological and biochemical phenotype may characterise T2DM, PDM or metabolic syndrome diagnosed through screening, with ethnicity-specific differences. This is investigated in more detail in Chapters 3-5. Waist circumference, skinfold thicknesses, bioelectrical impedance analysis and dual energy X-ray absorptiometry are used to determine differences in body fat composition in WE and SA across the glucose spectrum. Circulating risk markers such as C-reactive protein and the adipocytokines adiponectin, leptin and resistin are measured and compared in these two ethnic groups across the glucose spectrum.

Following diagnosis, it is essential to maintain strict glycaemic control as well as modify cardiovascular risk factors to reduce morbidity and mortality from macrovascular and microvascular complications. New and emerging therapies are available which may lead to improved management of this chronic condition.

Chapter 6 reviews the use of insulin glargine in T1DM followed by a report of the Glargine and Aspart study (GLASS) in Chapter 7 where glargine and NPH insulin are compared in a basal bolus regimen with aspart in a nine-month randomised cross-over study. In Chapter 6, there is a literature review of the meglitinides repaglinide and nateglinide followed by the PICNIC study in Chapter 8 describing dual oral combinations including nateglinide in early T2DM.

Summary of Main Findings

The main findings and recommendations are as follows:-

- No significant difference in mortality, microvascular or macrovascular outcomes were detected between known and screened T2DM subjects approximately a decade after screening
- No differences were detected in long-term outcomes between WE and SA
- Findings are limited by small numbers of events and short follow-up
- These data may be useful in power calculations for longer randomised controlled screening trials (RCT)
- Body fat, which increases with worsening glucose tolerance, is higher in SA than WE for a given BMI
- Ethnicity and BMI, but not age, predicts total and abdominal fat using DEXA scanning

- Waist circumference correlates with BMI in only WE males and SA females
- BMI underestimates body fat and other methods need to be validated and used to determine CVD and diabetes risk
- Differences are observed in circulating risk marker concentrations across the glucose spectrum and between WE and SA living in the UK
- After adjustment for age, BMI, WHR, gender, smoking and drug history, there are no differences in adiponectin and resistin concentration between SA and WE
- Leptin concentration is predicted by age, gender and smoking in WE but only gender in SA
- BMI predicts hsCRP in both groups while age and smoking predicts TNF α in SA
- Longitudinal cohort studies are needed to determine impact of lifestyle and therapeutic interventions on risk markers in different ethnic groups
- Insulin glargine results in a small but significant glycaemic improvement without significantly increased hypoglycaemia, weight gain or reduced patient satisfaction when used in a basal bolus regimen with aspart compared with NPH insulin (GLASS) in T1DM
- In the PICNIC study, four different dual combinations of oral agents in early T2DM all result in significant glycaemic improvement without increasing hypoglycaemia or patient dissatisfaction over six months
- There are no significant differences between combinations of pioglitazone/nateglinide, metformin/gliclazide, metformin/pioglitazone and metformin/nateglinide
- Longer RCT are required to determine duration of glycaemic improvement and emerging differences between these combinations

In conclusion, improved morbidity and mortality outcomes were not observed approximately ten years after screening in a multiethnic UK population although differences were detected in morphological and biochemical phenotype between ethnic groups and across the glucose spectrum. Following diagnosis, improved glycaemic control is achieved using insulin glargine in T1DM in a basal bolus regimen. Dual oral combination therapy improves glycaemic control regardless of agents used in early T2DM. Justification for diabetes screening will need reassessment following the completion of large multicentre randomised trials. In the meantime, intensive management of both types of diabetes is essential to minimise the significant burden associated with complications.

CHAPTER ONE

INTRODUCTION

1:1 General Aims

The worldwide prevalence of T2DM is predicted to increase to 220 million by 2010 (1). The enormous burden of this chronic disease is manifested by development of macrovascular and microvascular complications such as CVD, stroke, amputation, blindness and renal failure. UKPDS, a landmark study of over five thousand participants with T2DM, showed that intensive management of glycaemic control significantly decreased the development and/or progression of microvascular complications and there was a trend towards improvement of macrovascular complications. Inevitably, glycaemic control deteriorated with time (2).

Delayed diagnosis of T2DM leads to development and progression of undetected microvascular complications such as retinopathy (3). This delay is estimated at 7-12 years with around 50% of patients asymptomatic at presentation (4). Earlier identification of asymptomatic patients allows multifactorial intervention and monitoring of T2DM and its complications (5). A screening programme identifying asymptomatic patients by targeting those at risk is one way of lessening the long-term impact. In the UK, a systematic programme of widespread screening has not been advocated as robust data are not currently available to support its implementation.

In Chapter 2, long-term outcomes of screening for T2DM and its precursor of IGT are reviewed. These data are extrapolated from a screening study conducted in the early 1990s in Leicestershire when subjects were initially identified by postal screening for glycosuria and were then diagnosed with T2DM or IGT using an oral glucose tolerance test (OGTT) (6). Approximately ten years on, rates of all-cause and cardiovascular mortality and development of macrovascular and microvascular complications in screen-positive subjects

have been analysed, and compared with known diabetic patients at the time of screening and those who originally screened negative.

The “thrifty genotype” hypothesis has been postulated to explain the development of insulin resistance as a selection advantage in hunter-gatherers alternating between periods of feast and famine (7). Risk of developing T2DM is probably determined by a specific phenotype with notable differences according to ethnicity. Increasing obesity is associated with development of T2DM, and both location and quantity of adipose tissue are important in determining risk. A number of circulating inflammatory markers such as C-reactive protein as well as hormones secreted by adipose tissue, known as adipocytokines, have been linked with increased risk of developing PDM, defined by IFG and/or IGT, as well as T2DM and CVD (8-11). Metabolic syndrome describes the constellation of factors such as hypertension, lipid abnormalities and glucose intolerance that combine with obesity to increase risk of developing T2DM and CVD.

In Chapters 3-5, the morphological and biochemical phenotype of screened subjects is described in those with T2DM or PDM and compared with normal glucose tolerant subjects. These data were derived from two large population-based screening studies in Leicestershire, the “Screening Those At Risk” (STAR) study (12) and the Anglo-Danish-Dutch Study of Intensive Treatment and Complication Prevention in Type 2 Diabetic Patients Identified by Screening in Primary Care (ADDITION) (13), where around 30% of the screened population was of South Asian (SA) ethnicity. SA are known to have much-increased risk of both T2DM and CVD compared with the native White European (WE) population and this occurs at relatively lower body mass index (BMI). The association of circulating risk markers with metabolic syndrome is examined in Chapter 5. Their phenotype is characterised by examining demographic data, measurement of body fat

composition using simple anthropometry, bioelectrical impedance analysis (BIA) and dual-energy x-ray absorptiometry (DEXA), and measuring biochemical analysis of risk markers for CVD.

Following a diagnosis of both T1DM and T2DM, tight glycaemic control is essential to delay onset and progression of macrovascular and microvascular complications (14,15). This is often difficult to achieve despite intensive treatment with traditional oral hypoglycaemic agents as demonstrated by UKPDS in T2DM and with insulin in T1DM as shown by DCCT (14). In Chapter 7, the use of some emerging therapies is reviewed.

Insulin glargine was the first genetically engineered basal insulin available and its longer duration with no pronounced peak allows a more physiological mode of action with the potential for less hypoglycaemia, especially nocturnal (16). One of the problems with the intensive insulin treatment arm in DCCT was increased hypoglycaemia. The GLASS study is described in Chapter 7. This is a randomised cross-over trial of insulin glargine compared with NPH insulin, both in combination with meal-time aspart, in subjects with T1DM.

Newer oral agents, which have a more physiological mode of action, are potentially more effective especially when combined in a rational manner and given early in the natural history of T2DM. They target insulin resistance and impaired insulin secretion which characterise the pathophysiology of T2DM.

A randomised controlled pilot study, PICNIC, which compares four different oral hypoglycaemic combinations used early in the natural history of T2DM, is described in Chapter 8. Long-established agents such as sulphonylureas and metformin are compared

with newer ones such as thiazolidinediones and meglitinides and the effects of dual therapy on glycaemic control, weight gain and patient satisfaction are examined over six months.

In the final part, Chapter 9, findings from the various studies in this thesis are discussed, as well as the ways in which T1DM, T2DM and the at-risk individual may be better managed in the future and implications of the research described in this thesis.

1:2 South Asian Population in the United Kingdom

Diabetes and cardiovascular risk

Certain ethnic groups are at greater risk of T2DM and CVD. One such high-risk group is the SA population comprising of individuals of Indian, Pakistani, Bangladeshi or Sri Lankan descent. Overall increased risk persists despite heterogeneity in cultural practices and eating habits (17). Compared with WE, SA have 40% higher CVD mortality (18). CVD mortality rates for SA men in the UK are 46% higher and for SA women 51% higher than in non-Asians (19). T2DM affects around 20% of SA aged over 50 years in the UK (20) and is increasingly prevalent in urban populations in the Indian sub-continent (21). Risk of hyperglycaemia and hypertension increases with urbanization regardless of body fat percentage (BF%) and distribution (22). SA present at an earlier age, on average up to five years earlier, compared with WE in the UK (23,24). CVD and renal disease are more prevalent in UK SA (25,26), with CVD mortality four-fold higher (27).

In UK SA aged less than 40 years, 25% had evidence of at least one complication of T2DM at diagnosis following opportunistic screening (28). SA had higher prevalence of established macrovascular and microvascular disease, and lower high density lipoprotein (HDL) cholesterol and higher blood pressure, contributing to increased CVD risk when compared with WE. Other notable differences were greater waist-hip ratio (WHR) and lower insulin sensitivity in SA, which were also observed in UKPDS (29).

Conventional risk factors such as hypertension and smoking are less prevalent in India. For example, one study in India, where cigarette smoking is practically unheard of amongst women, found rates of CVD as high or higher than in men (30). Even amongst pre-menopausal SA women, three-vessel coronary disease was more common. Many SA

are vegetarian but obesity and dyslipidaemia are prevalent. Specific lipid abnormalities include higher triglycerides, apolipoprotein B and lipoprotein(a) concentrations with lower HDL cholesterol concentrations, and other emerging risk factors are more prevalent, such as homocysteine, fibrinogen, plasminogen-activator inhibitor type 1 (PAI-1), high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) (31,32). Identification and optimal management of lipid abnormalities are a key aspect of reducing CVD morbidity and mortality (33). Other findings in SA are impaired insulin-mediated vasodilatation and lower adiponectin concentrations (34,35). Adiponectin has anti-inflammatory and anti-atherogenic properties and is secreted by adipose tissue. How early these abnormalities develop remains unclear. Furthermore, there are little data comparing these biomarkers in SA and WE screened for T2DM and PDM.

Obesity and Metabolic Syndrome in the South Asian Population

CVD is associated with T2DM, IGT and metabolic syndrome, and obesity is a key risk factor for these three conditions. BMI has been used to define obesity but SA have greater insulin resistance, dyslipidaemia and CVD risk compared with Caucasians of the same BMI and age (36). Greater WHR and abdominal fat are seen in SA living in North America for a specific BMI (36,37). Location of fat in the abdominal compartment and around organs, that is, visceral rather than subcutaneous, is more closely linked to T2DM. A good predictor of risk of insulin resistance and metabolic syndrome is the measurement of waist circumference (WC) (38).

In urban Asian Indians, T2DM was strongly associated with visceral and central abdominal fat (as measured by computed tomography and DEXA), and these two measures correlated well with each other as well as with WC and sagittal abdominal diameter (39).

Metabolic syndrome refers to a cluster of risk factors, including insulin resistance, obesity, lipid abnormalities, high blood pressure and glucose intolerance, that have been linked with increased development of CVD (40) and is discussed more fully in Chapter 5. It has been variously defined but only the IDF definition recognises the importance of different WC cut-offs for obesity according to ethnic group (41). In contrast, the NCEP ATP III definition does not require insulin resistance or abnormal glucose tolerance to diagnose metabolic syndrome (42). Metabolic syndrome is more prevalent in SA living in both India (43) and in the UK (44). Canadian SA had greater prevalence of metabolic syndrome compared with Europeans and Chinese and was associated with more atherosclerosis and elevated PAI-1 (45). Sagittal abdominal diameter predicts metabolic syndrome in both SA and WE males in the UK (46), and has been suggested as a useful clinic or bedside tool for determining risk. Adiponectin is lower in SA in India with metabolic syndrome (47). There are very few studies investigating adiponectin concentrations in migrant SA.

South Asian population in Leicestershire

The county of Leicestershire has a culturally diverse current population of over 950,000, with approximately one third (320,000) resident in the city of Leicester. According to the 2001 census, 33% of Leicester citizens are of SA origin. Leicestershire SA have acute CVD rates twice as high as the Caucasian population (48).

In Leicester, a unique opportunity exists to compare the phenotype of indigenous WE subjects and the substantial migrant SA population. The majority of this cohort originates from the state of Gujarat in Northern India either through direct immigration or via previous settlement in sub-Saharan Africa.

Efforts to tackle this burden of disease in SA have concentrated on lifestyle modification involving increased activity levels, promotion of weight loss and improvement of diet, for example, the community scheme Project Dil (49). Pharmacological management of CVD risk factors such as hypertension, diabetes and dyslipidaemia are necessary but emphasis must be given to maintaining compliance and ensuring understanding of the need for multiple medications. The possibility that subtle but definite differences in phenotype exist could allow more tailored therapy to be provided.

Understanding of social and cultural aspects that determine health beliefs and behaviour are of paramount importance when tailoring therapies in this high risk population (50). When calculating CVD risk, lower thresholds for example obesity, blood pressure and dyslipidaemia are needed to avoid underestimation and under-treatment (19).

A further concern is that risk is present at an early age in SA. Comparison of body size and cord blood leptin and insulin concentrations in Indian and Caucasian babies showed that Indian babies had relatively greater adiposity, hyperinsulinaemia and hyperleptinaemia (51) despite Indian mothers being smaller. A key priority is the maintenance of optimal maternal health to ensure a favourable uterine environment.

Fat distribution of peripubertal Asian females tends to be less gynoid than white females when measured by skinfolds and DEXA (52). Insulin resistance and BF% are also increased in UK SA adolescents compared with WE counterparts (53). This difference is not restricted to SA as more subcutaneous adipose tissue is found in Singaporean Chinese compared with Dutch adolescents (54). Ethnic specific growth charts are required especially with the rising incidence of childhood and adolescent overweight and obesity in the UK. All these findings suggest that an unfavourable metabolic environment is already present at early developmental stages. There is an urgent need to address adverse lifestyle factors in second and third generation descendants of migrant SA populations (19).

1:3 New and Emerging Therapies in Type 1 and Type 2 Diabetes

The increasing prevalence of diabetes in most populations, especially T2DM, has placed an enormous burden on health care systems worldwide (55,56). Factors such as increasing obesity, sedentary lifestyle, ageing population, improved medical care and decreasing mortality rates are all contributory factors. The economic impact is considerable and was estimated at £1 billion to the NHS for England and Wales for both types of diabetes resulting in consumption of at least 5% of health resources in the 1990s (57,58).

Two landmark studies, DCCT (14) and UKPDS (59), showed that in T1DM and T2DM respectively, intensive management was essential to delay or prevent development of complications. However, intensive management as defined by maintaining HbA1c<7% has been difficult to achieve, especially as hypoglycaemia increases with tightening glycaemic control (2,14,60). Hypoglycaemia is likely to be an increasing problem as glycaemic control targets are lowered further in both T1DM and T2DM.

1:3:1 Glargine

Glargine was the first commercially available DNA-recombinant long-acting insulin analogue. Replacement of asparagine by glycine and addition of two arginine molecules in the molecular structure of insulin results in glargine having a longer, often 24-hour profile which is described as “peakless” compared with other basal insulins such as Neutral Protamine Hagedorn (NPH) and Ultralente.

Prior to biosynthetically produced human insulin, which has been available for approximately thirty years, insulin was derived by purification and extraction from porcine and bovine sources. Several different regimens and formulations of insulin are available.

Insulin may be given as a twice daily pre-mixed formulation where short-acting and intermediate-acting insulin are combined. Although simple and convenient, this formulation does not closely mimic physiological insulin profiles. Endogenous insulin secretion is better approximated by short-acting insulin such as soluble insulin or rapid-acting analogues for example lispro or aspart at meal-times, usually thrice-daily, combined with intermediate or long-acting insulin once or twice daily, the so-called basal-bolus regimen. Alternatively, insulin may be provided by continuous subcutaneous infusion (CSII) using soluble insulin or short-acting insulin analogues, known as the 'insulin pump'. On the horizon are alternative insulin administration methods such as inhaled insulin.

Original long-acting insulins such as Ultralente and intermediate-acting insulins like NPH were characterised by variable subcutaneous absorption, delayed onset of action, and peaks and troughs in profile, exposing patients to increased risk of hypoglycaemia, especially nocturnal, and periods of relative hyperglycaemia (61). The search for an ideal long-acting basal insulin led to the development of glargine with its relatively peak-free near 24-hour duration and reduced intersubject variability.

Aspart has been extensively studied in combination with NPH insulin in T1DM and represents a significant proportion of the rapid-acting analogue market currently prescribed in the UK. Insulin glargine has been studied in combination with other short-acting insulins such as Lispro. Little data are available on efficacy of combining glargine and aspart in a basal bolus regimen, and this was the rationale for the Glargine and Aspart Study (GLASS), described in Chapter 7.

1:3:2 Meglitinides

Since the 1950s, metformin and sulphonylureas have formed the mainstay of oral therapy for T2DM. Metformin targets insulin resistance probably by increasing peripheral glucose uptake and utilization and suppressing hepatic glucose output. It may have other mechanisms of actions which are not completely understood. UKPDS showed that metformin was effective in lowering HbA1c, and in particular was the only agent to confer cardiovascular benefits (62). However, like sulphonylureas and insulin, metformin did not maintain good glycaemic control. It is also associated with significant gastrointestinal side-effects resulting in around 10% of patients being unable to tolerate therapy and may rarely cause lactic acidosis.

Sulphonylureas such as gliclazide and glimepiride are insulin secretagogues which bind to the sulphonylurea receptor of the pancreatic β cell promoting closure of ATP-dependent potassium channels. They are effective at improving glycaemic control but associated with weight gain and increased risk of hypoglycaemia. Incidence of severe hypoglycaemic episodes with sulphonylureas is approximately 0.2/1000 patient-years. About 20-25% of patients with T2DM are initially unresponsive to sulphonylureas and secondary failure occurs in 5-10% of individuals on an annual basis.

Alpha glucosidase inhibitors such as acarbose are used either as monotherapy or in combination with metformin and sulphonylureas to reduce carbohydrate absorption from the small intestine. UKPDS showed that acarbose was less effective in lowering HbA1c compared with other oral agents. The STOP-NIDDM trial showed that, with acarbose, fewer patients progressed to T2DM from IGT (acarbose vs. placebo, 32% vs. 42%). However, 31% had to discontinue acarbose due to gastrointestinal side-effects.

More recent oral agents include thiazolidinediones or peroxisome proliferator-activated receptor γ (PPAR γ) agonists which enhance endogenous insulin action on target organs such as skeletal muscle, liver and adipose tissue. The first launched was troglitazone but had to be withdrawn following hepatotoxicity. Rosiglitazone and pioglitazone are currently available and do not appear to be hepatotoxic. They have a modest effect on blood pressure and lipid profile thus potentially improving CVD risk and these areas continue to be explored.

A new class of drugs known as meglitinides have recently been launched on the international market and have been developed to improve early phase insulin secretion which is one of the earliest pathophysiological manifestations of T2DM. They are derived from the meglitinide portion of sulphonylureas. Repaglinide is derived from the non-sulphonylurea moiety of glibenclamide whereas nateglinide is derived from an amino acid. Meglitinides are rapid-acting insulin secretagogues (or prandial glucose regulators) which have a fast onset and short duration of action resulting in more physiological insulin secretion. Meglitinides have a glucose-dependent mechanism of action and this has important implications for lessening the risk of hypoglycaemia. The question remains as to whether these newer agents lower HbA1c and sustain it for longer without increasing hypoglycaemia risk.

In the pioglitazone in combination with nateglinide in care of early type 2 diabetes (PICNIC) study described in Chapter 8, the efficacy of the meglitinide nateglinide is investigated in combination with pioglitazone or metformin over a six month period.

CHAPTER TWO

LONG TERM OUTCOMES OF SCREENING FOR DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

2:1 Introduction

The Need for a Screening Programme

UKPDS provided clear evidence that T2DM is asymptomatic for several years before diagnosis, during which time macrovascular complications such as CVD and microvascular complications such as retinopathy or nephropathy develop in a significant number of patients (63). Diagnostic delay has been estimated at 7-12 years with approximately 50% asymptomatic at diagnosis (4).

The Steno type 2 randomised study showed that intensified multifactorial intervention in patients with T2DM and microalbuminuria slowed progression to eventual nephropathy, and further progression of retinopathy and autonomic neuropathy (15). Intensive treatment consisted of behaviour modification with additional pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria. In UKPDS, intensive treatment for hyperglycaemia and hypertension had fewer diabetes-related endpoints than when blood glucose was targeted alone (64). Identifying patients earlier in the disease process potentially enables multifactorial risk intervention and intensive management of the overall CVD risk profile (15).

A targeted screening programme for subjects at high risk of T2DM would help in the prevention and delay of complications but little robust data are available to support this. Recent data from UKPDS identified that those with lower initial fasting glycaemia have significantly reduced risk of progression of retinopathy and development of microalbuminuria and less reduction in vibration sensory potential (65).

SA patients have greater rates of CVD and T2DM compared with WE. A 28-year prospective cohort study in insulin-treated SA (n=828) and non-SA (n=27 962) patients in the UK showed very high mortality in the SA cohort (66).

The History of Screening Programmes

The earliest organised screening programmes were conducted among insurance applicants during the early 1900s. During World Wars I and II, recruits to the armed services were also screened for diabetes. High false positive and false negative rates and overall poor performance of diabetes screening tests were a major problem with these early screening programmes.

The Bedford survey was one of the first UK screening studies and conducted in the 1960s (67). However, screened subjects did not undergo long-term follow-up and clinical endpoints were not evaluated. Another screening study conducted during this decade performed repeat screening after a five year interval on Leicestershire villagers and detected an increase in T2DM incidence, with multiparous women identified at greater risk of developing disease (68).

Subsequently there have been few large UK screening studies. Notable are those conducted in Leicestershire, East Anglia and Coventry in the late 1980s and early 1990s (6,69-73). These form a unique and valuable resource to investigate long-term outcomes in patients screened for T2DM compared with those with known T2DM.

East Anglia data showed that patients identified through screening had modifiable risk factors that would benefit from earlier treatment (74). Since then, there has been little

evidence in the literature investigating whether screening programmes provide a “window of opportunity” for addressing risk factors and reducing micro- and macrovascular complications and all-cause mortality.

In 1978 Panzram and Ruttman showed that there was no survival benefit in 250 patients screening positive for glycosuria. No difference was identified between groups for mortality, survival times and vascular complications at 10 and 20 years. Their conclusion was that screening groups with high diabetes risk would be expected to yield higher effectiveness than the mass screening they had performed (75).

Another German study showed that patients admitted to hospital with positive glycosuria screening lived one year longer than those who attended with clinical symptoms (76,77). However, this study lacked robust evidence of reduced mortality rates.

An Italian study compared 105 patients with screen-detected diabetes with 104 matched patients (by age, sex and weight, family history, therapy and smoking) who had been diagnosed clinically. After six years of follow-up, average glycaemia was significantly less in the screen-detected group. However, there was no difference in development of retinopathy, cataracts, neuropathy, cardiovascular or peripheral vascular disease (78).

A study conducted in Melton Mowbray, Leicestershire, identified that elderly diabetic subjects screened for diabetes were 4.5 times more likely to die than subjects who had normal glucose tolerance detected by OGTT (69).

The UK National Screening Committee has not yet recommended a screening programme because of lack of robust evidence in several areas (79). One of the main gaps is long-term

data showing that screening improves patient outcomes. Unfortunately most of the above-mentioned studies were not designed or powered enough to analyse long-term outcomes.

Screening programmes for diabetes may be associated with physical, psychological and social disadvantages and need to be undertaken using the best possible and most cost-effective strategy. It has been suggested that individuals aged more than 40 years with at least one diabetes risk factor would benefit from screening. Screening for diabetes fulfils the criteria recommended in a screening programme by the World Health Organisation (Box 1) (80).

Box 1 Criteria for instituting a screening programme (80)

Disease	Serious High prevalence of preclinical stage Natural history understood Long period between first signs and overt disease
Diagnostic test	Sensitive and specific Simple and cheap Safe and acceptable Reliable
Diagnosis and treatment	Facilities are adequate Effective, acceptable, and safe treatment available

The Screened Subject

Screening needs to be distinguished from diagnostic testing. Screening detects asymptomatic disease and differentiates high risk from low risk subjects. Methods used need to be quick, simple and safe, such as risk assessment questionnaires, capillary blood testing or laboratory-based measurements. Conversely, diagnostic testing is carried out when patients have symptoms or signs of disease. Increased mortality is associated with a positive questionnaire-based risk score even if biochemical testing is normal (5).

Screen-detected individuals would be expected to have some advantages. Earlier diagnosis leads to identification of complications such as cardiovascular and renal disease with appropriate referral and management. The patient has an earlier opportunity to address smoking, obesity and reduced activity. However, the ability to manage these risk factors and others such as hypertension and hyperlipidaemia would not be a justification per se for screening.

Importantly, screening is associated with adverse effects. Early diagnosis leads to labelling and there are the restrictions of intensive management. There is considerable variation in compliance with complex treatment regimens involving polypharmacy. Patients diagnosed early may be more compliant. Conversely, lack of symptoms may deter them from complying with optimal management.

Despite these provisos, the current evidence is strongly in favour of detecting and managing T2DM, hyperlipidaemia and hypertension earlier if better outcomes are to be achieved, as demonstrated by major studies such as UKPDS, The Scandinavian Simvastatin Survival Study and Steno study (15,81,82).

Assessing benefits of screening

The benefits of screening can be assessed using the following measures:-

- The relative reduction in morbidity or mortality rates
- The absolute reduction in morbidity and mortality rates
- The number of patients needed to treat to prevent one adverse event (in a given time period)
- The total cohort mortality rate (all causes of mortality, not just diabetes related)

Randomized controlled trials (RCT) are the best way of evaluating benefits and risks of diabetes screening programmes because they measure the effect of the screening procedure alone and not other health behaviours that make an individual submit to screening. In an RCT, a control group where subjects are not screened and receive currently available routine care after clinical diagnosis usually at onset of hyperglycaemic symptoms could be compared with an intervention group diagnosed earlier, that is, before symptomatic hyperglycaemia, following active screening.

Although this would yield valid results, it has not been conducted to date and there are ethical and economic considerations. Large numbers of subjects and long-term follow-up are necessary. Currently a large randomised controlled trial of diabetes, the ADDITION study, is being conducted in Leicester in collaboration with other UK and European centres (13).

In the meantime, observational data may allow some evidence to be derived as to effectiveness of screening.

Biases affecting analysis of screening programmes

Selection bias

Better outcomes may be seen if healthier subjects tend to participate in screening programmes. Prevention or delay in diabetic complications may occur as they are more likely to follow recommendations, rather than because of their early diagnosis.

Lead-time bias

Lead time bias refers to increased survival time which is expected when subjects are diagnosed earlier through screening rather than following clinical presentation. Comparing survival, or time to development of complications, is affected by this bias between groups. Longer “survival” following detection includes a period for the screened group during which no symptoms or signs of disease are present. Overall survival may not be improved. However, this is always an issue of screening.

Lead time bias may be expected to have an effect on improved survival when comparing screened with clinically diagnosed patients. There is little published evidence comparing longer term outcomes in screened and clinically diagnosed groups. In the study described in this chapter, there is an opportunity to evaluate formally screened and clinically diagnosed groups after ten years to see if the screened patients do in fact fare better. In interpreting the results, the effects of lead-time bias need to be considered.

Length time bias

This is a function of severity of disease. Subjects with less severe or slowly progressing disease would be expected to do better than those with more severe disease, and would be less likely to be diagnosed. This latter group may be detected in screening, thus introducing a bias between screen-detected and clinically diagnosed groups, leading to artificially large differences in survival or other outcomes. Retrospectively, little can be done to alleviate this bias, but the effects can be considered when evaluating and interpreting study results.

Overdiagnosis

Errors in diagnosis may occur as a consequence of overzealous screening in individuals without disease.

2:2 Key Research Questions

1. Does screening for T2DM and IGT reduce all-cause and cardiovascular mortality?
2. Does screening for T2DM and IGT improve long-term macrovascular and microvascular outcomes by introduction of therapeutic interventions and monitoring early in the disease process?
3. Can the results of this study contribute to the power calculations for randomised controlled trials such as the ADDITION study designed to look at long-term outcomes?

2:3 Patients and Methods

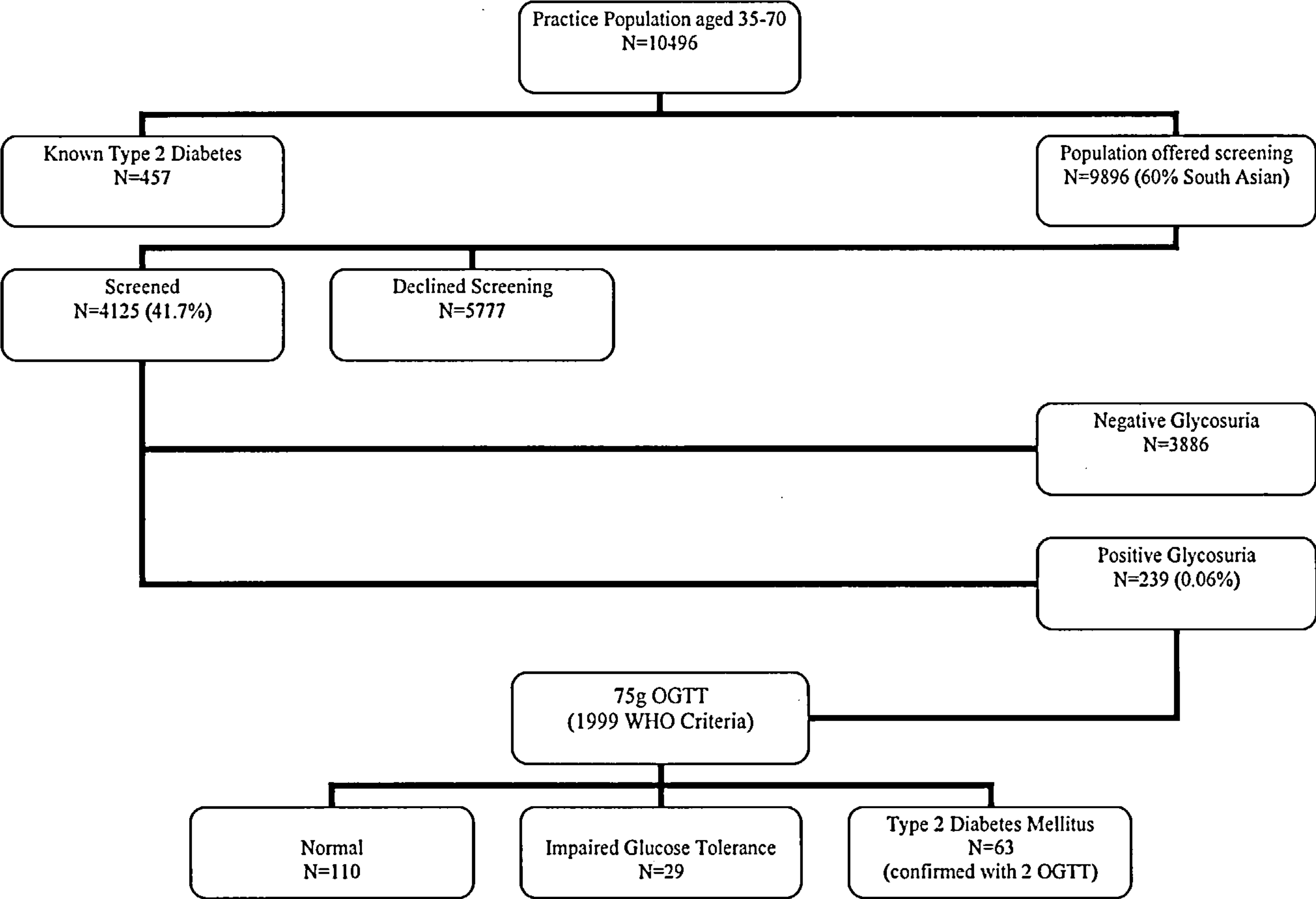
In 1993-4, 9896 subjects were screened for T2DM and IGT using self-testing for post-prandial glycosuria in Leicestershire (74). They were obtained from two randomly selected primary care practices. Patients themselves were not randomised but consent was obtained from all.

In the original study, screening was performed in two local general practices with a large proportion of registered patients of SA ethnicity. A register of all patients aged 35-70 years was provided by the practices and this was used to exclude patients with known diabetes (types 1 and 2) and also those who had moved from the area. All remaining patients (n=9896, 6198 = SA, 3698 = WE) were sent individual instruction cards and foil wrapped urine testing sticks (Clinistix, Bayer Diagnostics Ltd, Newbury, UK). A letter was also sent explaining the procedure and inviting them to participate in screening.

One hour after the main meal of the day, subjects were instructed to self-test for glycosuria. To facilitate ease of understanding, instruction and response cards were sent to SA subjects in Punjabi and Gujarati.

Subjects with documented glycosuria were invited to attend for a 75g OGTT at the local hospital. 1985 WHO criteria were used to classify glucose tolerance (83). Subjects and their general practitioners were informed of OGTT results on the same day. If an abnormal result was recorded, an invitation was sent for a second OGTT two weeks later. Patients were considered normal if the second OGTT was normal. Figure 2:1 illustrates the outcomes from this study.

Figure 2:1. Screening Outcomes from Original Leicestershire Diabetes Screening Study



The present study focused on comparing mortality rates of the group with screen-detected T2DM with the population with known T2DM. In addition, those patients with screen-detected IGT were compared with

1. screen-detected T2DM subjects
2. subjects with normal OGTT
3. glycosuria-negative subjects.

A list of patients from Leicestershire, who were subjects in the initial research study, was compiled with contact details, including postcode and National Health Service number,

Tracing was performed by the Leicestershire Health Informatics Service, which has an established record linkage system and includes a variety of routine data on all Leicestershire residents registered with general practices in the district. The core of the system is the Family Health Service (FHS) patient register. This links to acute in-patient data sets with historical data back to the late 1980s, outpatient and accident and emergency sets, and mortality with a complete record set since 1993.

The Diabetes Register was record-linked to the FHS register allowing accurate outcome information such as mortality, coronary heart disease-related admissions and amputations to be obtained. Mortality and patient migration details are updated at regular intervals.

It was also possible to link data from the Health Authority with the list of screened-positive and known T2DM patients, allowing mortality status and causes of death to be available. The outcome events determined were

1. myocardial infarction (MI) – macrovascular complication
2. coronary artery bypass grafting (CABG) – macrovascular complication
3. amputation – macrovascular complication
4. renal failure – microvascular complication
5. death.

Retinopathy was not used as it was not available as an endpoint in the hospital coding system.

Analyses of survival from positive screening were compared amongst the following groups:-

1. newly diagnosed T2DM at screening
2. established T2DM
3. IGT
4. normal – negative glycosuria

Age-sex standardised mortality for causes of death was compared with the screening group.

2:4 Statistical Analyses

Sample size was estimated with all cause mortality as the primary endpoint, using the Sample computer program (Medical Statistics, University of Southampton, Version 3.1). Substantial mortality was anticipated in both the diagnosed and screen-detected T2DM group.

The Melton screening study conducted in the 1980s-1990s, with people aged over 60 years, and with 5 years of follow-up, suggested mortality rates of 52% in known and 37% in discovered diabetes subjects (69). In the current study, the screening age range was younger at 45-70 years, but the follow-up period longer at approximately 10 years. The high prevalence of SA people in the current Leicester study sample (more than 70%) in both screened and diagnosed groups was expected to raise mortality rates relative to the previously reported data. The old study suggested a relative risk of 1.8 for mortality in diagnosed compared to screened groups.

To detect a difference in proportions of deaths in the current study, 52% vs 37%, with 80% power and a one-sided test significance level of 5%, 135 subjects in each group with 1:1 allocation, was required. Using an allocation ratio of 2:1 or 3:1, 100 or 89 subjects per group were needed respectively. The total numbers of subjects available, allowing for dropouts and some variation from the suggested mortality differential therefore provided adequate numbers to detect differences.

2:5 Results

In the original study, over 40% of those who attended for OGTT were subsequently found to have abnormal glucose tolerance. However, there was a relatively low response rate to the initial screening invitation with only 41.7% of SA and 54.2% of WE returning urine-testing sticks (6). In comparison, in the predominantly White European East Anglia study, the response rate was 75% (70).

Ten years later, record retrieval was 86%, 94%, 86% and 95% for those with known diabetes (KDM), screened diabetes (SDM), screened IGT and normal OGTT respectively. Table 2:1 shows the baseline characteristics of the screened groups and the KDM group. From the original study, data were obtained on 393 subjects with KDM, 59 with SDM, 25 with screen-detected IGT and 107 who had normal OGTT but were originally glycosuria positive.

Following adjustment for age, gender and ethnicity, OR compared to screened normal subjects were 2.0 (0.89 to 4.48, $p=0.09$) for KDM, 1.68 (0.59 to 4.84, $p=0.33$) for SDM, and 0.55 (0.06 to 4.82, $p=0.59$) for screened IGT.

On specifically comparing KDM and SDM, there were no significant differences between the groups for gender or ethnicity. Relative risk (RR) for males was 0.97 (0.77 to 1.21) and SA 1.01 (0.89 to 1.24). Odds ratios (95% CI) in KDM vs. SDM for all-cause mortality were 1.2 (0.6 to 2.5), MI 2.7 (0.8 to 8.8), CABG 1.9 (0.4 to 8.1), and renal failure 1.7 (0.5 to 5.6).

Table 2:2 shows the absolute number of events across the groups. SA were younger across all groups and had fewer events.

Table 2:3 shows outcome analyses for all-cause mortality and MI. The wide confidence intervals indicate the relatively small number of outcome events that were recorded. Overall there was a difference in all-cause mortality between groups in the 10-year period following screening. Using logistic regression and comparing with those with normal OGTT, OR (95% CI) were 2.6 (1.2 to 5.6, $p=0.01$), 2.2 (0.8 to 6.0, $p=0.13$), and 0.5 (0.1 to 4.2, $p=0.52$), for KDM, SDM and screen-detected IGT respectively.

Compared with OGTT normal subjects, OR for cardiovascular mortality was 1.83 (0.62 to 5.39, $p=0.27$) for KDM and 1.08 (0.59 to 1.97, $p=0.81$) for SDM. There were no cardiovascular deaths in the screened IGT group.

Following adjustment for age, sex and ethnicity, there was no significant difference in outcomes for all-cause mortality or MI between the groups.

The recorded causes of death in the 8 WE patients diagnosed with T2DM following screening were as follows: - bronchopneumonia, carcinomatosis due to right breast carcinoma, cardiac arrest, metastatic pancreatic carcinoma, congestive cardiac failure, cardiac failure, pneumonia, and coronary atherosclerosis. In the one SA patient with screen-detected diabetes who died the cause of death was pulmonary embolism.

Table 2:1 – Baseline Characteristics of Study Population - N (%)

	Known T2DM N=393	Screened T2DM N=59	Screened IGT/IFG N=25	Screened normal N=107
<i>Gender</i> ^a				
Males	226 (58)	35 (59)	17 (68)	83 (79)
Females	167 (43)	24 (41)	8 (32)	22 (21)
<i>Ethnic Group</i> ^b				
South Asian	302 (77)	43 (73)	18 (72)	73 (70)
White/other	91 (23)	16 (27)	7 (28)	32 (31)
<i>Age (y)</i> ^c	56.9 (9.4)	56.3 (9.2)	51.1 (9.5)	52.2 (9.8)
<i>Duration of Diabetes (y)</i> ^d	18.4 (5.0-63.0)	n/a	n/a	n/a

a - $\chi^2 = 16.887$, 3df, P=0.001

b - $\chi^2 = 2.646$, 3df, P=0.450. One Chinese patient is included in the White/Other group

c - analysis of variance (ANOVA), F=8.971, P<0.001

d- mean (range)

Table 2:2 Outcome Events by Group - N (%)

	Known T2DM N=393	Screened T2DM N=59	Screened IGT N=25	Screened normal N=107
All-cause mortality	69 (18)	9 (15)	1 (4)	8 (7.5)
Acute MI	29 (7)	2 (3)	1 (4)	1 (1)
CABG	18 (5)	2 (3)	1 (4)	3 (2.8)
Amputation	3 (0.7)	0	0	0
Renal Failure	30 (8)	3 (5)	0	1 (1)

Table 2:3 Outcome Analyses for All Cause Mortality and Myocardial Infarction

	Known T2DM	Screened T2DM	Screened IGT	Screened normal	P value
Death OR (95% CI)	2.6 (1.2-5.6)	2.2 (0.8-6.0)	0.5 (0.1-4.2)	1	0.03
Adjusted OR (95% CI)	1.8 (0.8-4.0)	1.7 (0.6-4.9)	0.7 (0.1-5.8)	1	NS
MI OR(95% CI)	8.3 (1.1-61.6)	3.6 (0.3-41.1)	4.3 (0.3-71.8)	1	NS
Adjusted OR (95% CI)	8.9 (1.2-66.9)	3.8 (0.3-43.5)	4.7 (0.7-77.9)	1	NS

Adjusted for age, gender and ethnicity

2:6 Discussion

There are very few longitudinal studies reporting outcomes in people with screen-detected T2DM (68,69,75-78). In contrast to some of these studies, the results of this observational study do not show significantly improved outcomes in the ten-year period following a screening programme for T2DM. Although small, this study indicates that there is increased all-cause mortality in subjects diagnosed with T2DM through screening compared to those who were screened normal. However, this was not statistically significant when adjusted for age, sex and ethnicity.

Outcomes for all measured macrovascular and microvascular outcomes were higher in the known T2DM group. They were not statistically significant which may be a result of the relatively small numbers of observed outcomes. During the decade following screening, there were relatively few outcomes across all groups. This could be partly attributed to small numbers in this study but may also reflect changing diabetes management practice in the UK for all complications.

The American Diabetes Association and other national and international organisations have promoted guidelines for screening of T2DM based on the high prevalence of both detected and undetected T2DM (84). However, no national screening programme has been recommended and uncertainties remain as to value and cost-effectiveness of such programmes (79). Screening those with established risk factors would be more justified than universal screening, especially in populations with a high prevalence of undiagnosed T2DM and CVD.

To date, no outcome data are available from RCT to confirm the impact of detecting T2DM early in the disease process and the subsequent effects on subjects. A number of RCT in the UK and elsewhere are currently being conducted and will eventually clarify the issue. However, early detection would allow management leading to an improvement in cardiovascular complications as seen for example in the Malmo Study (85). Early interventions to target cardiovascular risk factors are likely to provide greatest benefit.

Various biases that may affect estimates of outcomes in long-term follow-up of screening study participants have already been discussed in the introduction to this section. Lead-time bias means that screened subjects are detected earlier in the disease process and are therefore likely to have better outcomes. Subjects within screen-defined groups may have differing levels of disease severity, which could affect outcomes years after screening (length-time bias). Selection bias occurs when subjects volunteering for screening may be more health-conscious or alternatively may present from high-risk groups. Adequately interpreting and explaining observed data in the presence of these biases is difficult and potentially unsatisfactory. In the original study, initial uptake of screening was low especially in SA. In contrast, WE were more likely to participate in the screening programme. Greater uptake in a predominantly WE population was observed in another screening study performed in East Anglia (70).

In the current study, compared with the screened normal but glycosuric group, those with screen detected T2DM had elevated risk of mortality and combined MI or CABG. In neither case were these excesses statistically significant. However, the number of events and differences observed were small. It is likely that the study had insufficient power to detect any real difference which might exist. In addition, testing for post-prandial glycosuria does not allow identification of subjects with IGT or IFG which are associated

with increased cardiovascular risk. More cases of pre-diabetes and diabetes would have been detected using 2001 WHO diagnostic criteria. There were non-significant differences on comparing the screen detected and known T2DM groups for mortality and combined MI and CABG. These differences were smaller than anticipated from the power calculations and again the study may have been too small to detect any real differences. The numbers actually screened ten years ago limited study size, and therefore simply increasing the sample studied on the basis of few observed events was not possible. This is an important consideration in observational screening follow-up studies.

As well as larger differences, more total events were anticipated in the groups studied and the limited number of adverse outcomes is probably reassuring and possibly reflects generally improved management of T2DM with fewer complications than in previous cohorts. Given the accumulating evidence over the past 10 years, improved and intensified care for patients with T2DM might be expected to benefit those detected through screening or clinical diagnosis (15).

This observational study does not clearly demonstrate significant differences in outcome between known and screened T2DM and IGT patients a decade after screening. However, there were relatively few outcome events during this period and it would be useful to determine outcomes 15 to 20 years following diagnosis. Larger RCT are needed to determine the impact of screening on outcomes. The results from this study could be useful in informing the power calculations for these RCT, ensuring that a sufficient number of outcomes are obtained. The Screening Those At Risk (STAR) study, described in Chapter 3, was developed from the original Leicester study.

Above all, management of T2DM and cardiovascular risk in the post-screening period needs to be carefully analysed, as this is likely to have a major impact on outcomes in the long-term.

2:7 Conclusion

The results of this small observational study do not show significantly improved outcomes in the ten-year period following a screening programme for T2DM. These findings reflect some of the other studies which did not show increased outcomes in people with screen-detected diabetes. Larger RCT with analysis of post-screening interventions are required to determine the long-term impact of diabetes screening programmes. The all-cause and cardiovascular mortality rates from this study may be useful in informing the power calculations for these larger trials and should be considered at the time of study design.

CHAPTER THREE

PHENOTYPE OF SUBJECTS WITH SCREEN-DETECTED DIABETES

Body Fat Composition

3:1 Introduction

It has already been discussed in the preceding chapters that subjects diagnosed with T2DM are at high risk of developing macrovascular and microvascular complications. Even if they have PDM, their risk of developing CVD remains higher than the general population (86,87). Obesity predisposes to both T2DM and PDM. Quantity and location of adipose tissue are important in determining risk. Adipose tissue is not an inert storage depot for triglycerides as previously thought but a highly metabolic organ producing several different substances with varying effects on glucose and lipid metabolism (88). Most of these substances increase insulin resistance and lipid abnormalities but a notable exception is adiponectin which is linked to insulin sensitivity (89).

When obesity, glucose and lipid abnormalities and high blood pressure co-exist, a diagnosis of metabolic syndrome is made. The “common soil” hypothesis suggests that underpinning all these metabolic derangements is an antecedent period of chronic but mild inflammation (8). Normally the acute phase response to tissue injury is beneficial and protective but when this is augmented, it may be the mechanism leading to T2DM and its complications.

It could be postulated that subjects in the pre-clinical stages of T2DM have a distinct phenotype, both morphological and biochemical, which is different to those with normal glucose tolerance. Identification of this “at risk” phenotype would be useful for the purposes of population-based screening and appropriate subsequent interventions. However even small increases in glucose concentration are a potentially modifiable CVD risk factor (90).

In this chapter, the current knowledge regarding obesity and cardiovascular risk is reviewed, before a number of techniques are described for quantifying the amount and distribution of adipose tissue. In the following chapter, Chapter 4, biochemical differences are determined by comparing adipose tissue products and inflammatory marker concentrations between WE and SA subjects with worsening glucose tolerance.

Body Mass Index and Body Composition

The World Health Organisation (WHO) has classified overweight and obesity according to BMI as a risk marker for T2DM and CVD. In 1993, an expert committee proposed BMI cut-off points of 25.0-29.9 kg/m² for overweight grade 1, 30.0-39.9 kg/m² for grade 2, and ≥40.0 kg/m² for grade 3 (91). In 1997, this classification was amended to recognise an additional subdivision of 35.0-39.9 kg/m² (92).

There is increasing concern that conventional use of BMI fails to acknowledge varying levels of body fat percentage (BF%), especially in at risk populations (93). In the SA population it has been recommended that more definitive measurements such as skinfold thickness or BIA are used to measure BF% rather than BMI to avoid risk underestimation (93). T2DM incidence and prevalence vary greatly among ethnic groups despite similar BMI, such as Japanese and Taiwanese Americans compared with European populations (94). The problem with using BMI as a measure of adiposity is that it also includes fat-free mass and is related to body build, with Asians tending to be more slender and potentially less muscular.

The continued debate surrounding application of BMI cut-off points regardless of ethnic population led to a recent WHO expert consultation (95), which concluded that Asian

people were at high risk of T2DM and CVD at BMI levels substantially lower than the traditional cut-off of 25 kg/m² for overweight. However, there was little evidence to indicate an advisable cut-off in this population for overweight or obesity. Potential public health action points were identified along a BMI continuum of 23.0, 27.5, 32.5 and 37.5kg/m². Importantly, the consultation recognised the importance of using WC as a key measurement for determining cardiovascular and metabolic syndrome risk. Finally, it was recommended that meaningful body composition studies using valid methodology should be undertaken to address this important issue.

Body Fat Composition

Total quantity of adipose tissue is not as good a predictor of CVD and T2DM as the amount of fat stored in the abdomen, so-called central or visceral adipose tissue (94,96-99).

Visceral adipose tissue is twice as common in men than in pre-menopausal women but is more detrimental in the latter (97,99-102). Relative CVD risk is increased eight-fold in women with the highest WC or WHR compared with only two-fold in men. This indicates that increased visceral adiposity lessens the relative cardioprotection of the pre-menopausal state.

In both men and women with IGT, a high level of visceral adipose tissue is associated with abnormal lipid profiles which may partly explain their increased cardiovascular risk (103,104). In elderly men and women, excess visceral adiposity is associated with increased risk of developing T2DM (105). Specifically, a visceral adipose tissue level of $\geq 106 \text{ cm}^2$, estimated using CT scanning, is associated with elevated risk of coronary heart disease, that is, with low HDL cholesterol concentrations, hypertriglyceridaemia, high

LDL/HDL cholesterol ratio, impaired glucose tolerance, and hyperinsulinaemia in women (106). In comparison, leg fat accumulation was protective in the Hoorn study against disturbed glucose metabolism, especially in women (107).

In a comparison of healthy European American and Asian American subjects, the latter group had higher visceral adipose tissue in women but not in men despite adjusting for age and total body fat, with differences more pronounced after the age of 30 years (108).

Importantly however, some individuals who are clinically obese may still be “metabolically healthy” and this is associated with relatively little visceral fat deposition (109).

Assessment of Body Fat Composition

More precise measurements of body fat composition would help to elucidate those who are at greater risk. Body fat composition can be measured using either criterion methods or prediction methods and these are further subdivided into direct and indirect estimates.

Physical properties such as chemical or anatomical components are measured by criterion methods. Examples are direct measurement such as total body water using the deuterium dilution space, or indirect measurements of other components of body composition, for example, BF% from total body water (110).

There are a number of available criterion methods, such as underwater weighing or hydrodensitometry (which is considered the “gold standard” and based on Archimedes’

principle), potassium 40 counting, total body water from tritium or deuterium dilution, and in-vivo neutron activation. These methods are associated with random technical errors and non-random and/or systematic errors due to individual deviations from the assumed normal range related to factors such as age, gender and ethnicity (110).

Prediction methods are less specific and utilise measurements derived from body circumferences, skinfold thicknesses, or BIA. Equations used to determine BF% are obtained from values calibrated against criterion methods (110).

Simple anthropometry, that is, measurement of height, weight, waist/hip circumferences and skinfold thicknesses, and BIA are commonly used prediction methods. Errors in measurement can occur due to technical difficulties and there are also errors as a consequence of the limitations of the criterion method used for calibration. Equations are available for predicting fat-free mass (FFM) and total BF% but they have mostly not been cross-validated to determine accuracy especially when applied to other populations. Early studies suggested that BIA and skinfold thickness measurements were not comparable especially at either extreme of body fat (111). Skinfold measurement tended to overestimate fat mass in lean subjects and underestimate in obesity when compared with BIA (110).

Reference methods such as in-vivo neutron activation analysis, computed tomography (CT) and magnetic resonance imaging (MRI) involve the use of cumbersome, expensive equipment and specialised personnel. CT involves large amounts of ionizing radiation (110). These factors limit their widespread application for measuring body composition.

Dual-energy x-ray absorptiometry (DEXA) is a relatively new criterion method for body composition measurement and was originally used to measure bone density. Regional and whole-body estimates of fat, lean mass, and bone mass are obtained using DEXA at reasonable cost although trained personnel and expensive scanning equipment are required. Radiation risk is much lower than with CT scanning. However, it needs to be properly validated before widespread use as it can be affected by depth and tissue thickness and variations in tissue hydration (112,113).

Accuracy of Measurements

When measuring body composition, values are converted into amounts of bone, muscle and fat. There is some concern as to the validity of the assumptions underpinning estimates of body composition. The simple two-compartment model or Siri's equation is used most commonly (114) and divides the body into fat and FFM on the basis of body density from underwater weighing. This equation is derived from the assumption that fat and FFM densities are 0.9g/ml and 1.1 g/ml respectively (115). Depending on relative proportions of its components, mainly water, protein, and osseous and non-osseous mineral and the age and race of the individual, the density of FFM can vary greatly (116). Small variations from assumed densities can translate into proportionately greater errors in BF%. When compared with a four-compartment model, DEXA tended to underestimate BF% in leaner individuals (117).

A four-compartment model improves estimations of body fat composition. Whereas in a two-compartment model, there are FFM and fat divisions only, in the four-compartment model, FFM is further subdivided into water, bone mineral, and protein. Non-osseous mineral and carbohydrates are considered within the protein compartment, as it is a relatively small fraction of FFM at around 1.5% in young adults.

Water is the largest fraction of FFM and is estimated at 73% in young adults. Some studies suggest that this figure is slightly higher in women and with increased adiposity (118-120). The overall density of FFM will increase with water content, but decreased by greater bone mineral content. The fraction of protein, non-osseous mineral and carbohydrate is assumed to be relatively constant but this may be misleading due to ethnic and gender differences.

The equation for the four-compartment model is: -

$$1/D = F/df + TBW/dw + B/db + C$$

where 1/D is the sum of the volumes (fractions of weight/density) for fat (F), total body water (TBW), total bone mineral (B) and protein plus small amounts of non-osseous mineral and glycogen (C).

The majority of body composition studies have been performed on Caucasians and much of the information regarding validity methods and assumptions are only available on this group. Before the widespread application of the four-compartment model, the amount of difference in the densities of the body compartments among gender and ethnic groups needs to be established. Otherwise, significant errors of unknown magnitude could result.

3:2 Key Research Questions

1. Are there characteristic phenotypic features for body fat distribution and anthropometric measurements that predict disease in patients screened for T2DM and PDM?
2. Are these phenotypic features different in White Europeans compared with South Asians?
3. Which simple method of measuring body composition is the most accurate?

3:3 Subjects and Methods

Subjects who had undergone T2DM screening as part of the STAR (12) and ADDITION (13) programmes were randomly selected by the author for measurement of weight, height, WC, WHR, skinfold thicknesses and BIA. Written consent was obtained from all subjects as per the Helsinki Declaration and the local ethics committee approved the study.

These population-based programmes were conducted in surgeries, hospital sites and a mobile screening unit in Leicestershire, UK, between 2001 and 2004 (12,13). Male and female WE aged 40-75 years and male and female SA aged 25-75 years were invited to undergo OGTT with a 75g glucose load to determine glucose tolerance status. A diagnosis of PDM or T2DM was made using 1999 WHO criteria (121). Measurements were undertaken prospectively while patients were screened and also in a designated diabetes clinic for those diagnosed with T2DM through screening.

Weight was measured to the nearest 0.1kg using standard weighing scales. Height was measured to the nearest 0.5cm using a stadiometer. WC was measured to the nearest 0.1cm using a non-stretching measuring tape over the tops of the iliac crests and hip circumference over the greatest protrusion of the gluteal muscles.

Skinfold measurements

Using the left side of the body in all subjects, skinfold measurements were performed over the biceps, triceps, subscapular and upper suprailiac regions using a non-stretching tape measure and Harpenden skinfold callipers (CMS Instruments, London, UK). All measurements were obtained by a single fully trained investigator (the author) to minimise intra-operator error and conducted according to standard operating procedures. Measurements were recorded to 0.1mm accuracy. Three readings were taken from each

site and the mean value calculated. BF% obtained by this method was derived using the Durnin and Womersley and Siri equations as below (114,122).

Calculations

1. total skinfolds = average triceps skinfold + average biceps skinfold + average subscapular skinfold + average upper suprailiac skinfold

2. density = c – [m x log total skinfolds]

where c and m are found according to the subject’s age from the table below.

Age	16-19	20-29	30-39	40-49	50+
C	1.1549	1.1599	1.1423	1.1333	1.1339
M	0.0678	0.0717	0.0632	0.0612	0.0645

3. BF% = $\left[(4.95/\text{density}) - 4.5 \right] \times 100$ (Siri’s equation)

Bioelectrical Impedance Analysis

For this measurement, subjects were asked to fast overnight. However, those undertaking OGTT consumed 394ml of Lucozade prior to this part of the study. Following skinfold thickness measurement, subjects removed all metal objects from their person and lay supine on a couch for up to five minutes. Electrodes were applied over the right metacarpophalangeal joints, wrist, tarsophalangeal joints and ankle after wiping with alcohol to remove surface grease. Bioelectrical impedance was measured using the

Quadscan 4000 device (Bodystat, Isle of Man, UK). The data were initially stored in the device before being downloaded onto a computer database. The author carried out all the measurements and collected and analysed the data.

Dual Energy X-Ray Photoabsorptiometry

Subjects diagnosed with T2DM through STAR and ADDITION were invited to undergo DEXA scanning to determine body composition. Scanning was conducted by fully trained nursing staff and took place in the Menopause Unit, Leicester Royal Infirmary, using a Lunar Prodigy scanner (GE, Madison, WI, USA). The actual scan lasted ten minutes during which subjects were asked to lie very still on the table within anatomically defined regions. The scan was subsequently analysed using Encore software. Following the scan, subjects were sent a copy of the results with advice on healthy lifestyle management.

3:4 Statistical Analyses

A previous study showed up to 1% difference in BF% with up to 3% difference in standard deviation among Chinese, Malay and Indian subjects in Singapore (123).

In the study described in this chapter, using power calculations, it was estimated that to detect a difference in mean BF% of 1% and standard deviation of 3% with a power of 80% at type 1 error of 0.05, each of the two ethnic groups would need to consist of at least 75 patients.

All measurements are given as mean \pm standard deviation (SD) or mean \pm standard error of mean (SEM) unless otherwise stated. Significance was taken as $p < 0.05$. Student's T test, Pearson's correlations, ANOVA and multiple linear regression were used to determine

differences between measurements for WE and SA. Bland and Altman plots were used to assess degree of agreement between measurement techniques. Receiver operator characteristic (ROC) curves were used to compare sensitivity and specificity rates for different cut-off values for skinfold thicknesses and BIA in WE and SA. The statistical package used for all calculations was SPSS version 14 (SPSS, Chicago, IL, USA).

3:5 Results

Baseline characteristics of subjects assessed for body fat composition are given in Tables 3:1 and 3:2. In total, 120 (59.7%) WE and 81 (38.5%) SA subjects across the glucose spectrum underwent measurement of skinfold thickness and BIA. Male subjects made up 46% of the cohort.

Anthropometry, skinfold thicknesses and BIA were used to measure body fat composition in 120 WE (mean age 59.7 ± 10.9 y, mean BMI 29.1 ± 5.8 kg/m², mean waist WC 96.3 ± 12.6 cm) and 81 SA (mean age 49.9 ± 12.0 y, mean BMI 26.3 ± 4.5 kg/m², mean WC 88.9 ± 13.8 cm) who had undergone OGTT screening. A further 39 subjects (20 WE, 19 SA) diagnosed with T2DM through screening agreed to attend for DEXA scanning.

It is important to note that subjects with normal glucose tolerance still had at least one cardiovascular risk factor and were not therefore strictly “normal.”

There was a significant difference in age of approximately ten years between WE and SA ($p < 0.001$) (Table 3:1). This was to be expected as SA were screened from the age of 25 years to reflect their increased risk at an earlier age compared with WE who were screened from the age of 40 years.

Mean BMI increased with worsening glucose tolerance. In women but not in men, BMI differed significantly between ethnic groups with higher BMI observed in WE women. This was probably because of the wide standard deviation seen with BMI in normal glucose tolerant males. In PDM and T2DM, mean BMI in WE was much higher than SA despite similar BF% (Table 3:1).

WC was higher in WE but tended to increase with abnormal glucose tolerance in both ethnic groups ($p=0.01$). Interestingly, WC was lower in both WE and SA females with T2DM. This may be attributable to weight loss associated with unrecognised osmotic symptoms of T2DM.

Mean BF% by skinfold thickness did not differ significantly between WE and SA males ($p=0.08$). However, in females there was a significant difference in skinfold thickness across the glucose spectrum ($p=0.001$).

In males, mean BF% was much higher in WE than SA in the control group using both skinfold thicknesses (35% vs 31%) and BIA (27.3% vs 23.0%). However, differences in BF% were much less in the pre-diabetic and diabetic groups ($<2\%$). In females, mean BF% varied by less than 2% for all three methods and glucose tolerance groups.

Multiple linear regression showed that ethnicity and BMI but not age predicted the amount of total body and abdominal fat percentage using DEXA scanning (Tables 3.3-4).

Only in WE males did BMI correlate significantly with WC, WHR and BF% using both skinfolds and BIA ($p<0.05$). In SA males, BMI strongly correlated with skinfold and BIA but not with WC and WHR (Table 3:9). The same pattern was seen with WE females. In SA females, BMI significantly correlated with WC but not WHR (Table 3:10).

In subjects with T2DM diagnosed through screening, BF% was greater with DEXA in both WE and SA females. In WE and SA males, skinfold thickness measurements gave higher BF% readings (Figure 3:1).

Figures 3:2 and 3:3 show Bland and Altman plots of differences between methods of estimating BF %. 95% limits of agreement were -9.79% to 11.33% between DEXA and skinfold thickness, and -6.53% to 11.99% between DEXA and BIA.

There was a significant difference in body fat as measured by skinfold thicknesses between WE and SA males with normal glucose tolerance (35.0% vs 31.0%, $p=0.03$). WC differed between WE and SA females with screen-detected diabetes (95.7cm vs 85.4cm, $p=0.026$).

Summary of Findings

The main findings from this part of the study were

- BMI, WC and BF% (measured by both skinfold thickness and BIA) all tended to increase with worsening glucose tolerance in both WE and SA
- BMI correlated significantly with BF% as measured by BIA and skinfold thickness in both male and female WE and SA
- WC only correlated with BMI in WE males and SA females
- In the diabetic sub-population who underwent DEXA, ethnicity and BMI were significant factors in predicting total and abdominal BF%. BF% was approximately 10% higher than normal in these subjects. In females, BF% was higher with DEXA and in males it was higher with BIA. However numbers in this part of the study were very small.

- The 90% limits of agreement between DEXA and skinfold thickness were -7.9% to 9.5%, and between DEXA and BIA were -4.9% to 10.3%, indicating that up to 10% differences in BF% are likely to occur using these methods.

Table 3:2 Baseline Characteristics of Diabetic Study Population
undergoing DEXA Scanning

	Type 2 Diabetes		
	White European	South Asian	P Value
Males			
N	10	8	
Age* (y)	70.1 (4.0)	55.2 (11.6)	0.007
BMI* (kg/m ²)	27.6 (4.3)	26.3 (3.3)	0.51
Total body fat [§] (%)	32.1 (1.3)	33.7 (2.1)	0.54
Total body fat [§] (kg)	26.1 (2.3)	23.7 (2.5)	0.48
Leg fat [§] (kg)	7.4 (0.6)	6.4 (0.8)	0.33
Trunk fat [§] (kg)	18.6 (4.1)	14.5 (1.4)	0.35
Ratio of trunk to total body fat	71%	61%	
Females			
N	10	11	
Age* (y)	66.8 (8.1)	55.0 (11.6)	0.01
BMI*(kg/m ²)	27.9 (3.8)	26.9 (6.3)	0.66
Total body fat [§] (%)	41.9 (1.7)	44.2 (1.8)	0.35
Total body fat [§] (kg)	28.7 (2.5)	27.3 (3.1)	0.72
Leg fat [§] (kg)	9.0 (1.1)	8.9 (1.0)	0.96
Trunk fat [§] (Kg)	15.6 (1.1)	14.9 (1.8)	0.74
Ratio of trunk to total body fat	54%	55%	

*mean (SD), [§] mean (SEM)

Significance assessed using independent samples T test

Table 3:3 Multiple Linear Regression of Total Body Fat Percentage using DEXA Scanning

Variable	Coefficient Estimate	95% Confidence Interval	P value
Race *	5.69	0.45 to 10.92	0.034
Age (y)	0.12	-0.12 to 0.37	0.308
BMI (kg/m ²)	1.02	0.55 to 1.49	<0.001
(Constant)	0.30	-23.62 to 24.23	0.980

* SA relative to WE

Table 3:4 Multiple Linear Regression of Abdominal Fat Percentage using DEXA Scanning

Variable	Coefficient Estimate	95% Confidence Interval	P value
Race *	6.95	2.53 to 11.36	0.003
Age (y)	0.13	-.072 to 0.34	0.196
BMI (kg/m ²)	0.97	0.58 to 1.37	<0.001
(Constant)	3.50	-16.69 to 23.68	0.727

* SA relative to WE

Table 3:5 Correlation between Measurement Methods for Body Fat Composition in Male Subjects Screened for Diabetes

	<i>Correlation Coefficients</i>	BMI	waist-hip ratio	waist circumference	body fat % (skinfolds)	body fat % (BIA)
White European Males N=55	BMI (kg/m²)	1	0.30(*)	0.38(**)	0.72(**)	0.80(**)
	waist-hip ratio	0.30(*)	1	0.17	0.15	0.37(**)
	waist circumference (cm)	0.38(**)	0.17	1	0.60(**)	0.48(**)
	body fat % (skinfolds)	0.72(**)	0.15	0.60(**)	1	0.69(**)
	body fat % (BIA)	0.80(**)	0.37(**)	0.48(**)	0.69(**)	1
South Asian Males N=38	BMI (kg/m²)	1	0.15	0.78	0.64(**)	0.56(**)
	waist-hip ratio	0.24	1	-0.14	0.19	0.38(*)
	waist circumference (cm)	0.05	-0.14	1	0.22	-0.03
	body fat % (skinfolds)	0.64(**)	0.19	0.22	1	0.52(**)
	body fat % (BIA)	0.56(**)	0.38(*)	-0.03	0.52(**)	1

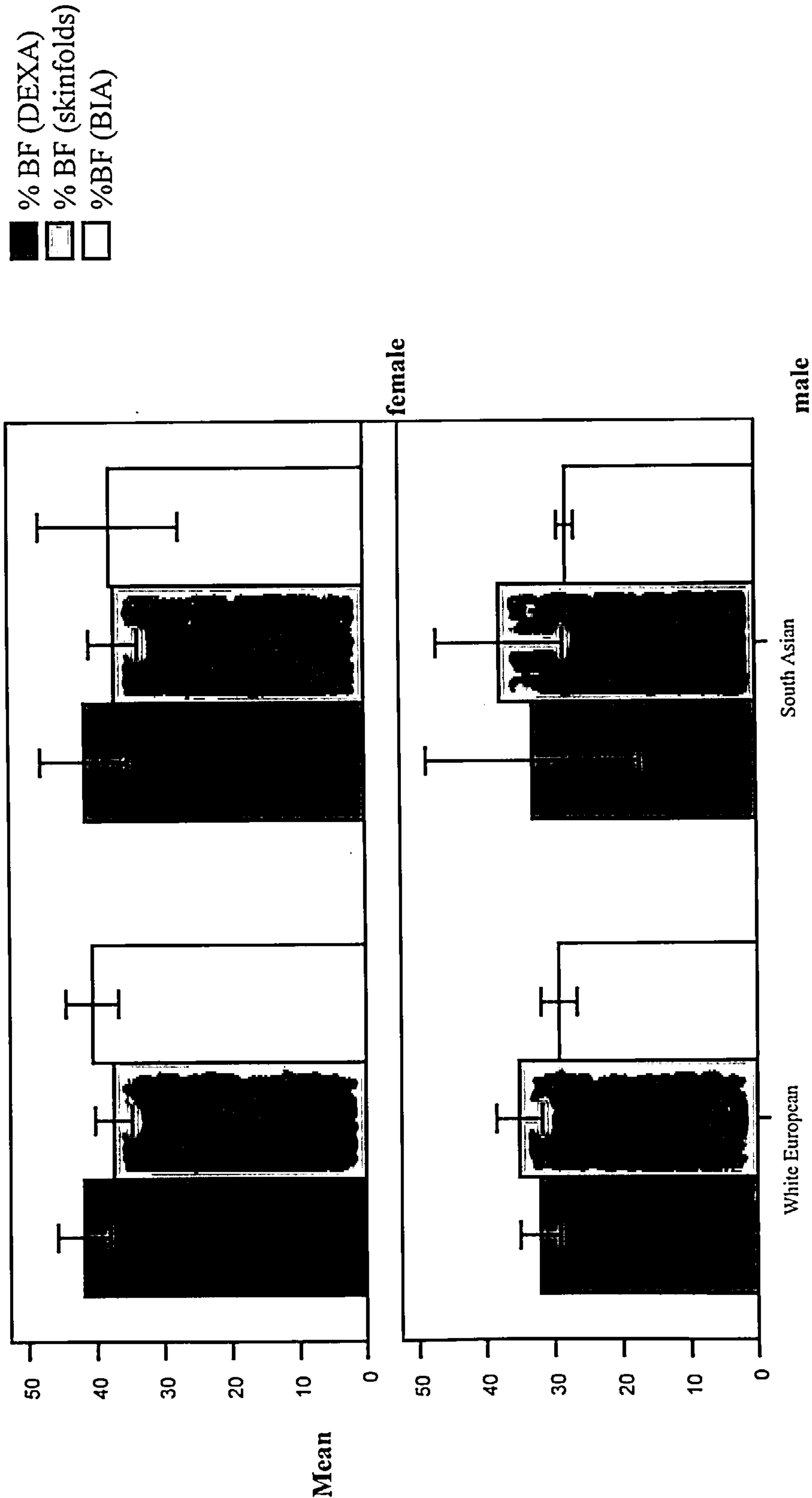
* p<0.05
** p<0.01

Table 3:6 Correlation between Measurement Methods for Body Fat Composition in Female Subjects Screened for Diabetes

	<i>Correlation Coefficients</i>	BMI	waist-hip ratio	waist circumference	body fat % (skinfolds)	body fat % (BIA)
White European Females N=65	BMI (kg/m²)	1	-0.13	0.22	0.77(**)	0.85(**)
	waist-hip ratio	-0.13	1	-0.05	-0.001	-0.01
	waist circumference (cm)	0.22	-0.05	1	0.24	0.17
	body fat % (skinfolds)	0.77(**)	-0.001	0.24	1	0.76(**)
	body fat % (BIA)	0.85(**)	-0.01	0.17	0.76(**)	1
South Asian Females N=43	BMI (kg/m²)	1	0.14	0.59(**)	0.62(**)	0.72(**)
	waist-hip ratio	0.14	1	0.32(*)	0.28	0.24
	waist circumference	0.59(**)	0.32(*)	1	0.35(*)	0.40(**)
	body fat % (skinfolds)	0.62(**)	0.28	0.35(*)	1	0.74(**)
	body fat % (BIA)	0.72(**)	0.24	0.40(**)	0.74(**)	1

* p<0.05
** p<0.01

Figure 3:1 Body Fat Percentage in Subjects with Screen-detected T2DM using Three Different Methods of Measurement



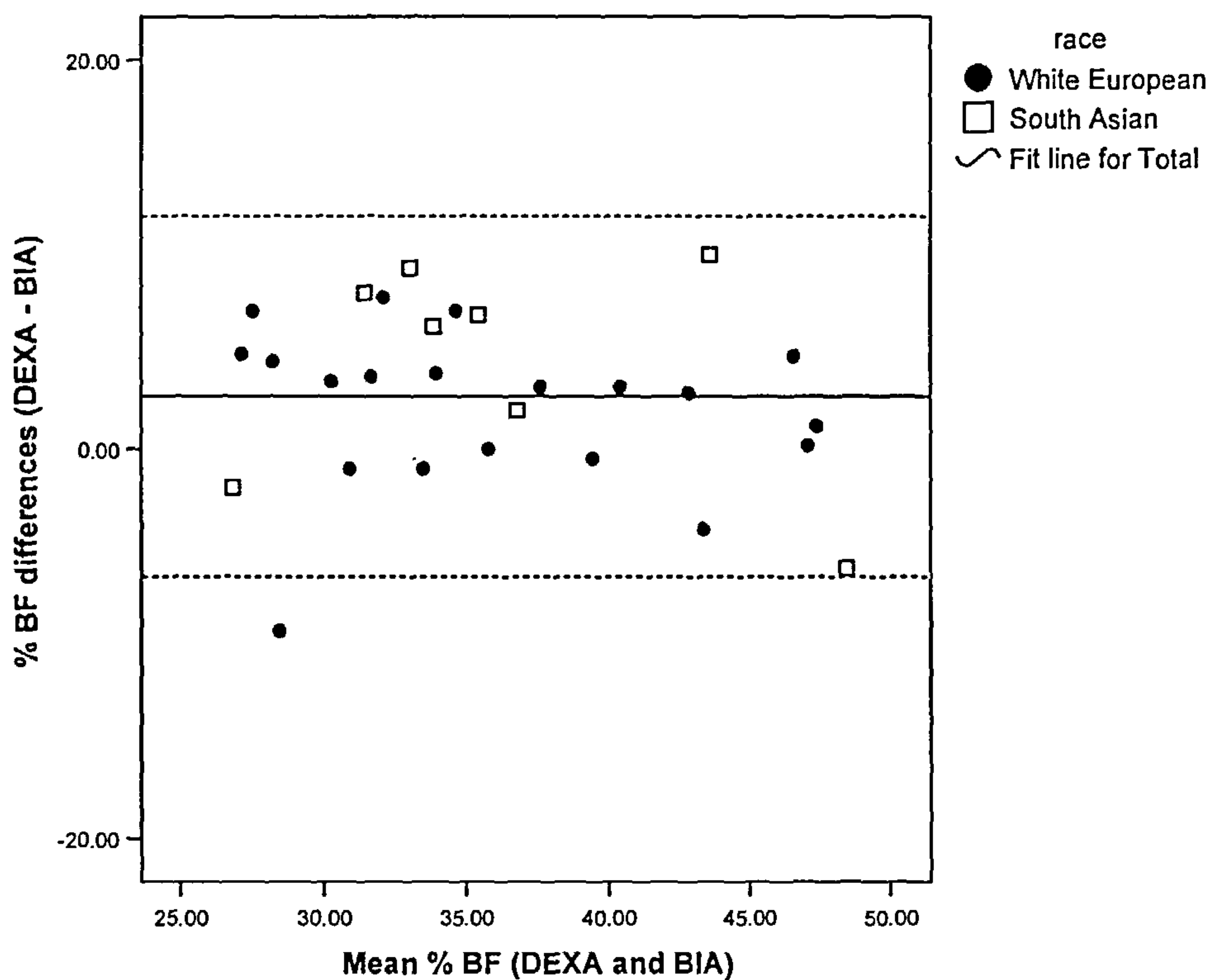


Fig 3:2 Bland and Altman plot of %BF differences between DEXA and BIA

Mean differences \pm SD $2.73 \pm 4.63\%$
Range of limits of agreement -6.53% to 11.99%

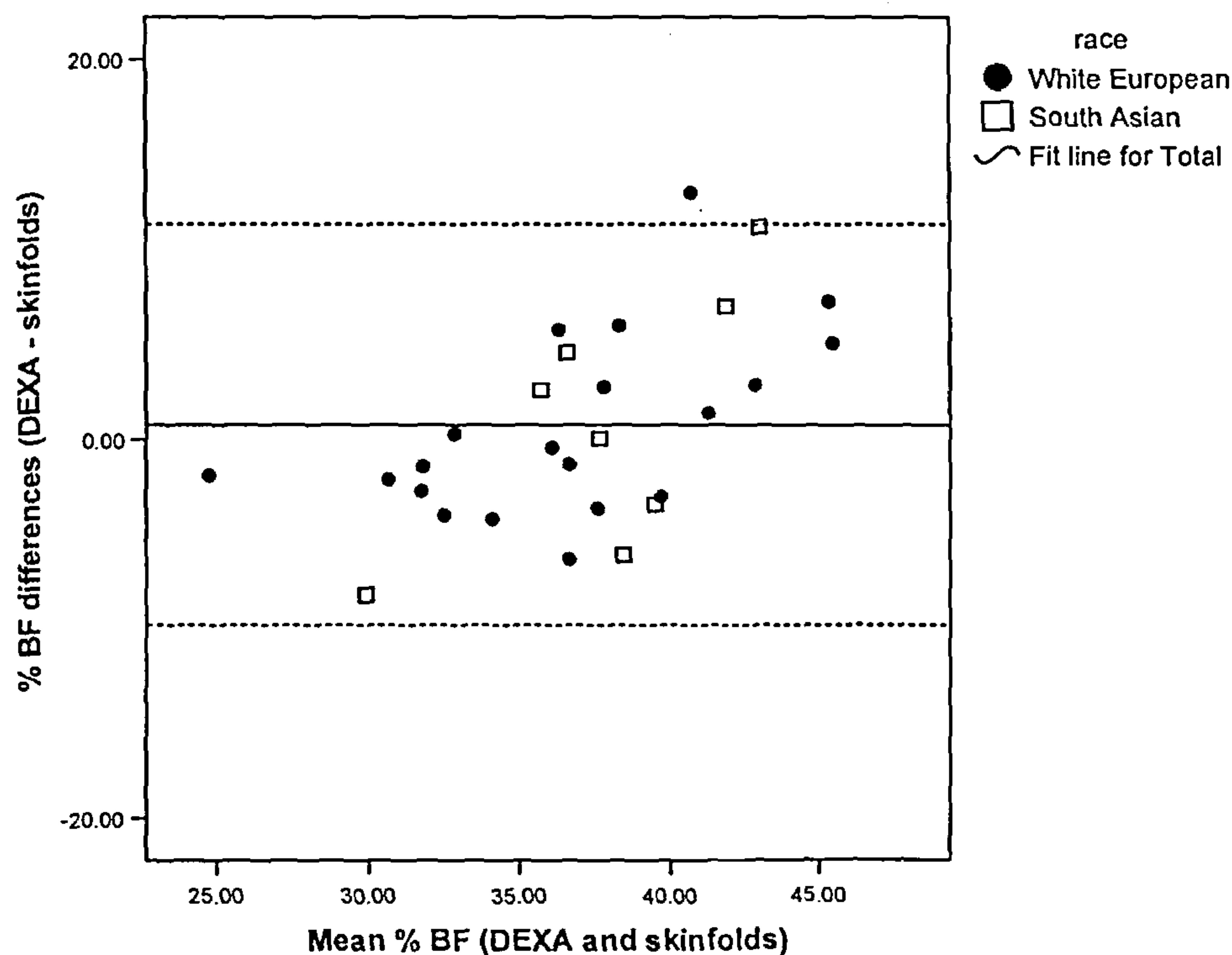


Fig.3:3 Bland and Altman plot of %BF differences between DEXA and skinfolds

Mean differences \pm SD $0.77 \pm 5.28\%$
Range of limits of agreement -9.79% to 11.33%

3:6 Discussion

In this study, one of the main findings was that ethnicity and BMI significantly affected total and abdominal BF% but age was not a significant factor. Being SA and/or having greater BMI were predictors of increased BF%.

DEXA scanning did not differentiate between visceral and subcutaneous adiposity and therefore the ratio of these two compartments cannot be reported. It is possible that WE have relatively more subcutaneous than visceral fat which would be more cardiovascularly protective.

The evidence that simple bedside measurements can improve the ability to detect increased risk of CVD continues to accumulate. INTERHEART (124) and the IDEA study (125) which are global multiethnic studies have demonstrated the ability of WC and WHR to determine CVD risk irrespective of age and BMI.

In INTERHEART, which looked at 27 000 individuals in 52 countries, WHR showed a more significant association with acute MI than BMI, especially at higher levels of adiposity. In IDEA, CVD risk changed from 21% to 40% when WC increased by 14cm in men and 14.9cm in women.

WHR, WC and sagittal abdominal diameter are useful surrogate measurements for detection of visceral adiposity in both WE and SA populations and can be used with minimum effort in the clinical setting (46,124). Other more expensive and cumbersome methods such as CT or MRI scanning (often used in research) are therefore not necessary to determine adipose tissue distribution and cardiovascular risk. Other methods such as

DEXA are less expensive but are still relatively inconvenient for widespread measurement of body fat composition. DEXA underestimates BF% in lean subjects which is probably of less significance in a predominantly overweight population such as our cohort (117,126). Although DEXA does not appear to be affected by hydration status, its validity can be decreased by differences in age, body mass, BMI and gluteal girth (117).

Skinfold thickness, BIA and DEXA have been compared in other populations, for example patients with chronic renal failure undergoing haemodialysis (127). Skinfolts were considered preferable to BIA in determining BF% as there was greater agreement with the gold standard of DEXA used in the study. This population had a much lower mean BMI than in the study described in this chapter (23.5kg/m^2 vs 27.7 kg/m^2). Skinfold measurements are easier to perform and therefore prone to less inter-observer errors in leaner subjects. Differences of up to 10% in BF% have previously been reported when using BIA (128) although in another study good reliability has been shown with impedance measurements (129). In healthy children, BF% derived from the DEXA method was significantly higher than with BIA or skinfolts (130).

Another study of 100 subjects suggested that DEXA underestimates lean body mass and body fat compared with BIA but concluded that both methods were suitable for body composition studies (131). The differences were assumed to be related to different assumptions about the constants in equations used to calculate BF%.

The Durnin and Wormersley equation was used in the study described here to assess BF% and this was also calculated by the BIA device used. It has been shown that this equation can predict BF% values approximately 10% above and below the subject's actual BF% (132). Often this equation underestimates BF% suggesting that, in our subjects, values

were likely to be higher than actually obtained. This has been borne out by other studies (93). Furthermore, in subjects with more than 30% BF, Brozek's rather than Siri's equation may be more reliable (133).

The discrepancy between BMI and BF% has been well-documented in both native and migrant SA populations (93,123,134-137). In fact, obesity and BF% appear to be increased in other migrant populations as well, for example, white European migrants living in Sweden (138). This suggests that there may be some factors associated with migration that predispose to relatively greater adiposity compared with the native population. This is partly dependent on the environment to which the migrant is exposed, that is, whether it is obesity promoting. From this perspective, migrants to North America are more susceptible than those to Sweden although the comparative studies looked at Asian and WE populations respectively (139,140). BMI tends to increase with increasing length of stay in the country of migration (141).

Further exploration is needed to determine how much lifestyle factors, including amount of exercise, smoking and alcohol consumption and high fat and carbohydrate diets, play a part in determining diabetes and cardiovascular risk. For example, smokers were reported to have greater WHR than non-smokers with comparable body weight (142). This is especially important as migrants differ in their degrees of assimilation with the native population's lifestyle. Socioeconomic factors may also be important as poorer social groups are associated with greater CVD and diabetes risk. The probable interaction with genetic susceptibility remains unclear.

The case for reducing visceral adipose tissue continues to strengthen with several interventional studies. For example, substantial improvements in oral glucose tolerance,

fasting plasma glucose and insulin sensitivity have been seen with removal of small amounts of intra-abdominal adipose tissue (<1kg) (143). Conversely despite a reduction in WC of more than 12cm with liposuction of subcutaneous abdominal fat, no significant improvement in cardiovascular risk was achieved (144).

As T2DM and CVD increase with rising obesity, the level of risk that is perceived in SA is clearly being underestimated. In the data reported here, BF% was very similar in WE and SA with PDM and T2DM despite much lower BMI and WC in the latter group. The need for different cut-offs is clear if risk is not to be under-estimated.

3:7 Conclusion

The well-documented variability in different methods for determining body fat composition was observed with the study described in this chapter. The difficulty of applying the same equation to different ethnic populations makes the results somewhat difficult to interpret. Nevertheless, it was found that regardless of method used, there was a clear increase in BF% with worsening glucose tolerance in both WE and SA and this was observed using simple measures such as WC as well as those requiring specialised equipment such as skinfold measurements and BIA. With DEXA in diabetic subjects, total and abdominal BF% was affected by differences in race and BMI.

It can be concluded that continuing to use BMI as the sole obesity marker to measure CVD risk in different populations is inherently misleading. The adoption of simple measures such as WC and WHR and, if resources permit, methods such as BIA, skinfold thickness and DEXA to delineate actual BF%, need to be considered if risk stratification is to be more effective in different populations. The relatively small size of this study did not allow cut-offs to be determined which could be used to predict different levels of glucose tolerance.

Further longitudinal and randomised controlled interventional studies of sufficient magnitude comparing WE with SA are required to determine prevalence of abdominal and visceral obesity and the effects of its reduction in at risk populations.

CHAPTER FOUR

PHENOTYPE OF SUBJECTS WITH SCREEN-DETECTED DIABETES

Circulating Risk Markers and their Association with Glucose Tolerance

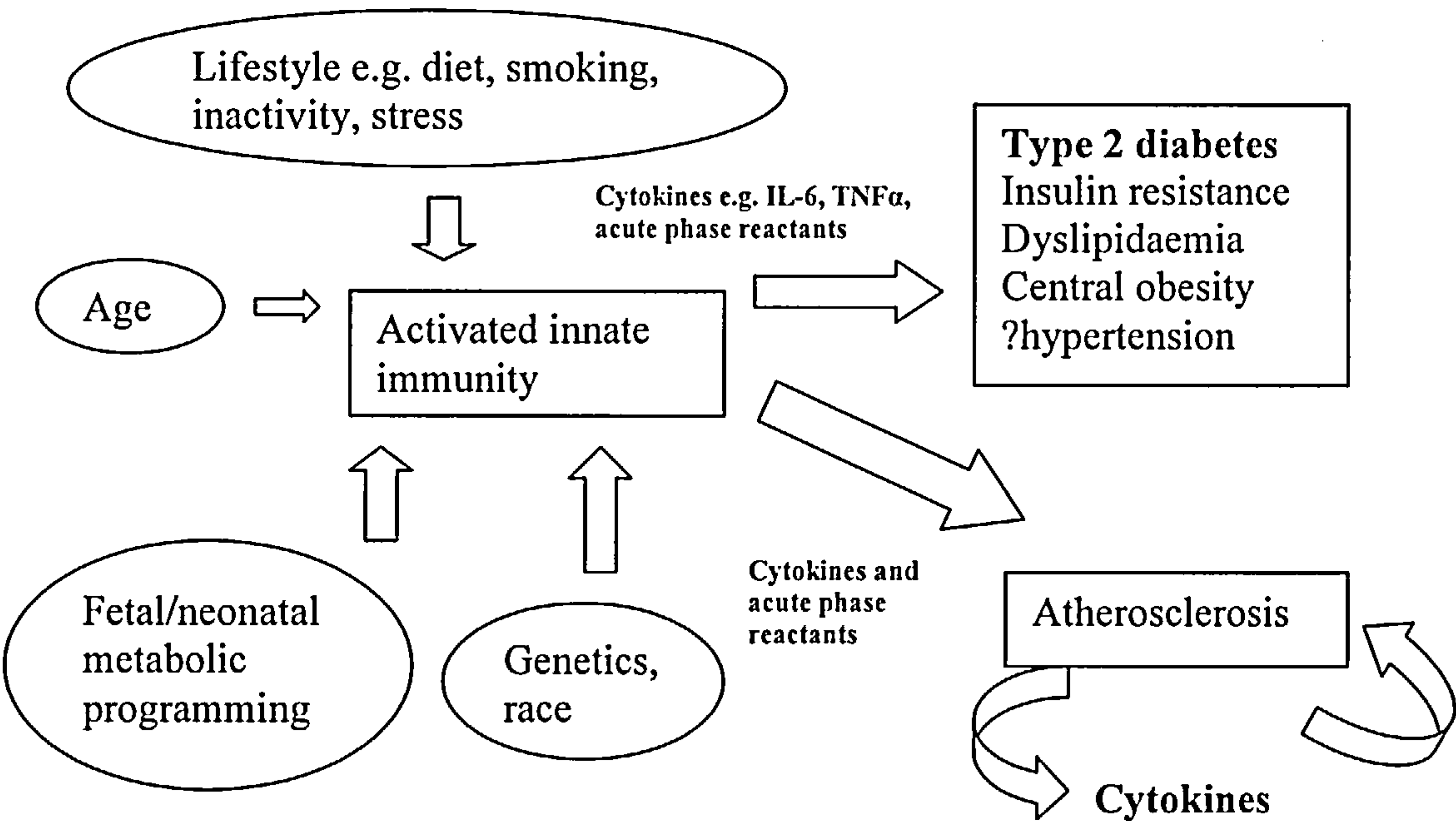
4:1 Introduction

In the previous chapter, the morphological phenotype of screened subjects was discussed and examined. The relative adiposity of subjects screening positive for PDM or T2DM was identified. What are the risks of increased amounts of adipose tissue? One of the most exciting current areas of research is in exploring the cytokines produced by adipocytes and the interaction between organs such as adipose tissue, muscle and liver in a metabolic environment of chronic mild inflammation and dyslipidaemia (8).

This chapter explores the biochemical phenotype of screened subjects by investigating and then discussing the difference in concentrations of circulating inflammatory risk markers across the glucose spectrum and in WE and SA populations screened for abnormal glucose tolerance.

The role of inflammation as a preceding event in development of T2DM and CVD has been intensely debated over the last few years (8-11). The “common soil” hypothesis suggests that low levels of chronic inflammation are responsible for triggering the abnormal metabolic features associated with these conditions (145). Normally, the acute phase response to inflammation is entirely appropriate and conducive to long-term survival. However, chronic exposure to stressful stimuli such as ageing, increased fat and glucose intake, and a sedentary lifestyle transforms a protective mechanism into a harmful one that predisposes to increased morbidity and mortality (Fig. 4:1) (11).

Figure 4:1 The Role of Activated Innate Immunity as the Antecedent of Type 2 Diabetes and Atherosclerosis (adapted from (8))



Hyperglycaemia has been linked to inflammation by demonstration of simultaneous inflammation, endothelial dysfunction and insulin resistance at the pathophysiological level (146). Reducing hyperglycaemia alone did not decrease the number of cardiovascular events in several studies such as the large UKPDS (65) and the smaller Kumamoto study (147). It is possible that the link between CVD and diabetes is the inflammatory processes underlying both conditions (9) and that targeting pro-inflammatory cytokines would enable greater reductions in atherosclerosis related complications.

A number of circulating biochemical substances have been identified which can provide a surrogate marker of cardiovascular risk in subjects with T2DM and PDM. These include C-reactive protein (CRP), interleukin-6 (IL-6), adipocytokines such as adiponectin, leptin, resistin and tumour necrosis factor α (TNF α), and apolipoproteins A-1 and B (apo A-1 and apo B).

Pharmacological agents such as aspirin and HMG Co-A reductase inhibitors (statins) have been extensively studied to determine their effects on circulating risk markers. In a small study of nine subjects with T2DM treated with two weeks of high dose aspirin (approximately 7g/day) there was a 25% reduction in fasting plasma glucose, 15% reduction in CRP concentration, 50% reduction in triglycerides and 30% reduction in insulin clearance (148). The optimal dose of aspirin for reducing chronic low-grade inflammation and its association with atherosclerosis has yet to be determined and long-term intervention studies are needed to investigate this further (149).

CRP concentrations are lowered by atorvastatin in patients with T2DM (150) and by pravastatin in those who have had a myocardial infarction (151). Pravastatin also appears

to reduce the risk of developing T2DM as shown in the West of Scotland Coronary Prevention Study (152) .

It has been suggested that inflammation is not solely induced by chronic hyperglycaemia and that the inflammatory response may be reduced by improving glycaemic control (8). Thiazolidinediones or “glitazones” are PPAR- γ agonists used in the treatment of T2DM and improve insulin sensitivity. Furthermore, they have beneficial but small effects on lipid profile and blood pressure. Troglitazone, now withdrawn from the global market, reduces reactive oxygen species generation and nuclear factor- κ B binding activity by 50 in obese subjects (153). Rosiglitazone has been shown to reduce CRP concentrations (154). In the PRO-ACTIVE study, pioglitazone was used in patients with T2DM at high risk of macrovascular disease and there was a non-significant decrease in all events including mortality in the pioglitazone group after approximately three years of follow-up (155). It is possible that reducing chronic inflammation led to improvement in macrovascular outcomes in this study. Interestingly, TNF- α also down-regulates PPAR- γ expression (156). Troglitazone and pioglitazone stop the progression of intima-media thickness in the carotid artery of diabetic subjects within three months of administration and the benefits appear to continue for at least six months (157,158). Adiponectin gene expression and circulating adiponectin levels are increased by thiazolidinediones in insulin-resistant obese human subjects (159).

High Sensitivity C-Reactive Protein

Normal individuals have low circulating CRP concentrations which are synthesised in the liver in response to inflammatory substances such as IL-6 released from macrophages and activated T cells (160,161). With acute inflammation, CRP concentrations are as high as

40-200 mg/L. However in healthy individuals the median concentration is 0.8-1.1 mg/L and assay-dependent.

Traditional immunophelometric or immunoturbidimetric automated methods used in the clinical laboratory have a sensitivity of around 3-5 mg/L when detecting CRP. However, to assess CVD risk, the analytical method used to measure CRP must have greater sensitivity e.g. below 1 mg/L and therefore is termed 'high sensitivity' CRP (hsCRP). Studies have shown that CRP is higher in diabetes than in the normal population (162-164) and in healthy subjects, CRP is predicted by BMI and 2-hour post-challenge glucose (165). CRP is a risk factor for the development of T2DM (166,167) and insulin resistance (168). In the West of Scotland Coronary Prevention Study, CRP>4.18mg/l was associated with more than three-fold risk of developing T2DM at five years in middle-aged men (169).

Elevated CRP is associated with increasing HbA1c levels (170). In 1018 North American patients with T2DM, it was found that, after controlling for age, ethnicity, sex, smoking, diabetes duration, insulin and BMI, HbA1c was significantly associated with increased likelihood of elevated CRP for HbA1c>9% by more than two-fold and for HbA1c>11% by more than four-fold. This study was limited by the self-reported nature of the data, including diabetes diagnosis, anti-inflammatory medication usage and smoking status.

CRP selectively binds to low-density lipoprotein especially within atherosclerotic plaques, which results in complement activation and promotes inflammation, potentially contributing to atherosclerosis. It may also increase macrophage production of tissue factor, which initiates coagulation and is responsible for occlusive thrombotic events. Raised CRP levels have been linked to increased risk of thrombotic events including MI (171-173).

A large cohort study of 746 American men with T2DM aged 46-81 years were followed up for around five years and high CRP levels were associated with increased risk of cardiovascular events. This was independent of lifestyle risk factors, lipid profile and glycaemic control (174). HsCRP is useful in predicting development of future cardiovascular events in stable and unstable angina (175).

CRP is markedly different according to ethnicity. In a Canadian study, asymptomatic SA had higher CRP levels than Chinese or European subjects despite adjustment for glucose metabolism, body weight or abdominal obesity (176). Combined increases in both visceral and total body adiposity appear to be more critically associated with a rise in CRP levels than increases in either parameter alone (177). CRP is higher in SA than WE in the UK (178). Another study showed median CRP levels were nearly double in SA compared with WE women (179).

Adipocytokines

Previously thought to be just an inert storage organ, adipose tissue is now established as a highly metabolic endocrine gland with adipocytes capable of producing a number of hormones such as TNF α , adiponectin, leptin and resistin (Fig. 4:2) (88). Adipose tissue mass expands by an angiogenesis-dependent mechanism (180). These hormones have been linked to insulin resistance and metabolic syndrome. In this way, they can be surrogate markers of cardiovascular risk.

Tumour Necrosis Factor α

TNF α is a pro-inflammatory cytokine produced by neutrophils and macrophages, which is involved in mechanisms leading to development of atherosclerosis and CVD. It is also

secreted by adipose tissue and is elevated in obese subjects (181). Inflammatory cytokines such as TNF α are thought to impair insulin action by various mechanisms. They can attenuate insulin-induced suppression of hepatic glucose production, enhance hepatic production of triglycerides and free fatty acids and may also inhibit insulin-stimulated glucose uptake (182). Specifically, down-regulation of TNF α receptors appears to be associated with improvements in blood pressure and insulin resistance (183).

TNF α also increases levels of IL-6, a major pro-inflammatory cytokine. Whereas TNF α concentrations have been reported as normal in PDM (184), other studies have shown elevated levels in T2DM (185-187). Dietary restriction and weight loss reduce TNF α (188). In post-MI patients, TNF α negatively correlated with HDL cholesterol (189). TNF α mRNA has been found within human atherosclerotic plaques (190,191).

There are little data on the prevalence of TNF α in migrant SA. However, one study in India showed that TNF α concentration is elevated in urban compared with rural SA (192).

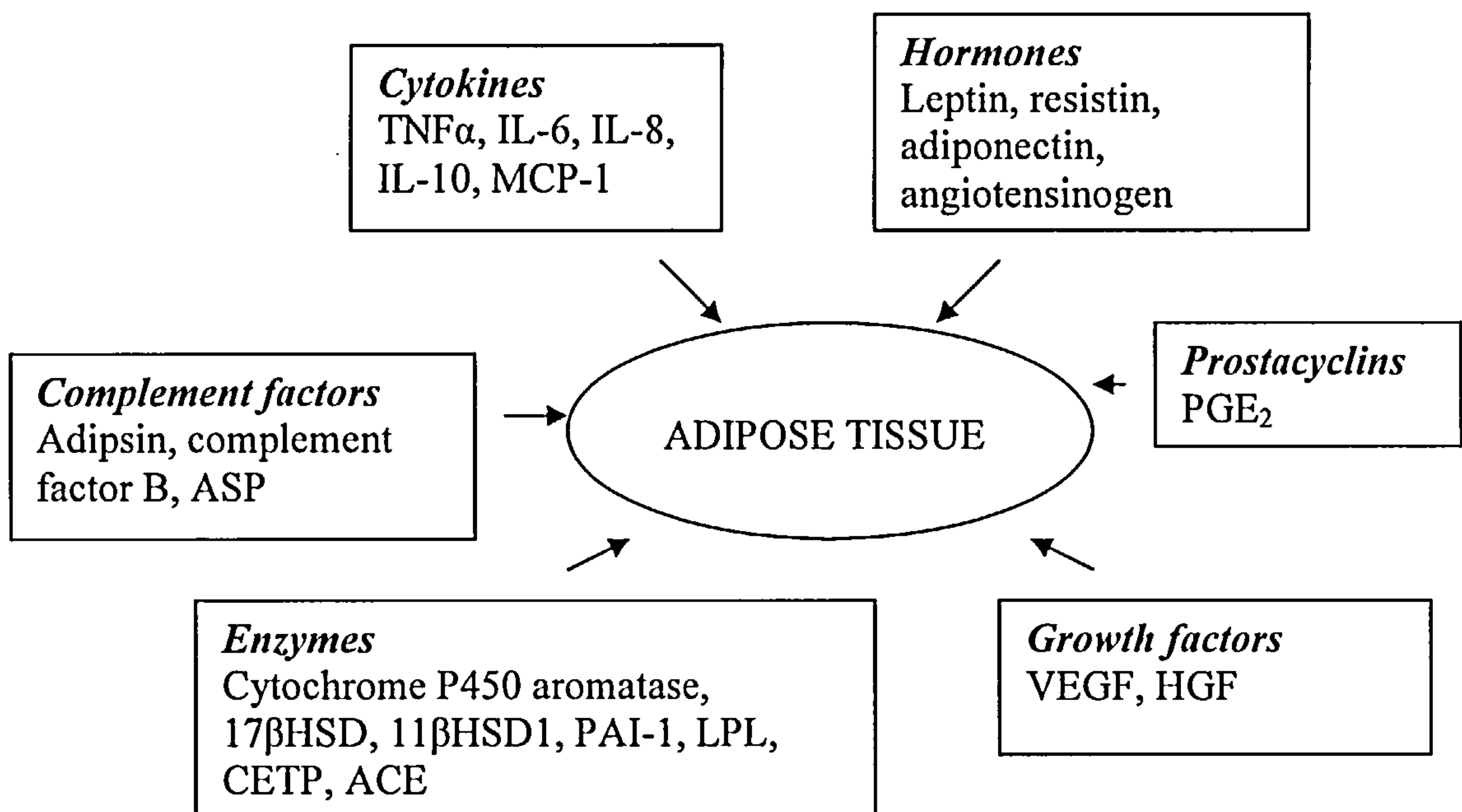


Fig. 4:2 Proteins derived from Adipose Tissue (adapted from (193))

17βHSD, 17β-hydroxysteroid dehydrogenase; 11βHSD1, 11β-hydroxysteroid dehydrogenase-1; LPL, lipoprotein lipase; CETP, cholesterol ester transfer protein; PAI-1, plasminogen activator-inhibitor-1; ACE, angiotensin-converting enzyme; ASP, acylation-stimulating protein; HGF, hepatic growth factor; MCP-1, monocyte chemoattractant protein-1; PGE₂, prostaglandin E2; VEGF, vascular endothelial growth factor.

Adiponectin

One of the most extensively researched adipocytokines, adiponectin is a hormone exclusively expressed and secreted by adipose tissue (89). Uniquely, it is a protective adipocytokine with low concentrations in obesity which increase after weight loss (194,195). Adiponectin is also low in association with insulin resistance, CVD and T2DM (196). In particular, adiponectin has anti-inflammatory and antiatherogenic properties (197) and suppresses TNF α secretion (198,199). Reduced inflammation with better glycaemic and lipid profiles is associated with increased adiponectin concentrations in male T2DM subjects (200). Reduced adiponectin was independently associated with increased risk of T2DM and metabolic syndrome in 372 elderly Korean subjects (201).

Effects of lifestyle modification are uncertain. Adiponectin did not increase in young Finnish men in military service on a six month low-calorie diet (202). However, a low-energy Mediterranean style diet and increased physical activity in obese Italian women was associated with significantly increased adiponectin levels (203).

Serum adiponectin exists in trimeric, hexameric and high-molecular-weight (HMW) forms (204) which exhibit different biological activities. Interestingly, only the HMW isoform is increased after weight loss in obese individuals (205) and after thiazolidinedione treatment (206).

Future CVD risk in women was not predicted by adiponectin levels although they were associated with insulin resistance (207). In Indo-Asian subjects, HDL cholesterol is the best predictor of adiponectin levels and is lower than in BMI-matched Caucasians (208). Another sub-population with decreased adiponectin levels are women with previous

gestational diabetes (209). Of concern is that levels in this study were low regardless of BMI or insulin sensitivity.

Leptin

Leptin is a product of the *ob* gene (210) and is produced by differentiated adipocytes as well as skeletal muscle tissue, liver, placenta and stomach (211). Leptin levels increase with increasing body fat and are associated with insulin resistance and hypertension. It binds to hypothalamic receptors and increases satiety (212,213). Elevated leptin is a risk factor for development of T2DM (214). Its production is regulated by insulin, glucocorticoid, TNF α , interleukin-1 and TGF β . Recombinant leptin is not beneficial in morbidly obese subjects. After weekly injections of long-acting pegylated human leptin for eight weeks, there was no change in metabolic or inflammatory status of 28 healthy males and females (215).

Differences in leptin in migrant SA have been noted in studies in several countries. There were significantly higher leptin levels in UK SA with T2DM compared with those with normal glucose tolerance or IGT (216). Leptin levels are much higher in offspring aged 18-30 years of SA immigrants living in North America compared with the native white population (217).

Resistin

The gene family of resistin and its tissue-specific distribution was first described in 2000 (218) and it was thought to induce insulin resistance (219). It reduces the insulin-stimulated uptake of glucose by tissues, thus decreasing insulin sensitivity in obese mice (220). It has high expression in adipocytes. It has been suggested that resistin induces obesity and is related to insulin sensitivity but this role as yet remains unproven (221,222).

In 65 Chinese patients with hypertension, fasting resistin concentrations were significantly higher in those with T2DM compared with those with IGT or normal glucose tolerance (223).

In 231 Japanese subjects with T2DM, adiponectin, leptin and resistin correlated with visceral and subcutaneous fat. A correlation was also demonstrated between adipocytokines and carotid intima-media thickness (224). In a cross-sectional study of 150 SA in the UK with worsening glucose tolerance, resistin was inversely correlated with adiponectin (216).

Apolipoproteins A-1 and B

Diabetes is commonly associated with deranged lipid profiles and this may contribute to the increased risk of CVD. The combined cholesterol in low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and very low density lipoprotein (VLDL) sub-fractions appears to result in greater cardiovascular risk than LDL cholesterol alone. Total apolipoprotein B (apo B) levels are highly correlated with non-HDL cholesterol, as there is one apo B molecule per particle of LDL, IDL and VLDL (225).

An increasing number of studies indicate that lipid sub-fractions such as non-HDL cholesterol and total apolipoproteins B and A-1 are stronger markers of cardiovascular risk than LDL cholesterol (226,227).

A study in 313 Swedish men identified that the apoB / apoA-1 ratio was strongly associated with metabolic syndrome and change in carotid artery intima media thickness after three years (228).

Adiponectin is positively associated with HDL cholesterol and inversely associated with triglycerides and apoB100. As increasing levels of adiponectin improve insulin sensitivity, raised levels of apoB100 may increase insulin resistance (229).

In SA living in Canada, apoB/apoA-1 ratio was significantly associated with increased body fat as measured by WHR and BMI but interestingly not with actual BF% (230).

Circulating Risk Markers in South Asian Population

It has already been discussed that SA represent a particularly high risk population for development of T2DM and CVD. Table 4:1 summarises the evidence to date showing associations between the above circulating risk markers and the SA population.

Table 4:1 Key Associations of Risk Markers in South Asian Population in UK and Globally

Risk Marker	Association
hsCRP	Higher in SA than WE in UK (231) and Canada (232)
Adiponectin	Low in SA (233) Predicted by HDL chol (234)
Leptin	Higher in SA with T2DM in UK (216) Higher in offspring of SA immigrants in N.America (235)
TNF alpha	Higher in urban than rural SA in India (236)
Resistin	Inverse correlation with adiponectin in UK SA (216)
Apo B/apo A-1 ratio	Significantly associated with increased body fat in SA in Canada (230)

4:2 Key Research Questions

1. Are there characteristic circulating levels of conventional and non-conventional cardiovascular risk factors in patients screened for T2DM and PDM?
2. Are these cardiovascular risk markers associated with disease in White Europeans and South Asians?

4:3 Subjects and Methods

At the time of screening in the STAR study, baseline demographic data were collected including age, sex, ethnicity, drug and smoking history, BMI and WHR. Plasma and serum samples were taken for fasting and 2 hour glucose, fasting insulin, HbA1c and renal function. Urine samples were obtained for estimation of urinary albumin excretion. Further serum samples were removed for storage in a -70° freezer for subsequent analysis of circulating inflammatory markers. The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all subjects. The local ethics committee approved the study.

T2DM was confirmed with two positive OGTT results using 1999 WHO criteria (121). PDM was diagnosed by a single OGTT result, and was monitored by annual re-screening.

Biochemical Analyses

From this cohort, serum samples from 85 WE (47 PDM and 38 T2DM) and 80 SA (49 PDM, 31 T2DM) were randomly selected by the author. Plasma samples from age, sex and ethnicity- matched controls were also selected for analysis. All the biochemical analyses were performed by the author at the Unit for Diabetes and Metabolism at Warwick Medical School.

The serum samples were transferred in dry ice to the laboratory and 2ml samples were aliquoted into five further 200µl tubes to minimise repeated defrosting cycles. HsCRP was analysed using standard ELISA techniques (Life Diagnostics® Inc., West Chester, PA,

USA). Intra-assay coefficient of variation was 2.3-7.5% and inter-assay coefficient of variation was <20%.

All other circulating inflammatory markers, namely adiponectin, leptin, resistin, TNF α apo A-1, apo B and IL-6 were analysed using bioplex assay (Linco[®] Research, St.Charles, MO, USA). This relatively novel technique involves mixing serum molecules with antibody-coated microspheres, which are then read by a laser in the bioplex analyser. The technique allows several analytes to be measured simultaneously. Each sample was analysed in duplicate using standard techniques. For bioplex, intra-assay coefficient of variation was 1.4-7.9% and inter-assay coefficient of variation was <21%.

4:4 Statistical Analysis

All values are given as mean \pm standard deviation (SD) unless otherwise stated. Linear regression analyses (following logarithmic transformation as markers were not normally distribute) were used to determine differences in circulating risk markers between ethnic groups. Correlation coefficients are stated with 95% confidence intervals. Significance was assumed if $p < 0.05$. All statistical analyses were carried out using SPSS statistical software version 14.0 (SPSS, Chicago, IL, USA).

4:5 Results

Samples from 118 WE (50% male) and 113 SA (48% male) were analysed. Baseline characteristics of the 231 subjects are summarised in Tables 4.2 and 4.3. Age increased progressively with abnormal glucose tolerance and WE tended to be slightly older than SA. BMI and WHR increased with PDM and T2DM in both groups. Systolic and diastolic blood pressure, triglycerides, HbA1c and fasting plasma glucose all increased with deterioration in glucose tolerance. Total cholesterol remained relatively stable and HDL cholesterol fell with PDM and T2DM.

Mean concentrations of circulating risk markers according to ethnicity and glucose status are shown in Tables 4.4 and 4.5. Leptin, TNF α and hsCRP all increased in WE with worsening glucose tolerance, whereas IL-6 initially fell slightly with PDM. Adiponectin levels decreased in WE with PDM and T2DM. In SA, trends were less consistent. There was an increase in leptin and hsCRP, and a decrease in adiponectin with abnormal glucose tolerance. However, resistin increased markedly with PDM before falling again in those with T2DM. Conversely TNF α and IL-6 fell initially with PDM before rising again with T2DM.

TNF α , adiponectin and resistin were significantly different between WE and SA males with normal glucose tolerance ($p=0.04$, $p=0.002$ and $p=0.04$ respectively). In the diabetic state, hsCRP differed between WE and SA males (8.16 mg/l vs 4.44 mg/l, $p=0.03$). Leptin was significantly different between WE and SA controls (6.62 vs 18.12 ng/ml, $p=0.02$). Following adjustment for age, BMI, WHR, smoking, BP and lipid treatment and gender, predictors of leptin concentration were age, BMI and gender in WE, but only gender in SA

(Table 4:6). There were no significant predictors of adiponectin or resistin after adjustment for these variables (Tables 4:7 and 4:8). Age and current smoking were predictors of TNF α in SA (Table 4:9). BMI predicted hsCRP in WE and SA (Table 4:10). The change in circulating risk markers across the glucose spectrum is shown for both ethnic groups in Figures 4:4 and 4.5.

Table 4:2. Baseline Characteristics of Male Subjects – mean (SD) unless otherwise stated

Characteristics	Controls			Pre-Diabetes			Diabetes		P Value
	White Europeans N=16	South Asians N=15		White Europeans N=23	South Asians N=23		White Europeans N=20	South Asians N=15	
Age (y)	57.06 (11.47)	52.53 (11.34)		64.00 (8.36)	56.04 (10.94)		61.30 (9.17)	55.47 (11.81)	0.002
BMI (kg/m²)	22.95 (1.30)	23.66 (1.22)		27.33 (3.58)	25.64 (2.52)		30.92 (3.54)	28.92 (5.80)	0.09
Waist-hip ratio	0.87 (0.06)	0.91 (0.05)		0.97 (0.12)	0.96 (0.04)		0.98 (0.07)	0.98 (0.07)	0.74
SBP (mmHg)	138.00 (17.59)	128.73 (17.67)		144.70 (20.49)	132.22 (14.62)		139.25 (23.97)	146.00 (24.25)	0.13
DBP (mmHg)	81.00 (9.40)	77.87 (11.99)		79.96 (11.40)	79.83 (7.81)		80.50 (11.07)	85.27 (11.98)	0.85
Total chol (mmol/l)	5.06 (0.99)	5.59 (1.08)		4.90 (0.88)	5.63 (1.37)		5.20 (1.02)	5.18 (1.18)	0.03
LDL chol (mmol/l)	3.18 (0.82)	3.77 (0.74)		3.00 (0.79)	3.64 (1.02)		3.18 (0.83)	2.78 (0.90)	0.04
HDL chol (mmol/l)	1.31 (0.37)	1.07 (0.25)		1.27 (0.54)	1.12 (0.26)		1.10 (0.30)	1.36 (1.04)	0.57
TG (mmol/l)	1.23 (0.51)	1.66 (0.69)		1.41 (0.70)	2.00 (1.52)		2.77 (2.53)	2.91 (2.90)	0.31
HbA1c (%)	5.43 (0.55)	5.65 (0.62)		6.10 (0.61)	6.05 (0.40)		7.31(2.11)	7.70 (1.43)	0.74
FPG (mmol/l)	4.89 (0.49)	5.08 (0.42)		5.56 (0.53)	5.43 (0.66)		8.15 (3.21)	8.39 (2.45)	0.84
MAC ratio	0.53 (0.31)	0.45 (0.19)		2.78 (10.47)	0.77 (0.91)		1.47 (3.08)	1.83 (2.50)	0.42
BMI>30 (%)	0	0		26	5		75	43	0.008
Current smoker (%)	69	20		39	13		20	33	0.023
Ex-Smoker (%)	13	7		35	9		35	27	0.045
BP treatment (%)	19	40		50	39		60	50	0.79
Lipid treatment (%)	0	0		45	17		20	29	0.26

p values derived using one way ANOVA comparing PDM and T2DM with controls

Table 4:3. Baseline Characteristics of Female Subjects – mean (SD) unless otherwise stated

Characteristics	Controls			Pre-Diabetes		Diabetes		P Value
	White Europeans N=17	South Asians N=18		White Europeans N=24	South Asians N=26	White Europeans N=18	South Asians N=15	
Age (y)	54.53 (9.61)	48.22 (11.17)		58.04 (9.91)	52.12 (9.87)	62.11 (10.67)	51.87 (9.54)	<0.001
BMI (kg/m ²)	22.55 (1.81)	23.14 (2.06)		31.43 (6.75)	29.47 (4.48)	31.67 (6.03)	29.61 (5.33)	0.22
Waist-hip ratio	0.81 (0.09)	0.87 (0.09)		0.90 (0.08)	0.87 (0.08)	0.91 (0.09)	0.88 (0.06)	0.59
SBP (mmHg)	121.06 (21.23)	116.72 (15.39)		126.13 (13.41)	128.46 (18.90)	143.39 (15.39)	147.07 (22.82)	0.93
DBP (mmHg)	73.82 (10.13)	73.94 (9.51)		75.63 (9.96)	75.08 (9.09)	81.67 (9.88)	86.13 (12.54)	0.77
Total chol (mmol/l)	5.75 (1.14)	5.26 (0.99)		5.68 (0.91)	5.43 (1.00)	5.52 (0.99)	5.46 (1.03)	0.15
LDL chol (mmol/l)	3.43 (0.82)	3.36 (0.64)		3.48 (0.86)	3.45 (0.84)	3.37 (0.91)	3.48 (0.88)	0.99
HDL chol (mmol/l)	1.75 (0.59)	1.33 (0.29)		1.40 (0.31)	1.24 (0.23)	1.26 (0.23)	1.13 (0.20)	0.001
TG (mmol/l)	1.59 (1.16)	1.23 (0.84)		1.80 (0.92)	1.63 (0.72)	1.96 (0.71)	2.25 (1.55)	0.52
HbA1c (%)	5.43 (0.37)	5.68 (0.31)		5.88 (0.37)	6.03 (0.53)	6.55 (0.82)	7.17 (0.72)	0.05
FPG (mmol/l)	4.57 (0.55)	4.99 (0.56)		5.30 (0.30)	5.33 (0.55)	6.95 (1.23)	7.49 (1.41)	0.41
MAC ratio	0.82 (1.31)	0.63 (0.47)		0.54 (0.31)	1.01 (0.83)	2.48 (7.42)	0.89 (0.59)	0.53
BMI>30 (%)	0	6		58	36	50	47	0.27
Current smoker (%)	76	0		33	19	22	13	<0.001
Ex-Smoker (%)	6	0		21	4	33	0	0.001
BP treatment (%)	6	17		52	15	78	50	0.01
Lipid treatment (%)	0	0		26	4	39	7	0.002

p values derived using one way ANOVA comparing PDM and T2DM with controls

Table 4:4. Concentrations of Circulating Risk Markers in Males – Mean (SEM)

Risk Marker	Control	South Asian N=12	P value	Pre-Diabetes	South Asian N=21	P value	Diabetes	South Asian N=12	P value
	White European N=14			White European N=19			White European N=16		
TNF alpha (pg/ml)	5.87 (0.90)	9.39 (1.24)	0.04	5.68 (1.07)	4.74 (0.61)	0.45	5.30 (0.73)	8.20 (1.50)	0.11
Adiponectin (µg/ml)	29.87 (4.13)	13.54 (3.88)	0.002	17.41 (3.52)	12.31 (2.67)	0.26	17.65 (4.81)	10.30 (5.33)	0.33
Leptin (ng/ml)	4.19 (1.79)	27.17 (14.56)	0.13	18.99 (9.39)	9.40 (1.58)	0.33	17.28 (5.0)	30.31 (12.0)	0.34
Resistin (pg/ml)	20.64 (2.07)	13.75 (2.37)	0.04	21.69 (2.53)	24.92 (6.64)	0.65	18.52 (1.47)	14.70 (3.16)	0.31
HsCRP (mg/l)	8.23 (3.00)	5.19 (1.04)	0.38	7.52 (7.80)	6.57 (6.45)	0.69	8.16 (1.13)	4.44 (1.13)	0.03
Apo A-1 (mcg/ml)	1151.38 (307.88)	842.66 (229.56)	0.43	992.10 (264.90)	1614.74 (926.18)	0.53	1175.78 (354.88)	958.67 (169.76)	0.59
Apo B (mcg/ml)	75.76 (32.12)	65.56 (18.86)	0.793	67.75 (19.66))	66.50 (8.79)	0.96	96.54 (36.04)	60.82 (16.63)	0.39

p values derived using one way ANOVA comparing PDM and T2DM with controls

Table 4:5. Concentrations of Circulating Risk Markers in Females – Mean (SEM)

Risk Marker	Control	South Asian N=18	P value	Pre- Diabetes White European N=16	South Asian N=21	P value	Diabetes White European N=16	South Asian N=12	P value
TNF alpha (pg/ml)	White European N=14 3.81 (0.45)	5.53 (0.77)	0.07	5.28 (0.73)	5.72 (0.63)	0.65	9.34 (1.97)	6.03 (1.40)	0.19
Adiponectin (µg/ml)	26.80 (4.88)	24.15 (4.92)	0.71	22.45 (4.37)	12.78 (2.89)	0.08	20.97 (3.37)	11.51 (3.57)	0.07
Leptin (ng/ml)	6.62 (1.79)	18.12 (4.0)	0.018	52.71 (20.32)	53.07 (16.34)	0.99	69.19 (22.60)	38.89 (15.84)	0.28
Resistin (pg/ml)	23.75 (2.48)	13.37 (1.66)	0.003	20.86 (2.24)	20.18 (6.85)	0.93	28.81 (7.04)	17.38 (2.27)	0.15
HsCRP (mg/l)	4.51 (1.22)	5.90 (1.34)	0.45	7.88 (2.01)	8.43 (1.37)	0.82	10.27 (2.39)	13.59 (3.20)	0.42
Apo A-1 (mcg/ml)	2254.83 (367.98)	1369.55 (249.26)	0.07	1113.99 (227.57)	997.71 (119.88)	0.66	881.28 (173.31)	1390.81 (216.73)	0.08
Apo B (mcg/ml)	86.90 (12.57)	89.54 (19.65)	0.91	63.38 (16.55)	69.00 (17.57)	0.82	55.04 (10.21)	131.64 (20.53)	0.007

p values derived using one way ANOVA comparing PDM and T2DM with controls

Table 4:6 Multiple Linear Regression of Leptin*

Adjusted Variable		Coefficient Variable	95% Confidence Interval	P value
White European	Age (y)	0.02	0.004 to 0.03	0.01
	BMI (kg/m ²)	0.06	0.03 to 0.09	<0.001
	Waist-hip ratio	0.46	-0.85 to 1.77	0.49
	Current smoker	-0.07	-0.32 to 0.19	0.60
	BP treatment	-0.08	-0.39 to 0.22	0.60
	Lipid treatment	0.07	-0.24 to 0.38	0.63
	Gender	0.43	0.19 to 0.68	0.001
	(Constant)	0.29	-1.10 to 1.68	0.68
South Asian	Age (y)	0.01	-0.001 to 0.02	0.08
	BMI (kg/m ²)	0.01	-0.01 to 0.04	0.21
	Waist-hip ratio	-0.99	-2.46 to 0.49	0.19
	Current smoker	0.24	-0.02 to 0.51	0.07
	BP treatment	0.08	-0.18 to 0.33	0.55
	Lipid treatment	0.04	-0.34 to 0.43	0.82
	Gender	0.30	0.07 to 0.53	0.01
	(Constant)	3.76	2.24 to 5.29	<0.001

*log transformed

Table 4:7 Multiple Linear Regression of Adiponectin*

Adjusted Variable		Coefficient Variable	95% Confidence Interval	P value
White European	Age (y)	-0.01	-0.02 to 0.01	0.41
	BMI (kg/m ²)	-0.01	-0.04 to 0.02	0.41
	Waist-hip ratio	-0.40	-1.73 to 0.93	0.55
	Current smoker	-0.06	-0.33 to 0.20	0.63
	BP treatment	0.27	-0.06 to 0.61	0.10
	Lipid treatment	-0.23	-0.58 to 0.12	0.20
	Gender	0.14	-0.15 to 0.43	0.34
	(Constant)	8.00	6.37 to 9.63	<0.0001
South Asian	Age (y)	0.01	0.0001 to 0.02	0.05
	BMI (kg/m ²)	-0.02	-0.05 to 0.01	0.19
	Waist-hip ratio	-1.31	-2.86 to 0.24	0.10
	Current smoker	-0.19	-0.45 to 0.07	0.15
	BP treatment	0.02	-0.22 to 0.26	0.87
	Lipid treatment	-0.30	-0.77 to 0.18	0.22
	Gender	0.05	-0.19 to 0.30	0.67
	(Constant)	8.11	6.56 to 9.66	<0.0001

*log transformed

Table 4:8 Multiple Linear Regression of Resistin*

Adjusted Variable		Coefficient Variable	95% Confidence Interval	P value
White European	Age (y)	0.001	-0.005 to 0.008	0.70
	BMI (kg/m ²)	0.01	-0.002 to 0.02	0.13
	Waist-hip ratio	0.19	-0.34 to 0.71	0.48
	Current smoker	0.05	-0.06 to 0.16	0.36
	BP treatment	-0.10	-0.23 to 0.03	0.14
	Lipid treatment	-0.03	-0.18 to 0.12	0.70
	Gender	0.06	-0.06 to 0.17	0.34
	(Constant)	3.80	3.14 to 4.46	<0.0001
South Asian	Age (y)	0.003	-0.003 to 0.01	0.37
	BMI (kg/m ²)	-0.004	-0.02 to 0.01	0.63
	Waist-hip ratio	0.53	-0.4 to 1.50	0.28
	Current smoker	-0.10	-0.26 to 0.07	0.24
	BP treatment	0.12	-0.03 to 0.28	0.11
	Lipid treatment	0.19	-0.10 to 0.50	0.19
	Gender	0.05	-0.10 to 0.20	0.52
	(Constant)	3.55	2.58 to 4.52	<0.0001

*log transformed

Table 4:9 Multiple Linear Regression of TNFα*

Adjusted Variable		Coefficient Variable	95% Confidence Interval	P value
White European	Age (y)	0.004	-0.003 to 0.01	0.30
	BMI (kg/m ²)	0.002	-0.01 to 0.02	0.78
	Waist-hip ratio	0.14	-0.51 to 0.79	0.66
	Current smoker	-0.08	-0.20 to 0.05	0.24
	BP treatment	0.06	-0.09 to 0.21	0.41
	Lipid treatment	-0.12	-0.27 to 0.04	0.14
	Gender	0.04	-0.08 to 0.16	0.46
	(Constant)	0.25	-0.45 to 0.95	0.47
South Asian	Age (y)	0.006	0.001 to 0.01	0.02
	BMI (kg/m ²)	-0.01	-0.02 to 0.003	0.11
	Eaist-hip ratio	-0.57	-1.43 to 0.30	0.19
	Current smoker	0.15	0.001 to 0.31	0.05
	BP treatment	0.11	-0.05 to 0.26	0.17
	Lipid treatment	0.04	-0.20 to 0.28	0.72
	Gender	-0.06	-0.20 to 0.08	0.37
	(Constant)	1.23	0.34 to 2.13	0.01

*log transformed

Table 4:10 Multiple Linear Regression of HsCRP*

Adjusted Variable		Coefficient Variable	95% Confidence Interval	P value
White European	Age (y)	0.001	-0.02to 0.02	0.93
	BMI (kg/m ²)	0.05	0.02 to 0.07	0.002
	Waist-hip ratio	0.20	-1.31 to 1.70	0.80
	Current smoker	0.15	-0.16 to 0.47	0.34
	BP treatment	-0.04	-0.40 to 0.32	0.83
	Lipid treatment	-0.33	-0.71 to 0.05	0.09
	Gender	-0.15	-0.47 to 0.16	0.33
	(Constant)	-0.66	-2.45 to 1.13	0.47
South Asian	Age (y)	0.009	-0.004 to 0.02	0.17
	BMI (kg/m ²)	0.04	0.005 to 0.07	0.03
	Waist-hip ratio	-0.66	-2.60 to 1.27	0.50
	Current smoker	0.12	-0.24 to 0.48	0.50
	BP treatment	0.02	-0.31 to 0.35	0.91
	Lipid treatment	-0.34	-0.81 to 0.12	0.15
	Gender	0.12	-0.2- to 0.44	0.45
	(Constant)	-0.47	-2.52 to 1.58	0.65

*log transformed

Figure 4:3 Concentrations of Resistin, Adiponectin and Leptin According to Glucose Tolerance and Ethnicity (mean \pm 95 CI)

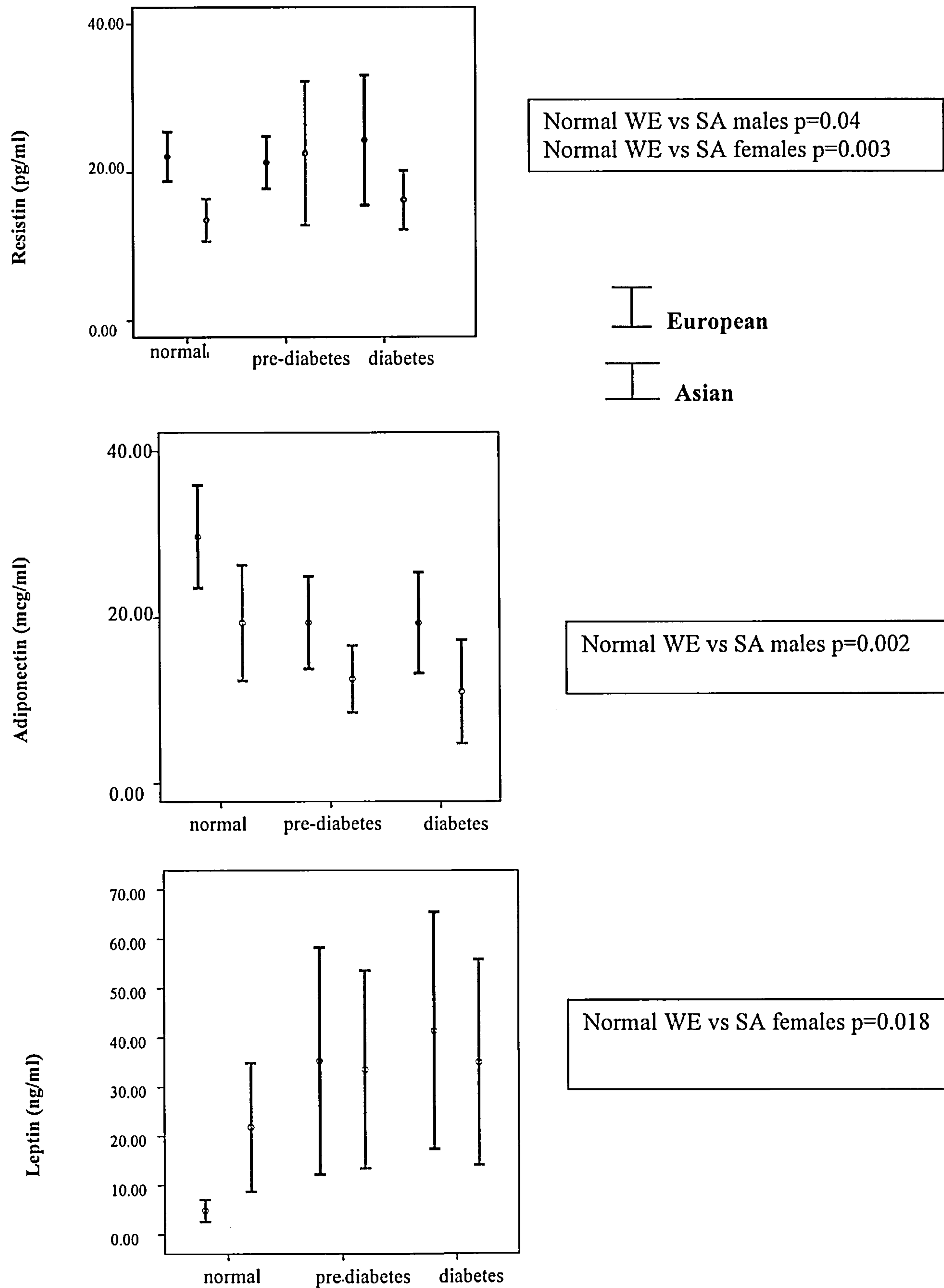
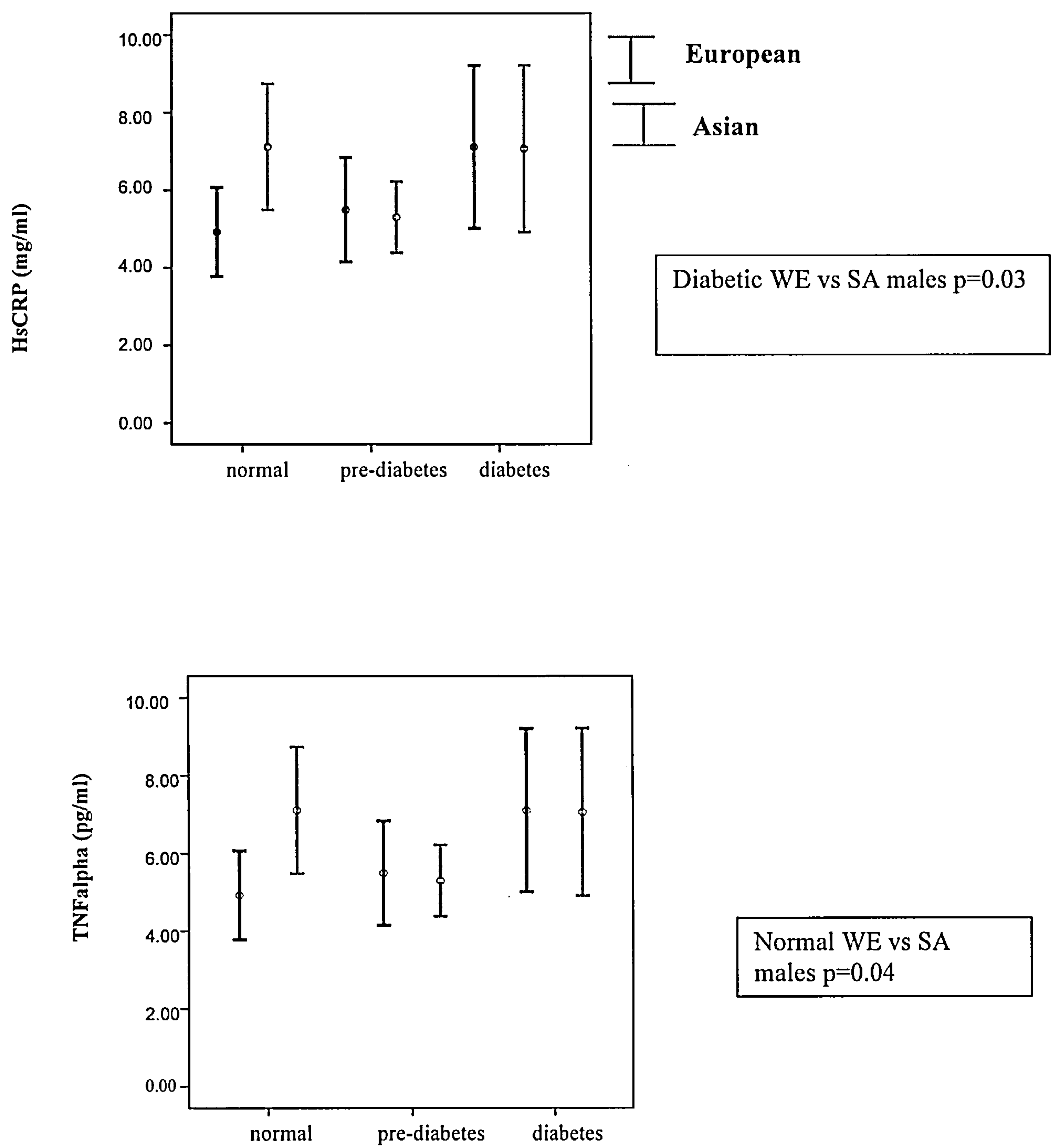


Figure 4:4 Concentrations of hsCRP and TNFα According to Glucose Tolerance
and Ethnicity (mean ± 95 CI)



4:6 Discussion

This study shows that there are differences in concentrations of circulating risk markers across the glucose spectrum between WE and SA living in the UK. However, after adjustment for variables such as age, BMI, WHR, gender, smoking and drug history, there were no differences with adiponectin and resistin. Leptin was predicted by age, gender and smoking in WE and only gender in SA. BMI predicted hsCRP in both groups and age and smoking predicted TNF α in SA.

Mean adiponectin in this study was significantly lower in SA diabetic subjects compared with WE prior to adjustment, which might explain the increased risk of T2DM and CVD in this ethnic group. In other studies in patients with CVD and IFG, who have a high rate of conversion to T2DM, elevated adiponectin levels were associated with reduced risk of developing diabetes (237).

In this study, mean adiponectin was consistently lower in SA compared with WE across the glucose tolerance spectrum. The mean adiponectin concentration in the SA controls with normal glucose tolerance was lower than that measured in healthy SA subjects living in the United States (32). However, the US subjects were younger (mean age 35 years) and they did not have cardiovascular risk factors such as diabetes, hypertension, coronary artery disease or hyperlipidaemia although BMI was similar compared with our study population. Lower levels of adiponectin are predictive of T2DM in SA. In SA living in India, adiponectin levels in normal, IGT and T2DM groups decreased progressively with worsening glucose tolerance. As in the study in this thesis, women had higher mean adiponectin values (238). The reason for this remains unclear.

Leptin is produced by adipose tissue and has a key role in food intake and energy metabolism. The concept of hyperleptinaemia leading to a state of leptin resistance in obese individuals with detrimental effects on cardiovascular function is now well-established (239).

Leptin was markedly higher in our SA control subjects compared with WE. Leptin concentrations have been measured in urban middle class, urban slum and rural Indians (240). In our study, median leptin in the SA control group was higher than in all these social groups. However, median BMI was also higher in our study (24.0 vs 22.3 kg/m²).

In this study, the significantly lower level of resistin in SA controls was an unexpected result. It might be assumed that resistin would be higher in SA as it has been suggested that this hormone induces insulin resistance. However, no correlation has been found between body weight, adiposity and insulin resistance, and resistin mRNA level (241,242). More recent work has also found that resistin, contrary to previous opinion, is not strongly associated with insulin resistance (243).

These differences in adipocytokine profile between WE and SA may be of significance in targeting at risk individuals with specific agents. The observation that adiponectin is significantly lower in SA who have T2DM might suggest that they would benefit from thiazolidinedione therapy which specifically targets adiponectin mRNA expression. However, genetic variations in the adiponectin gene may possibly alter the response to thiazolidinediones, as has been shown with rosiglitazone (244). Glimepiride, a long-acting sulphonylurea, has also been shown to increase adiponectin concentrations in subjects with T2DM (245,246). Although not yet available, adiponectin analogues developed in the future could conceivably increase insulin sensitivity in hypoadiponectinaemic individuals.

Adiponectin concentration is reduced and inversely correlated with the degree of proteinuria in subjects with T2DM (247). As shown in our study with SA males, adiponectin was significantly lower in relatively healthy SA compared with WE in another study (248). Weight loss with sibutramine did not increase adiponectin levels in obese subjects with T2DM (249). Current cigarette smokers and a family history of hypertension are both associated with lower levels of adiponectin (250,251). The antihypertensive agent valsartan has been shown to increase adiponectin levels (252). Decreasing concentrations of adiponectin have been correlated with increased risk of cerebrovascular disease (253).

The effects of leptin are somewhat harder to determine. Recombinant leptin therapy in obese individuals has not been shown to be associated with weight reduction (215) although leptin receptor deficiency is linked to morbid obesity states.

The benefits of exercise training on adipocytokines has been shown by a study in fifty inactive men aged between 65 and 78 years with BMI 28.7-30.2 kg/m² who underwent different intensities of exercise for six months and then detrained over six months (254). There was a significant decrease in leptin with all intensities of training but a significant increase in adiponectin only with high intensity training. Once detrained, changes only remained in the high intensity exercise group.

Although no significant differences were detected in TNF α , IL-6 and hsCRP levels between the two ethnic groups (apart from TNF α in normal WE and SA men), all three circulating markers increased with worsening glucose tolerance. Other studies have shown that hsCRP is higher in T2DM compared with normal subjects. In this study, the normal subjects still had at least one cardiovascular risk factor. TNF α is markedly upregulated in obese states and promotes insulin resistance by interfering with insulin receptor signalling

(255). Thiazolidinediones prevent the inhibitory effect of TNF α on adiponectin expression in adipose tissue (256). It has been shown that TNF α concentration is elevated in urban compared with rural SA living in India (257). In this study, median concentrations of TNF α were 30.9, 39.3 and 2.57 pg/ml respectively. Median TNF α in our control group was 6.77 pg/ml, which is much closer to the rural TNF α concentration. As with IL-6, the differences in TNF α between the Indian urban and rural populations and the Leicester population could be attributable to socioeconomic and environmental factors.

A limitation of this study is that the size of the cohort may not be sufficiently large enough to detect the differences observed in previous analyses, for example as seen with hsCRP and IL-6 concentrations in different ethnic groups. Longitudinal studies are required to determine the change with time of these risk markers especially after lifestyle interventions of weight loss and exercise as well as introduction of therapies such as metformin or thiazolidinediones.

Interestingly, in the Indian Diabetes Prevention Programme, there was no additional benefit in combining lifestyle modification with metformin (258). Both the individual interventions resulted in significant risk reduction in the progression of IGT to T2DM in native Indian middle-class men and women. In the USA, the Diabetes Prevention Programme also showed that lifestyle modification was effective in preventing T2DM in migrant SA although they represented a very small proportion (4.4%) of the total study population (259).

As described earlier, a study in 120 Italian obese pre-menopausal women of the effect of a Mediterranean diet, weight loss of 10% or more, and increased physical activity over two

years demonstrated decreased CRP and IL-6 concentrations whereas adiponectin concentration increased when compared with placebo (260).

Rimonabant, a selective cannabinoid-1 receptor blocker, has recently been shown in the RIO study to be effective in reducing weight and WC and may have beneficial effects on circulating risk markers (261).

Notably, there have been few previous studies in a multiethnic population especially of SA who are at high risk of T2DM and CVD. The strengths of this study are that all subjects had OGTT confirming T2DM and PDM according to WHO criteria and all underwent the same measurement as this was a nested case control study.

In summary, the main findings from this part of the study are as follows:-

- Mean adiponectin is significantly lower in SA diabetic subjects compared with WE prior to adjustment for age, BMI, WHR, gender, smoking and drug history
- Mean leptin is significantly higher in SA normal subjects compared with WE
- Leptin is predicted by age, gender and smoking in WE but only gender in SA
- Resistin was significantly lower in SA control subjects
- No significant differences were detected in IL-6 and hsCRP levels between WE and SA subjects
- hsCRP was predicted by BMI in both WE and SA subjects
- TNF α was significantly different between normal WE and SA men and is predicted by age and smoking in SA

4:7 Conclusion

In summary, this study found differences in adipocytokine profile in SA and WE, which are consistent with findings from other studies. These differences may have important implications in detecting undiagnosed T2DM and PDM. Following identification of these abnormal glucose tolerance states, lifestyle modifications such as increased activity and weight loss need to be instituted. Further work to elucidate exactly how early on these differences between ethnic groups develop and the impact of interventions is needed.

CHAPTER FIVE

PHENOTYPE OF SCREENED SUBJECTS

Circulating Risk Markers in Metabolic Syndrome

5.1 Introduction

Since Reaven first described the condition in his Banting lecture in 1988, much interest and research has been focused on a constellation of cardiovascular risk factors variously termed metabolic syndrome, syndrome X or insulin resistance syndrome (262). This syndrome comprises of abnormal glucose tolerance, hypertension, hyperlipidaemia and obesity and is thought to confer increased risk for the development of CVD and T2DM.

Metabolic syndrome has been defined by a number of expert committees, in particular the World Health Organisation (WHO) (121), the National Cholesterol Evaluation Program (NCEP) in North America (263) and more recently the International Diabetes Federation (IDF) (264). To avoid underestimating risk in certain ethnic groups, IDF has specifically recognised that different waist circumference cut-offs are required when diagnosing obesity in this syndrome. The criteria required to define metabolic syndrome by each of these definitions are shown in Table 5:1.

In 2005, the concept of the metabolic syndrome was keenly challenged by the major international diabetes organisations ADA and EASD on the basis that it is not precisely defined, the pathogenesis is uncertain and its value as a cardiovascular risk marker was questionable (265). Although other authorities resisted abandoning the definition altogether, the term cardiometabolic disease is now being used more frequently to describe the clustering of abnormalities that increase CVD and T2DM risk. The term was first coined by an exercise physiologist (266).

In the same year, the American Heart Association issued a scientific statement in association with the National Heart, Lung and Blood Institute outlining the areas which needed further research in metabolic syndrome. Key areas that were identified were

abnormal body fat distribution, atherogenic dyslipidaemia, dysglycaemia, insulin resistance, vascular dysregulation, the proinflammatory and prothrombotic states, and hormonal factors such as the corticosteroid axis and polycystic ovary syndrome (40).

In this chapter, the association of the circulating risk markers described in Chapter 4 with metabolic syndrome is considered. These fall under the heading of proinflammatory state (hsCRP, adipocytokines including adiponectin) and atherogenic dyslipidaemia (apo A-1 and B).

Table 5:1 Major Definitions for Diagnosis of Metabolic Syndrome

Criteria	WHO (modified) (121)	NCEP (ATPIII) (267)	IDF (268)
Insulin resistance	Presence		
IFG (mmol/l)	≥6.1	≥6.1	≥5.6 or previously diagnosed T2DM
IGT (mmol/l)	≥7.8		
WHR (waist:hip ratio)	Males >0.9 Females > 0.85		
Waist circumference (cm)		Males >102 Females > 88	Males >94 Females > 80
BMI (kg/m ²)	>30		
Blood pressure (mmHg)	≥ 140/90	≥ 130/85	≥ 130/85
Triglycerides (mmol/l)	≥ 1.7	≥ 1.7	≥ 1.7
HDL cholesterol (mmol/l)	Males < 0.9 Females < 1.0	Males <1.04 Females <1.29	Males ≤ 0.9 Females ≤ 1.1
Number of components for diagnosis	IR or IFG or IGT plus ≥ 2 other components: central obesity (using WHR and/or BMI), ↑BP, dyslipidaemia (↑TG and/or ↓ HDL cholesterol)	≥ 3 of the components above	Central obesity (waist circumference) plus two other components. Waist circumference defined for different ethnic groups.

WHO World Health Organisation

NCEP ATPIII National Cholesterol Evaluation Program Adult Treatment Panel III

IDF International Diabetes Federation

5:2 Key Research Questions

1. What is the prevalence of metabolic syndrome using WHO, NCEP and IDF criteria in White Europeans and South Asians screened for T2DM and PDM?
2. What is the association between metabolic syndrome and circulating risk markers in these screened subjects overall and by ethnicity?

5:3 Subjects and Methods

The subjects and methods for this part of the study are as described in Chapter 4.

5:4 Results

Using WHO, NCEP and IDF criteria respectively, prevalence of metabolic syndrome in WE (N=118, mean age 59.5y, mean BMI 27.8 kg/m²), was 58%, 38% and 57%, whereas in SA, (N=113, mean age 52.7y, mean BMI 26.8 kg/m²), it was 44% (p=0.03), 31% (NS) and 54% (NS) respectively (Fig 5:1). Prevalence of metabolic syndrome varied according to the definition used but was more prevalent in WE, and was only significantly different in the two populations using the WHO definition.

Tables 5:2-5:4 show baseline characteristics of subjects with and without metabolic syndrome using each of the three definitions. Subjects with metabolic syndrome were slightly older and, in keeping with the definition, had greater BMI, WHR and WC. BMI in metabolic syndrome was lower in SA than WE despite similar mean values in the non-metabolic syndrome state.

Pearson correlations between circulating risk markers and presence of metabolic syndrome are shown in Table 5:5. Using IDF criteria, the only one to take into account ethnic cut-offs, there was a negative correlation between adiponectin concentration and presence of metabolic syndrome in WE (r=-0.29, p=0.01). In addition, there was a positive correlation between leptin concentration and metabolic syndrome in WE (r=0.30, p=0.009). In SA, there was only a significant positive correlation between resistin and metabolic syndrome (r=0.31, p=0.02).

There was a negative correlation with Apo A-1 in WE with metabolic syndrome ($r=-0.31$, $p=0.02$) and a positive correlation with Apo B in SA with metabolic syndrome ($r=0.33$, $p=0.02$). Correlations of metabolic syndrome using NCEP and WHO criteria are also shown in Table 5:5.

Table 5:6 shows differences between ethnic groups with and without metabolic syndrome (using any one of the three definitions) for each marker. There was a significant difference in mean adiponectin ($p=0.021$), leptin ($p=0.01$), resistin ($p<0.001$) and apoA-1 ($p=0.04$) concentrations between SA and WE without metabolic syndrome. However, only adiponectin was significantly different between SA and WE with metabolic syndrome ($p=0.03$).

ROC analysis showed that only leptin was highly associated with prevalent metabolic syndrome (area under curve 0.80, 95% CI 0.67 to 0.94, $p=0.001$).

Table 5:2 Baseline Characteristics of Subjects with and without Metabolic Syndrome using IDF Definition – Mean (SD)

Metabolic Syndrome (IDF)		Age (y)	BMI (kg/m ²)	Waist Circumference (cm)	SBP (mmHg)	DBP (mmHg)	Total Chol (mmol/L)	HDL chol (mmol/L)	TG (mmol/L)	HbA1c (%)	FPG (mmol/L)
European	No (N=50)	58.8 (9.6)	24.5(4.1)	85.5 (11.2)	131.3 (21.6)	76.2 (10.3)	5.4 (1.1)	1.5 (0.5)	1.4 (0.8)	5.6 (0.6)	5.3 (1.8)
	Yes (N=67)	60.3 (10.5)	31.0 (5.2)	104.4 (10.0)	138.3 (19.2)	80.5 (10.5)	5.3 (1.0)	1.2 (0.4)	2.1 (1.6)	6.5 (1.4)	6.4 (1.8)
Asian	No (N=52)	50.4 (11.0)	24.7 (3.6)	87.4 (10.7)	125.6 (19.8)	77.4 (10.3)	5.4 (1.0)	1.2 (0.3)	1.5 (1.2)	6.0 (1.0)	5.4 (1.3)
	Yes (N=60)	54.8 (10.3)	28.7 (4.6)	98.0 (9.9)	138.0 (20.3)	80.6 (11.5)	5.5 (1.2)	1.2 (0.5)	2.3 (1.7)	6.6 (0.9)	6.4 (1.8)

Table 5:3 Baseline Characteristics of Subjects with and without Metabolic Syndrome using NCEP Definition – Mean (SD)

Metabolic Syndrome (NCEP)		Age (y)	BMI (kg/m ²)	Waist circumference (cm)	SBP (mmHg)	DBP (mmHg)	Total Chol (mmol/L)	HDL chol (mmol/L)	TG (mmol/L)	HbA1c (%)	FPG (mmol/L)
European	No (N=72)	59.0 (10.0)	25.8 (5.4)	89.8 (12.8)	131.0 (18.2)	76.8 (9.6)	5.4 (1.1)	1.5 (0.5)	1.4 (0.8)	5.7 (0.5)	5.2 (0.8)
	Yes (N=45)	60.7 (10.3)	32.0 (4.1)	106.8 (8.6)	142.2 (22.2)	81.7 (11.5)	5.3 (0.9)	1.1 (0.2)	2.5 (1.8)	6.9 (1.5)	7.1 (2.5)
Asian	No (N=77)	53.1 (11.3)	25.6 (3.5)	90.2 (10.1)	128.6 (19.3)	76.7 (10.2)	5.4 (1.1)	1.2 (0.3)	1.5 (1.0)	6.0 (0.6)	5.4 (0.9)
	Yes (N=35)	52.1 (9.9)	29.7 (5.5)	99.9 (11.7)	140.2 (22.3)	84.3 (11.0)	5.4 (1.1)	1.1 (0.7)	2.7 (2.1)	7.0 (1.3)	7.3 (2.2)

Table 5:4 Baseline Characteristics of Subjects with and without Metabolic Syndrome using WHO Definition – Mean (SD)

Metabolic Syndrome (WHO)	Age (y)	BMI (kg/m ²)	Waist Circumference (cm)	SBP (mmHg)	DBP (mmHg)	Total Chol (mmol/L)	HDL chol (mmol/L)	TG (mmol/L)	HbA1c (%)	FPG (mmol/L)
European	No (N=49)	24.0 (3.8)	85.5 (11.6)	130.1 (19.6)	76.7 (9.9)	5.3 (1.1)	1.5 (0.5)	1.3 (0.8)	5.6 (0.5)	5.0 (0.8)
	Yes (N=68)	31.2 (5.0)	104.1 (10.0)	139.0 (20.4)	80.1(10.9)	5.4 (1.0)	1.2 (0.3)	2.2 (1.6)	6.5 (1.4)	6.6 (2.2)
Asian	No (N=63)	25.7 (4.3)	89.5 (12.0)	127.9 (20.2)	77.5(11.2)	5.4 (1.0)	1.3 (0.5)	1.4 (0.8)	6.1 (1.0)	5.7 (1.8)
	Yes (N=49)	28.3 (4.7)	98.0 (8.8)	137.8 (20.7)	81.1 (10.5)	5.5 (1.3)	1.1 (0.3)	2.5 (2.0)	6.5 (0.9)	6.3 (1.4)

Table 5:5 Correlations of Markers with Different Definitions for Metabolic Syndrome

		Marker	Correlation Coefficient	P value
<i>IDF criteria</i>				
Europeans		Adiponectin	-0.29	0.01
		Leptin	0.30	0.009
		Resistin	-0.06	0.65
		TNF α	0.19	0.08
		HsCRP	0.04	0.71
		Apo A-1	-0.31	0.02
		Apo B	-0.27	0.10
		Insulin	0.53	<0.001
Asians		Adiponectin	-0.05	0.72
		Leptin	0.18	0.12
		Resistin	0.31	0.02
		TNF α	0.10	0.40
		HsCRP	0.16	0.12
		Apo A-1	-0.04	0.77
		Apo B	0.33	0.02
		Insulin	0.32	0.009
<i>NCEP criteria</i>				
Europeans		Adiponectin	-0.36	0.001
		Leptin	0.33	0.004
		Resistin	0.07	0.61
		TNF α	0.23	0.035
		HsCRP	0.07	0.54
		Apo A-1	-0.25	0.07
		Apo B	-0.23	0.15
		Insulin	0.60	<0.001
Asians		Adiponectin	-0.12	0.34
		Leptin	0.08	0.51
		Resistin	0.19	0.14
		TNF- α	-0.09	0.46
		HsCRP	0.13	0.22
		Apo A-1	-0.06	0.64
		Apo B	0.39	0.006
		Insulin	0.33	0.007
<i>WHO criteria</i>				
Europeans		Adiponectin	-0.17	0.16
		Leptin	0.35	0.002
		Resistin	0.12	0.36
		TNF α	0.14	0.20
		HsCRP	0.18	0.08
		Apo A-1	-0.29	0.04
		Apo B	-0.14	0.40
		Insulin	0.50	<0.001
Asians		Adiponectin	-0.08	0.61
		Leptin	0.09	0.47
		Resistin	0.15	0.26
		TNF α	0.08	0.49
		HsCRP	0.004	0.97
		Apo A-1	0.12	0.34
		Apo B	0.27	0.07
		Insulin	0.32	0.008

Figure 5:1 Prevalence of Metabolic Syndrome according to Definition in White European and South Asian Subjects

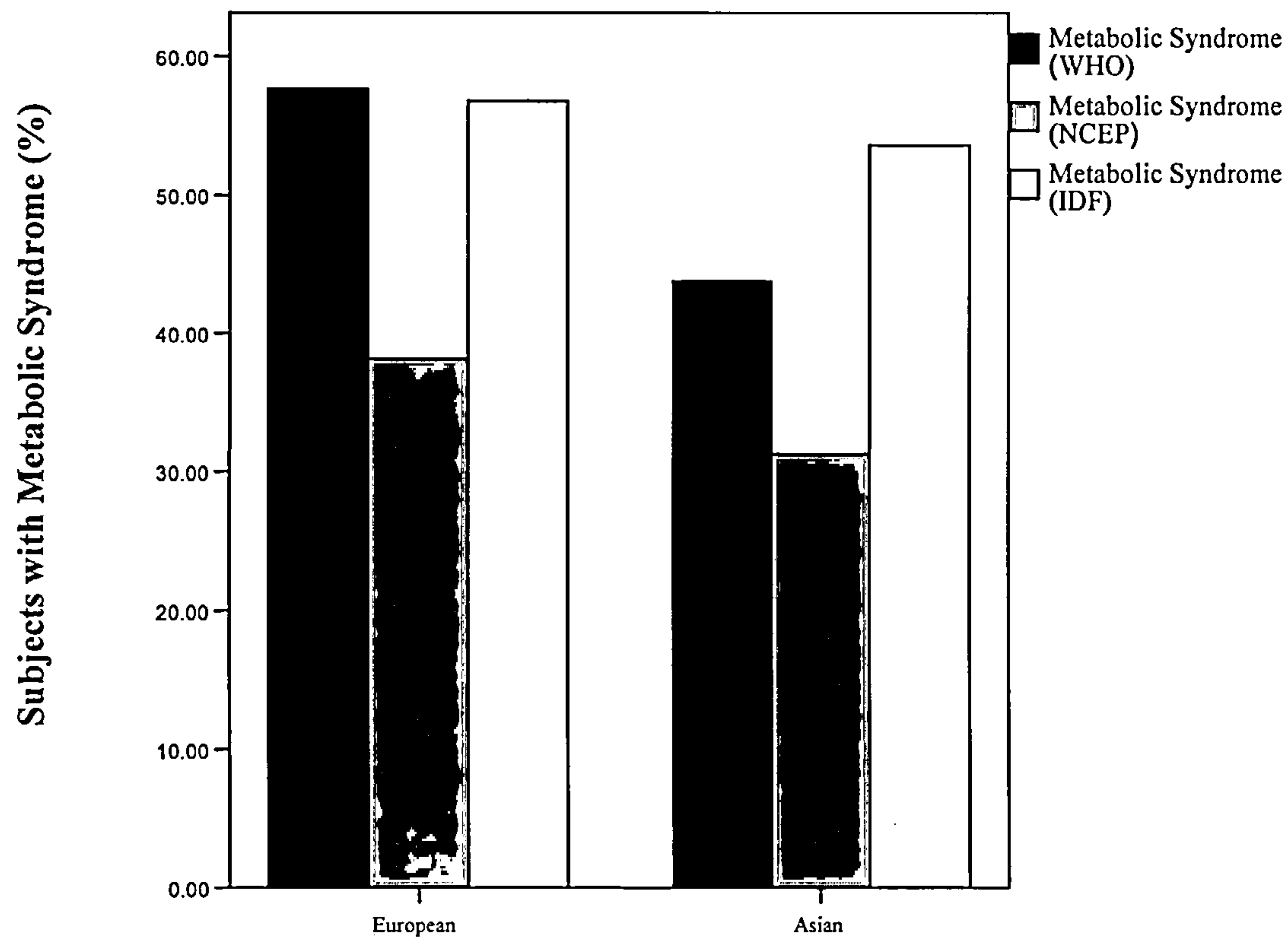


Table 5:6 Differences in Risk Markers between SA and WE with and without Metabolic Syndrome

Metabolic Syndrome	Risk Marker Concentration	Mean difference in concentrations (WE - SA)	95% Confidence Interval	P value
No	Adiponectin (mcg/ml)	10.26	2.40 to 18.11	0.01
	Leptin (ng/ml)	-19.87	-35.07 to -4.66	0.01
	Resistin (pg/ml)	8.88	4.94 to 12.81	<0.001
	TNFalpha (pg/ml)	-1.35	-3.01 to 0.30	0.11
	HsCRP (mg/ml)	1.67	-1.62 to 4.97	0.31
	Apo A-1 (mcg/ml)	612.93	34.56 to 1191.30	0.04
	Apo B (mcg/ml)	37.03	-2.42 to 76.48	0.06
Yes	Adiponectin (mcg/ml)	6.58	0.65 to 12.50	0.03
	Leptin (ng/ml)	7.61	-14.99 to 30.21	0.51
	Resistin (pg/ml)	1.40	-6.61 to 9.40	0.73
	TNFalpha (pg/ml)	0.05	-1.70to1.80	0.98
	HsCRP (mg/ml)	0.13	-2.54 to 2.80	0.92
	Apo A-1 (mcg/ml)	-270.42	-809.42 to 268.60	0.32
	Apo B (mcg/ml)	-28.50	-59.62 to 2.63	0.07

5:5 Discussion

No previous studies have examined the association of these circulating risk markers in subjects screened for T2DM and PDM and compared WE with SA. This study was population-based and representative of the general population. However, it was cross-sectional which limits the implications of the results.

The prevalence of metabolic syndrome in our study varied between 30-60% with the lowest rate obtained using the NCEP criteria. Underestimation of metabolic syndrome using NCEP has been recognized previously in Asian populations and modified Asian criteria are recommended (269). Our prevalence rate in UK SA was virtually identical to urban Indians using NCEP criteria (270). The IDF criteria showed greatest similarity in prevalence of metabolic syndrome between the two ethnic groups.

This study shows that adipocytokine and lipid sub-fraction concentrations are significantly associated with metabolic syndrome in both WE and SA. In line with other studies, adiponectin concentrations were found to be lower with metabolic syndrome (47,271,272). However, one study suggests that the high molecular weight isoform of adiponectin is more predictive of metabolic syndrome than total plasma adiponectin concentrations (273).

Leptin, resistin and TNF α concentrations all increased in the presence of metabolic syndrome.

The link between resistin and metabolic syndrome remains controversial. The finding in this study that resistin is associated with development of metabolic syndrome is in contrast to

another study in North American subjects (274). Resistin was also not associated with insulin sensitivity but weakly associated with body fat. However, the Study of Inherited Risk of Coronary Atherosclerosis found slightly higher resistin concentrations with metabolic syndrome (275).

Furthermore, adiponectin and resistin are lower in SA compared with WE whereas leptin and TNF α are higher. Apo A-1, the “good” sub-fraction of the lipid profile falls significantly in WE subjects with metabolic syndrome whereas apo B, the “bad” sub-fraction tends to increase in SA subjects.

Unlike other studies (276), no difference was found in inflammatory markers such as hsCRP but this may have been because of the much smaller cohort, reducing the power required to detect significant differences.

The importance of detecting at risk individuals cannot be underestimated. Mass population screening requires simple bedside tools of assessing risk. WC measurement as a surrogate marker of increased cardiovascular risk may be recommended as an effective and simple screening tool (277).

Identification of metabolic syndrome enables primary and secondary intervention strategies to be implemented with the aim of reducing CVD risk and T2DM, as recommended by IDF (278). Primary intervention includes encouraging increased physical activity, reduced calorie intake and improved dietary composition in order to achieve weight loss. Even small degrees of weight loss have prevented progression to T2DM in obese subjects with IGT in Finnish (279,280) and American prevention studies (281). In the Diabetes Prevention Program, there

was already a high baseline prevalence rate of 53% for metabolic syndrome (282). At three years, fewer participants developed metabolic syndrome with metformin therapy compared with placebo (55% vs 61%). With intensive lifestyle modification, the prevalence rate of metabolic syndrome at three years actually decreased from 51% to 43%.

A study of increased physical activity in adolescents showed improved insulin sensitivity and reduction in systemic low grade inflammation but adiponectin, leptin and TNF- α were not shown to contribute substantially to these benefits (283). The study was conducted in France with no further details of ethnicity.

Secondary prevention strategies need to be incorporated when primary strategies are insufficient and include adding pharmacological agents in order to combat the metabolic derangements. Insulin resistance and hyperglycaemia in PDM is improved with metformin (284), thiazolidinediones (285), acarbose (286) and orlistat (287). Metformin improved cardiovascular outcomes in UKPDS and pioglitazone non-significantly improved cardiovascular outcomes in the PRO-ACTIVE study (288). Hypertension needs to be treated but no particular agent has been recommended above another. ACE inhibitors and angiotensin receptor blockers reduce development of T2DM (289,290). Dyslipidaemia needs to be targeted with HMG-CoA reductase inhibitors (“statins”) or fibrates, primary aims of therapy being to reduce LDL cholesterol, triglyceride and apo B levels and raise HDL and apo A-1 levels. Statin therapy is confirmed to be beneficial by numerous clinical studies such as HPS, 4S and CARE (291-293). The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed significant cardiovascular benefit with the fibrate gemfibrozil (294). T2DM patients on fenofibrate for 5 years had significant reductions in total CVD events, particularly nonfatal MI and coronary revascularization. However, the primary endpoint of

major coronary events was not significantly reduced by fenofibrate compared with placebo (295).

5:6 Conclusion

It can be concluded that changes in adipocytokines and lipid sub-fractions are significantly associated with metabolic syndrome and may have a potential role in screening for this condition. Long-term intervention studies in subjects with and without metabolic syndrome will reveal whether improvements in adipocytokines and lipid abnormalities improve cardiovascular outcomes.

CHAPTER SIX

NEW AND EMERGING THERAPIES IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

6:1 Glargine in T1DM

Since its discovery by Banting and Best in 1922, insulin therapy in diabetes has advanced considerably both in terms of action profile and delivery. Early modifications of insulin structure produced several classes of insulins with varying pharmacokinetics but did not sufficiently mimic physiological insulin release.

Genetic engineering led to the development of novel long and short-acting insulin analogues, the so-called “designer insulins”, in the 1990s, paving the way for more physiological insulin therapy, with improvements in hypoglycaemia and patient satisfaction.

Insulin glargine (Lantus®, Sanofi-Aventis) was first launched in Germany in 2000 followed shortly by availability in the rest of Western Europe and the United States. Glargine is a basal or long-acting insulin analogue which has been genetically modified resulting in an approximately 24-hour, relatively peak-free profile with little variability in subcutaneous absorption. It is usually administered as part of a basal bolus regimen in combination with meal-time soluble insulin or rapid-acting insulin analogues.

Insulin glargine is produced by genetic modification using a non-pathogenic laboratory strain of *Escherichia coli* as the production organism. Glargine differs from human insulin at position A21 where the amino acid asparagine is replaced by glycine, and at the C-terminus of the B chain due to the addition of two arginine molecules. The chemical structure is 21^A-Gly^B-30^B-L-Arg-human insulin, the molecular weight is 6063 Da and the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆.

Genetic modifications to human insulin allow glargine to have low aqueous solubility at neutral pH by shifting the isoelectric point. It is therefore completely soluble in the injection solution which has a pH of 4. On injection into subcutaneous tissue, the acidic solution is neutralised forming microprecipitates of glargine which are slowly released as the hexameric structure breaks down into monomers. The addition of zinc delays absorption further. This leads to the relatively peak-free 24-hour profile of glargine, enabling it to be subcutaneously administered as a once-daily basal insulin usually in the abdomen or thigh.

The clear solution is usually administered as a single dose at bedtime but may be injected at other times of the day. As the diluent of insulin glargine has a low pH, it should not be mixed with other insulins.

In T1DM, median onset of action of glargine (defined as time to 50% decrease in insulin infusion rate) was 1.11 h compared with 0.71 h with NPH insulin ($p<0.08$) (16). 30 minutes of exercise did not increase absorption rate of insulin glargine when injected subcutaneously in patients with T1DM (296).

Peak plasma concentration four hours after administration of insulin glargine (0.15 U/kg with zinc 80 mg/L) is 5.75 U/L and the time to disappearance of 25% dose from the injection site is 11 h (297). Interindividual variability is lower with glargine than with NPH or Ultralente (298). However, there is lower within-subject variability with insulin detemir compared with glargine or NPH in T1DM (299).

A number of RCT have compared insulin glargine with NPH in T1DM as part of a basal bolus regimen (297,300-302). Two studies were of only four weeks' duration (300,301)

and regular soluble insulin was used as the prandial insulin. Three studies (297,301,302) did not find statistically significant differences in HbA1c between glargine and NPH at the end of the study. In these studies, mean change in HbA1c was -0.06% to -0.4% with glargine and - 0.03% to 0.4% with NPH. In the fourth study (300), conducted in 333 T1DM subjects, there was a significant HbA1c reduction with glargine compared with NPH (-0.14%, $p=0.0037$).

In a trial of 121 patients with T1DM, subjects were randomised to 12 months' treatment with either four times daily NPH or once daily glargine along with lispro at mealtimes. At study end, subjects in the glargine arm had lower HbA1c and improved responses to hypoglycaemia compared with NPH (7.1% vs 6.7%, $p<0.05$) (303).

A 32 week randomised cross-over study of 28 adolescents (mean age 14.8 years) receiving basal bolus therapy of either glargine and lispro or NPH and soluble insulin showed no significant difference in HbA1c levels (8.7% vs 9.1%, $p=0.13$) (304).

A retrospective study of 196 subjects comparing those on basal bolus therapy with glargine or NPH and found that there was no change in HbA1c after 13 months (305). However, severe hypoglycaemic events were significantly lower with glargine (0.5 vs 1.2, $p=0.04$).

The efficacy of four times daily NPH has been compared with once daily glargine in a basal bolus regimen in 51 patients in a 3 month randomised study (306). The simpler glargine regimen was associated with a greater HbA1c decrease and hypoglycaemia frequency. More steady plasma insulin concentrations at night and before meals were seen with glargine than with NPH ($p<0.05$).

Although the data regarding improved HbA1c levels are somewhat equivocal, significant differences in fasting plasma glucose (FPG) or fasting blood glucose (FBG) levels have been observed with glargine in most studies (see Table 6:1). In a 4-week study of 256 patients, adjusted mean FPG levels were reduced by 2.2mmol/l ($p=0.0001$) (297). However, a significant difference in reduction in FPG was only observed when glargine was compared with twice-daily NPH rather than once daily NPH. A clinically meaningful FPG effect was seen as early as week 1.

Most studies did not show significant differences in insulin dose between glargine and NPH at study end (297,302,303,306,307). Two studies (297,300) where NPH had been used once daily, showed that subjects taking glargine once daily had an increase in mean dosage of insulin at study end of 2 and 1.8 U/day respectively compared with baseline. In the NPH arm of two studies (297,301) there was an increased dose of insulin at study end compared with baseline of 1.8 U and an unspecified amount respectively, although one study showed a decrease in NPH of 0.5 U/day at study end (300). When the pre-trial regimen was NPH twice daily, insulin glargine decreased by between 4 and 7 U/day compared with baseline (297,300,301).

The gold standard of insulin therapy is continuous subcutaneous insulin infusion (CSII) as it provides physiological insulin replacement. Studies have shown that CSII results in equivalent or better glycaemic control than multiple daily injection (MDI) therapy (308-311). However, the benefits of CSII have to be counterbalanced with problems such as increased cost, need for a high level of professional support and the risks of pump failure.

A randomised multicentre cross-over study of 100 patients of 10 weeks' duration compared CSII using aspart and MDI consisting of bedtime glargine and mealtime aspart (311). All patients underwent 1-week run-in with CSII using aspart initially. As study duration was short, fructosamine was used to assess efficacy and was significantly lower with CSII than with MDI using glargine ($p=0.0001$). Glucose exposure was also lower with CSII as measured by area under the curve. The number of hypoglycaemic events was similar with both regimens.

Hypoglycaemia is the commonest side-effect seen with insulin therapy. Several studies have demonstrated that the use of insulin glargine in T1DM is associated with less nocturnal hypoglycaemia compared with NPH insulin (300,302).

In a study of 534 patients with T1DM, the incidence of diurnal and nocturnal hypoglycaemia, as defined by a blood glucose of $<2\text{mmol/l}$, was significantly lower in those treated with glargine compared with those on NPH insulin (302). In this study, there was no improvement in severe hypoglycaemia with insulin glargine. A four-week randomised multicentre study in 333 patients showed less nocturnal hypoglycaemia with glargine compared with NPH (36% vs 55%, $p=0.0037$) but overall frequency of hypoglycaemia did not differ between treatment groups and was only significant compared with NPH once daily, not twice daily (300).

Another longer study (16 weeks) did not show any differences in hypoglycaemia, including nocturnal hypoglycaemia, between NPH and glargine (301) .

Nocturnal hypoglycaemia occurs more frequently if glargine is injected at dinner (71.9%) or bedtime (77.5%) compared with breakfast (59.5%) ($p=0.005$) (312).

One study showed that plasma adrenaline and symptom responses improved with glargine more than NPH and this may account for the observed differences in hypoglycaemia rate (303).

Effect on body weight has varied with studies and some trials did not report their results. A sixteen week study of glargine or NPH in a basal bolus regimen showed that weight gain was 0.12 kg with glargine and 0.54 kg with NPH (301). Another 30 week study showed that glargine resulted in 1.97 kg weight gain compared with 2.34 kg with NPH (307). Other studies have shown no significant differences in weight gain between glargine and NPH at study end (297,303).

Glargine has been associated with more injection site pain than NPH (297,300,301). However, these episodes were mild and transient in nature and did not usually result in discontinuation of glargine. No significant changes in antibody titres for insulin or E.coli have been observed.

Summary of Effects of Glargine in T1DM

- Insulin glargine results in at least equivalent glycaemic control as measured by HbA1c when compared with NPH insulin in a basal bolus regimen
- FPG and FBG tend to be lower with glargine treatment
- Insulin glargine is superior to once daily NPH in reducing nocturnal hypoglycaemia but not when compared with twice daily NPH
- There is less weight gain and greater patient satisfaction with glargine compared with NPH
- Glargine in combination with prandial soluble insulin or analogues such as lispro are effective in improving glycaemic control in a basal bolus regimen
- few studies have investigated efficacy of glargine with prandial aspart – hence the rationale for the Glargine and Aspart study (GLASS) described in Chapter 7

6:2 Meglitinides in T2DM

UKPDS clearly demonstrated that improved glycaemic control reduces microvascular complications (313). It also showed that metformin and sulphonylurea therapy does not delay the natural history and progression of T2DM (314). 50% of patients required combination therapy three years into the study and after 9 years this number rose to 75%. In addition, HbA1c increased with time even in the intensively treated group with median HbA1c values of 6.6%, 7.5% and 8.1% over successive 5-year periods of follow-up. Compared with the conventionally treated group, there was significant weight gain and increased risk of hypoglycaemia in the intensively treated group.

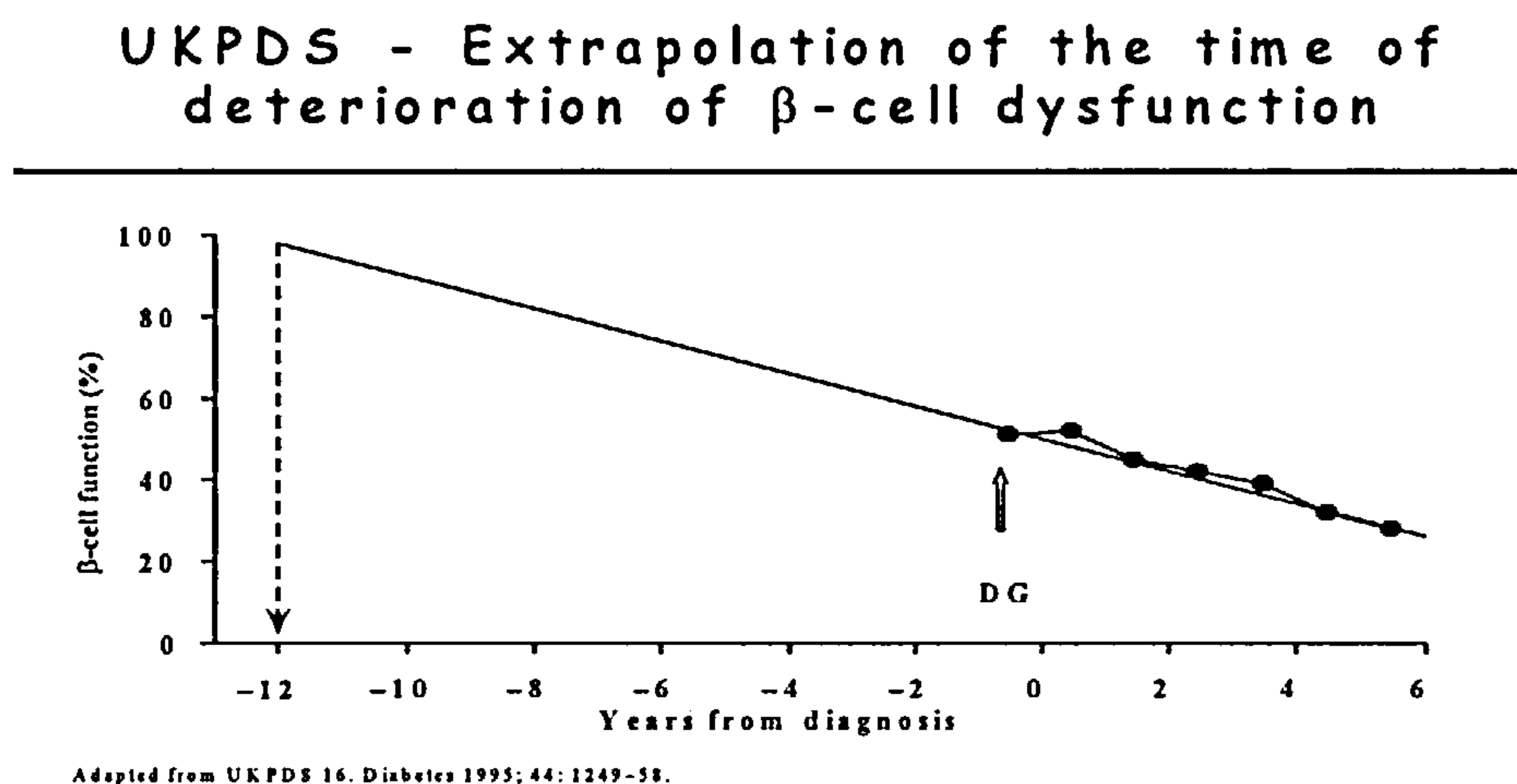
The need for new durable oral hypoglycaemic agents with the potential to change the natural history of T2DM is clear from the UKPDS findings. Two rapid-acting insulin secretagogues, repaglinide and nateglinide (also known as prandial glucose regulators) are available on the UK market. As a consequence of their shorter duration of action and glucose-dependent insulin secretion, they more closely reflect physiological insulin secretion than sulphonylureas. This mechanism of action means that they are more effective at controlling glucose excursions after meals (post-prandial hyperglycaemia) leading to the term “prandial glucose regulator”. Repaglinide, which is structurally related to the non-sulphonylurea moiety of glibenclamide, is licensed for use as monotherapy in T2DM, and at present nateglinide, a novel amino acid derivative, is licensed to be given in combination with metformin.

This chapter will begin by exploring the current evidence supporting the issue of postprandial hyperglycaemia (PPH) and its clinical implications. Repaglinide and nateglinide will each be discussed in detail including their pharmacological activity, pharmacokinetic profile, therapeutic dosage, efficacy and use in specific patient groups and in combination with other therapy. The safety profile of each drug will also be discussed. Finally there will be a summary describing where the prandial glucose regulators fit into the overall management of T2DM.

Pathophysiology of T2DM

In T2DM, the relentless deterioration in glycaemic control with time is associated with progressive failure of β cells whereas insulin resistance remains relatively unchanged (315). This deterioration appears to be independent of BMI and whether or not metformin or sulphonylureas are used. Extrapolation of data from UKPDS would indicate that β cell dysfunction probably begins around 12 years prior to clinical diagnosis of T2DM (Fig.6:1).

Fig. 6:1 (DG=diagnosis)



Insulin secretion is divided into two phases. There is a rapid early phase response that peaks at 2-4 min after an acute secretagogue challenge and is over after about 10 min. A second late phase response occurs which usually lasts around 2-3 hours. The importance of the early phase response is related to its association with normal glucose tolerance and it has also been shown to prime tissues sensitive to insulin. In particular hepatic glucose production is reduced (316).

This important early-phase insulin secretion is already lost in patients with IGT (317) and also in ethnic populations such as Pima Indians who are noted for their severe insulin resistance. Loss of early-phase insulin response is a reliable indicator of subsequent progression to T2DM (318). It results in suppressed hepatic glucose output, postchallenge hyperglycaemia and late hyperinsulinaemia (319). The most obvious manifestation of loss of early-phase insulin secretion is elevated blood glucose after meals or PPH.

The prandial glucose regulators, repaglinide and nateglinide, are insulin secretagogues whose mechanism of action is to stimulate early-phase insulin secretion in the post-prandial situation. Their rapid onset and short duration of action make them ideal for premeal administration and patients have cited the ability to miss or skip meals as a therapeutic advantage.

Potential Significance of Postprandial Hyperglycaemia (PPH) and Cardiovascular Outcomes

T2DM is characterized by both fasting and post-prandial hyperglycaemia. Traditionally, more emphasis has been placed on the importance of fasting plasma glucose levels and patients are

often instructed to self-monitor before meals. The contribution of PPH to HbA1c has been recognised (320). Recent evidence suggest that post-prandial glucose levels correlate better with HbA1c and that treatment targeting post-prandial as well as fasting glucose tends to more effective in improving glycaemic control (321,322).

Little data exist directly linking PPH in T2DM and cardiovascular outcomes. The Diabetes Intervention Study showed that post-meal but not fasting glucose is associated with adverse macrovascular outcomes (323). A number of epidemiological studies largely in subjects without diabetes have suggested a link between post-challenge or post-prandial glucose and cardiovascular outcomes and they are summarized in table 6:1.

Table 6:1. Association between Post-prandial Glucose Values and the Risk of Cardiovascular Heart Disease across the Spectrum of Glucose Tolerance

Study	Characteristics	Cardiovascular Outcomes
Honolulu Heart Program (324)	6005 men 45-70 years 12 year follow-up	CHD incidence and mortality increase stepwise with increasing 1-hour post-challenge glucose
DECODE Study Group (325)	18408 men 7316 women 13 European centres 28 year follow-up	CHD mortality is more related to 2 hour post meal glucose than fasting plasma glucose
Whitehall, Paris Prospective and Helsinki Policeman Studies (72)	17285 men 44-55 years 20 year follow-up	Men in upper 2.5% of 2hour post-meal glucose distribution had significantly higher CHD mortality
Hoorn Study (326)	2363 subjects 50-75 years 8 years follow-up	High plasma glucose levels especially 2 hour post load glucose concentrations and to a lesser extent HbA1c values indicate a risk of CHD mortality

Post-Prandial Hyperglycaemia in Clinical Practice

The only data to show that post-prandial monitoring improves outcomes is from a randomised study in women with gestational diabetes (327). The two glucose monitoring protocols used were pre-prandial monitoring before meals and at bedtime, or post-prandial glucose before breakfast and 1 hour after each meal and treated to target levels. In the group assigned to target post-prandial glucose, there was a significant improvement in fetal outcomes and a 5-fold reduction in HbA1c.

The ADA has produced a consensus statement recognizing the importance of PPH. This stresses the need for further intervention and outcome studies.

A number of theoretical disadvantages of PPH have been postulated. These include production of increased free radicals with subsequent oxidative stress (328), and endothelial dysfunction and damage (329). Any drugs which lower PPH have the potential to lessen these detrimental effects on cardiovascular outcomes, although outcome data to support this hypothesis are still awaited. It is in this area of diabetes management that repaglinide and nateglinide may assume an important role since their mechanism of action is linked to reduction in PPH.

Compared with glyburide, treatment with repaglinide in 175 drug-naïve men and women over twelve months was associated with increased regression of carotid intima media thickness, as

well as greater reductions in CRP and IL-6 levels (330). These findings were attributed to reduced PPH.

Acarbose, an α glucosidase inhibitor, whose main mechanism of action is lowering PPH, reduced progression to T2DM and improved cardiovascular outcomes in the STOP-NIDDM trial (331).

Repaglinide

Indication

This prandial glucose regulator, the first of its class to be launched in the UK, has been available since 1998. It is indicated for treatment of T2DM either as monotherapy or in combination with metformin when metformin alone is inadequate. It is licensed for use in mild-to-moderate renal impairment and is recommended for patients between 18-75 years.

Pharmacology

Repaglinide is chemically related to the non-sulphonylurea moiety of glibenclamide although it is structurally distinct, being derived from a carbamoylmethyl benzoic acid. The mode of action of repaglinide in initiating insulin secretion is by closure of the K^+_{ATP} channel of the sulphonylurea receptor on the beta cell. Unlike sulphonylureas, repaglinide has no direct biosynthetic activity and is not taken up internally by the pancreatic islet cells (332). Repaglinide has a very short half-life resulting in peak insulin concentrations at 1-2 h after a meal. After 4 h repaglinide is no longer detectable in the circulation and additionally plasma insulin resumes fasting levels by 6 h (333,334). A direct benefit of this fast onset and short duration of action is that the risk of hypoglycaemia is significantly reduced, in contrast to more conventional sulphonylureas like glibenclamide (335).

Pharmacokinetics

Repaglinide undergoes hepatic metabolism into inactive substances by the CYP3A4 isoform of the P450 cytochrome enzyme which are then excreted via bile. Renal excretion occurs for only 6% of metabolites and this enables it to be used in patients with mild to moderate renal impairment (336,337).

Recommended Doses

The initial recommended dose for repaglinide is 500mcg to be taken within 15 to 30 minutes of a main meal. A higher dose of 1 mg may be used if the patient was previously on another oral hypoglycaemic agent. The dose of repaglinide should be adjusted at intervals of 1-2 weeks according to response. The maximum single dose is 4mg and the total daily dose is 16mg.

Efficacy of Repaglinide

A number of clinical trials have demonstrated the efficacy of repaglinide as monotherapy and also in combination with metformin or a thiazolidinedione.

In a placebo-controlled cross-over design study of 10 patients with T2DM, participants were treated with repaglinide 3-9mg daily. There was a non-significant decline in HbA1c and an increase in area under the curve insulin during the first-phase insulin secretion test. This indicates that repaglinide augments first-phase insulin secretion (338).

A study of 320 subjects showed that compared with the sulphonylurea glibenclamide over 12 months, repaglinide showed no significant difference in terms of efficacy and safety when used in a fixed-dose regimen (339).

In an open randomized group comparison study of 12 weeks' duration, 44 patients with T2DM received either repaglinide or glibenclamide twice daily. Repaglinide significantly lowered post-prandial glucose whereas glibenclamide had a greater effect on fasting blood glucose (340).

A randomized study consisting of three arms looked at the use of metformin in combination with repaglinide in 83 subjects with T2DM. The patients were randomized to metformin alone, metformin and repaglinide, or repaglinide alone. There was a significant reduction in HbA1c of 1.4% associated with a fall in fasting plasma glucose of 2.2mmol/l. In the combination group, patients gained a mean 3kg in weight. Combination therapy with repaglinide and metformin was more effective at improving glycaemic control than monotherapy with either agent. Repaglinide monotherapy was as effective as metformin monotherapy (341).

A larger study in the real life setting has established the practical advantages of administering repaglinide as a flexibly dosed drug in more than 5000 patients with T2DM. Repaglinide was used either as monotherapy or in combination with metformin, the patient having been switched from a sulphonylurea. The results showed a significant reduction in HbA1c of around 1%, a significant fall in both fasting and post-prandial glucose levels and a fall in body weight of approximately 1.2kg. There was also improvement in quality of life. A particular advantage cited by patients was the ability to either postpone or even skip a meal (335).

An area of potential use of repaglinide is in combination with insulin. There is evidence to show the benefits of combining insulin with metformin in T2DM (342). In contrast the use of sulphonylureas with insulin although potentially advantageous as shown by a large meta-analysis (343), is associated with an increased risk of hypoglycaemia.

A more recent study has indicated that metformin alone is superior to repaglinide alone when combined with bedtime NPH insulin and was associated with less weight gain. The improvement in HbA1c with metformin and the deterioration with repaglinide were statistically non-significant (344).

The obvious combination is to use both repaglinide and metformin with bedtime insulin. A study which compared twice-daily insulin and metformin to bedtime isophane insulin, metformin and premeal repaglinide, showed that in the repaglinide group the HbA1c reduction was clinically significant with the actual dose of insulin lower than with the twice daily insulin and metformin group (345).

Side-Effects

The following side-effects have been reported with repaglinide:- hypoglycaemia, rash, flushing, constipation, diarrhoea, flatulence, nausea, vomiting, micturition frequency, and fatigue (346). Two large 1-year studies have shown that repaglinide has an adverse event profile similar to that of glibenclamide. Hypoglycaemia was the most frequently reported adverse event in both studies (339,347).

Contra-indications

Repaglinide should not be given in ketoacidosis, severe hepatic impairment, during pregnancy and lactation. Careful titration is recommended in mild to moderate renal impairment.

Long Term Safety

Long-term clinical trials have shown that the incidence of serious adverse events with repaglinide is low (10%) and similar to the average incidence reported with sulphonylureas (11.6%). Use of repaglinide was associated with less than 1% of serious adverse events (348).

Plasma half-life of repaglinide is extended in severe renal impairment ($t_{1/2}$ increased from 1.5 to 3.6 hours) (336). It is not contraindicated in mild to moderate renal impairment. Repaglinide is currently contraindicated in severe liver impairment since this results in significantly higher and more prolonged serum drug concentrations (349).

Nateglinide

Indication

This agent is currently licensed for use in combination with metformin when metformin alone is inadequate. It is not licensed for patients less than 18 years of age.

Pharmacology

Nateglinide has no sulphonylurea moiety and is a novel amino acid derived from D-phenylalanine.

Nateglinide appears to work in a different way to repaglinide and glibenclamide, as shown in various in vitro experiments using isolated rat islets. Early phase insulin secretion is restored

by the fast association/dissociation kinetics of nateglinide at the level of the β cell. Inhibition of the K^+_{ATP} channel occurs much faster with nateglinide compared with repaglinide but more slowly than with glibenclamide. Insulin levels return to baseline 2 h after administration which is about three-fold faster than with repaglinide (350).

Clinical studies have confirmed the very rapid onset of action and minimal insulin exposure that has been seen with nateglinide in the experimental setting. Nateglinide may produce enhancement of islet glucose sensitivity (350). By this mechanism, nateglinide may potentially produce less hypoglycaemia than is seen with other agents.

One small study of 15 non-diabetic subjects showed that although postprandial insulin secretion rate increased three-fold with nateglinide compared to placebo, by 2 h insulin concentration was similar in both placebo and treated groups (351). A randomized study of 289 patients with T2DM showed that nateglinide is effective in minimizing post-prandial hypoglycaemia while stimulating β cell insulin secretion (352). Patients received 120mg of nateglinide three times daily for 12 weeks with consequent lowering of the mean fasting plasma glucose by 1.4mmol/L. There were no reports of hypoglycaemia associated with the use of nateglinide.

Pharmacokinetics

Nateglinide is also metabolized by the liver although 10% undergoes renal excretion. CYP2C9 and CYP3A4 isoenzymes of cytochrome P450 are believed to be involved in hepatic metabolism (353,354).

Recommended Doses

The initial dose of nateglinide is 60mg three times daily taken within 30min of a main meal. The dose should subsequently be adjusted according to response to a maximum of 180mg three times daily.

Efficacy

Several studies have shown the efficacy of nateglinide either alone or in combination with other oral hypoglycaemic agents such as metformin or troglitazone (now withdrawn).

In a large randomised study 701 patients with T2DM were assigned to one of four different groups namely placebo, nateglinide monotherapy, metformin monotherapy, nateglinide and metformin combination (355). After 24 weeks of double-blind therapy, combination therapy proved to be the most effective in lowering both HbA1c and fasting plasma glucose by 1.9% and 2.4mmol/l respectively. Nateglinide alone reduced HbA1c by 0.9% and fasting plasma glucose by 0.7mmol/L whereas metformin reduced HbA1c by 1.2% and fasting plasma glucose by 1.2%. Nateglinide decreased mealtime glucose excursions after a liquid meal challenge (adjusted area under the curve [AUC]_{0-130min}-2.1mmol/h/l) and an even greater effect was observed with combination therapy ([AUC]_{0-130min} -2.5mmol/h/l). Metformin mainly affected FPG.

Another study evaluated 467 metformin-treated T2DM patients (356). In this multicentre double-blind parallel group trial, there was a significant reduction in HbA1c in the metformin and nateglinide group compared with metformin and placebo. In the nateglinide 60mg-plus-metformin group HbA1c fell by 0.36% and in the nateglinide 120mg-plus-metformin group by 0.51% at end-point. There was no increased rate of hypoglycaemia in the treatment group,

and a mean weight gain of 0.9kg which although statistically significant, was lower than that observed with sulphonylureas (357) and repaglinide (341).

Safety

Unwanted effects

None of the combination trials have found additional adverse events compared with monotherapy regimens.

Nateglinide was well tolerated in a randomized double-blind placebo controlled multicentre study of 289 patients with T2DM mellitus who received either nateglinide 30mg daily, 60mg daily, 120mg daily or 180mg daily or placebo before three main meals for 12 weeks (352). Only five patients in the pooled nateglinide group discontinued the study due to adverse events compared with two patients in the placebo group. Although the incidence of adverse events was higher in the pooled nateglinide group, most were mild symptoms suggestive of hypoglycaemia such as increased sweating, tremor, dizziness, increased appetite and asthenia. The main causes for these symptoms were strenuous exercise or a missed or delayed meal. There were no haematological or biochemical differences between the two groups and no relevant electrocardiographic differences. Changes in body weight ranged from 0.38 to 0.72 kg in the nateglinide 120mg group.

Other reported side-effects are hypersensitivity reactions, increased liver enzymes, gastrointestinal side-effects, headache and respiratory infections. These have been reported with similar incidence to placebo.

Precautions

At present nateglinide is not used in monotherapy. In the presence of fever, trauma, infection or surgery resulting in loss of glycaemic control, nateglinide therapy may need to be substituted by insulin therapy. Extra caution is needed in patients with liver impairment although studies have shown that adjustment of nateglinide dosage is not required in patients with mild to moderate cirrhosis (358).

Contraindications

Nateglinide is contra-indicated if there is hypersensitivity to any of its components, in patients with T1DM, during pregnancy and lactation, and in severe hepatic impairment.

Drug Interactions

The following drugs may interact with nateglinide:-ACE inhibitors, diuretics, corticosteroids, β_2 agonists, cytochrome P450 inhibitors. Concomitant beta-blockers may mask symptoms of hypoglycaemia.

Specific Patient Groups

By virtue of their rapid onset and short duration of action, repaglinide and nateglinide may be particularly suited to specific groups of patients. For those whose mealtimes may be erratic, such as shift workers, the ability to skip a meal due to the flexible dosage of these agents is particularly useful. Another potential area for the use of prandial glucose regulators is during religious events such as Ramadan when participants fast throughout daylight hours. Patients at risk of hypoglycaemia and its consequences such as the elderly may also benefit from first

line therapy with these agents. However repaglinide is not licensed for use in patients above the age of 75 years.

T2DM represents a significant burden on the usage and cost of prescription drugs based on data derived from the Department of Audit and Research at Tayside (DARTS) (359). Although difficult to determine directly, part of the increased cost may be attributed to variable compliance with drug therapy (360). The ability to dose flexibly with prandial glucose regulators may help improve compliance with drug therapy, although thrice daily dosing is prohibitive for some patients.

The recent National Institute for Health and Clinical Excellence (NICE) guidelines have recommended an algorithm for the management of blood glucose in adults with T2DM. Although generic sulphonylureas remain first line therapy, insulin secretagogues such as repaglinide and nateglinide may be prescribed in patients who have a BMI below 25kg/m². They may also have a role in attaining tight glucose control in patients with non-routine daily patterns.

Summary

UKPDS showed that use of traditional oral hypoglycaemic agents such as metformin and sulphonylureas does not change the natural history of T2DM. Sulphonylureas in particular are associated with weight gain and increased risk of hypoglycaemia.

The new rapid acting insulin secretagogues, repaglinide and nateglinide appear to be a useful addition to treatment of patients with T2DM. Repaglinide is least as effective as sulphonylureas in lowering HbA1c and in its safety profile when used in a fixed dose regimen. When used in a flexible dose regimen, it decreases HbA1c and results in less weight gain. Nateglinide in combination with metformin appears to be safe, effective and well-tolerated.

The increasing link between post-prandial glucose levels and increased cardiovascular risk suggests that this is a specific area of diabetes control that may need to be targeted. Currently there are no outcome studies with either of these drugs. An ongoing study in impaired glucose tolerance and nateglinide will shed light on whether lowering PPH will result in improved cardiovascular outcomes. At present, they may be useful as second line agents in combination with metformin in the treatment of T2DM, especially in those who require flexible dosing.

CHAPTER SEVEN

GLARGINE VS NPH INSULIN: EFFICACY IN COMPARISON WITH INSULIN ASPART IN A BASAL BOLUS REGIMEN IN TYPE 1 DIABETES

THE GLARGINE AND ASPART STUDY (GLASS)

7:1 Introduction

As discussed in Chapter 6, DCCT showed conclusively that intensified insulin therapy results in improved glycaemic control, leading to reduction in incidence and delaying progression of existing microvascular and macrovascular complications in T1DM (14,361,362). Intensified insulin therapy can be achieved with basal insulin in combination with short-acting insulins. Insulin analogues with more physiological profiles such as the basal analogue glargine and the short-acting analogue aspart allow intensified insulin therapy without the problems of nocturnal hypoglycaemia and morning fasting hyperglycaemia encountered with unmodified insulins.

Several studies have shown that insulin glargine reduces HbA1c, FPG and nocturnal hypoglycaemia rate (297,300,302-304,306,312,363). Insulin glargine also results in improved treatment satisfaction scores and psychological wellbeing compared with NPH insulin (364).

Reduced insulin dose, less severe hypoglycaemia and insignificant weight change have been observed when switching from NPH to glargine (305,365). There is greater efficacy of insulin glargine and Lispro compared with NPH and lispro in multiple daily injection regimens (303,363).

Insulin glargine has been studied in combination with other short-acting insulins, but not with insulin aspart. Insulin aspart has already been extensively studied in combination with NPH insulin in type 1 diabetes and represents a significant portion of the rapid-acting analogue market currently prescribed in the United Kingdom. There are little data on the efficacy of combining insulin glargine and aspart in a basal bolus regimen and this was

therefore the rationale for the Glargine and Aspart study (GLASS), which was conducted in a single centre in the UK.

7:2 Key Research Questions

1. How effective is insulin glargine compared with NPH insulin when combined with aspart in a basal bolus regimen?
2. What is the effect of insulin glargine on weight gain, hypoglycaemia and patient satisfaction compared with NPH insulin?

7:3 Patients and Methods

Design

The Glargine and Aspart study (GLASS) was a 36-week, open-label, single-centre cross-over study comparing insulin glargine (Lantus[®], Aventis Pharma, Frankfurt, Germany) as a once-daily basal insulin with NPH insulin (Insulatard[®], Novo Nordisk, Crawley, West Sussex, UK) as a twice-daily basal insulin, in combination with the rapid-acting analogue insulin aspart (Novorapid[®], Novo Nordisk) in a basal bolus regimen in T1DM. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all subjects. Recruitment took place between January 2002 and January 2004.

Subjects with T1DM on either twice daily or multiple dose insulin injections were recruited from a single specialist outpatient clinic. The inclusion criteria were: - aged between 18 and 75 years, T1DM on insulin for at least six months, BMI less than 45, baseline HbA1c 6-11%, and ability and willingness to perform self-blood glucose monitoring.

Subjects completed a four-week run-in period during which they received thrice-daily pre-prandial insulin aspart and twice-daily NPH. Subsequently, they were allocated to receive insulin aspart in combination with either once-daily insulin glargine or twice-daily NPH. Allocation was based on opening consecutively numbered sealed envelopes in which the name of the basal insulin had previously been randomly inserted.

Subjects were instructed to administer glargine once daily at bedtime and NPH approximately 30 minutes before breakfast and their evening meal. Aspart was injected immediately before meals. The Optipen[®] Pro 1 injection device (Aventis) was used to administer insulin glargine and the Novopen[®] 3 (Novo Nordisk) was used to administer insulin aspart and NPH.

Insulin glargine or NPH was continued for 16 weeks before crossing over to the other basal insulin. The number of units of insulin equal to that administered at the end of the first treatment period was prescribed, unless previous home glucose monitoring suggested a dosage modification.

On switching from glargine to NPH, the current basal dose of insulin was increased by 20% to compensate for switching from a once daily basal regimen to a twice-daily basal regimen. Conversely, when switching from NPH to glargine, the basal dose of insulin was reduced by 20%.

Visits took place at screening (visit 1), two weeks after screening (visit 2), baseline (visit 3) and then every eight weeks until the end of the study (visits 5-7) (Fig 7:1).

Subjects self-monitored blood glucose levels daily at home using the Precision[®] QID monitor (Medisense, Abingdon and Witney, Oxfordshire, UK). Insulin dosage was adjusted according to a local algorithm with targets of 4-6.7 mmol/l before meals, 4-8 mmol/l at bedtime and <8 mmol/l two hours after main meals. Telephone contact was made twice weekly to advise on changes in insulin dosage.

At visit 1, subjects were provided with dietetic input based on conventional advice for insulin analogues. They were supplied with a diary and blood-glucose meter and auxiliary supplies sufficient for the period between visit 1 and visit 3 and instructed in self-monitoring blood glucose throughout the trial to enable continuous dose adjustment. It was recommended that blood glucose should be measured prior to injecting and 120 min after the start of a meal.

Participants were advised about symptoms of hypoglycaemia and instructed to record the following information in a diary: - date, time of episode, time of last injection prior to episode, time of last meal prior to episode, type of insulin, blood glucose value at the time of episode, whether or not there were symptoms, and whether or not glucagon or intravenous glucose was required. Hypoglycaemia was categorised as symptoms only, documented or confirmed, severe and nocturnal (occurring between 2400 and 0800 h). Severe hypoglycaemia was defined as a hypoglycaemic episode requiring third-party assistance and/or intravenous glucose or intramuscular glucagon. Documented or confirmed hypoglycaemia was defined as a capillary glucose measurement of less than 2.8 mmol/L.

Blood samples for HbA1c, FPG and lipids were taken at visit 1 (screening), and at visits 3, 4, 5, 6 and 7. Weight was also recorded at these visits.

Subjects wore a continuous glucose monitoring system (CGMS) (MiniMed MMT-7102; Medtronic, Northridge, Ca) for up to 72 h at start of treatment (visit 3), at cross-over (visit 5) and at the end of the trial (visit 7). The monitor sampled the signals every 10 seconds

and then stored a mean value every 5 minutes. Data were downloaded to a computer via a communication device.

Patients were asked to complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Audit of Diabetes-Dependent Quality of Life questionnaire (ADDQoL) at visits 1,3,5 and 7 (366,367) (see Appendix).

The author was involved in actively recruiting subjects, conducting study visits, advising with regard to dose titration and adverse reactions, developing and maintaining the database, and analysing and reporting the data.

7:4 Statistical Analysis

The primary endpoint was HbA1c. 59 subjects were needed to achieve 80% power for a maximal difference of 0.5% in HbA1c between means with a common standard deviation of 1.35 at a significance level (α) of 5%. The data on HbA1c were analysed using mixed models analysis of variance with the subject effect as random. Terms within the model included sequence, period and treatment. Secondary endpoints were frequency of reported severe hypoglycaemic episodes and overall frequency of both severe and non-severe hypoglycaemic events during the last 12 weeks of each treatment period. Other secondary endpoints were FPG, weight, fasting lipids and questionnaire-based patient satisfaction. Safety endpoints were adverse event recording and vital signs namely pulse and blood pressure.

The data on the total number of hypoglycaemic episodes (severe and non-severe) were analysed using generalised linear models fitting a Poisson distribution.

Data from the DTSQ and ADDQoL questionnaires were analysed using standardised criteria. Data are stated as mean and mean difference \pm SE (95% CI) unless otherwise indicated.

7:5 Results

Characteristics of Study Population at Screening

A total of 60 subjects with T1DM were recruited to this single centre study of which 58 were White European and 2 were South Asian. Baseline characteristics are shown in Table 7:1. During run-in, all subjects were treated with standardised therapy consisting of twice daily NPH (human or porcine) and thrice daily pre-prandial insulin aspart. Most patients were on a basal bolus regimen with human insulins prior to run-in (Table 7:2). Three subjects withdrew before randomisation, with one experiencing an adverse reaction to insulin aspart.

Following randomisation, 25 received glargine and 33 received NPH first. One subject, who was randomised to NPH first, withdrew after three weeks and was therefore not included in the analysis. Three subjects, who all received glargine first, failed to complete both periods of the study. One subject from each group violated the protocol and was not included in the per protocol population.

Glycaemic Control

HbA1c

At the beginning of the first period, mean HbA1c was 8.51% for subjects randomised initially to NPH, and 8.57% for those randomised to glargine.

At the end of the study, mean HbA1c was lower with glargine and aspart compared with NPH and aspart (8.07 vs. 8.26%, -0.19 ± 0.09 (-0.36 to 0.01), $p=0.04$). At the end of the first period, HbA1c was 7.89% on glargine and 8.36% on NPH (-0.68 vs -0.15; glargine vs NPH). After the second period, subjects who switched from glargine to NPH

experienced an increase in HbA1c of 0.16%, whereas subjects who switched to glargine from NPH experienced a reduction in HbA1c of 0.1%. Figure 7:2 illustrates the change in HbA1c throughout the study.

Fasting Plasma Glucose (FPG)

At the end of the study, mean FPG was 3 mmol/L lower with glargine and aspart compared with NPH and aspart (8.42 vs. 11.42mmol/L, -3.00 (-4.80 to -1.20), $p<0.01$). At the end of the first period, FPG was 9.06mmol/L with glargine and 10.68 mmol/L with NPH. Following the second period, FPG was 7.78 mmol/L with glargine and 12.17 mmol/L with NPH.

Hypoglycaemia Rate

The mean incidence of both severe and non-severe hypoglycaemia was similar with glargine compared with NPH (80.7 vs 77.2%, 1.21 (0.56 to 2.64), $p=0.63$). The odds ratio for the incidence of hypoglycaemia on glargine compared to NPH was 1.2 (95% CI 0.55 to 2.59). Only one subject on glargine and one on NPH experienced a severe hypoglycaemic episode. Five subjects did not report hypoglycaemia on either treatment. Five subjects experienced hypoglycaemia on glargine but not on NPH insulin, whereas four had hypoglycaemia on NPH insulin but not on glargine.

In the first period, subjects randomised to glargine reported 170 episodes of hypoglycaemia of which 18 (10.6%) were symptomatic only, 152 (90.5%) were confirmed or documented by capillary glucose measurement, and 10 (0.06%) were nocturnal. Subjects randomised to NPH reported 167 episodes of hypoglycaemia of which 38 (22.8%) were symptomatic only, 129 (77.2%) were confirmed, and 15 (0.09%) were nocturnal.

There were no episodes of severe hypoglycaemia during the first period with either basal insulin.

In the second period, after crossing over to the other basal insulin, subjects on glargine reported 164 hypoglycaemic episodes of which 31 (18.9%) were symptomatic only, 133 (81.1%) were confirmed, 1 (0.006%) was severe and 11 (0.07%) were nocturnal. Those on NPH insulin in the second period reported 175 episodes of hypoglycaemia of which 26 (14.9%) were symptomatic only, 149 (85.1%) were confirmed, 1 (0.006%) was severe and 12 (0.07%) were nocturnal.

No significant difference in hypoglycaemia frequency was detected in the first or second periods between NPH and glargine ($p>0.05$ for all categories of hypoglycaemia).

Continuous Glucose Monitoring System (CGMS)

Only 27 patients had complete data for all three visits. In the majority of patients, “flat lines” appeared on the traces indicating failure of blood glucose measurement. From these limited data, no statistical differences were found between the two basal insulins for overall hypoglycaemia, nocturnal hypoglycaemia or glucose excursions after meals.

Insulin Doses

Basal dose

The mean basal insulin dose for all subjects after four weeks’ run-in was 38.4 (20.6) IU. In those subjects who were initially randomised to glargine, the basal insulin dose was 33.9 (21.0) IU at the end of the first period. Following crossover to NPH, the basal dose was 39.4 (19.4) IU at the end of the second period. For those subjects randomised to NPH first,

basal insulin dose was 40.9 (18.6) IU at the end of the first period and 39.7 (29.1) IU at the end of the second period.

Prandial dose

Mean prandial dose was 31.4 (20.5) IU after four weeks' run-in. In those randomised first to glargine, the prandial dose was 36.1 (19.0) IU at the end of the first period, and 35.1 (14.7) IU at the end of the second period. For those randomised to NPH first, prandial dose was 30.6 (15.6) IU at the end of the first period, and 32.6 (21.8) IU at the end of the second period.

There was no difference between the two basal insulins with either mean basal or prandial dose ($p=0.21$ and $p=0.46$ respectively) using analysis of variation (ANOVA). However, there were some outlying values and using non-parametric analyses there was a significant difference between glargine and NPH ($p=0.0002$) for basal dose but not prandial dose ($p=0.44$).

Other Secondary Endpoints

There was no significant difference between glargine and NPH for change in weight (Table 7:2). At the end of treatment, mean weight with glargine was 81.68kg and with NPH insulin 81.92kg (mean difference -0.24, 95% CI -0.87 to 0.39, $p=0.45$). Similarly, no differences were detected between the two basal insulins for total cholesterol or triglyceride levels after 16 weeks' treatment (Table 7:2).

Patient Satisfaction

DTSQ

A statistically significant difference between treatments ($p=0.001$) was only observed on analysis of DTSQ for the second period. Overall, satisfaction was greater with glargine by a mean of 4 points on the change scale compared with NPH. There was no difference between glargine and NPH in the perception of hyperglycaemia ($p=0.34$) or hypoglycaemia ($p=0.76$). Regardless of the insulin received first, subjects experienced more hypoglycaemia in the first period after run-in.

ADDQoL

There was no difference in overall quality of life and overall impact of diabetes on quality of life using ADDQoL. The profiles of the responses to the individual items were very similar for both insulins, with a slight divergence only noted on the item describing freedom of what to drink. No difference was detected in the average weighted impact score between the insulins ($p=0.8$).

7:6 Discussion

This study shows that treatment with insulin glargine resulted in a small but significant improvement in HbA1c and FPG compared with NPH in a basal bolus regimen in T1DM without a significant increase in hypoglycaemia rate or weight gain and associated with greater patient satisfaction.

In this study, HbA1c differed overall by 0.19% between the basal insulins, with notably greater reductions in the first treatment period in favour of insulin glargine (-0.68 vs -0.15; glargine vs NPH) and a deterioration in control at cross-over to NPH (-0.1 vs +0.16; glargine vs NPH). Although a large reduction in HbA1c was not achieved, this was a single centre study and therefore these subjects were a more representative sample of a T1DM population. Other studies have found a similar reduction in HbA1c of around 0.16-0.5% (297,300,302-306,312,363,365). A recent systematic review concluded that the majority of studies reporting on the use of glargine have been statistically underpowered or inconsistently analysed (368). However the results from suitably analysed and powered studies indicate that treatment with glargine results in statistically significant reductions in FPG at endpoint compared with both baseline and NPH, although this is not always associated with significant improvements in HbA1c.

One large study of 534 patients with well-controlled T1DM demonstrated that HbA1c levels decreased by 0.16% with glargine and 0.21% with NPH. However, in this study, lower FPG levels and fewer episodes of hypoglycaemia were recorded with glargine compared with once or twice daily NPH (302).

Compared with the gold standard therapy of continuous subcutaneous insulin infusion (CSII), glargine is either similar or less effective at reducing HbA1c (369-371), regardless

of whether lispro or aspart is used as the insulin infusion. In addition, a lower daily dose of insulin produced a greater effect with CSII. It was suggested that the effectiveness of glargine could be improved by a further 0.1% if the percentage of basal insulin was kept between 40-60%. Smaller but longer-term studies have shown that glargine and CSII have equivalent effects on HbA1c, FPG, triglycerides, and severe hypoglycaemia (369). Another small study compared night-time blood glucose control between glargine and CSII and found that subjects on glargine spent significantly more time outside target sensor glucose ranges (371). The current NICE guidance is that patients with T1DM should be managed with glargine in a basal bolus regimen before being referred for CSII therapy (372).

The flatter profile and longer duration of glargine is likely to lead to less glucose excursions during the twenty-four period. Notably, there was a significant difference in FPG between basal insulins in this study, which may reflect the more physiological pharmacokinetics of insulin glargine. However, the marked difference in FPG may be attributed to the different timings of the evening basal insulin, that is, NPH was injected before the evening meal whereas glargine was administered at bedtime.

In GLASS, a difference in hypoglycaemia was not detected although this has been reported in previous studies (302,365). Severe hypoglycaemia was reduced with glargine compared with NPH in intensively treated adults with T1DM although there was no difference in HbA1c (365). However in GLASS, improved glycaemic control was achieved on glargine without increasing hypoglycaemia. Furthermore, comparison of dose titration and final basal doses suggests that the glargine dose could have been more optimally titrated, especially as HbA1c at the end of the study was higher than the currently recommended target of 6.5-7% despite the use of a treat-to-target regimen. The

fact that this was an open-label study may also have affected optimal titration. However, as glargine is a clear insulin and NPH is cloudy, blinding would have been difficult to achieve.

A study of 121 subjects with T1DM found that the responses of plasma adrenaline, cortisol and growth hormone improved more with glargine than with NPH, indicating that counter-regulatory hormone responses to hypoglycaemia were more favourable with glargine (303). This was associated with improved glycaemic thresholds and magnitudes. CGMS has been shown to be reliable and reproducible in the assessment of hypoglycaemia in type 1 diabetes in some studies (373) but one study showed that spurious results for nocturnal hypoglycaemia could be obtained (374). However, in this study, CGMS was successfully obtained in less than 50% of subjects. The limited data caused difficulties with statistical analysis and were not useful in assessing frequency of hypoglycaemia.

Weight gain is often associated with insulin therapy. In GLASS, there was less than 1 kg increase in weight with both basal insulins. It has been shown elsewhere that weight gain occurs more with NPH than with glargine (305). Weight gain was significantly greater when glargine was administered as a split daily dose (365).

Subjects achieved greater treatment satisfaction on glargine compared with NPH when assessed using validated questionnaires. The ability to inject at different times of the day with significantly increasing glycaemic control might be expected to improve satisfaction further.

The increasing use of structured education programmes in T1DM such as Dose Adjustment for Normal Eating (DAFNE) programme has the potential to lead to better glycaemic

outcomes using glargine as the basal insulin. Up to 1% reduction in HbA1c without increased hypoglycaemia or weight gain was seen in a DAFNE randomised controlled trial in the UK (375). However this was prior to the wide availability of glargine as a basal insulin and the insulin regimens used in this study were not detailed.

Insulin aspart in combination with glargine is used extensively at present in the UK. The other commonly prescribed short-acting insulin analogue lispro has been well documented to improve glycaemic control in combination with glargine when compared with NPH (303,304,363,365). GLASS is the first study to compare the short-acting insulin analogue aspart in combination with either glargine or NPH.

7:6 Conclusion

The results of the Glargine and Aspart study (GLASS) suggest that the combination of once daily insulin glargine with aspart in a basal bolus regimen is an effective form of insulin therapy in T1DM.

Figure 7:1 Schematic Diagram of Study Design for GLASS

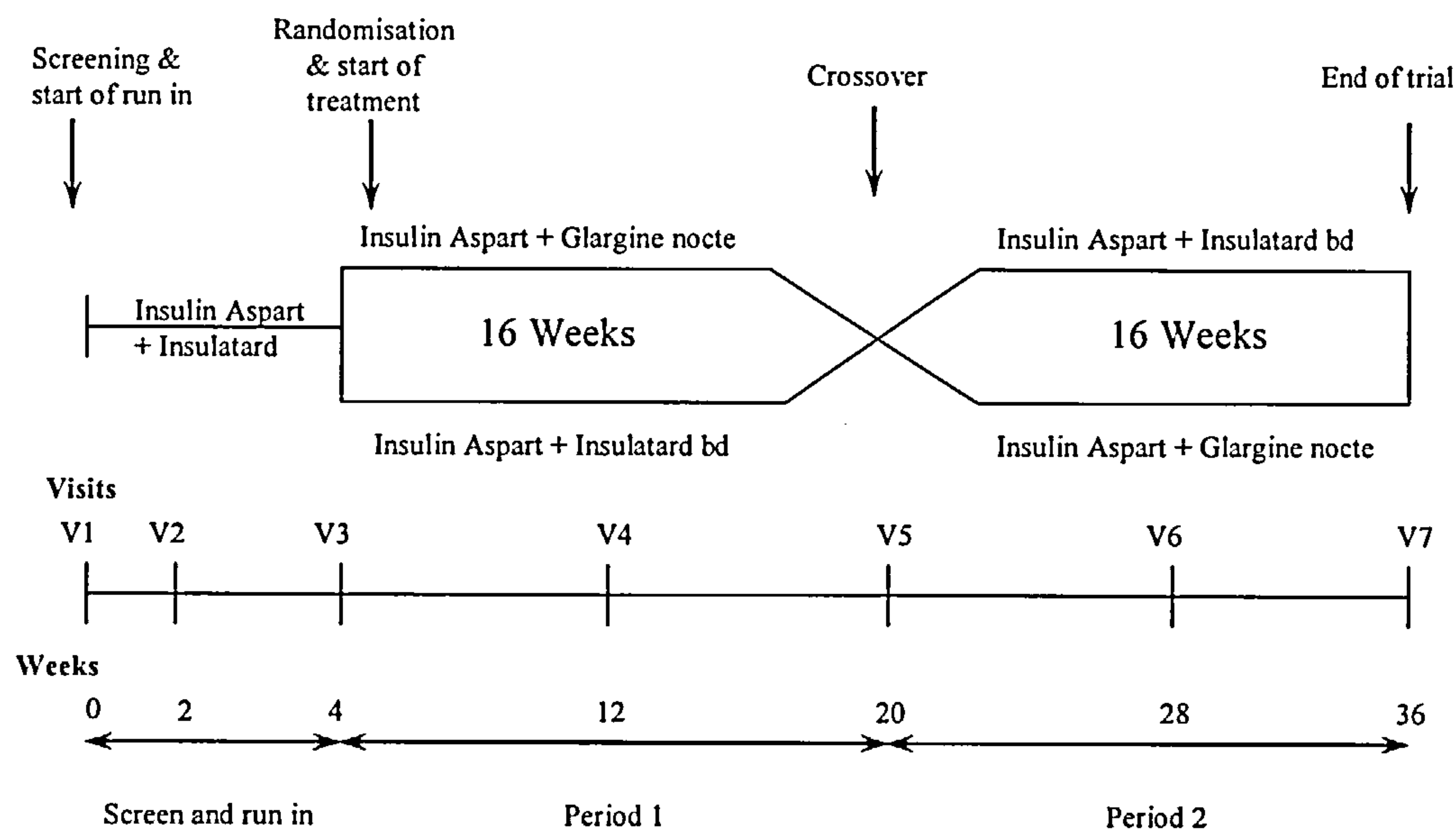


Figure 7:2. Change in HbA1c during Study

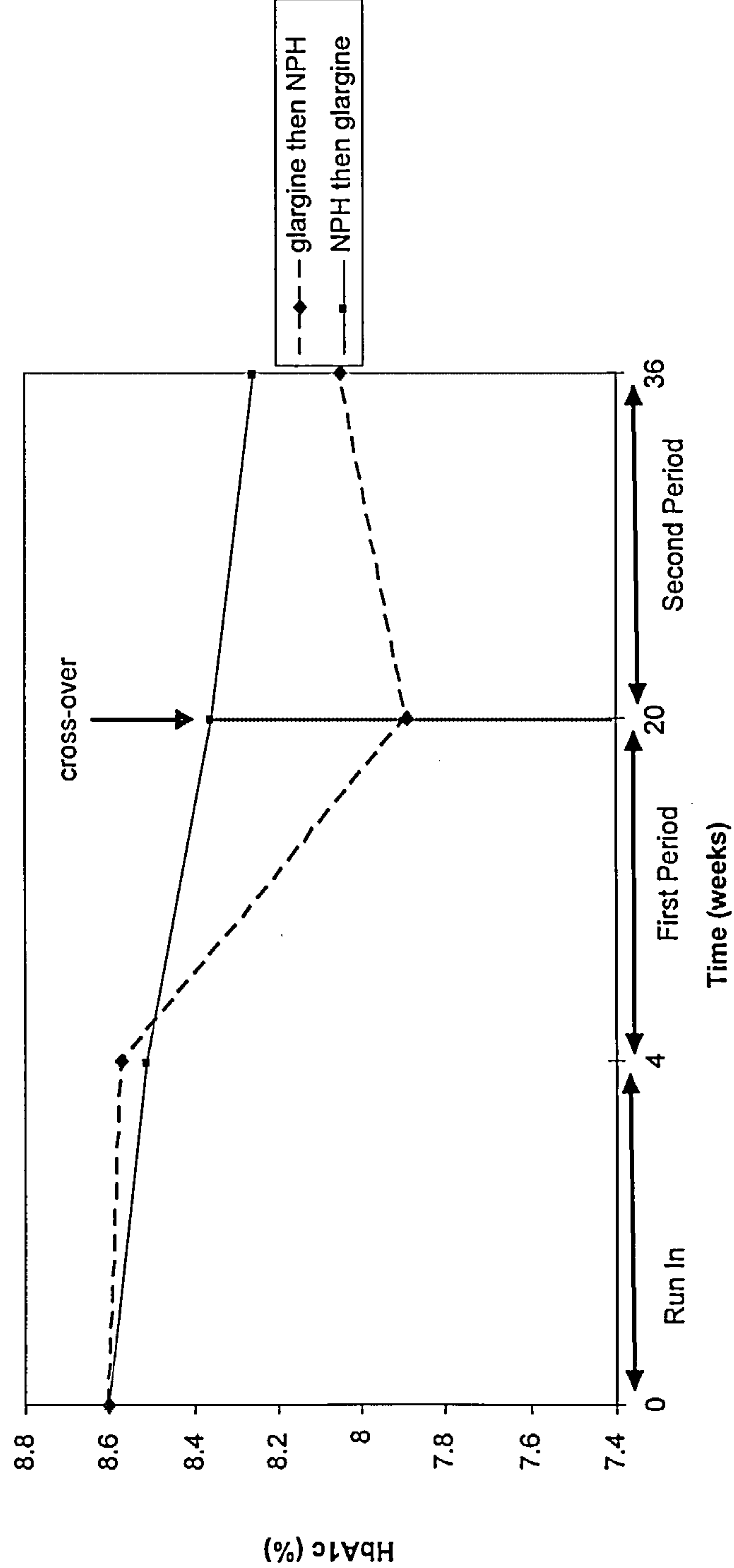


Table 7:1 Baseline Characteristics of GLASS Population

Variable	Mean ± SD or n (%)
N	60
Sex (M:F)	35:25
Mean age (years)	42.9 (12.5)
Duration of diabetes (years)	18.2 (11.8)
Weight (kg)	81.0 (14.0)
BMI (kg/m ²)	27 (4.2)
Haemoglobin A1c (%)	8.53 (1.15)
Fasting Plasma Glucose (mmol/l)	11.5 (5.4)
Total Cholesterol (mmol/l)	4.7 (0.8)
Triglycerides (mmol/l)	1.0 (0.6)
Systolic BP (mmHg)	139 (16)
Diastolic BP (mmHg)	83 (9)
Insulin dose (IU/kg)	0.86 (0.29)
<i>Insulin therapy prior to study</i>	
Basal bolus regimen	40 (66.7)
Twice daily regimen	17 (28.3)
Other	2 (3.0)
Human	43 (71.7)
Porcine or human/porcine mixture	15 (25)
Bovine	2 (3.0)

Table 7:2 Summary of Treatment Differences in GLASS

Variable	glargine	NPH	Difference (glargine- NPH)	95% CI	p-value
HbA _{1c} (%)	8.07	8.26	-0.19	(-0.36 to -0.01)	0.04
Fasting plasma glucose (mmol/L)	8.42	11.42	-3.00	(-4.80 to -1.20)	<0.01
Incidence of hypos (%)	80.7%	77.2%	1.21*	(0.56 to 2.64)*	0.63
Weight (kg)	81.68	81.92	-0.24	(-0.87 to 0.39)	0.45
Cholesterol (mmol/L)	4.74	4.84	-0.10	(-0.25 to 0.05)	0.18
Triglyceride (mmol/L) (Geometric means)	0.82	0.80	1.02*	(0.93 to 1.12)*	0.63

*Ratio

CHAPTER EIGHT

EARLY THERAPEUTIC INTERVENTIONS TO IMPROVE GLYCAEMIC CONTROL IN TYPE 2 DIABETES - THE PIOGLITAZONE IN COMBINATION WITH NATEGLINIDE IN CARE OF TYPE 2 DIABETES (PICNIC) STUDY

8:1 Introduction

Once the diagnosis of T2DM is made, whether through screening or following clinical presentation, the goal of management is to obtain optimal glycaemic control rapidly and to modify other cardiovascular risk factors such as hypertension, hyperlipidaemia and smoking. With the target for glycaemic control decreasing steadily over the last few years, and the increasing choice of oral therapies, it is essential to determine the best combination of agents that will reduce blood glucose effectively and safely soon after diagnosis.

T2DM is a progressive disease and UKPDS showed that inevitably combination therapy was required with time (2). Treatment with conventional agents, including insulin, sulphonylureas and metformin, did not appear to change the natural progression of the disease process, a combination of progressive β cell function and insulin resistance.

Since the 1950s, the mainstays of oral hypoglycaemic therapy have been the sulphonylureas and metformin. However, sulphonylureas such as gliclazide are associated with increased risk of hypoglycaemia and weight gain, whereas metformin causes gastrointestinal side effects in a significant proportion of patients and is contra-indicated in those with moderate renal impairment. In the UK, metformin and gliclazide remain the most commonly prescribed agents for the treatment of T2DM as monotherapy or in combination, but newer oral agents have now arrived on the scene.

Thiazolidinediones such as pioglitazone and rosiglitazone target insulin resistance whereas β cell dysfunction is reduced by the meglitinides namely repaglinide and nateglinide. Both these types of agents are potential candidates for early combination therapy.

8:2 Key Research Questions

1. How effective are dual oral combination therapies in early T2DM?
2. Which is the best oral hypoglycaemic combination in treatment of early T2DM?

8:3 Patients and Methods

The aim of this study was to determine the effectiveness of combination therapy early in the disease process for T2DM using one of the following four groups of drugs: - pioglitazone and nateglinide, gliclazide and metformin, metformin and nateglinide, and metformin and pioglitazone.

The primary outcome was change in HbA1c at 6 months. Secondary outcome measures were quality of life, change in weight, episodes of reported hypoglycaemia, FPG and 2 hour post-prandial glucose recordings from home blood glucose monitoring. Ethical approval from the local ethics committee was obtained for this study and it was conducted in accordance with the Declaration of Helsinki. Inclusion criteria were as follows:-

- Patients with T2DM
- Aged between 30-80 years
- HbA1c $\geq 6.5\% \leq 10\%$
- BMI $< 45\text{kg/m}^2$
- Patient on diet only or monotherapy with either a sulphonylurea up to 50% of maximum dose or metformin up to 1.7g per day.

Exclusion criteria were as follows:-

- Creatinine $>150 \mu\text{mol/L}$
- Abnormal liver function tests
- Known or suspected allergy to trial product or related products
- Pregnancy, breast-feeding, intention of becoming pregnant or judged not to be using adequate contraceptive measures. (Adequate contraceptive measures are an intrauterine device, oral contraceptives and barrier methods).

- A history of drug abuse or alcohol dependence within the last 5 years.
- Severe, uncontrolled hypertension (sitting systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg).
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation.
- Any disease or condition that might interfere with the trial.

Sample Selection

Patients were selected through attendance at secondary care diabetes clinics and direct referrals from primary care practices. In primary care, general practitioners and practice nurses searched computer databases and compiled a list of suitable patients who were then sent letters of invitation and information leaflets in the post. Once patients consented to participate, they were randomised to treatment groups using random number envelopes. A 2:2:1:1 randomisation approach was used. Block randomisation was used to ensure adequate numbers of patients in the two main arms of the study, namely metformin/gliclazide and pioglitazone/nateglinide.

Data Collection

The study visit schedule is shown in Table 8:1.

Table 8:1 PICNIC Study Visit Schedule

	Visit 1	Visit 2	Visit 3	Visit 4
Month	0	0.5	3	6
Consent	X			
Past Med Hx	X			
Demographics	X			
HbA1c	X		X	X
Weight	X		X	X
Height	X		X	X
BMI	X		X	X
Questionnaires	X		X	X
Fasting Lipids/Glucose	X		X	X
7 point profile			X	X
Titration of Medication		X		
Recording of Hypos		X	X	X
Dispense Medication	X			
Adverse Events	X	X	X	X

7 Point Profile and Home Blood Glucose Monitoring

Patients were asked to check a 7 point profile for 2 consecutive days prior to Visits 3 and 4. This involved home capillary glucose monitoring before and after each main meal and before bed.

At Visit 1, all subjects were supplied with the same blood-glucose meter and were instructed in its use, which included regular calibration in accordance with the manufacturer's instructions. Written instructions were also provided. The subjects were instructed in home blood glucose monitoring throughout the trial to enable continuous dose adjustment. It was recommended that patients should test their blood at least once at different times of the day. Values were recorded in the patients' study diary. Patients were also asked to record any episodes of hypoglycaemia in the diary.

Subjects were informed of the targets for glycaemic control as below:-

- 4-7 mmol/l before meals
- 5-8 mmol/l at bedtime
- <8 mmol/l two hours after main meals.

Dose Titration

At Visit 2, patients were assessed with regard to up-titration of drug dosage. Titration occurred in everyone unless they reported significant hypoglycaemia and/or troublesome side-effects from therapy. Following titration, subjects continued on these doses for the duration of the study. The doses used were as follows:- metformin 500mg thrice daily and gliclazide 80mg twice daily; pioglitazone 30mg once daily and nateglinide 120mg thrice daily; metformin 500mg thrice daily and nateglinide 120mg thrice daily; and metformin

500mg thrice daily and pioglitazone 30mg once daily. If subjects were new to metformin, the dose was titrated slowly over 2-3 weeks to minimise gastro-intestinal side-effects.

Patient Satisfaction Questionnaires

Patients were asked to complete quality of life questionnaires at Visits 1, 3 and 4 using Audit of Diabetes-Dependent Quality of Life (ADDQoL). At these visits, treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (status and change versions - DTSQs and DTSQc) (see Appendix).

The author was responsible for actively recruiting subjects to the study, conducting study visits, advising with regard to titration and adverse events, as well as developing and maintaining the database and analysing the data.

Ethical Issues

Local Research Ethics committee approval and University Hospitals of Leicester NHS Trust Trust Approval was sought for the study before it commenced. This ensured that all ethical and indemnity issues were dealt with.

Patients were given a patient information sheet (see Appendix) to read before they registered their interest in taking part in the study. This was either by post or by hand depending on the method of referral. They were asked to return the interest slip from the introduction letter accompanying the information sheet to register their interest. This allowed adequate time for the patient to consider participation. At the first appointment

patients were asked to sign a consent form to take part in the study and this was sought by the study physician.

Data were collected on an Access database. This database was protected with a minimum number of users to deal with patient confidentiality issues. All hospital notes and study records were kept in a locked filing cabinet.

8:4 Statistical Analysis

Data were analysed with parametric and non parametric tests where appropriate using SPSS version 11 (SPSS, Chicago, IL, USA). The distribution of the primary variable, HbA1c, was examined. As these values were not normally distributed, all values were logarithmically transformed before analysing the ratios of group geometric means. Secondary variables were FPG and rates of hypoglycaemia. The main groups under consideration were pioglitazone/nateglinide and gliclazide/metformin. Unpaired T tests were used to compare changes from baseline (Visit 1). Variant T test rather than standard T test output was used for reporting analysis. The main comparison of interest was between the primary groups, that is, pioglitazone/nateglinide and gliclazide/metformin.

Results are presented as the treatment effect with 95% CI and p value, and were interpreted with respect to the minimum difference of clinical interest from sample size calculation. An intention-to-treat analysis was used. Hypoglycaemia data were analysed as any episodes occurring between 0 to 2 weeks (Visit 2), 2 weeks to 3 months (Visit 3), and 3 months to 6 months (Visit 4). For patient satisfaction, paired T test and one-way ANOVA were used to determine differences.

8:5 Results

In total, 100 patients were enrolled in the study. One patient dropped out prior to randomisation as they did not wish to take the recommended medication doses. The baseline (Visit 1) characteristics of the study population are shown in Table 8:1. 99 male and female subjects were randomised to six months' treatment with one of four drug combinations, namely, pioglitazone/nateglinide (n=36), metformin/gliclazide (n=33), metformin/pioglitazone (n=15) and metformin/nateglinide (n=15). The difference in numbers was attributable to the 2:2:1:1 randomisation protocol. At baseline, mean (SD) age was 57.1 (10.4) y, duration of diabetes 47.2 (68.8) months, males 72.7%, 58% white Europeans, BMI 29.7 (5.4) kg/m², baseline HbA1c 7.8 (1.3) %, and FPG 8.4 (2.5) mmol/l.

13 subjects failed to complete the study. 1 subject withdrew prior to randomisation, 4 subjects stopped due to side-effects, 1 subject withdrew as he was a bus-driver and was afraid of hypoglycaemia, 2 subjects were protocol violators, 4 subjects failed screening, and 1 subject withdrew due to depression. At Visit 2, when response to medication was assessed, titration did not occur in 16 (16%) subjects due to hypoglycaemia, gastrointestinal side-effects or both.

Primary outcome - HbA1c

After six months, HbA1c was significantly reduced with all four combinations (p<0.001) (Table 8:3 and Fig 8:1). There was a significant difference in HbA1c between metformin/gliclazide and pioglitazone/nateglinide only at three months (6.41% vs 7.12%, p=0.018). At six months, HbA1c was similar in both groups (6.57% vs 6.58%, NS). HbA1c was also significantly different between metformin/gliclazide and metformin/nateglinide at 3 months (6.41% vs 6.91%, p=0.023) but not at six months

(6.57% vs 6.47%, NS). There were no significant differences between any of the groups for change in HbA1c between Visit 1 and Visits 3 or 6.

Secondary outcomes

Mean FPG was reduced significantly with all four combination groups ($p < 0.05$) with the greatest reduction seen with metformin/pioglitazone (2.78 mmol/l). There was significant weight gain from baseline to study end in the pioglitazone/nateglinide group (83.3kg vs 84kg, mean difference 1.67kg, $p = 0.02$), and significant weight gain between baseline and visit 3 with gliclazide/metformin (82.2kg vs 85.9kg, mean difference 1.64kg, $p < 0.001$) (Table 8:4). At six months there was a significant difference between metformin/gliclazide and pioglitazone/nateglinide in creatinine (80.4 vs 110.7 $\mu\text{mol/l}$, $p = 0.005$) and alanine transaminase (ALT) (33.8 vs 23.7 IU/l, $p = 0.02$).

Hypoglycaemia

Hypoglycaemic episodes were recorded at Visits 2, 3 and 4 (Table 8:5). At Visit 2, 2 subjects from each group reported minor hypoglycaemic episodes but only one in each group documented the plasma glucose value. As numbers were small, only metformin/gliclazide and pioglitazone/nateglinide groups were compared and there were no significant differences in frequency of hypoglycaemia. No episodes of severe hypoglycaemia were documented.

Patient Satisfaction

Table 8:6 shows the change in patient satisfaction using DTSQs at Visit 1 and DTSQc at Visits 3 and 4. In all four groups there was a reduction in satisfaction after six months of therapy. However this was non-significant. There was a significant difference in mean scores between Visit 1 and Visit 3 for the combinations pioglitazone/nateglinide and

metformin/nateglinide. There were no significant differences between the groups for DTSQ score during any of the visits.

The results of the ADDQoL questionnaire survey are summarised in Table 8:7. Using this questionnaire the maximum negative impact of diabetes is -9 and the maximum positive impact is +9. No significant difference was detected between the groups during any of the visits. However there was a significant difference between visit 1 and visit 4 for the gliclazide/metformin combination with an increase in the negative impact of diabetes ($p=0.026$, 95% CI 0.12 to 1.76).

Table 8:2 Baseline Characteristics of PICNIC Study Population (N=99)

	N	Mean	Range	SD
<i>Gender</i>				
Male	72			
Female	27			
<i>Ethnicity</i>				
White European	58			
South Asian	37			
Other	4			
<i>Smoker</i>				
Never	45			
Current	15			
Previous	37			
<i>Drug combination following randomisation</i>				
gliclazide/metformin	33			
pioglitazone/nateglinide	36			
metformin/nateglinide	15			
metformin/pioglitazone	15			
Age (yr)	99	57.9	30.3 to 79.2	10.4
Height (m)	99	1.69	1.53 to 1.85	0.08
Weight (kg)	99	84.63	52.25 to 145.20	17.99
BMI (kg/m ²)	99	29.7	21.5 to 48.0	5.4
Duration of diabetes (mth)	99	47.2	1.0 to 350.0	68.8
Systolic BP (mmHg)	99	137	96 to 199	19
Diastolic BP (mmHg)	99	81	56 to 100	9
Resting pulse (bpm)	99	71	40 to 108	12
HbA1c (%)	98	7.80	5.9 to 13.4	1.30
Fasting Plasma Glucose (mmol/l)	97	8.40	4.7 to 17.4	2.54
Total cholesterol (mmol/l)	99	4.87	2.5 to 7.7	1.04
LDL cholesterol (mmol/l)	83	2.97	1.0 to 5.8	0.87
HDL cholesterol (mmol/l)	99	1.2	0.6 to 9.0	0.9
Triglycerides (mmol/l)	98	1.83	0.5 to 12.6	1.45
Creatinine (umol/l)	99	88	47 to 126	16.0
Urea (mmol/l)	99	6	3 to 64	6.2
Alanine Transaminase (mmol/l)	99	35	4 to 191	25.0

Table 8:3 Change in HbA1c after Six Months' Treatment with each Dual Combination of Oral Hypoglycaemic Agents

Drug Combination		Mean HbA1c (%)	95% Confidence Interval	P value
gliclazide/metformin	Visit 1	7.49	7.18 to 7.81	<0.001
	Visit 3 ^{a,b}	6.41	6.12 to 6.70	
	Visit 4	6.57	6.21 to 6.93	
pioglitazone/nateglinide	Visit 1	8.05	7.48 to 8.62	<0.001
	Visit 3 ^a	7.12	6.60 to 7.64	
	Visit 4	6.58	6.25 to 6.91	
metformin/nateglinide	Visit 1	8.07	7.36 to 8.77	<0.001
	Visit 3 ^b	6.91	6.57 to 7.24	
	Visit 4	6.95	6.54 to 7.36	
metformin/pioglitazone	Visit 1	7.61	7.01 to 8.23	<0.001
	Visit 3	6.61	6.08 to 7.14	
	Visit 4	6.47	6.13 to 6.81	

^a significant difference between combinations in HbA1c at 3 months (6.41% vs 7.12%, p=0.018)

^b significant difference between combinations in HbA1c at 3 months (6.41% vs 6.91%, p=0.023)

Table 8:4 Change in Weight During PICNIC Study

Drug Combination		Mean Difference in Weight	95% Confidence Interval	P value
Gliclazide/Metformin	Weight(V1) - Weight (V3) (kg)	-1.64	-2.45 to -0.83	<0.001
	Weight (V1) - Weight (V4) (kg)	0.65	-5.80 to 7.09	0.84
Pioglitazone/Nateglinide	Weight(V1) - Weight (V3) (kg)	-0.34	-1.62 to 0.93	0.58
	Weight (V1) - Weight (V4) (kg)	-1.67	-3.10 to -0.24	0.02
Metformin/Nateglinide	Weight(V1) - Weight (V3) (kg)	-0.09	-0.86 to 0.69	0.81
	Weight (V1) - Weight (V4) (kg)	0.17	-1.09 to 1.43	0.77
Metformin/Pioglitazone	Weight(V1) - Weight (V3) (kg)	-0.80	-2.50 to 0.90	0.32
	Weight (V1) - Weight (V4) (kg)	-1.56	-3.90 to 0.78	0.17

Figure 8:1 Change in HbA1c According to Drug Combination over Study Period

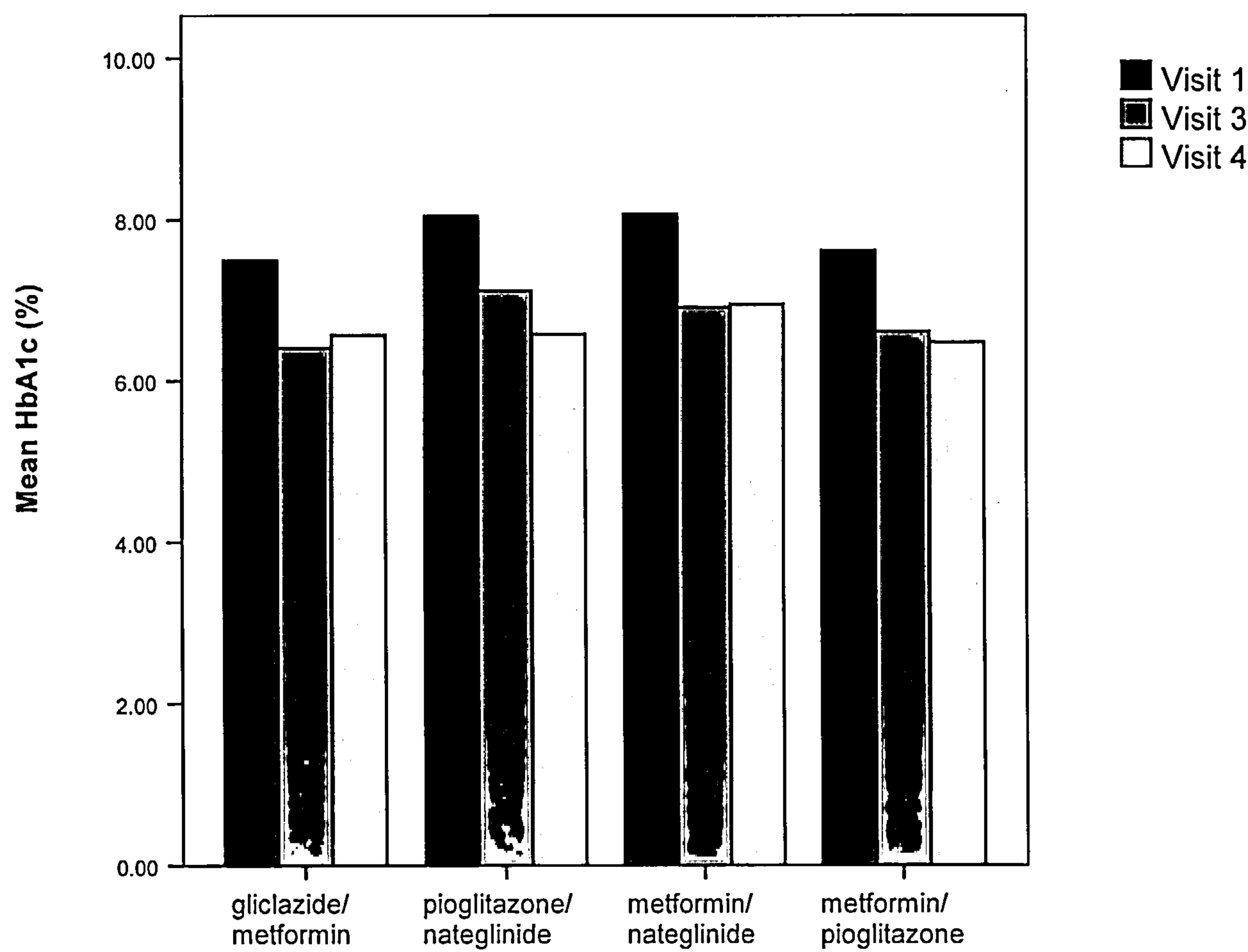


Table 8:5 Frequency of Hypoglycaemia with each Drug Combination during Study

Drug Combination	Visit 2		Visit 3		Visit 4	
	No. of hypos	Mean BM (mmol/l)	No. of hypos	Mean BM (mmol/l)	No. of hypos	Mean BM (mmol/l)
Metformin/Gliclazide (n=33)	2 (6%)	3.9	8 (24%)	3.1	5 (15%)	2.9
Pioglitazone/Nateglinide (n=36)	2 (5.5%)	2.9	7 (19%)	3	6 (17%)	2.8
Metformin/Nateglinide (n=15)	2 (13%)	2.8	3 (20%)	2.5	1 (6.6%)	2.6
Metformin/Pioglitazone (n=15)	2 (13%)	3.8	2 (13%)	2.9	0 (0%)	n/a

Table 8:6 Patient Satisfaction using DTSQ

Drug Combination	Mean DTSQs score (Visit 1)	Mean difference in DTSQc score (Visit 3 – Visit 1)	Mean difference in DTSQc score (Visit 4 – Visit 1)
Metformin/Gliclazide	14.5	-2.5	-2.1
Pioglitazone/Nateglinide ^a	14.7	-4.43	-1.9
Metformin/Nateglinide ^b	15.2	-3.6	-1.2
Metformin/Pioglitazone	14.1	-2.0	-0.9

^a difference between visit 1 and 3 scores (p=0.011, 95% CI -0.91 to 6.25)

^b difference between visit 1 and 3 scores (p=0.049, 95% CI -0.023 to 7.18)

Table 8:7 Patient Satisfaction using ADDQoL

Drug Combination	Mean ADDQoL score (visit 1)	Mean ADDQoL score (visit 3)	Mean ADDQoL score (visit 4)
Metformin/Gliclazide ^a	2.05	1.25	1.47
Pioglitazone/Nateglinide	2.01	1.89	1.69
Metformin/Nateglinide	1.83	2.31	1.88
Metformin/Pioglitazone	1.86	2.28	2.75

^a significant difference in mean score between visit 1 and visit 4 (p=0.026, 95% CI 0.12 to 1.76)

Seven Point Glucose Profile

Seven point glucose profiles were carried out over a 48 hour period within a week of visits 3 (Fig.8:2) and 4 (Fig.8:3). At visit 3, the metformin/gliclazide group tended to have lower capillary glucose levels than the other groups. However, there were no significant differences in mean capillary blood glucose between groups at any point in the day.

Side-Effects

Overall, patients complained of few side-effects. The main side-effects reported were minor hypoglycaemia and gastrointestinal symptoms such as nausea, vomiting and diarrhoea.

Figure 8:2 Seven Point Glucose Profile – Visit 3

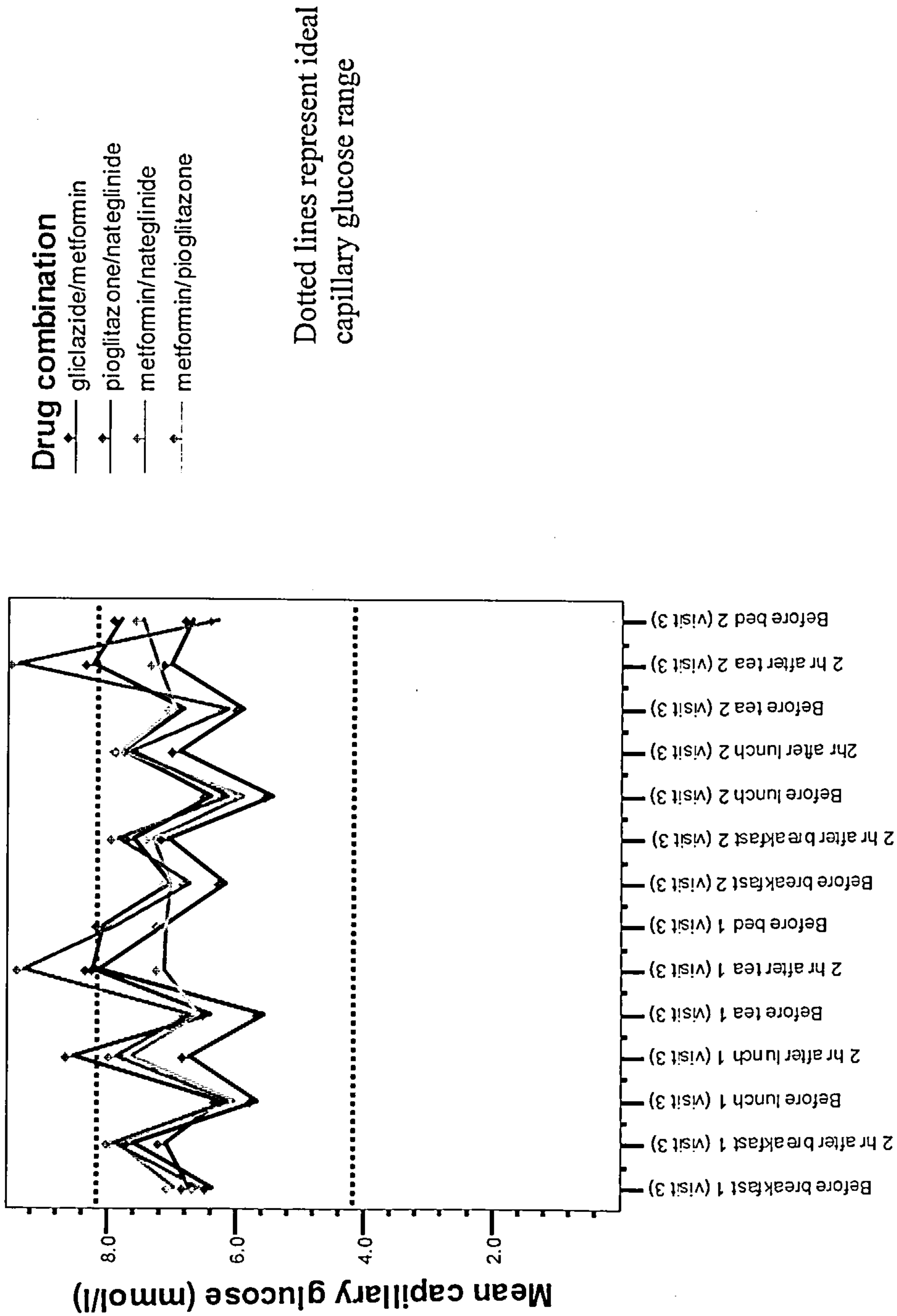
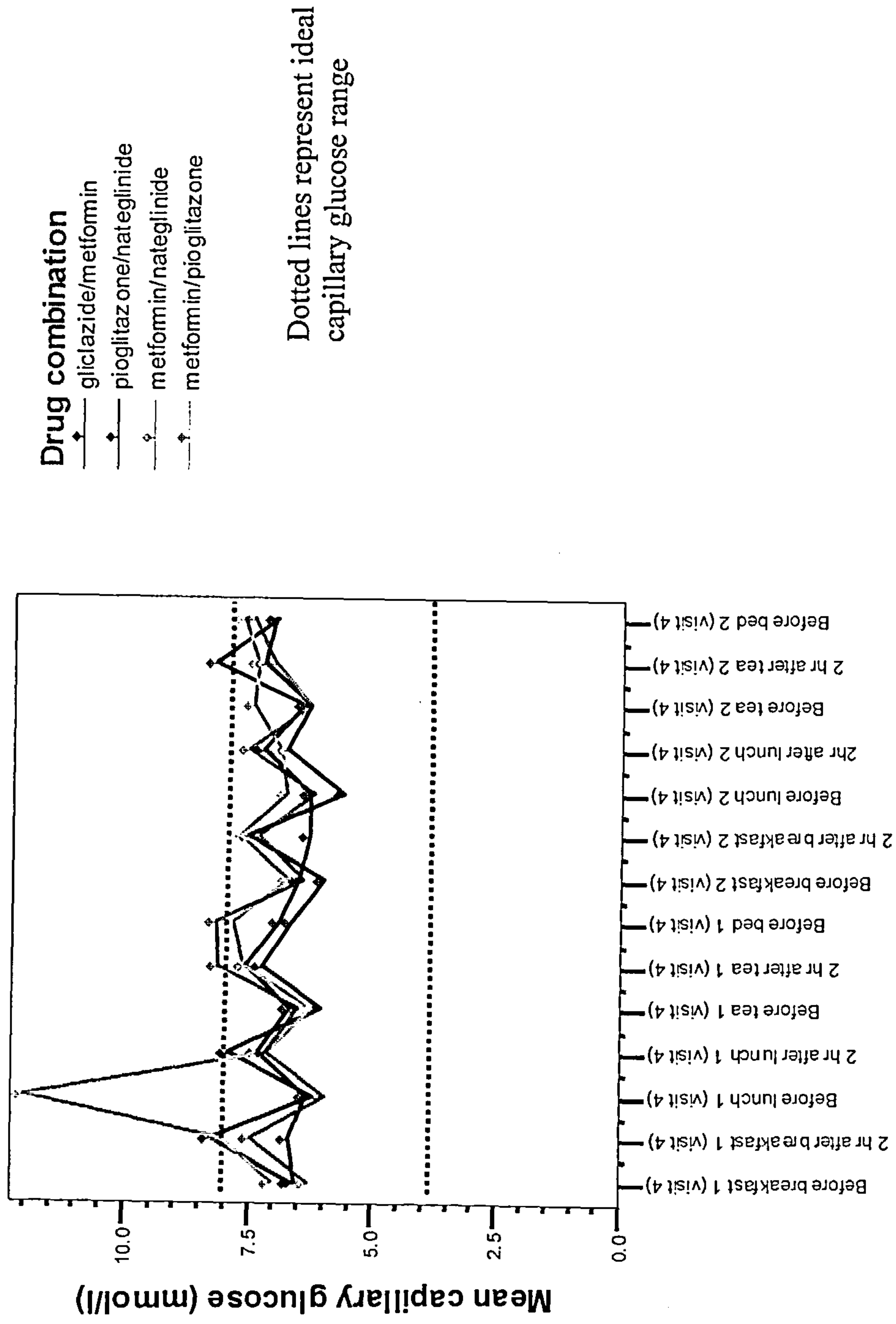


Figure 8:3 Seven Point Glucose Profile – Visit 4



8:6 Discussion

This study shows that six months' treatment with four different dual oral hypoglycaemic agents achieves significant improvements in glycaemic control as assessed by HbA1c and FPG. No difference was detected between the combination of traditional agents metformin and gliclazide with newer combinations such as nateglinide and pioglitazone, metformin and pioglitazone or metformin and nateglinide. A significant difference between treatments was seen at three months with a lower HbA1c with gliclazide/metformin than with the other combinations. These findings are similar to another recently published study where no differences were seen between nateglinide/metformin and gliclazide/metformin combinations although both resulted in significant improvements in HbA1c (376). However, the combination of nateglinide and metformin was associated with better post-prandial glucose control.

Although this was a small pilot study looking at treatment over a short period of time, it is clear that intensive treatment with dual agents can be effective in achieving good glycaemic control with relatively few adverse events and no significant differences in patient satisfaction or weight gain at study end.

The choice of agent does not appear to be important in attaining good control and as gliclazide and metformin have been used for many years, they are known to be agents with a good long-term safety profile and low cost. However as UKPDS demonstrated, patients with T2DM inevitably required insulin therapy after a few years' treatment with these agents, and only metformin was associated with improved cardiovascular outcomes.

The advent of the newer agents pioglitazone and nateglinide has been associated with much interest and promise. However, initial major clinical trials have not provided much

evidence to warrant their widespread use. For example, in the PRO-ACTIVE study, there was a suggestion that there was a reduction in macrovascular endpoints in patients treated with pioglitazone but the primary outcome was not statistically significant (155).

NICE guidelines for the management of T2DM using oral therapy recommends using metformin as the first line agent in all patients followed by the addition of a sulphonylurea (377). If either metformin or a sulphonylurea is contraindicated or not tolerated, a thiazolidinedione may be added instead as a second-line agent. Although NICE has made no specific recommendations for meglitinides, they may be useful in selected cases, such as shift-workers or those with erratic lifestyles and meal-times.

Simple algorithms for initiating and titrating oral medication in T2DM are useful in ensuring optimal glycaemic control as early as possible in the natural history of the disease. The place of newer agents compared with metformin and sulphonylureas remains uncertain.

8:7 Conclusion

Significant improvements in glycaemic control over six months in early T2DM can be achieved regardless of oral combination used. Further studies are needed to determine the long-term impact of newer agents such as nateglinide and pioglitazone in reducing macrovascular and microvascular complications and delaying the need for insulin therapy.

CHAPTER NINE

DISCUSSION AND ISSUES FOR FUTURE RESEARCH

9:1 Introduction

The preceding chapters have discussed the implications of screening for T2DM and PDM, the morphological and biochemical phenotype of the screened subject in WE and SA ethnic groups, and finally the early therapies that are available for the treatment of T1DM and T2DM.

This chapter discusses the importance of these findings and how they can be used to improve patient care and well-being as well as areas for future research.

Areas for Further Research

Long Term Outcomes of Screening

As the incidence of T2DM continues to rise inexorably and patients succumb to complications at the time of diagnosis, it is imperative to diagnose and manage the condition as early as possible. However, the long-term implications of screening for diabetes remain unknown and until the results of major international randomised controlled trials such as ADDITION are presented, the implementation of widespread screening is controversial. Certainly most small studies, including the one described in this thesis, have failed to show convincingly that there is major benefit in terms of outcomes to subjects undergoing diabetes screening.

This may simply be a reflection of the small numbers of subjects in these studies as well as insufficient length of follow-up. However these studies give an indication of the sample size needed to detect significant differences in larger studies and the importance of appropriate follow-up. The impact of appropriate interventions not only for glucose control but also other major cardiovascular risk factors such as hypertension and hyperlipidaemia need to be assessed in screened subjects. High risk ethnic groups such as SA need to be targeted early and their response to intervention determined.

It is just as important to detect patients with PDM in view of their high cardiovascular risk and this subgroup may particularly benefit from early and aggressive intervention, thus preventing or delaying development of T2DM. More evidence is accumulating which confirms the need to identify and manage these patients in the primary care setting without simply waiting for them to develop T2DM before interventions are put in place. Lifestyle modifications such as weight management, increased activity, healthy diet and stopping

smoking need to be implemented as soon as the diagnosis of PDM is made on screening for T2DM.

This begs the question as to how early to perform screening. Rather than concentrating on individual risk, the risk of the whole family needs to be taken into account, especially in ethnic minority groups. Local and national projects to raise awareness of T2DM and who is at risk are essential to stem the tide of new cases.

The possible fetal origins of cardiovascular and metabolic disease cannot be ignored and maternal and fetal health remains a priority in preventing or delaying the onset of new cases.

As can be seen therefore, screening for T2DM is just part of the spectrum of initiatives required to combat this modern-day epidemic. Without the input of the individual, the health profession, families and government, the future looks bleak indeed.

Summary of Conclusions and Further Research

- Small screening studies do not show improved long-term outcomes
- Early intensive lifestyle interventions need to be in place to prevent/delay development of new cases of T2DM
- At risk groups need to be targeted during screening
- Large multiethnic randomised controlled trials are needed to determine benefits of screening and long-term outcomes – several are currently underway

Morphological Phenotype of the Screened Subject

The limitations of BMI as an effective tool for screening for obesity-related diabetes and cardiovascular risk are becoming more clearly established.

The difficulties of accurately measuring body composition in human subjects make it necessary to find a surrogate method which can approximate the more detailed information obtained by gold standard techniques. If large populations are to be assessed quickly and effectively for obesity, a technique needs to be available that fulfils these criteria. In the study described in this thesis, skinfold thickness measurement by callipers, BIA and DEXA were used to determine BF%. These were then compared with BMI, WC and WHR.

Just as it is incorrect to assume that the Asian population is homogeneous, clear differences in BF% have also been found between European and North American Caucasian populations for a given BMI (378). Using prediction formulae derived from one population should therefore be interpreted with caution in another ethnic group.

Further advancement in software programs, for example Hippo Fat™ which quantifies adipose tissue areas using MRI without user inputs, could enable quicker more accurate determination of visceral adiposity (379).

Summary of Conclusions and Further Research

- Visceral adiposity is a key risk factor for CVD
- BMI will not fully determine risk especially in high risk populations such as South Asians

- Simple measures such as waist circumference are needed to determine risk in population screening
- South Asians are considerably more at risk compared with Europeans matched for age and sex
- Longitudinal and interventional studies are needed to determine prevalence of visceral adiposity and the effect of interventions on cardiovascular and diabetes risk

Biochemical Phenotype of the Screened Subject

Pre-Diabetes and Type 2 Diabetes

Adverse adipocytokine profiles are increasingly being reported in high risk groups but the important question is whether interventions can make a difference to these markers of cardiovascular risk. There is evidence that even modest weight loss as demonstrated by a reduction in WC achieved using oral weight-loss therapy (orlistat or sibutramine) results in an increase in adiponectin concentration, and a reduction in leptin, resistin and CRP (380). Weight loss and dietary restriction reduce CRP (188) as does physical exercise (381). Other studies have suggested that it is more important to target visceral adipose tissue by omentectomy (143) rather than subcutaneous fat by liposuction (144) if meaningful differences in metabolic abnormalities are to be achieved.

In UKPDS, metformin, in comparison with sulphonylureas or insulin, was the only agent to improve cardiovascular outcomes (382). Metformin reduces CRP levels in T2DM and in polycystic ovary syndrome (383,384). Insulin is also anti-inflammatory but its effects may be lost in chronic hyperinsulinaemia. In a study comparing insulin with sulphonylurea treatment, CRP concentrations only fell with insulin (385).

There are suggestions that ACE inhibitors and angiotensin receptor blockers have an anti-inflammatory action which may explain why some studies have shown reduced incidence of T2DM associated with the use of ramipril (289) and losartan (290). Similarly β -blockers reduce reactive oxygen species formation (386) and are associated with fewer cardiovascular events (387).

Summary of Conclusions and Further Research

- Earlier changes in cardiovascular risk markers are seen with South Asians compared with White Europeans
- Adiponectin is significantly lower in SA controls compared with WE controls
- Leptin is significantly higher in SA controls compared with WE controls
- Longitudinal and interventional studies are needed to determine concentrations of risk markers and the effect of interventions on subsequent cardiovascular and diabetes risk

Metabolic Syndrome

Although now a controversial definition, metabolic syndrome and its components are associated with increased CVD risk. Prevalence varies markedly according to definition used and population surveyed. As described in this thesis, there appear to be clear differences in circulating risk markers such as adiponectin and leptin that may be useful in screening for metabolic syndrome and devising appropriate management strategies. For example, in the Diabetes Prevention Programme, lifestyle modification succeeded in reducing the incidence of metabolic syndrome by 41% whereas metformin therapy reduced it by 17% (282).

Summary of Conclusions and Further Research

- Increasing prevalence of metabolic syndrome as predictor of CVD risk
- Differences in adipocytokines such as adiponectin and leptin in those with and without metabolic syndrome
- Lifestyle modification can reduce incidence of metabolic syndrome
- Further work needed to identify impact of interventions on different ethnic groups with metabolic syndrome

Early Therapies for Improving Glycaemic Control

Glargine

Basal bolus regimens using insulin analogues are now well-established for treatment of T1DM and have proven effective with associated reduction in hypoglycaemia and increased patient satisfaction. The Glargine and Aspart Study (GLASS) showed that a small but significant improvement in HbA1c is achieved with glargine combined with aspart when compared with NPH insulin.

Summary of Conclusions and Further Research

- Glargine is effective in a basal bolus regimen with aspart in T1DM
- Further long-term multi-centre randomised controlled trials needed to determine continued efficacy and impact on hypoglycaemia, weight gain and patient satisfaction
- Head-to-head studies with other basal insulin such as detemir

Meglitinides

The meglitinides repaglinide and nateglinide are newly available prandial glucose regulators which target post-prandial hyperglycaemia. In the PICNIC study, nateglinide was combined with either metformin or pioglitazone to determine efficacy in T2DM over six months compared with other more traditional combinations such as gliclazide and metformin. The study showed that all four combinations were equally effective at lowering HbA1c significantly over this period without significant differences in weight gain, hypoglycaemia or patient satisfaction. No differences were detected between the groups although as expected combinations with pioglitazone took at least six months to achieve better control. Cost implications must be considered before recommending a combination of pioglitazone/nateglinide before gliclazide/metformin.

Summary of Conclusions and Further Research

- The PICNIC study shows improvement in early T2DM regardless of oral agents used in dual therapy
- Dual oral combination therapy is therefore feasible, well-tolerated and effective in early T2DM
- Further long-term RCT needed to determine efficacy of dual combinations in T2DM
- Cost-effectiveness analysis required

FINAL CONCLUSION

CVD is the greatest cause of morbidity and mortality in patients with T2DM. The risk is associated with increased visceral adiposity, deranged metabolic parameters and polygenic factors. Improving not only the glycaemic control but also the chronic inflammation associated with T2DM with a complement of lifestyle modifications and therapeutic agents is likely to reduce progression to CVD. Future research needs to focus on improving these abnormalities in at risk populations. Prospective longitudinal multiethnic interventional studies are needed to determine the impact of these measures.

REFERENCES

1. Amos AF, McCarty DJ, and Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet.Med.* 14(suppl 5), 1-85. 1997.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-853, 1998
3. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 34:877-890, 1991
4. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 15:815-819, 1992
5. Spijkerman AM, Adriaanse MC, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ: Diabetic patients detected by population-based stepwise screening already have a diabetic cardiovascular risk profile. *Diabetes Care* 25:1784-1789, 2002
6. Davies MJ, Ammari F, Sherriff C, Burden ML, Gujral J, Burden AC: Screening for Type 2 diabetes mellitus in the UK Indo-Asian population. *Diabet Med* 16:131-137, 1999
7. NEEL JV: Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14:353-362, 1962
8. Pickup JC: Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 27:813-823, 2004
9. Dandona P, Aljada A, Chaudhuri A, Bandyopadhyay A: The potential influence of inflammation and insulin resistance on the pathogenesis and treatment of atherosclerosis-related complications in type 2 diabetes. *J Clin Endocrinol Metab* 88:2422-2429, 2003
10. Tataranni PA, Ortega E: A burning question: does an adipokine-induced activation of the immune system mediate the effect of overnutrition on type 2 diabetes? *Diabetes* 54:917-927, 2005
11. Fernandez-Real JM, Ricart W: Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 24:278-301, 2003
12. Davies, M. J., Tringham J.R, Farooqi A, Jarvis J, Raymond, N. T., Skinner C, Thomson J, and Khunti K. STAR: Screening those at risk: study design and recruitment. *Diabet.Med.* (Suppl 2), P68. 2003.
13. Lauritzen, T, Griffin, S. J., Borch-Johnsen, K., Wareham, N. J., Wolffenbuttel, B. H. R, and Rutten, G. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. *Int.J.Obesity* 24 (suppl 3), S6-S11. 2000.

14. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-986, 1993
15. Gaede P, Vedel P, Parving HH, Pedersen O: Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 353:617-622, 1999
16. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordini C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142-2148, 2000
17. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KG, Harland J, Patel S, Ahmad N, Turner C, Watson B, Kaur D, Kulkarni A, Laker M, Tavridou A: Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ* 319:215-220, 1999
18. Balarajan R: Ethnicity and variations in the nation's health. *Health Trends* 27:114-119, 1995
19. Khunti K, Samani NJ: Coronary heart disease in people of south-Asian origin. *Lancet* 364:2077-2078, 2004
20. Mather HM, Chaturvedi N, Fuller JH: Mortality and morbidity from diabetes in South Asians and Europeans: 11-year follow-up of the Southall Diabetes Survey, London, UK. *Diabet Med* 15:53-59, 1998
21. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M: Rising prevalence of NIDDM in an urban population in India. *Diabetologia* 40:232-237, 1997
22. Lubree HG, Rege SS, Bhat DS, Raut KN, Panchnadikar A, Joglekar CV, Yajnik CS, Shetty P, Yudkin J: Body fat and cardiovascular risk factors in Indian men in three geographical locations. *Food Nutr Bull* 23:146-149, 2002
23. Mather HM, Keen H: The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. *Br Med J (Clin Res Ed)* 291:1081-1084, 1985
24. Samanta A, Burden AC, Fent B: Comparative prevalence of non-insulin-dependent diabetes mellitus in Asian and white Caucasian adults. *Diabetes Res Clin Pract* 4:1-6, 1987
25. Mather HM, Chaturvedi N, Kehely AM: Comparison of prevalence and risk factors for microalbuminuria in South Asians and Europeans with type 2 diabetes mellitus. *Diabet Med* 15:672-677, 1998
26. Burden AC, McNally PG, Feehally J, Walls J: Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. *Diabet Med* 9:641-645, 1992

27. Chaturvedi N, Fuller JH: Ethnic differences in mortality from cardiovascular disease in the UK: do they persist in people with diabetes? *J Epidemiol Community Health* 50:137-139, 1996
28. Chowdhury TA, Lasker SS: Complications and cardiovascular risk factors in South Asians and Europeans with early-onset type 2 diabetes. *QJM* 95:241-246, 2002
29. UK Prospective Diabetes Study. XII: Differences between Asian, Afro-Caribbean and white Caucasian type 2 diabetic patients at diagnosis of diabetes. UK Prospective Diabetes Study Group. *Diabet Med* 11:670-677, 1994
30. Enas EA, Senthilkumar A, Juturu V, Gupta R: Coronary artery disease in women. *Indian Heart J* 53:282-292, 2001
31. Forouhi NG, Rumley A, Lowe GD, McKeigue P, Sattar N: Specific elevation in plasma tissue plasminogen activator antigen concentrations in South Asians relative to Europeans. *Blood Coagul Fibrinolysis* 14:755-760, 2003
32. Raji A, Gerhard-Herman MD, Warren M, Silverman SG, Raptopoulos V, Mantzoros CS, Simonson DC: Insulin resistance and vascular dysfunction in nondiabetic Asian Indians. *J Clin Endocrinol Metab* 89:3965-3972, 2004
33. Superko HR, Enas EA, Kotha P, Bhat NK, Garrett B: High-density lipoprotein subclass distribution in individuals of Asian Indian descent: the National Asian Indian Heart Disease Project. *Prev Cardiol* 8:81-86, 2005
34. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A: Plasma adiponectin is an independent predictor of type 2 diabetes in Asian indians. *Diabetes Care* 26:3226-3229, 2003
35. Chambers JC, McGregor A, Jean-Marie J, Kooner JS: Abnormalities of vascular endothelial function may contribute to increased coronary heart disease risk in UK Indian Asians. *Heart* 81:501-504, 1999
36. Raji A, Seely EW, Arky RA, Simonson DC: Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab* 86:5366-5371, 2001
37. Ramachandran A, Snehalatha C, Viswanathan V, Viswanathan M, Haffner SM: Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. *Diabetes Res Clin Pract* 36:121-125, 1997
38. Ascaso JF, Romero P, Real JT, Lorente RI, Marti, nez-Valls J, Carmena R: Abdominal obesity, insulin resistance, and metabolic syndrome in a southern European population. *Eur J Intern Med* 14:101-106, 2003
39. Anjana M, Sandeep S, Deepa R, Vimalaswaran KS, Farooq S, Mohan V: Visceral and central abdominal fat and anthropometry in relation to diabetes in Asian Indians. *Diabetes Care* 27:2948-2953, 2004
40. Grundy SM, Cleeman JJ, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F: Diagnosis and management of the metabolic syndrome: an American Heart Association/National

Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 112:2735-2752, 2005

41. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005
42. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
43. Ramachandran A, Snehalatha C, Latha E, Satyavani K, Vijay V: Clustering of cardiovascular risk factors in urban Asian Indians. *Diabetes Care* 21:967-971, 1998
44. Tillin T, Forouhi N, Johnston DG, McKeigue PM, Chaturvedi N, Godsland IF: Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: a UK population-based cross-sectional study. *Diabetologia* 48:649-656, 2005
45. Anand SS, Yi Q, Gerstein H, Lonn E, Jacobs R, Vuksan V, Teo K, Davis B, Montague P, Yusuf S: Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. *Circulation* 108:420-425, 2003
46. Valsamakis G, Chetty R, Anwar A, Banerjee AK, Barnett A, Kumar S: Association of simple anthropometric measures of obesity with visceral fat and the metabolic syndrome in male Caucasian and Indo-Asian subjects. *Diabet Med* 21:1339-1345, 2004
47. Mohan V, Deepa R, Pradeepa R, Vimalaswaran KS, Mohan A, Velmurugan K, Radha V: Association of low adiponectin levels with the metabolic syndrome--the Chennai Urban Rural Epidemiology Study (CURES-4). *Metabolism* 54:476-481, 2005
48. Addressing inequalities in health: Annual report of the Director of Public Health. 1-3-2002. Leicestershire Health Authority.
49. Farooqi A, Bhavsar M: Project Dil: a co-ordinated Primary Care and Community Health Promotion Programme for reducing risk factors of coronary heart disease amongst the South Asian community of Leicester--experiences and evaluation of the project. *Ethn Health* 6:265-270, 2001
50. Barnett AH, Dixon AN, Bellary S, Hanif MW, O'hare JP, Raymond NT, Kumar S: Type 2 diabetes and cardiovascular risk in the UK south Asian community. *Diabetologia* 49:2234-2246, 2006
51. Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS, Joglekar CV, Yudkin JS: Adiposity and hyperinsulinemia in Indians are present at birth. *J Clin Endocrinol Metab* 87:5575-5580, 2002
52. He Q, Horlick M, Thornton J, Wang J, Pierson RN, Jr., Heshka S, Gallagher D: Sex-specific fat distribution is not linear across pubertal groups in a multiethnic study. *Obes Res* 12:725-733, 2004

53. Ehtisham S, Crabtree N, Clark P, Shaw N, Barrett T: Ethnic differences in insulin resistance and body composition in United Kingdom adolescents. *J Clin Endocrinol Metab* 90:3963-3969, 2005.
54. Deurenberg P, Bhaskaran K, Lian PL: Singaporean Chinese adolescents have more subcutaneous adipose tissue than Dutch Caucasians of the same age and body mass index. *Asia Pac J Clin Nutr* 12:261-265, 2003
55. Colagiuri S, Borch-Johnsen K, Glumer C, Vistisen D: There really is an epidemic of type 2 diabetes. *Diabetologia* 48:1459-1463, 2005
56. Wareham NJ, Forouhi NG: Is there really an epidemic of diabetes? *Diabetologia* 48:1454-1455, 2005
57. Key features of a good diabetes service. 1997. London, Department of Health. Report No.HSG(97)45.
58. McKinnon M. Providing diabetes care in general practice. (3rd Edition). 1998. London, Class Publishing. A Practical Guide for the Primary Care Team.
59. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405-412, 2000
60. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 287:2563-2569, 2002
61. Barnett AH: A review of basal insulins. *Diabet Med* 20:873-885, 2003
62. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:854-865, 1998
63. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 44:1249-1258, 1995
64. Stratton IM, Cull CA, Adler AI, Matthews DR, Neil HA, Holman RR: Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). *Diabetologia* 49:1761-1769, 2006
65. Colagiuri S, Cull CA, Holman RR: Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: U.K. prospective diabetes study 61. *Diabetes Care* 25:1410-1417, 2002
66. Swerdlow AJ, Laing SP, Dos SS, I, Slater SD, Burden AC, Botha JL, Waugh NR, Morris AD, Gatling W, Bingley PJ, Patterson CC, Qiao Z, Keen H: Mortality of South Asian patients with insulin-treated diabetes mellitus in the United Kingdom: a cohort study. *Diabet Med* 21:845-851, 2004
67. Sharp CL, Butterfield WJ, Keen H: Diabetes Survey in Bedford 1962. *Proc R Soc Med* 57:193-202, 1964

68. Walker JB, Brown PE. Early Diabetes: A Five Year Follow-up of Diabetes in an English Community. *Lancet* 189:246-248, 1964
69. Croxson SC, Price DE, Burden M, Jagger C, Burden AC: The mortality of elderly people with diabetes. *Diabet Med* 11:250-252, 1994
70. Davies MJ, Williams DR, Metcalfe J, Day JL: Community screening for non-insulin-dependent diabetes mellitus: self-testing for post-prandial glycosuria. *Q J Med* 86:677-684, 1993
71. Simmons D, Williams DR, Powell MJ: Prevalence of diabetes in a predominantly Asian community: preliminary findings of the Coventry diabetes study. *BMJ* 298:18-21, 1989
72. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360-367, 1998
73. Williams DR, Wareham NJ, Brown DC, Byrne CD, Clark PM, Cox BD, Cox LJ, Day NE, Hales CN, Palmer CR. Undiagnosed glucose intolerance in the community: the Isle of Ely Diabetes Project. *Diabet Med* 12:30-35, 1995
74. Davies, M. J., Grenfell A, and Day, J. L. Clinical characteristics and follow-up of subjects with non-insulin-dependent diabetes mellitus diagnosed by screening. *Practical Diabetes International* 13, 75-78. 1996.
75. Panzram G, Ruttman B: [Prognosis of diabetes mellitus after an early diagnosis by means of glucosuria screening. Results of a 10 year course control]. *Schweiz Med Wochenschr* 108:221-225, 1978
76. Schneider H, Lischinski M, Jutzi E: Survival time after onset of diabetes: 29-year follow-up mortality study in a diabetes cohort from a rural district. *Diabete Metab* 19:152-158, 1993
77. Schneider H, Ehrlich M, Lischinski M, and Schneider H. Did the intensive screening of the sixties and seventies in East Germany improve the survival prognosis of early detected diabetics? *Diab.Stoffw* 5, 33-38. 1996.
78. Morsiani M, Beretta P, Pareschi PL, Manservigi D, Bottoni L: Long-term results in preventive medicine for type II diabetes. *Acta Diabetol Lat* 22:191-202, 1985
79. Wareham NJ, Griffin SJ: Should we screen for type 2 diabetes? Evaluation against National Screening Committee criteria. *BMJ* 322:986-988, 2001
80. Wilson, J. M. G and Jungner, G. Principles and Practice of Screening for Disease. 1968. Geneva, World Health Organisation.
81. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 44:1249-1258, 1995

82. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383-1389, 1994
83. World Health Organisation:Diabetes Mellitus:Report of a WHO Study Group. 1985. Geneva, World Health Organisation. Technology Report Series No.727.
84. American Diabetes Association: Screening for diabetes (Position Statement). *Diabetes Care* 23(suppl 1), S20-S23. 2000.
85. Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 34:891-898, 1991
86. Qiao Q, Jousilahti P, Eriksson J, Tuomilehto J: Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care* 26:2910-2914, 2003
87. Jarrett RJ: The cardiovascular risk associated with impaired glucose tolerance. *Diabet Med* 13:S15-S19, 1996
88. Kershaw EE, Flier JS: Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 89:2548-2556, 2004
89. Berg AH, Combs TP, Scherer PE: ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab* 13:84-89, 2002
90. Gerstein HC, Yusuf S: Dysglycaemia and risk of cardiovascular disease. *Lancet* 347:949-950, 1996
91. WHO.Physical status:the use and interpretation of anthropometry.Report of a WHO expert consultation. WHO Technical Report . 1-1-1995. 854.
92. WHO.Obesity:preventing and managing the global epidemic. 3-6-0006. Geneva. Report on a WHO Consultation on Obesity.
93. Bhat DS, Yajnik CS, Sayyad MG, Raut KN, Lubree HG, Rege SS, Chougule SD, Shetty PS, Yudkin JS, Kurpad AV: Body fat measurement in Indian men: comparison of three methods based on a two-compartment model. *Int J Obes (Lond)* 29:842-848, 2005
94. Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, Shofer JB, Wahl PW: Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care* 22:1808-1812, 1999
95. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 363:157-163, 2004
96. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE: Abdominal adiposity and coronary heart disease in women. *JAMA* 280:1843-1848, 1998

97. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L: Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J (Clin Res Ed)* 289:1257-1261, 1984
98. Despres JP, Lemieux I, Prud'homme D: Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 322:716-720, 2001
99. Lemieux S: Contribution of visceral obesity to the insulin resistance syndrome. *Can J Appl Physiol* 26:273-290, 2001
100. Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F: Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. *Am J Clin Nutr* 44:739-746, 1986
101. Larsson B, Svardstam K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G: Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 288:1401-1404, 1984
102. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP: Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 58:463-467, 1993
103. Pascot A, Despres JP, Lemieux I, Bergeron J, Nadeau A, Prud'homme D, Tremblay A, Lemieux S: Contribution of visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. *Diabetologia* 43:1126-1135, 2000
104. Pascot A, Despres JP, Lemieux I, Almeras N, Bergeron J, Nadeau A, Prud'homme D, Tremblay A, Lemieux S: Deterioration of the metabolic risk profile in women. Respective contributions of impaired glucose tolerance and visceral fat accumulation. *Diabetes Care* 24:902-908, 2001
105. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, Schwartz AV, Kritchevsky S, Newman AB: Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care* 26:372-379, 2003
106. Nicklas BJ, Penninx BW, Ryan AS, Berman DM, Lynch NA, Dennis KE: Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. *Diabetes Care* 26:1413-1420, 2003
107. Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Yudkin JS, Heine RJ, Nijpels G, Seidell JC: Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care* 27:372-377, 2004
108. Park YW, Allison DB, Heymsfield SB, Gallagher D: Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res* 9:381-387, 2001
109. Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, Poehlman ET: What are the physical characteristics associated with a normal metabolic

profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 86:1020-1025, 2001

110. Chumlea, C. and Baumgartner, RN. Body composition, morbidity and mortality. Body composition and physical performance. 175-184. 1992. National Academy Press.
111. Vansant G, Van Gaal L, De L, I: Assessment of body composition by skinfold anthropometry and bioelectrical impedance technique: a comparative study. *JPEN J Parenter Enteral Nutr* 18:427-429, 1994
112. Laskey MA, Lyttle KD, Flaxman ME, Barber RW: The influence of tissue depth and composition on the performance of the Lunar dual-energy X-ray absorptiometer whole-body scanning mode. *Eur J Clin Nutr* 46:39-45, 1992
113. Pietrobelli A, Wang Z, Formica C, Heymsfield SB: Dual-energy X-ray absorptiometry: fat estimation errors due to variation in soft tissue hydration. *Am J Physiol* 274:E808-E816, 1998
114. Siri WE. Body composition from fluid spaces and density: analysis of methods. Brozek J and Henschel A. Techniques for measuring body composition , 224-244. 2006. Washington DC, National Academy of Sciences.
115. Pace N and Rathburn EN. The body water and chemically combined nitrogen content in relation to fat content. *J Biol Chem* 158, 685-691. 1945. Studies on body composition, III.
116. Lohman TG. Applicability of body composition techniques and constants for children and youths. *Exerc Sport Sci Rev* 14, 325-357. 1986.
117. van der Ploeg GE, Withers RT, Laforgia J: Percent body fat via DEXA: comparison with a four-compartment model. *J Appl Physiol* 94:499-506, 2003
118. Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B: Longitudinal studies of anthropometric data and body composition. The population study of women in Gotenberg, Sweden. *Am J Clin Nutr* 33:155-162, 1980
119. Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B: Longitudinal studies of anthropometric data and body composition. The population study of women in Gotenberg, Sweden. *Am J Clin Nutr* 33:155-162, 1980
120. Steen B, Bruce A, Isaksson B, Lewin T, Svanborg A: Body composition in 70-year-old males and females in Gothenburg, Sweden. A population study. *Acta Med Scand Suppl* 611:87-112, 1977
121. World Health Organization: Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. 1999. Geneva, World Health Organization.
122. Durnin JV, Womersley J: The relationship between skinfold thickness and body fat in adults of middle age. *J Physiol* 200:105P-106P, 1969
123. Deurenberg-Yap M, Schmidt G, van Staveren WA, Hautvast JG, Deurenberg P: Body fat measurement among Singaporean Chinese, Malays and Indians: a

comparative study using a four-compartment model and different two-compartment models. *Br J Nutr* 85:491-498, 2001

124. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Jr., Razak F, Sharma AM, Anand SS: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 366:1640-1649, 2005
125. Haffner, S. M, Despres, J-P, Balkau, B, Deanfield, J. E, Barter, P, Bassand, J-P. L, Fox, K. A. A, van Gaal, L, Wittgen, H-U, Tan, C. E, and Smith, S. C. Waist Circumference and Body Mass Index Are Both Independently Associated With Cardiovascular Disease: The International Day for the Evaluation of Abdominal Obesity (IDEA) Survey. P842-6. 2006. American College of Cardiology.
126. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y: Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr* 72:694-701, 2000
127. Kamimura MA, Avesani CM, Cendoroglo M, Canziani ME, Draibe SA, Cuppari L: Comparison of skinfold thicknesses and bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body fat in patients on long-term haemodialysis therapy. *Nephrol Dial Transplant* 18:101-105, 2003
128. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. *Am J Clin Nutr* 64:524S-532S, 1996
129. Heitmann BL: Impedance: a valid method in assessment of body composition? *Eur J Clin Nutr* 48:228-240, 1994
130. Gutin B, Litaker M, Islam S, Manos T, Smith C, Treiber F: Body-composition measurement in 9-11-y-old children by dual-energy X-ray absorptiometry, skinfold-thickness measurements, and bioimpedance analysis. *Am J Clin Nutr* 63:287-292, 1996
131. Bolanowski M, Nilsson BE: Assessment of human body composition using dual-energy x-ray absorptiometry and bioelectrical impedance analysis. *Med Sci Monit* 7:1029-1033, 2001
132. Peterson MJ, Czerwinski SA, Siervogel RM: Development and validation of skinfold-thickness prediction equations with a 4-compartment model. *Am J Clin Nutr* 77:1186-1191, 2003
133. Yao M, Roberts SB, Ma G, Pan H, McCrory MA: Field methods for body composition assessment are valid in healthy chinese adults. *J Nutr* 132:310-317, 2002
134. Chowdhury B, Lantz H, Sjostrom L: Computed tomography-determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males. *Metabolism* 45:634-644, 1996
135. Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE: Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab* 84:137-144, 1999

136. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM: Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. *J Clin Endocrinol Metab* 84:2329-2335, 1999
137. Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P: The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. *Int J Obes Relat Metab Disord* 24:1011-1017, 2000
138. Lahmann PH, Lissner L, Gullberg B, Berglund G: Differences in body fat and central adiposity between Swedes and European immigrants: the Malmo Diet and Cancer Study. *Obes Res* 8:620-631, 2000
139. Klatsky AL, Armstrong MA: Cardiovascular risk factors among Asian Americans living in northern California. *Am J Public Health* 81:1423-1428, 1991
140. Alfredsson L, Ahlbom A, Theorell T: Incidence of myocardial infarction among male Finnish immigrants in relation to length of stay in Sweden. *Int J Epidemiol* 11:225-228, 1982
141. Cairney J, Ostbye T: Time since immigration and excess body weight. *Can J Public Health* 90:120-124, 1999
142. Shimokata H, Muller DC, Andres R: Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA* 261:1169-1173, 1989
143. Thorne A, Lonnqvist F, Aelman J, Hellers G, Arner P: A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *Int J Obes Relat Metab Disord* 26:193-199, 2002
144. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS: Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 350:2549-2557, 2004
145. Stern MP: Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes* 44:369-374, 1995
146. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 19:972-978, 1999
147. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103-117, 1995
148. Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, Shoelson SE, Shulman GI: Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J Clin Invest* 109:1321-1326, 2002
149. Deans KA, Sattar N: "Anti-inflammatory" drugs and their effects on type 2 diabetes. *Diabetes Technol Ther* 8:18-27, 2006

150. Tan KC, Chow WS, Tam SC, Ai VH, Lam CH, Lam KS: Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 87:563-568, 2002
151. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E: Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 100:230-235, 1999
152. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A: Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 103:357-362, 2001
153. Ghanim H, Garg R, Aljada A, Mohanty P, Kumbkarni Y, Assian E, Hamouda W, Dandona P: Suppression of nuclear factor-kappaB and stimulation of inhibitor kappaB by troglitazone: evidence for an anti-inflammatory effect and a potential antiatherosclerotic effect in the obese. *J Clin Endocrinol Metab* 86:1306-1312, 2001
154. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI: Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 106:679-684, 2002
155. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Morkan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366:1279-1289, 2005
156. Tanaka T, Itoh H, Doi K, Fukunaga Y, Hosoda K, Shintani M, Yamashita J, Chun TH, Inoue M, Masatsugu K, Sawada N, Saito T, Inoue G, Nishimura H, Yoshimasa Y, Nakao K: Down regulation of peroxisome proliferator-activated receptor gamma expression by inflammatory cytokines and its reversal by thiazolidinediones. *Diabetologia* 42:702-710, 1999
157. Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y: Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 86:3452-3456, 2001
158. Minamikawa J, Tanaka S, Yamauchi M, Inoue D, Koshiyama H: Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 83:1818-1820, 1998
159. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y: PPAR gamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094-2099, 2001
160. Libby P, Ridker PM: Novel inflammatory markers of coronary risk: theory versus practice. *Circulation* 100:1148-1150, 1999

161. Ross R: Atherosclerosis--an inflammatory disease. *N Engl J Med* 340:115-126, 1999
162. Ford ES: Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22:1971-1977, 1999
163. Grau AJ, Bugge F, Becher H, Werle E, Hacke W: The association of leukocyte count, fibrinogen and C-reactive protein with vascular risk factors and ischemic vascular diseases. *Thromb Res* 82:245-255, 1996
164. Goldberg RB: Cardiovascular disease in diabetic patients. *Med Clin North Am* 84:81-93, viii, 2000
165. Hashimoto K, Kasayama S, Yamamoto H, Kurebayashi S, Kawase I, Koga M: Strong association of C-reactive protein with body mass index and 2-h post-challenge glucose in non-diabetic, non-smoker subjects without hypertension. *Diabet Med* 21:581-585, 2004
166. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327-334, 2001
167. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N: C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 51:1596-1600, 2002
168. Festa A, D'Agostino R, Jr., Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 51:1131-1137, 2002
169. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N: C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 51:1596-1600, 2002
170. King DE, Mainous AG, III, Buchanan TA, Pearson WS: C-reactive protein and glycemic control in adults with diabetes. *Diabetes Care* 26:1535-1539, 2003
171. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 97:2007-2011, 1998
172. Kervinen H, Palosuo T, Manninen V, Tenkanen L, Vaarala O, Manttari M: Joint effects of C-reactive protein and other risk factors on acute coronary events. *Am Heart J* 141:580-585, 2001
173. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 285:2481-2485, 2001

174. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB: C-reactive protein and incident cardiovascular events among men with diabetes. *Diabetes Care* 27:889-894, 2004
175. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB: Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 349:462-466, 1997
176. Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, Lonn E, Teo K, McQueen M, Yusuf S: C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol* 24:1509-1515, 2004
177. Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, Bergeron J, Despres JP: Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 21:961-967, 2001
178. Chambers JC, Eda S, Bassett P, Karim Y, Thompson SG, Gallimore JR, Pepys MB, Kooner JS: C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation* 104:145-150, 2001
179. Forouhi NG, Sattar N, McKeigue PM: Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *Int J Obes Relat Metab Disord* 25:1327-1331, 2001
180. Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, Folkman MJ: Adipose tissue mass can be regulated through the vasculature. *Proc Natl Acad Sci U S A* 99:10730-10735, 2002
181. Arner P: The adipocyte in insulin resistance: key molecules and the impact of the thiazolidinediones. *Trends Endocrinol Metab* 14:137-145, 2003
182. Nesto R: C-reactive protein, its role in inflammation, Type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. *Diabet Med* 21:810-817, 2004
183. Fernandez-Real JM, Lainez B, Vendrell J, Rigla M, Castro A, Penarroja G, Broch M, Perez A, Richart C, Engel P, Ricart W: Shedding of TNF-alpha receptors, blood pressure, and insulin sensitivity in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab* 282:E952-E959, 2002
184. Muller S, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, Giani G, Illig T, Thorand B, Kolb H: Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. *Diabetologia* 45:805-812, 2002
185. Katsuki A, Sumida Y, Murashima S, Murata K, Takarada Y, Ito K, Fujii M, Tsuchihashi K, Goto H, Nakatani K, Yano Y: Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 83:859-862, 1998

186. Winkler G, Salamon F, Salamon D, Speer G, Simon K, Cseh K: Elevated serum tumour necrosis factor-alpha levels can contribute to the insulin resistance in Type II (non-insulin-dependent) diabetes and in obesity. *Diabetologia* 41:860-861, 1998
187. Pickup JC, Chusney GD, Thomas SM, Burt D: Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. *Life Sci* 67:291-300, 2000
188. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T: Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab* 83:2907-2910, 1998
189. Jovinge S, Hamsten A, Tornvall P, Proudler A, Bavenholm P, Ericsson CG, Godslund I, de Faire U, Nilsson J: Evidence for a role of tumor necrosis factor alpha in disturbances of triglyceride and glucose metabolism predisposing to coronary heart disease. *Metabolism* 47:113-118, 1998
190. Barath P, Fishbein MC, Cao J, Berenson J, Helfant RH, Forrester JS: Detection and localization of tumor necrosis factor in human atheroma. *Am J Cardiol* 65:297-302, 1990
191. Kaartinen M, Penttila A, Kovanen PT: Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF-alpha. *Circulation* 94:2787-2792, 1996
192. Yudkin JS, Yajnik CS, Mohamed-Ali V, Bulmer K: High levels of circulating proinflammatory cytokines and leptin in urban, but not rural, Indians. A potential explanation for increased risk of diabetes and coronary heart disease. *Diabetes Care* 22:363-364, 1999
193. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57-58, 2002
194. Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K: Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 88:1594-1602, 2003
195. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM: Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 86:3815-3819, 2001
196. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930-1935, 2001
197. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y: Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 102:1296-1301, 2000

198. Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R, Ricart W: Novel interactions of adiponectin with the endocrine system and inflammatory parameters. *J Clin Endocrinol Metab* 88:2714-2718, 2003
199. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K: Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 14:561-566, 2003
200. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB: Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. *Diabetes Care* 27:1680-1687, 2004
201. Choi KM, Lee J, Lee KW, Seo JA, Oh JH, Kim SG, Kim NH, Choi DS, Baik SH: Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. *Clin Endocrinol (Oxf)* 61:75-80, 2004
202. Mousavinasab F, Tahtinen T, Jokelainen J, Koskela P, Vanhala M, Oikarinen J, Keinanen-Kiukaanniemi S: Lack of increase of serum adiponectin concentrations with a moderate weight loss during six months on a high-caloric diet in military service among a young male Finnish population. *Endocrine* 26:65-69, 2005
203. Esposito K, Pontillo A, Di PC, Giugliano G, Masella M, Marfella R, Giugliano D: Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 289:1799-1804, 2003
204. Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF: Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. *J Biol Chem* 278:50810-50817, 2003
205. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, Funahashi T, Matsuzawa Y: Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ Res* 94:e27-e31, 2004
206. Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE: Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J Biol Chem* 279:12152-12162, 2004
207. Lawlor DA, Davey SG, Ebrahim S, Thompson C, Sattar N: Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women. *J Clin Endocrinol Metab* 90:5677-5683, 2005
208. Valsamakis G, Chetty R, McTernan PG, Al Daghri NM, Barnett AH, Kumar S: Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. *Diabetes Obes Metab* 5:131-135, 2003
209. Winzer C, Wagner O, Festa A, Schneider B, Roden M, Bancher-Todesca D, Pacini G, Funahashi T, Kautzky-Willer A: Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. *Diabetes Care* 27:1721-1727, 2004
210. Friedman JM, Halaas JL: Leptin and the regulation of body weight in mammals. *Nature* 395:763-770, 1998

211. Meier U, Gressner AM: Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem* 50:1511-1525, 2004
212. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM: Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 269:543-546, 1995
213. Jacob RJ, Dziura J, Medwick MB, Leone P, Caprio S, During M, Shulman GI, Sherwin RS: The effect of leptin is enhanced by microinjection into the ventromedial hypothalamus. *Diabetes* 46:150-152, 1997
214. McNeely MJ, Boyko EJ, Weigle DS, Shofer JB, Chessler SD, Leonnetti DL, Fujimoto WY: Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. *Diabetes Care* 22:65-70, 1999
215. Hukshorn CJ, van Dielen FM, Buurman WA, Westerterp-Plantenga MS, Campfield LA, Saris WH: The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. *Int J Obes Relat Metab Disord* 26:504-509, 2002
216. Wasim H, Al-Daghri NM, Chetty R, McTernan PG, Barnett AH, Kumar S: Relationship of serum adiponectin and resistin to glucose intolerance and fat topography in South-Asians. *Cardiovasc Diabetol* 5:10, 2006
217. Kalhan R, Puthawala K, Agarwal S, Amini SB, Kalhan SC: Altered lipid profile, leptin, insulin, and anthropometry in offspring of South Asian immigrants in the United States. *Metabolism* 50:1197-1202, 2001
218. Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, Nelson C, Lowman HB, Wright BD, Skelton NJ, Frantz GD, Tumas DB, Peale FV, Jr., Shelton DL, Hebert CC: FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* 19:4046-4055, 2000
219. Steppan CM, Brown EJ, Wright CM, Bhat S, Banerjee RR, Dai CY, Enders GH, Silberg DG, Wen X, Wu GD, Lazar MA: A family of tissue-specific resistin-like molecules. *Proc Natl Acad Sci U S A* 98:502-506, 2001
220. Ukkola O: Resistin - a mediator of obesity-associated insulin resistance or an innocent bystander? *Eur J Endocrinol* 147:571-574, 2002
221. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, Xiao Q, Mistry JS, Retzlaff BM, Knopp RH, Kahn SE: Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia* 48:2330-2333, 2005
222. Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM: Resistin gene expression in human adipocytes is not related to insulin resistance. *Obes Res* 10:1-5, 2002
223. Zhang JL, Qin YW, Zheng X, Qiu JL, Zou DJ: Serum resistin level in essential hypertension patients with different glucose tolerance. *Diabet Med* 20:828-831, 2003

224. Matsuda M, Kawasaki F, Yamada K, Kanda Y, Saito M, Eto M, Matsuki M, Kaku K: Impact of adiposity and plasma adipocytokines on diabetic angiopathies in Japanese Type 2 diabetic subjects. *Diabet Med* 21:881-888, 2004
225. Abate N, Vega GL, Grundy SM: Variability in cholesterol content and physical properties of lipoproteins containing apolipoprotein B-100. *Atherosclerosis* 104:159-171, 1993
226. Frost PH, Davis BR, Burlando AJ, Curb JD, Guthrie GP, Jr., Isaacsohn JL, Wassertheil-Smoller S, Wilson AC, Stamler J: Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 94:2381-2388, 1996
227. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL: Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 161:1413-1419, 2001
228. Wallenfeldt K, Bokemark L, Wikstrand J, Hulthe J, Fagerberg B: Apolipoprotein B/apolipoprotein A-I in relation to the metabolic syndrome and change in carotid artery intima-media thickness during 3 years in middle-aged men. *Stroke* 35:2248-2252, 2004
229. Schulze MB, Rimm EB, Shai I, Rifai N, Hu FB: Relationship between adiponectin and glycemic control, blood lipids, and inflammatory markers in men with type 2 diabetes. *Diabetes Care* 27:1680-1687, 2004
230. Smith J, Cianflone K, Al-Amri M, Sniderman A: Body composition and the apoB/apoA-I ratio in migrant Asian Indians and white Caucasians in Canada. *Clin Sci (Lond)* 111:201-207, 2006
231. Chambers JC, Eda S, Bassett P, Karim Y, Thompson SG, Gallimore JR, Pepys MB, Kooner JS: C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation* 104:145-150, 2001
232. Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, Lonn E, Teo K, McQueen M, Yusuf S: C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol* 24:1509-1515, 2004
233. Valsamakis G, Chetty R, McTernan PG, Al Daghri NM, Barnett AH, Kumar S: Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. *Diabetes Obes Metab* 5:131-135, 2003
234. Valsamakis G, Chetty R, McTernan PG, Al Daghri NM, Barnett AH, Kumar S: Fasting serum adiponectin concentration is reduced in Indo-Asian subjects and is related to HDL cholesterol. *Diabetes Obes Metab* 5:131-135, 2003
235. Kalhan R, Puthawala K, Agarwal S, Amini SB, Kalhan SC: Altered lipid profile, leptin, insulin, and anthropometry in offspring of South Asian immigrants in the United States. *Metabolism* 50:1197-1202, 2001
236. Yudkin JS, Yajnik CS, Mohamed-Ali V, Bulmer K: High levels of circulating proinflammatory cytokines and leptin in urban, but not rural, Indians. A potential

explanation for increased risk of diabetes and coronary heart disease. *Diabetes Care* 22:363-364, 1999

237. Knobler H, Benderly M, Boyko V, Behar S, Matas Z, Rubinstein A, Raz I, Wainstein J: Adiponectin and the development of diabetes in patients with coronary artery disease and impaired fasting glucose. *Eur J Endocrinol* 154:87-92, 2006
238. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A: Plasma adiponectin is an independent predictor of type 2 diabetes in Asian indians. *Diabetes Care* 26:3226-3229, 2003
239. Ren J: Leptin and hyperleptinemia - from friend to foe for cardiovascular function. *J Endocrinol* 181:1-10, 2004
240. Yudkin JS, Yajnik CS, Mohamed-Ali V, Bulmer K: High levels of circulating proinflammatory cytokines and leptin in urban, but not rural, Indians. A potential explanation for increased risk of diabetes and coronary heart disease. *Diabetes Care* 22:363-364, 1999
241. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, O'Rahilly S: Resistin / Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. *Diabetes* 50:2199-2202, 2001
242. Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM: Resistin gene expression in human adipocytes is not related to insulin resistance. *Obes Res* 10:1-5, 2002
243. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, Xiao Q, Mistry JS, Retzlaff BM, Knopp RH, Kahn SE: Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia* 48:2330-2333, 2005
244. Kang ES, Park SY, Kim HJ, Ahn CW, Nam M, Cha BS, Lim SK, Kim KR, Lee HC: The influence of adiponectin gene polymorphism on the rosiglitazone response in patients with type 2 diabetes. *Diabetes Care* 28:1139-1144, 2005
245. Koshihara K, Nomura M, Nakaya Y, Ito S: Efficacy of glimepiride on insulin resistance, adipocytokines, and atherosclerosis. *J Med Invest* 53:87-94, 2006
246. Tsunekawa T, Hayashi T, Suzuki Y, Matsui-Hirai H, Kano H, Fukatsu A, Nomura N, Miyazaki A, Iguchi A: Plasma adiponectin plays an important role in improving insulin resistance with glimepiride in elderly type 2 diabetic subjects. *Diabetes Care* 26:285-289, 2003
247. Yenicesu M, Yilmaz MI, Caglar K, Sonmez A, Eyileten T, Kir T, Acikel C, Bingol N, Oguz Y, Ikizler TA, Vural A: Adiponectin level is reduced and inversely correlated with the degree of proteinuria in type 2 diabetic patients. *Clin Nephrol* 64:12-19, 2005
248. Raji A, Gerhard-Herman MD, Warren M, Silverman SG, Raptopoulos V, Mantzoros CS, Simonson DC: Insulin resistance and vascular dysfunction in nondiabetic Asian Indians. *J Clin Endocrinol Metab* 89:3965-3972, 2004

249. Hung YJ, Chen YC, Pei D, Kuo SW, Hsieh CH, Wu LY, He CT, Lee CH, Fan SC, Sheu WH: Sibutramine improves insulin sensitivity without alteration of serum adiponectin in obese subjects with Type 2 diabetes. *Diabet Med* 22:1024-1030, 2005
250. Furuhashi M, Ura N, Higashiura K, Miyazaki Y, Murakami H, Hyakukoku M, Shimamoto K: Low adiponectin level in young normotensive men with a family history of essential hypertension. *Hypertens Res* 28:141-146, 2005
251. Iwashima Y, Katsuya T, Ishikawa K, Kida I, Ohishi M, Horio T, Ouchi N, Ohashi K, Kihara S, Funahashi T, Rakugi H, Ogihara T: Association of hypoadiponectinemia with smoking habit in men. *Hypertension* 45:1094-1100, 2005
252. Nomura S, Shouzu A, Omoto S, Nishikawa M, Fukuhara S, Iwasaka T: Effect of valsartan on monocyte/endothelial cell activation markers and adiponectin in hypertensive patients with type 2 diabetes mellitus. *Thromb Res* 117:385-392, 2006
253. Chen MP, Tsai JC, Chung FM, Yang SS, Hsing LL, Shin SJ, Lee YJ: Hypoadiponectinemia is associated with ischemic cerebrovascular disease. *Arterioscler Thromb Vasc Biol* 25:821-826, 2005
254. Fatouros IG, Tournis S, Leontsini D, Jamurtas AZ, Sxina M, Thomakos P, Manousaki M, Douroudos I, Taxildaris K, Mitrakou A: Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. *J Clin Endocrinol Metab* 90:5970-5977, 2005
255. Hotamisligil GS, Spiegelman BM: Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes* 43:1271-1278, 1994
256. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y: PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094-2099, 2001
257. Yudkin JS, Yajnik CS, Mohamed-Ali V, Bulmer K: High levels of circulating proinflammatory cytokines and leptin in urban, but not rural, Indians. A potential explanation for increased risk of diabetes and coronary heart disease. *Diabetes Care* 22:363-364, 1999
258. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V: The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 49:289-297, 2006
259. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002
260. Esposito K, Pontillo A, Di PC, Giugliano G, Masella M, Marfella R, Giugliano D: Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 289:1799-1804, 2003

261. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 295:761-775, 2006
262. Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595-1607, 1988
263. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
264. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005
265. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 48:1684-1699, 2005
266. Pescatello LS, VanHeest JL: Physical activity mediates a healthier body weight in the presence of obesity. *Br J Sports Med* 34:86-93, 2000
267. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
268. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005
269. Tan CE, Ma S, Wai D, Chew SK, Tai ES: Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 27:1182-1186, 2004
270. Gupta R, Deedwania PC, Gupta A, Rastogi S, Panwar RB, Kothari K: Prevalence of metabolic syndrome in an Indian urban population. *Int J Cardiol* 97:257-261, 2004
271. Choi KM, Lee J, Lee KW, Seo JA, Oh JH, Kim SG, Kim NH, Choi DS, Baik SH: Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. *Clin Endocrinol (Oxf)* 61:75-80, 2004
272. Hulthe J, Hulthen LM, Fagerberg B: Low adipocyte-derived plasma protein adiponectin concentrations are associated with the metabolic syndrome and small dense low-density lipoprotein particles: atherosclerosis and insulin resistance study. *Metabolism* 52:1612-1614, 2003
273. Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T: Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. *Diabetes Care* 29:1357-1362, 2006

274. Utzschneider KM, Carr DB, Tong J, Wallace TM, Hull RL, Zraika S, Xiao Q, Mistry JS, Retzlaff BM, Knopp RH, Kahn SE: Resistin is not associated with insulin sensitivity or the metabolic syndrome in humans. *Diabetologia* 48:2330-2333, 2005
275. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ: Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 111:932-939, 2005
276. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 107:391-397, 2003
277. Khunti, K. Metabolic syndrome: time to weight or waist? *Practical Diabetes International* 23(7), 302-308. 2006.
278. Alberti KG, Zimmet P, Shaw J: Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 23:469-480, 2006
279. Lindstrom J, Louheranta A, Manninen M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J: The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26:3230-3236, 2003
280. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343-1350, 2001
281. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002
282. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S: The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 142:611-619, 2005
283. Platat C, Wagner A, Klumpp T, Schweitzer B, Simon C: Relationships of physical activity with metabolic syndrome features and low-grade inflammation in adolescents. *Diabetologia* 49:2078-2085, 2006
284. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002
285. Durbin RJ: Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. *Diabetes Obes Metab* 6:280-285, 2004
286. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486-494, 2003

287. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L: XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27:155-161, 2004
288. PROactive study shows reduced heart attacks and strokes in type 2 diabetics on pioglitazone HCl (Actos) therapy. *Cardiovasc J S Afr* 16:286-287, 2005
289. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253-259, 2000
290. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359:995-1003, 2002
291. Collins R, Armitage J, Parish S, Sleight P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005-2016, 2003
292. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K: Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 159:2661-2667, 1999
293. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 98:2513-2519, 1998
294. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D: Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care* 26:1513-1517, 2003
295. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366:1849-1861, 2005
296. Peter R, Luzio SD, Dunseath G, Miles A, Hare B, Backx K, Pauvaday V, Owens DR: Effects of exercise on the absorption of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 28:560-565, 2005
297. Rosenstock J, Park G, Zimmerman J: Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. *Diabetes Care* 23:1137-1142, 2000

298. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R: Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. *Diabetes Care* 23:813-819, 2000
299. Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C, Draeger E: Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 53:1614-1620, 2004
300. Pieber TR, Eugene-Jolchine I, Derobert E: Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. *Diabetes Care* 23:157-162, 2000
301. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 23:1666-1671, 2000
302. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 23:639-643, 2000
303. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L, Perriello G, Bolli GB: Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 21:1213-1220, 2004
304. Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acerini CL, Dunger DB: Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 26:799-804, 2003
305. Garg SK, Paul JM, Karsten JI, Menditto L, Gottlieb PA: Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. *Diabetes Technol Ther* 6:589-595, 2004
306. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E, Scionti L, Bolli GB: Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care* 26:1490-1496, 2003
307. Fulcher GR, Gilbert RE, Yue DK: Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern Med J* 35:536-542, 2005
308. Tsui E, Barnie A, Ross S, Parkes R, Zinman B: Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 24:1722-1727, 2001
309. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a

randomized study. The Study Group for the Development of Pump Therapy in Diabetes. *Diabetes Care* 23:1232-1235, 2000

310. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ: A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care* 25:2074-2080, 2002
311. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, Santiago OM, Kolaczynski JW: Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care* 28:533-538, 2005
312. Hamann A, Matthaei S, Rosak C, Silvestre L: A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 26:1738-1744, 2003
313. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-853, 1998
314. Turner RC: The U.K. Prospective Diabetes Study. A review. *Diabetes Care* 21 Suppl 3:C35-C38, 1998
315. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 44:1249-1258, 1995
316. DeFronzo RA: Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. *Diabetologia* 35:389-397, 1992
317. Davies MJ, Rayman G, Grenfell A, Gray IP, Day JL, Hales CN: Loss of the first phase insulin response to intravenous glucose in subjects with persistent impaired glucose tolerance. *Diabet Med* 11:432-436, 1994
318. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787-794, 1999
319. Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, Gerich J: Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22-29, 1992
320. Riddle MC: Evening insulin strategy. *Diabetes Care* 13:676-686, 1990
321. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822-1826, 1997
322. Bastyr EJ, III, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. *Diabetes Care* 23:1236-1241, 2000

323. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577-1583, 1996
324. Rodriguez BL, Lau N, Burchfiel CM, Abbott RD, Sharp DS, Yano K, Curb JD: Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. *Diabetes Care* 22:1262-1265, 1999
325. Balkau B: The DECODE study. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. *Diabetes Metab* 26:282-286, 2000
326. de Vegt F., Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 42:926-931, 1999
327. de VM, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237-1241, 1995
328. Ceriello A: The emerging role of post-prandial hyperglycaemic spikes in the pathogenesis of diabetic complications. *Diabet Med* 15:188-193, 1998
329. Lefebvre, P. J and Scheen, A. J. The post prandial state and risk of cardiovascular disease. *diabetic medicine* 15(suppl 4), 563-568. 1998.
330. Esposito K, Giugliano D, Nappo F, Marfella R: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 110:214-219, 2004
331. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072-2077, 2002
332. Vinambres C, Villanueva-Penacarrillo ML, Valverde I, Malaisse WJ: Repaglinide preserves nutrient-stimulated biosynthetic activity in rat pancreatic islets. *Pharmacol Res* 34:83-85, 1996
333. Owens DR: Repaglinide: a new short-acting insulintropic agent for the treatment of type 2 diabetes. *Eur J Clin Invest* 29 Suppl 2:30-37, 1999
334. Damsbo P, Clauson P, Marbury TC, Windfeld K: A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 22:789-794, 1999
335. Landgraf R, Frank M, Bauer C, Dieken ML: Prandial glucose regulation with repaglinide: its clinical and lifestyle impact in a large cohort of patients with Type 2 diabetes. *Int J Obes Relat Metab Disord* 24 Suppl 3:S38-S44, 2000
336. Schumacher S, Abbasi I, Weise D, Hatorp V, Sattler K, Sieber J, Hasslacher C: Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur J Clin Pharmacol* 57:147-152, 2001

337. Marbury TC, Ruckle JL, Hatorp V, Andersen MP, Nielsen KK, Huang WC, Strange P: Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin Pharmacol Ther* 67:7-15, 2000
338. Hollingdal M, Sturis J, Gall MA, Damsbo P, Pincus S, Veldhuis JD, Porksen N, Schmitz O, Juhl CB: Repaglinide treatment amplifies first-phase insulin secretion and high-frequency pulsatile insulin release in Type 2 diabetes. *Diabet Med* 22:1408-1413, 2005
339. Wolffenbuttel BH, Landgraf R: A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch and German Repaglinide Study Group. *Diabetes Care* 22:463-467, 1999
340. Wolffenbuttel BH, Nijst L, Sels JP, Menheere PP, Muller PG, Kruseman AC: Effects of a new oral hypoglycaemic agent, repaglinide, on metabolic control in sulphonylurea-treated patients with NIDDM. *Eur J Clin Pharmacol* 45:113-116, 1993
341. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, Donnelly T, Moffitt P, Hopkins H: Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 22:119-124, 1999
342. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M: Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 130:389-396, 1999
343. Johnson JL, Wolf SL, Kabadi UM: Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. *Arch Intern Med* 156:259-264, 1996
344. Furlong NJ, Hulme SA, O'Brien SV, Hardy KJ: Repaglinide versus metformin in combination with bedtime NPH insulin in patients with type 2 diabetes established on insulin/metformin combination therapy. *Diabetes Care* 25:1685-1690, 2002
345. Davies, M. J, Johnston, V, and Howe, J. Comparison of combination regimes of insulin, repaglinide and metformin in type 2 diabetes: an interim analysis. *Diabet.Med.* A44. 2001.
346. Goldberg RB, Einhorn D, Lucas CP, Rendell MS, Damsbo P, Huang WC, Strange P, Brodows RG: A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. *Diabetes Care* 21:1897-1903, 1998
347. Marbury T, Huang WC, Strange P, Lebovitz H: Repaglinide versus glyburide: a one-year comparison trial. *Diabetes Res Clin Pract* 43:155-166, 1999
348. Massi-Benedetti M, Damsbo P: Pharmacology and clinical experience with repaglinide. *Expert Opin Investig Drugs* 9:885-898, 2000
349. Hatorp V, Walther KH, Christensen MS, Haug-Pihale G: Single-dose pharmacokinetics of repaglinide in subjects with chronic liver disease. *J Clin Pharmacol* 40:142-152, 2000

350. Hu S, Wang S, Dunning BE: Glucose-dependent and glucose-sensitizing insulintropic effect of nateglinide: comparison to sulfonylureas and repaglinide. *Int J Exp Diabetes Res* 2:63-72, 2001
351. Kalbag JB, Walter YH, Nedelman JR, McLeod JF: Mealtime glucose regulation with nateglinide in healthy volunteers: comparison with repaglinide and placebo. *Diabetes Care* 24:73-77, 2001
352. Hanefeld M, Bouter KP, Dickinson S, Guitard C: Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care* 23:202-207, 2000
353. Karara AH, Dunning BE, McLeod JF: The effect of food on the oral bioavailability and the pharmacodynamic actions of the insulintropic agent nateglinide in healthy subjects. *J Clin Pharmacol* 39:172-179, 1999
354. Takesada H, Matsuda K, Ohtake R, Mihara R, Ono I, Tanaka K, Naito M, Yatagai M, Suzuki E: Structure determination of metabolites isolated from urine and bile after administration of AY4166, a novel D-phenylalanine-derivative hypoglycemic agent. *Bioorg Med Chem* 4:1771-1781, 1996
355. Horton ES, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S: Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 23:1660-1665, 2000
356. Marre M, Van GL, Usadel KH, Ball M, Whatmough I, Guitard C: Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab* 4:177-186, 2002
357. Hermann LS, Schersten B, Bitzen PO, Kjellstrom T, Lindgarde F, Melander A: Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. *Diabetes Care* 17:1100-1109, 1994
358. Choudhury S, Hirschberg Y, Filipek R, Lasseter K, McLeod JF: Single-dose pharmacokinetics of nateglinide in subjects with hepatic cirrhosis. *J Clin Pharmacol* 40:634-640, 2000
359. Morris AD: Considerations in assessing effectiveness and costs of diabetes care: lessons from DARTS. *Diabetes Metab Res Rev* 18 Suppl 3:S32-S35, 2002
360. Donnan PT, MacDonald TM, Morris AD: Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med* 19:279-284, 2002
361. Wang PH, Lau J, Chalmers TC: Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 341:1306-1309, 1993
362. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304-309, 1993
363. Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, Shutler SD, Stephens JW, Home PD: Improved glycaemic control with insulin glargine

plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes. *Diabet Med* 23:285-292, 2006

364. Bradley, C, Witthaus, E, and Stewart, J. Treatment satisfaction and psychological well being in patients with type 1 diabetes, treated with a new long acting insulin, insulin glargine (abstract). *Diabetes* 47, 353. 1999.
365. Garg SK, Gottlieb PA, Hisatomi ME, D'Souza A, Walker AJ, Izuora KE, Chase HP: Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. *Diabetes Res Clin Pract* 66:49-56, 2004
366. Bradley, C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. 111-132. 1994. Switzerland, Harwood Academic Publishers. Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice.
367. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R: The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 8:79-91, 1999
368. Wang F, Carabino JM, Vergara CM: Insulin glargine: a systematic review of a long-acting insulin analogue. *Clin Ther* 25:1541-77, discussion, 2003
369. Fahlen M, Eliasson B, Oden A: Optimization of basal insulin delivery in Type 1 diabetes: a retrospective study on the use of continuous subcutaneous insulin infusion and insulin glargine. *Diabet Med* 22:382-386, 2005
370. Lepore G, Dodesini AR, Nosari I, Trevisan R: Both continuous subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment. *Diabetes Care* 26:1321-1322, 2003
371. King AB, Armstrong D: A comparison of basal insulin delivery: continuous subcutaneous insulin infusion versus glargine. *Diabetes Care* 26:1322, 2003
372. National Institute for Clinical Excellence. Guidance on the Use of Continuous Subcutaneous Insulin Infusion in Diabetes. NICE Technology Appraisal Guidance 57. 2003. London, UK, National Institute for Clinical Excellence.
373. Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B: Reproducibility and reliability of hypoglycaemic episodes recorded with Continuous Glucose Monitoring System (CGMS) in daily life. *Diabet Med* 22:858-862, 2005
374. McGowan K, Thomas W, Moran A: Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 25:1499-1503, 2002
375. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 325:746, 2002
376. Ristic S, Collober-Maugeais C, Pecher E, Cressier F: Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with Type 2

diabetes mellitus inadequately controlled on maximum doses of metformin alone. *Diabet Med* 23:757-762, 2006

377. Technology appraisal guidance 63:Glitazones in the treatment of type 2 diabetes. 1-8-2003. NICE.
378. Deurenberg P, Yap M, van Staveren WA: Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord* 22:1164-1171, 1998
379. Demerath EW, Ritter KJ, Couch WA, Rogers NL, Moreno GM, Choh A, Lee M, Remsberg K, Czerwinski SA, Chumlea WC, Siervogel RM, Towne B: Validity of a new automated software program for visceral adipose tissue estimation. *Int J Obes (Lond)* 2006
380. Valsamakis G, McTernan PG, Chetty R, Al Daghri N, Field A, Hanif W, Barnett AH, Kumar S: Modest weight loss and reduction in waist circumference after medical treatment are associated with favorable changes in serum adipocytokines. *Metabolism* 53:430-434, 2004
381. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN: Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol* 22:1869-1876, 2002
382. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:854-865, 1998
383. Diamanti-Kandarakis E, Paterakis T, Alexandraki K, Piperi C, Aessopos A, Katsikis I, Katsilambros N, Kreatsas G, Panidis D: Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin. *Hum Reprod* 21:1426-1431, 2006
384. Carter AM, Bennett CE, Bostock JA, Grant PJ: Metformin reduces C-reactive protein but not complement factor C3 in overweight patients with Type 2 diabetes mellitus. *Diabet Med* 22:1282-1284, 2005
385. Yudkin JS, Panahloo A, Stehouwer C, Emeis JJ, Bulmer K, Mohamed-Ali V, Denver AE: The influence of improved glycaemic control with insulin and sulphonylureas on acute phase and endothelial markers in Type II diabetic subjects. *Diabetologia* 43:1099-1106, 2000
386. Dandona P, Karne R, Ghanim H, Hamouda W, Aljada A, Magsino CH, Jr.: Carvedilol inhibits reactive oxygen species generation by leukocytes and oxidative damage to amino acids. *Circulation* 101:122-124, 2000
387. Chen J, Marciniak TA, Radford MJ, Wang Y, Krumholz HM: Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. Results from the National Cooperative Cardiovascular Project. *J Am Coll Cardiol* 34:1388-1394, 1999

PUBLICATIONS ARISING FROM THIS THESIS

Chatterjee S, Jarvis J, Rengarajan T, McNally PG, Lawrence IG, Davies MJ. Glargine vs NPH Insulin: Efficacy in comparison with insulin aspart in a basal bolus regimen in Type 1 Diabetes -The Glargine and Aspart Study (GLASS). *Diabetes Research and Clinical Practice* 2007;77:215-22.

Chatterjee S, Tringham JR, Davies MJ. Insulin glargine and its place in the treatment of Type 1 and 2 Diabetes. *Expert Opinion on Pharmacotherapy* 2006; 7(10):1357-71

Chatterjee S, Davies MJ. Nateglinide and Repaglinide for Type 2 diabetes mellitus. *Drug and Therapeutics Bulletin* 2003; 41:52-54

Davies MJ, Chatterjee S. Meglitinides: Basic Aspects and Clinical Uses. Section editor Dr RR Holman. In *International Textbook of Diabetes* 3rd Ed. 2004.

Chatterjee S, Khunti K, Da Silva NF, Kumar S, McTernan PG, Taub N, Davies MJ. Adipocytokines are associated with development of metabolic syndrome in subjects screened for Type 2 diabetes. *Diab Med* 2006; 23(Suppl 2):P89

Poster presentation, Diabetes UK Annual Professional Conference, Birmingham 2006

Chatterjee S, Davies MJ, Al-Azzawi F, Taub N, Tringham JR, Farooqi A, Khunti K. Bioimpedance, a simple and cheap measure of body fat composition, is a reliable measure for use in patients with diabetes in a multi-ethnic population. *Diab Med* 2006; 23(Suppl 2):P262

Poster presentation, Diabetes UK Annual Professional Conference, Birmingham 2006

Chatterjee S, Da Silva NF, McTernan PG, Khunti K, Kumar S, Davies MJ. Abnormalities of adiponectin and leptin in white European and south Asian subjects screened for impaired glucose tolerance and Type 2 diabetes. *Diabetologia* 2005;48(suppl 1):A250

Poster presentation 41st Annual Meeting of EASD, Athens, Sept 2005

Davies MJ, Chatterjee S, Rengarajan T, Lawrence IG, McNally PG. Glargine vs insulatard: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes – the Glargine and Aspart study (GLASS). *Diabetologia* 2005;48(suppl 1):A329

Poster presentation 41st Annual Meeting of EASD, Athens, Sept 2005

Chatterjee S, Raymond NT, Blackledge H, Khunti K, Davies MJ. 10 year outcomes following screening for type 2 diabetes and impaired glucose tolerance in white Europeans and south Asians in Leicestershire. *Diab Med* 2005;22(Suppl 2):A94

Oral presentation, Diabetes UK Annual Professional Conference, Glasgow 2005

Chatterjee S, Insulatard vs. glargine: efficacy in combination with insulin aspart in type 1 diabetes mellitus (GLASS study). *Diab Med* 2004: 21(Suppl 2); P92

Poster presentation, Diabetes UK Annual Professional Conference, Birmingham 2004



Available online at www.sciencedirect.com



Diabetes Research and Clinical Practice xxx (2006) xxx–xxx

DIABETES RESEARCH
AND
CLINICAL PRACTICE

www.elsevier.com/locate/diabres

Glargine versus NPH insulin: Efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes—The glargine and aspart study (GLASS) A randomised cross-over study

S. Chatterjee *, J. Jarvis-Kay, T. Rengarajan, I.G. Lawrence,
P.G. McNally, M.J. Davies

Department of Diabetes, University Hospitals of Leicester, Leicester, UK

Received 2 October 2006; accepted 6 November 2006

Abstract

The aim of the study was to compare the efficacy of insulin glargine and aspart with NPH insulin and aspart in a basal bolus regimen in type 1 diabetes.

In this 36-week randomised open-label two-period cross-over trial, subjects received 16 weeks' treatment with either once-daily insulin glargine or twice-daily NPH insulin after 4-week run-in. Primary outcome was HbA1c and secondary outcomes were fasting plasma glucose (FPG), weight change, incidence of hypoglycaemia, effect on lipid profile and patient satisfaction.

Sixty patients with type 1 diabetes were recruited (33 male, mean age 42.7 years, mean HbA1c 8.53%) with 53 completing the study. At completion, HbA1c was lower with glargine and aspart than with NPH and aspart (8.07% versus 8.26%, difference -0.19 [95% CI $0.37-0.01$], $p = 0.04$). FPG was significantly different between glargine and NPH ($p = 0.002$), with mean FPG on glargine 3 mmol/L lower than on NPH at the end of the study. There were no differences in hypoglycaemia rate ($p = 0.63$), weight ($p = 0.45$) or lipid profile ($p = 0.18$). Patient satisfaction was greater with glargine (DTSQ, $p = 0.001$). Three patients discontinued as they wished to remain on glargine.

We suggest that glargine combined with aspart is an effective basal bolus regimen in type 1 diabetes.

© 2006 Published by Elsevier Ireland Ltd.

Keywords: Insulin glargine; Insulin aspart; Type 1 diabetes; HbA1c; Insulin analogues

1. Introduction

The Diabetes Control and Complications Trial (DCCT) showed conclusively that intensified insulin therapy results in improved glycaemic control, leading

to a reduction in incidence and delaying progression of existing microvascular and macrovascular complications in type 1 diabetes [1–3]. Intensified insulin therapy can be achieved with basal insulin in combination with short-acting insulins. Insulin analogues with more physiological profiles such as the basal analogue glargine and the short-acting analogue aspart allow intensified insulin therapy without the problems of nocturnal hypoglycaemia and morning fasting hyperglycaemia encountered with unmodified insulins.

* Corresponding author at: University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Close, Leicester LE1 5WW, UK. Tel.: +44 116 204 7819; fax: +44 116 204 7819.

E-mail address: sudesna.chatterjee@uhl-tr.nhs.uk (S. Chatterjee).

Insulin glargine has been modified using recombinant DNA technology by substituting a glycine residue for the 21 amino acid residue on the A chain of human insulin. This has produced a basal insulin which can be given once-daily and has a flat diurnal profile with minimal absorption variability [4].

Several studies have shown that insulin glargine reduces glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG) and nocturnal hypoglycaemia rate [5–13]. Insulin glargine also results in improved treatment satisfaction scores and psychological well-being compared with NPH insulin [14].

Reduced insulin dose, less severe hypoglycaemia and insignificant weight change have been observed when switching from NPH to glargine [15,16]. There is greater efficacy of insulin glargine and Lispro compared with NPH and lispro in multiple daily injection regimens [10,13].

Insulin glargine has been studied in combination with other short-acting insulins, but not with insulin aspart. Insulin aspart has already been extensively studied in combination with NPH insulin in type 1 diabetes and represents a significant portion of the rapid-acting analogue market currently prescribed in the United Kingdom. There are little data on the efficacy of combining insulin glargine and aspart in a basal bolus regimen and this was therefore the rationale for this study, which was conducted in a single centre in the UK.

2. Materials and methods

2.1. Design

GLASS (glargine and aspart Study) is a 36-week, open-label, single-centre cross-over study comparing insulin glargine (Lantus[®], Aventis Pharma, Frankfurt, Germany) as a once-daily basal insulin with NPH insulin (Insulatard[®], Novo Nordisk, Crawley, West Sussex, UK) as a twice-daily basal insulin, in combination with the rapid-acting analogue insulin aspart (Novorapid[®], Novo Nordisk) in a basal bolus regimen in type 1 diabetes. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all subjects. Recruitment took place between January 2002 and January 2004.

Subjects with type 1 diabetes on either twice-daily or multiple dose insulin injections were recruited from a single specialist outpatient clinic. The inclusion criteria were: age between 18 and 75 years, type 1 diabetes on insulin for at least 6 months, body mass index less than 45, baseline HbA1c 6–11%, and ability and willingness to perform self-blood glucose monitoring.

Subjects completed a 4-week run-in period during which they received thrice-daily pre-prandial insulin aspart and

twice-daily NPH. Subsequently, they were allocated to receive insulin aspart in combination with either once-daily insulin glargine or twice-daily NPH. Allocation was based on opening consecutively numbered sealed envelopes in which the name of the basal insulin had previously been randomly inserted.

Subjects were instructed to administer glargine once-daily at bedtime and NPH approximately 30 min before breakfast and their evening meal. Aspart was injected immediately before meals. The Optipen[®] Pro 1 injection device (Aventis) was used to administer insulin glargine and the Novopen[®] 3 (Novo Nordisk) was used to administer insulin aspart and NPH.

Insulin glargine or NPH was continued for 16 weeks before crossing over to the other basal insulin. The number of units of insulin equal to that administered at the end of the first treatment period was prescribed, unless previous home glucose monitoring suggested a dosage modification.

On switching from glargine to NPH, the current basal dose of insulin was increased by 20% to compensate for switching from a once-daily basal regimen to a twice-daily basal regimen. Conversely, when switching from NPH to glargine, the basal dose of insulin was reduced by 20%.

Visits took place at screening (visit 1), 2 weeks after screening (visit 2), baseline (visit 3) and then every 8 weeks until the end of the study (visits 5–7) (Fig. 1).

Subjects self-monitored blood glucose levels daily at home using the Precision[®] QID monitor (Medisense, Cambridge, UK). Insulin dosage was adjusted according to a local algorithm with targets of 4–6.7 mmol/L before meals, 4–8 mmol/L at bedtime and <8 mmol/L 2 h after main meals. Telephone contact was made twice weekly to advise on changes in insulin dosage.

At visit 1, subjects were provided with dietetic input based on conventional advice for insulin analogues. They were supplied with a diary and blood glucose meter and auxiliary supplies sufficient for the period from visit 1 to visit 3 and instructed in self-monitoring blood glucose throughout the trial to enable continuous dose adjustment. It was recommended that blood glucose should be measured prior to injecting and 120 min after the start of a meal.

The subject was advised about symptoms of hypoglycaemia and instructed to record the following information in a diary: date, time of episode, time of last injection prior to episode, time of last meal prior to episode, type of insulin, blood glucose value at the time of episode, whether or not there were symptoms, and whether or not glucagon or intravenous glucose was required. Hypoglycaemia was categorised as symptoms only, documented or confirmed, severe and nocturnal (occurring between 24:00 and 08:00 h). Severe hypoglycaemia was defined as a hypoglycaemic episode requiring third-party assistance and/or intravenous glucose or intramuscular glucagon. Documented or confirmed hypoglycaemia was defined as a capillary glucose measurement of less than 2.8 mmol/L.

Blood samples for HbA1c, FPG and lipids were taken at visit 1 (screening), and at visits 3–7. Weight was also recorded at these visits.

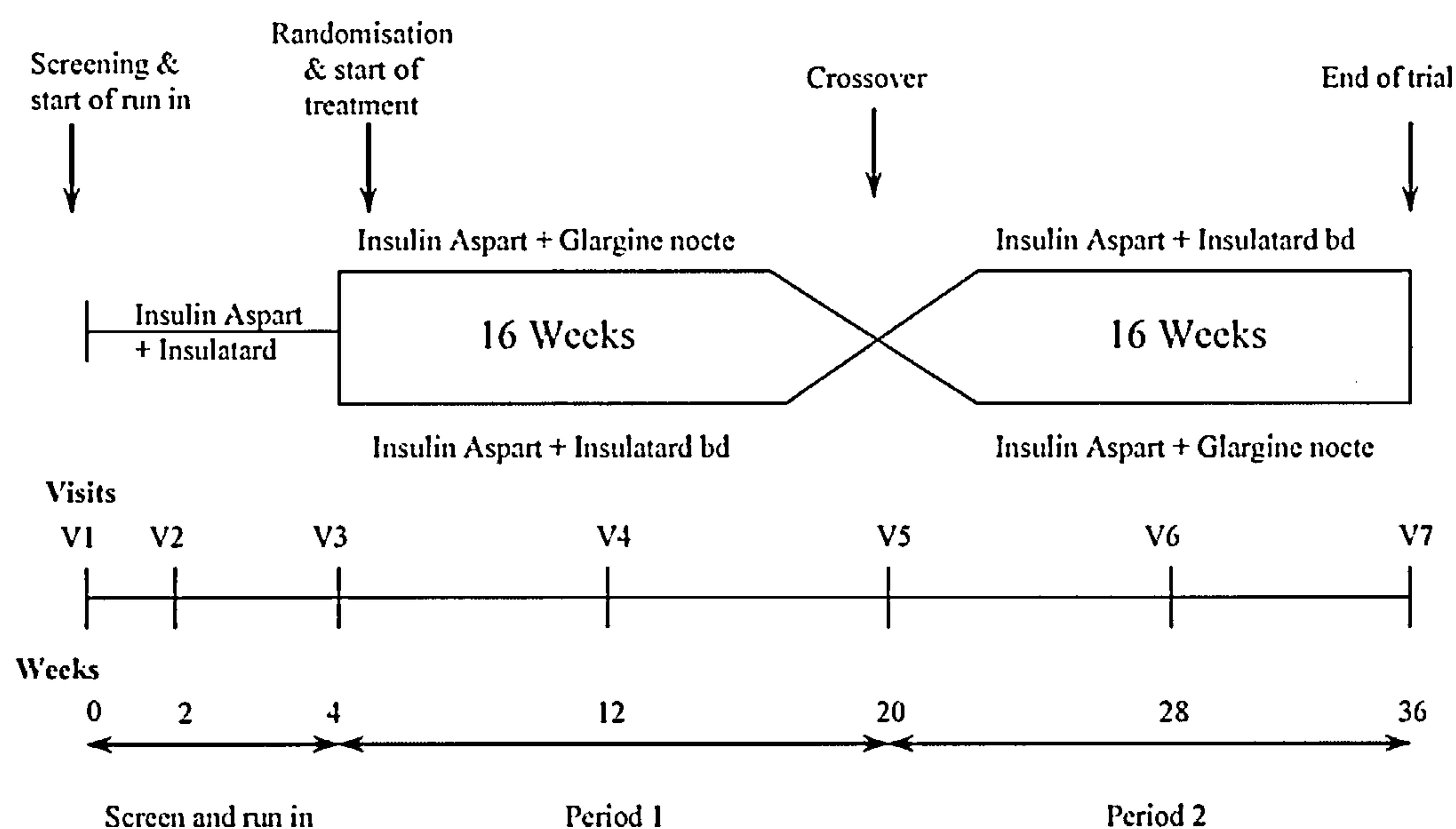


Fig. 1. Schematic diagram of study design.

Subjects wore a continuous glucose monitoring system (CGMS) (MiniMed MMT-7102; Medtronic, Northridge, CA) for up to 72 h at start of treatment (visit 3), at cross-over (visit 5) and at the end of the trial (visit 7). The monitor sampled the signals every 10 s and then stored a mean value every 5 min. Data were downloaded to a computer via a communication device.

Patients were asked to complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Audit of Diabetes-Dependent Quality of Life questionnaire (ADDQoL) at visits 1, 3, 5 and 7 [17,18].

2.2. Statistical analysis

The primary endpoint was HbA1c. Fifty-nine subjects were needed to achieve 80% power for a maximal difference of 0.5% in HbA1c between means with a common standard deviation of 1.35 at a significance level (α) of 5%. The data on HbA1c were analysed using mixed models analysis of variance with the subject effect as random. Terms within the model included sequence, period and treatment. Secondary endpoints were frequency of reported severe hypoglycaemic episodes and overall frequency of both severe and non-severe hypoglycaemic events during the last 12 weeks of each treatment period. Other secondary endpoints were FPG, weight, fasting lipids and questionnaire-based patient satisfaction. Safety endpoints were adverse event recording and vital signs namely pulse and blood pressure.

The data on the total number of hypoglycaemic episodes (severe and non-severe) were analysed using generalised linear models fitting a Poisson distribution.

Data from the DTSQ and ADDQoL questionnaires were analysed using standardised criteria [17,18].

Data are stated as mean and mean difference \pm S.E. (95% CI) unless otherwise indicated.

3. Results

3.1. Characteristics of study population at screening

A total of 60 subjects with type 1 diabetes were recruited to this single centre study of which 58 were White European and 2 were South Asian. Baseline characteristics are shown in Table 1. During run-in, all subjects were treated with standardised therapy consisting of twice-daily NPH (human or porcine) and thrice-daily pre-prandial insulin aspart. Most patients were on a basal bolus regimen with human insulins prior to run-in (Table 2). Three subjects withdrew before randomisation, with one experiencing an adverse reaction to insulin aspart.

Following randomisation, 25 received glargine and 33 received NPH first. One subject, who was randomised to NPH first, withdrew after 3 weeks and was therefore not included in the analysis. Three subjects, who all received glargine first, failed to complete both periods of the study. One subject from each group violated the protocol and was not included in the per protocol population.

Table 1
Baseline characteristics of study population

<i>n</i>	60
Sex (M:F)	35:25
Mean age (years)	42.9 (12.5)
Duration of diabetes (years)	18.2 (11.8)
Weight (kg)	81.0 (14.0)
BMI (kg/m ²)	27 (4.2)
Haemoglobin A1c (%)	8.53 (1.15)
Fasting plasma glucose (mmol/L)	11.5 (5.4)
Total cholesterol (mmol/L)	4.7 (0.8)
Triglycerides (mmol/L)	1.0 (0.6)
Systolic BP (mmHg)	139 (16)
Diastolic BP (mmHg)	83 (9)
Insulin dose (IU/kg)	0.86 (0.29)
Insulin therapy prior to study	
Basal bolus regimen	40 (66.7)
Twice-daily regimen	17 (28.3)
Other	2 (3.0)
Human	43 (71.7)
Porcine or human/porcine mixture	15 (25)
Bovine	2 (3.0)

Mean ± S.D. or *n* (%).

3.2. Glycaemic control

3.2.1. HbA1c

At the beginning of the first period, mean HbA1c was 8.51% for subjects randomised initially to NPH, and 8.57% for those randomised to glargine.

At the end of the study, mean HbA1c was lower with glargine and aspart compared with NPH and aspart (8.07% versus 8.26%, -0.19 ± 0.09 (-0.36 to 0.01), $p = 0.04$). At the end of the first period, HbA1c was 7.89% on glargine and 8.36% on NPH (-0.68 versus -0.15 ; glargine versus NPH). After the second period, subjects switched from glargine to NPH experienced an increase in HbA1c of 0.16%, whereas subjects switched to glargine from NPH experienced a reduction in HbA1c of 0.1%. Fig. 2 illustrates the change in HbA1c throughout the study.

Table 2
Summary of treatment differences

Variable	Glargine	NPH	Difference (glargine-NPH)	95% confidence interval	<i>p</i> -Value
HbA1c (%)	8.07	8.26	-0.19	-0.36 to -0.01	0.04
Fasting glucose (mmol/L)	8.42	11.42	-3.00	-4.80 to -1.20	<0.01
Incidence of hypos (%)	80.7%	77.2%	1.21 ^a	0.56 to 2.64 ^a	0.63
Weight (kg)	81.68	81.92	-0.24	-0.87 to 0.39	0.45
Cholesterol (mmol/L)	4.74	4.84	-0.10	-0.25 to 0.05	0.18
Triglyceride (mmol/L) (geometric means)	0.82	0.80	1.02 ^a	0.93 to 1.12 ^a	0.63

^a Ratio.

3.2.2. Fasting plasma glucose (FPG)

At the end of the study, mean FPG was 3 mmol/L lower with glargine and aspart compared with NPH and aspart (8.42 mmol/L versus 11.42 mmol/L, -3.00 (-4.80 to -1.20), $p < 0.01$). At the end of the first period, FPG was 9.06 mmol/L with glargine and 10.68 mmol/L with NPH. Following the second period, FPG was 7.78 mmol/L with glargine and 12.17 mmol/L with NPH.

3.3. Hypoglycaemia rate

The mean incidence of both severe and non-severe hypoglycaemia was similar with glargine compared with NPH (80.7% versus 77.2%, 1.21 (0.56–2.64), $p = 0.63$). The odds ratio for the incidence of hypoglycaemia on glargine compared to NPH was 1.2 (95% CI 0.55–2.59). Only one subject on glargine and one on NPH experienced a severe hypoglycaemic episode. Five subjects did not report hypoglycaemia on either treatment. Five subjects experienced hypoglycaemia on glargine but not on NPH insulin, whereas four had hypoglycaemia on NPH insulin but not on glargine.

In the first period, subjects randomised to glargine reported 170 episodes of hypoglycaemia of which 18 (10.6%) were symptomatic only, 152 (90.5%) were confirmed or documented by capillary glucose measurement, and 10 (0.06%) were nocturnal. Subjects randomised to NPH reported 167 episodes of hypoglycaemia of which 38 (22.8%) were symptomatic only, 129 (77.2%) were confirmed, and 15 (0.09%) were nocturnal. There were no episodes of severe hypoglycaemia during the first period with either basal insulin.

In the second period, after crossing over to the other basal insulin, subjects on glargine reported 164 hypoglycaemic episodes of which 31 (18.9%) were symptomatic only, 133 (81.1%) were confirmed, 1 (0.006%) was severe and 11 (0.07%) were nocturnal. Those on NPH insulin in the second period reported 175 episodes of hypoglycaemia of which 26 (14.9%) were

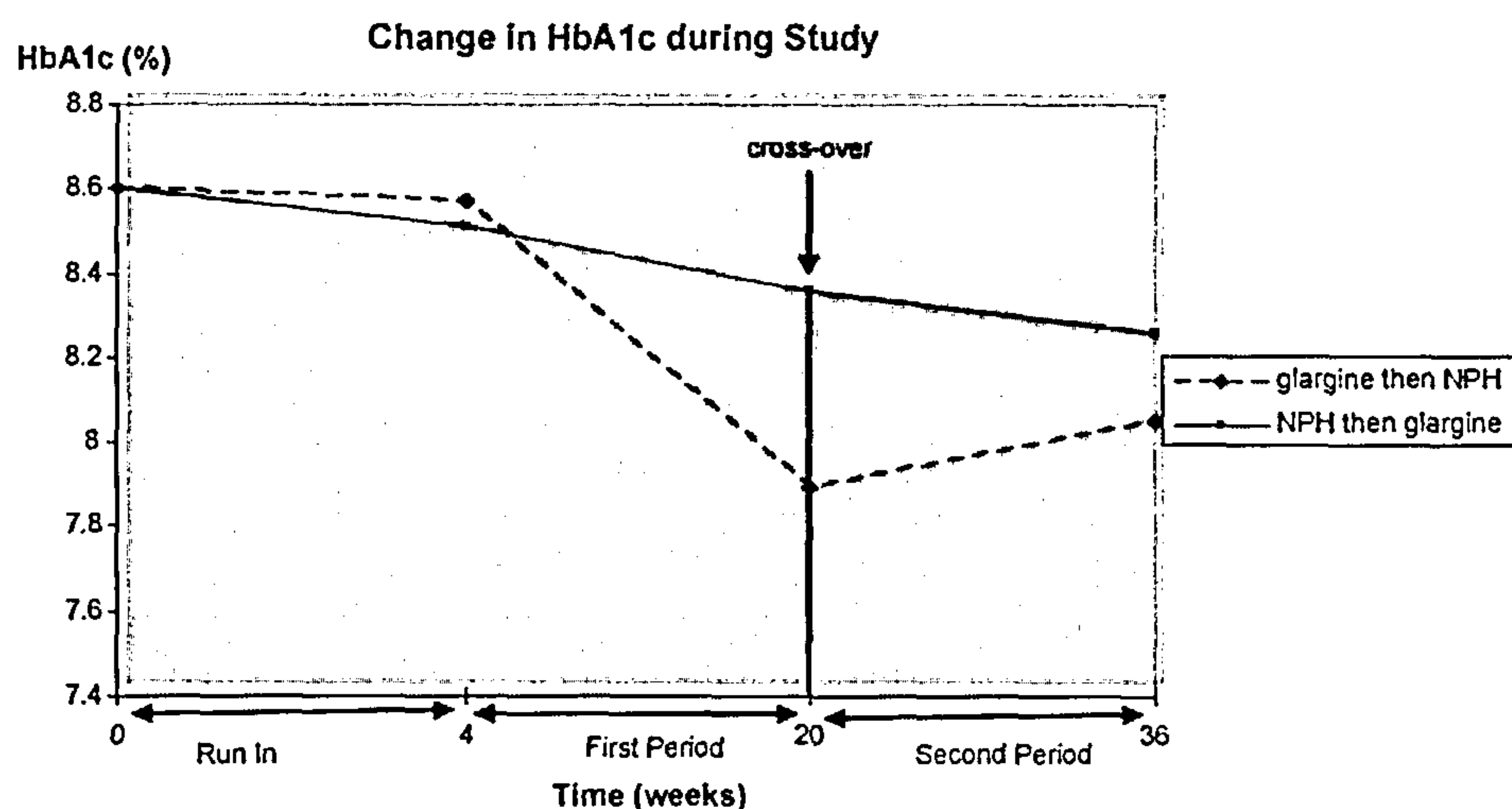


Fig. 2. Change in HbA1c during study.

symptomatic only, 149 (85.1%) were confirmed, 1 (0.006%) was severe and 12 (0.07%) were nocturnal.

No significant difference in hypoglycaemia frequency was detected in the first or second periods between NPH and glargine ($p > 0.05$ for all categories of hypoglycaemia).

3.4. Continuous glucose monitoring system (CGMS)

Only 27 patients had complete data for all three visits. From these limited data, no statistical differences were found between the two basal insulins for overall hypoglycaemia, nocturnal hypoglycaemia or glucose excursions after meals.

3.5. Insulin doses

3.5.1. Basal dose

The mean basal insulin dose for all subjects after 4 weeks' run-in was 38.4 (20.6) IU. In those subjects who were initially randomised to glargine, the basal insulin dose was 33.9 (21.0) IU at the end of the first period. Following cross-over to NPH, the basal dose was 39.4 (19.4) IU at the end of the second period. For those subjects randomised to NPH first, basal insulin dose was 40.9 (18.6) IU at the end of the first period and 39.7 (29.1) IU at the end of the second period.

3.5.2. Prandial dose

Mean prandial dose was 31.4 (20.5) IU after 4 weeks' run-in. In those randomised first to glargine, the prandial dose was 36.1 (19.0) IU at the end of the first period, and 35.1 (14.7) IU at the end of the second

period. For those randomised to NPH first, prandial dose was 30.6 (15.6) IU at the end of the first period, and 32.6 (21.8) IU at the end of the second period.

There was no difference between the two basal insulins with either mean basal or prandial dose ($p = 0.21$ and $p = 0.46$, respectively) using analysis of variation (ANOVA). However, there were some outlying values and using non-parametric analyses there was a significant difference between glargine and NPH ($p = 0.0002$) for basal dose but not prandial dose ($p = 0.44$).

3.6. Other secondary endpoints

There was no significant difference between glargine and NPH for change in weight (Table 2). At the end of treatment, mean weight with glargine was 81.68 kg and with NPH insulin 81.92 kg (mean difference -0.24 , 95% CI -0.87 to 0.39 , $p = 0.45$). Similarly, no differences were detected between the two basal insulins for total cholesterol or triglyceride levels after 16 weeks' treatment (Table 2).

3.7. Patient satisfaction

Thirty-five subjects (19 receiving glargine and 16 receiving NPH first) completed ADDQoL and DTSQ questionnaires at visits 1, 3, 5 and 7. The first 23 subjects received invalid questionnaires and were not included in the analysis. Item 2 relating to friends and social life was inadvertently omitted from all the ADDQoL questionnaires and therefore not completed by the subjects.

3.7.1. DTSQ

A statistically significant difference between treatments ($p=0.001$) was only observed on analysis of DTSQ for the second period. Overall, satisfaction was greater with glargine by a mean of 4 points on the change scale compared with NPH. There was no difference between glargine and NPH in the perception of hyperglycaemia ($p=0.34$) or hypoglycaemia ($p=0.76$). Regardless of the insulin received first, subjects experienced more hypoglycaemia in the first period after run-in.

3.7.2. ADDQoL

There was no difference in overall quality of life and overall impact of diabetes on quality of life using ADDQoL. The profiles of the responses to the individual items were very similar for both insulins, with a slight divergence only noted on the item describing freedom of what to drink. No difference was detected in the average weighted impact score between the insulins ($p=0.8$).

4. Discussion

This study shows that treatment with insulin glargine resulted in a small but significant improvement in HbA1c and FPG compared with NPH in a basal bolus regimen in type 1 diabetes without a significant increase in hypoglycaemia rate or weight gain and associated with greater patient satisfaction.

In our study, HbA1c differed overall by 0.19% between the basal insulins, with notably greater reductions in the first treatment period in favour of insulin glargine (-0.68 versus -0.15 ; glargine versus NPH) and a deterioration in control at cross-over to NPH (-0.1 versus $+0.16$; glargine versus NPH). Although we did not achieve a large reduction in HbA1c, this was a single centre study and therefore these subjects were a more representative sample of our type 1 diabetes population. Other studies have found a similar reduction in HbA1c of around 0.16–0.5% [5–16]. A recent systematic review concluded that the majority of studies reporting on the use of glargine have been statistically underpowered or inconsistently analysed [19]. However the results from suitably analysed and powered studies indicate that treatment with glargine results in statistically significant reductions in FPG at endpoint compared to both baseline and NPH, although this is not always associated with significant improvements in HbA1c.

One large study of 534 patients with well-controlled type 1 diabetes demonstrated that HbA1c levels

decreased by 0.16% with glargine and 0.21% with NPH. However, in this study, lower FPG levels and fewer episodes of hypoglycaemia were recorded with glargine compared with once- or twice-daily NPH [7].

Compared with the gold standard therapy of continuous subcutaneous insulin infusion (CSII), glargine has been shown to be either similar or less effective at reducing HbA1c [20–22], regardless of whether lispro or aspart is used as the insulin infusion. In addition, a lower daily dose of insulin produced a greater effect with CSII. It was suggested that the effectiveness of glargine could be improved by a further 0.1% if the percentage of basal insulin was kept between 40 and 60%. Smaller but longer-term studies have shown that glargine and CSII have equivalent effects on HbA1c, FPG, triglycerides, and severe hypoglycaemia [20]. Another small study compared night-time blood glucose control between glargine and CSII and found that subjects on glargine spent significantly more time outside target sensor glucose ranges [22]. The current NICE guidance is that patients with type 1 diabetes should be managed with glargine in a basal bolus regimen before being referred for CSII therapy [23].

The flatter profile and longer duration of glargine is likely to lead to less glucose excursions during the 24 period. Notably, there was a significant difference in FPG between basal insulins in this study, which may reflect the more physiological pharmacokinetics of insulin glargine. However, the marked difference in FPG may be attributed to the different timings of the evening basal insulin, that is, NPH was injected before the evening meal whereas glargine was administered at bedtime.

We did not find a difference in hypoglycaemia although this has been reported in previous studies [8,16]. Severe hypoglycaemia was reduced with glargine compared to NPH in intensively treated adults with type 1 diabetes although there was no difference in HbA1c [16]. However in our study, improved glycaemic control was achieved on glargine without increasing hypoglycaemia. Furthermore comparison of dose titration and final basal doses suggests that the glargine dose could have been more optimally titrated, especially as HbA1c at the end of the study was higher than the currently recommended target of 6.5–7% despite the use of a treat-to-target regimen. The fact that this was an open-label study may also have affected optimal titration. However, as glargine is a clear insulin and NPH is cloudy, blinding would have been difficult to achieve.

A study of 121 subjects with type 1 diabetes found that the responses of plasma adrenaline, cortisol and growth hormone improved more with glargine than NPH, indicating that counter-regulatory hormone response to hypoglycaemia were more favourable with glargine [10]. This was associated with improved glycaemic thresholds and magnitudes. CGMS has been shown to be reliable and reproducible in the assessment of hypoglycaemia in type 1 diabetes in some studies [24] but one study showed that spurious results for nocturnal hypoglycaemia could be obtained [25]. However, in our study, CGMS was successfully obtained in less than 50% of subjects. The limited data caused difficulties with statistical analysis and were not useful in assessing frequency of hypoglycaemia.

Weight gain is often associated with insulin therapy. In this study, there was less than 1 kg increase in weight with both basal insulins. It has been shown elsewhere that weight gain occurs more with NPH than with glargine [15]. Weight gain was significantly greater when glargine was administered as a split daily dose [16].

Subjects achieved greater treatment satisfaction on glargine compared with NPH when assessed using validated questionnaires. The ability to inject at different times of the day with significantly increasing glycaemic control might be expected to improve satisfaction further.

The increasing use of structured education programmes in type 1 diabetes such as DAFNE has the potential to lead to better glycaemic outcomes using glargine as the basal insulin. Up to 1% reduction in HbA_{1c} without increased hypoglycaemia or weight gain was seen in a DAFNE randomised controlled trial in the UK [26]. However this was prior to glargine being widely available as a basal insulin and in fact the insulin regimens used in this study were not detailed.

This is the first study to compare the short-acting insulin analogue aspart with the basal insulins glargine and NPH. Insulin aspart in combination with glargine is used extensively at present in the UK. The other commonly prescribed short-acting insulin analogue lispro has been well documented to improve glycaemic control in combination with glargine when compared with NPH [10,12,13,16].

We would suggest that the combination of once-daily insulin glargine with aspart in a basal bolus regimen is an effective form of insulin therapy in type 1 diabetes.

Acknowledgements

This study was supported by unconditional educational grants from Novo Nordisk and Aventis. The

authors thank Caroline Whately-Smith for help with statistical analysis.

References

- [1] The Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N. Engl. J. Med.* 329 (1993) 977–986.
- [2] P.H. Wang, J. Lau, T.C. Chalmers, Meta-analysis of effects of intensive blood glucose control on late complications in type 1 diabetes, *Lancet* 341 (1993) 1306–1309.
- [3] P. Reichard, B.Y. Nilsson, U. Rosenqvist, The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus, *N. Engl. J. Med.* 329 (1993) 304–309.
- [4] M. Lepore, S. Pampanelli, C. Fanelli, F. Porcellati, L. Bartocci, A. Di Vincenzo, et al., Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analogue glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro, *Diabetes* 49 (2000) 2142–2148.
- [5] J. Rosenstock, G. Park, J. Zimmerman, US insulin glargine (HOE901) type 1 diabetes investigator group 2000. Basal insulin glargine (HOE901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens, *Diabetes Care* 23 (2000) 1137–1142.
- [6] T.R. Pieber, I. Eugene-Jolchine, E. Derobert, et al., Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes, *Diabetes Care* 23 (2000) 157–162.
- [7] R.E. Ratner, I.B. Hirsch, J.L. Neifing, S.K. Garg, T.E. Mecca, C.A. Wilson, Less hypoglycaemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US study group of insulin glargine in type 1 diabetes, *Diabetes Care* 23 (2000) 639–643.
- [8] E. Schoenle, Insulin glargine (HOE901) lowers fasting blood glucose in children with type 1 diabetes mellitus without increasing the risk of hypoglycaemia (abstract), *Diabetologia* 42 (Suppl 1) (1999) A235.
- [9] P. Rossetti, S. Pampanelli, C. Fanelli, et al., Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime, *Diabetes Care* 26 (2003) 1490–1496.
- [10] F. Porcellati, P. Rossetti, S. Pampanelli, C.G. Fanelli, E. Torlone, L. Scionti, et al., Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time Lispro insulin, *Diabet. Med.* 21 (2004) 1213–1220.
- [11] A. Hamann, S. Matthaël, C. Rosak, et al., A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes, *Diabetes Care* 26 (2003) 1738–1744.
- [12] N.P. Murphy, S.Z. Keane, K.K. Ong, et al., Randomized cross-over trial of insulin glargine plus Lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens, *Diabetes Care* 26 (2003) 799–804.
- [13] S.G. Ashwell, S.A. Amiel, R.W. Bilous, et al., Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in patients with Type 1 diabetes, *Diabet. Med.* 23 (2006) 285–292.

- [14] C. Bradley, E. Witthaus, J. Stewart, Treatment satisfaction and psychological well being in patients with type 1 diabetes, treated with a new long acting insulin, insulin glargine (abstract), *Diabetes* 47 (1999) 353.
- [15] S.K. Garg, J.M. Paul, J.I. Karsten, L. Menditto, P.A. Gottlieb, Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes, *Diabetes Technol. Ther.* 6 (2004) 589–595.
- [16] S.K. Garg, P.A. Gottlieb, M.E. Hisatomi, A. D'Souza, A.J. Walker, K.E. Izuora, et al., Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine, *Diabetes Res. Clin. Pract.* 66 (2004) 49–56.
- [17] C. Bradley, The Diabetes Treatment Satisfaction Questionnaire: DTSQ, in: C. Bradley (Ed.), *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*, Harwood Academic Publishers, Chur, Switzerland, 1994, pp. 111–132.
- [18] C. Bradley, C. Todd, T. Gorton, E. Symonds, A. Martin, R. Plowright, The development of an individualised questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL, *Qual. Life Res.* 8 (1999) 79–91.
- [19] F. Wang, J.M. Carabino, C.M. Vengara, Insulin glargine: a systematic review of a long-acting insulin analogue, *Clin. Ther.* 25 (2003) 1541–1577.
- [20] M. Fahlen, B. Eliasson, A. Oden, Optimization of basal insulin delivery in type 1 diabetes: a retrospective study on the use of continuous subcutaneous insulin infusion and insulin glargine, *Diabet. Med.* 22 (2004) 382–386.
- [21] G. Lepore, A.R. Dodesini, I. Nosari, R. Trevisan, Both continuous subcutaneous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment, *Diabetes Care* 26 (2003) 1321–1332.
- [22] A.B. King, D. Armstrong, A Comparison of basal insulin delivery. Continuous subcutaneous insulin infusion versus glargine, *Diabetes Care* 26 (2003) 1322.
- [23] National Institute for Clinical Excellence, Guidance on the Use of Continuous Subcutaneous Insulin Infusion in Diabetes. NICE Technology Appraisal Guidance No. 57, National Institute for Clinical Excellence, London, UK, 2003.
- [24] T. Hoi-Hansen, U. Pedersen-Bjergaard, B. Thorsteinsson, Reproducibility and reliability of hypoglycaemic episodes recorded with Continuous Glucose Monitoring System (CGMS) in daily life, *Diabet. Med.* 22 (2005) 858–862.
- [25] K. McGowan, W. Thomas, A. Moran, Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes, *Diabetes Care* 25 (2002) 1499–1503.
- [26] DAFNE Study Group, Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial, *BMJ* 325 (2002) 746.

Expert Opinion

1. Background
2. Overview of the market
3. Introduction to the insulin analogue
4. Chemistry
5. Pharmacodynamics and pharmacokinetics
6. Efficacy and safety of insulin glargine in Type 1 diabetes
7. Efficacy and safety in Type 2 diabetes
8. Treatment satisfaction
9. Special populations
10. Cost implications
11. Expert opinion

Insulin glargine and its place in the treatment of Types 1 and 2 diabetes mellitus

Sudesna Chatterjee, Jennifer R Tringham & Melanie J Davies[†]
[†]*Department of Cardiovascular Sciences, University of Leicester, Diabetes Research Unit, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, LE1 5WW, UK*

Insulin treatment in Type 1 and Type 2 diabetes has come a long way since its discovery by Banting and Best in 1922. Early insulin therapy was life-saving, but was associated with practical problems and had side effects such as lipoatrophy. Initial modifications of insulin structure produced several classes of insulins with varying pharmacokinetics, but did not sufficiently mimic physiological insulin release. Novel long- and short-acting insulin analogues, the so-called 'designer insulins', developed through genetic engineering in the 1990s, paved the way for more physiological insulin therapy, which was theoretically less problematic in terms of hypoglycaemia and patient satisfaction. Insulin glargine (glargine) was the first DNA-recombinant long-acting insulin analogue. The replacement of asparagine with glycine and the addition of two arginine molecules in the molecular structure results in modified pharmacokinetics. Consequently, glargine has a longer, often 24-h profile, which is described as 'peakless' compared with other insulins such as neutral protamine Hagedorn insulin (NPH) and insulin ultralente. Since its launch, the use of glargine in Type 1 and Type 2 diabetes has been extensively reviewed to determine its place in the current insulin market. A potential advantage of glargine seems to be a lower risk of hypoglycaemia, particularly at night. The UK National Institute of Clinical Excellence has recommended that glargine is a treatment option for people with Type 1 diabetes. In Type 2 diabetes, it has been advised that glargine only be considered for: those who require assistance to administer insulin injections; those whose lifestyle is restricted significantly by recurrent symptomatic hypoglycaemic episodes; or those who would otherwise need twice-daily basal insulin injections in combination with oral glucose-lowering drugs.

Keywords: basal analogue, diabetes mellitus, hypoglycaemia, insulin glargine

Expert Opin. Pharmacother. (2006) 7(10):xxx-xxx

1. Background

The increasing prevalence of diabetes in most populations, especially Type 2 diabetes, has had a major impact on healthcare systems worldwide [1]. Factors such as obesity, sedentary lifestyle, ageing population, improved medical care and decreasing mortality rates all contribute to this prevalence. In 2005, it was estimated that there were 2,103,000 patients with both Types of diabetes in the UK [2]. Overall, 9% of the NHS budget is currently spent on treating diabetes and its complications [2,3].

The Diabetes Control and Complications Trial (DCCT) [4,5] and UK Diabetes Study (UKPDS) [6,7] indicated that in Type 1 and Type 2 diabetes, respectively, intensive glucose control delayed or prevented the development of complications. However, intensive glucose control, as defined by maintaining glycosylated haemoglobin (HbA_{1c}) < 7%, can be difficult to achieve. In the UK, the National Diabetes Audit predicted that only 56% of patients achieved HbA_{1c} of < 7.5% and 23%

achieved that of $< 6.5\%$ [8]. The attainment of adequate, yet safe, glycaemic control is likely to be further complicated by recent recommendations for HbA_{1c} targets $< 6.5\%$ [9].

Prior to biosynthetically produced human insulin, which has been available since the 1980s, insulin therapy was derived by purification and extraction from porcine and bovine sources. There are currently several different regimens and formulations of insulin available. Insulin may be given as a twice-daily premixed formulation, for example Human Mixtard® 30/70, in which short- and intermediate-acting insulin are combined. This formulation has advantages of simplicity and convenience but does not closely mimic physiological insulin profiles. Endogenous insulin secretion is better approximated by administering short-acting insulin such as soluble insulin or rapid-acting insulin analogues such as insulin lispro or insulin aspart at mealtimes, usually three-times daily, combined with intermediate- or long-acting insulin once or twice daily; this is referred to as a basal-bolus regimen. Alternatively, insulin may be provided by continuous subcutaneous infusion (CSII) using soluble insulin or rapid-acting insulin analogues, the so-called 'insulin pump'. More recently, inhaled insulin has become available commercially in the UK.

The original long-acting insulins, such as ultralente, and intermediate-acting insulins, such as NPH, were characterised by variable subcutaneous absorption, delayed onset of action and profiles characterised by a peak followed by diminution of action; these exposed patients to increased risk of hypoglycaemia, particularly nocturnal, and periods of relative hyperglycaemia [10]. The search for a more physiological long-acting basal insulin led to the development of insulin glargine (glargine) with its near 24-h duration, reduced intersubject variability and no pronounced peak. Glargine was the first basal insulin analogue to enter clinical practice.

2. Overview of the market

The estimated worldwide prevalence of diabetes is 194 million and this is expected to increase to 333 million by 2025 [11]. Over 80% of patients have Type 2 diabetes with a significant proportion remaining undiagnosed. Developing countries, in particular, have a rising incidence of Type 2 diabetes as a consequence of lifestyle factors.

Type 1 diabetes is a metabolic disorder resulting from absolute insulin deficiency secondary to autoimmune pancreatic β -cell destruction. Although the peak incidence occurs between the ages of 10 and 14 years, it can occur at any age [12]. The incidence and prevalence of Type 1 diabetes in children < 14 years of age varies globally with a very high incidence ($\geq 20/100,000$ per year) in the UK, Finland, Sweden, Canada and New Zealand and a much lower incidence ($< 1/100,000$ per year) in China and South America [13]. A diagnosis of Type 1 diabetes necessitates immediate insulin therapy, which is usually given as a twice-daily premixed formulation or as a basal-bolus regimen. The administration of

basal insulin maintains normoglycaemia in between meals and prevents lipolysis leading to ketoacidosis. Intensification of glycaemic control requires appropriate titration of insulin doses and is associated with increased hypoglycaemia.

The pathophysiology of Type 2 diabetes consists of relative insulin deficiency combined with insulin resistance, which increases with obesity. Lifestyle modification and oral glucose-lowering drugs are the initial management tools in Type 2 diabetes; deterioration of glycaemic control despite maximal oral therapy is followed by initiation of insulin. However, hypoglycaemia, weight gain, suboptimal dose initiation and titration are all barriers to the initiation of insulin therapy in Type 2 diabetes. In contrast to Type 1 diabetes, the insulin resistance associated with Type 2 diabetes requires the administration of higher insulin doses to achieve optimal glycaemic control. Some patients are treated with a single basal insulin dose in addition to maximal oral therapy to limit weight gain and the need for multiple injections.

Two new glucose-lowering therapies have recently been launched on the market. The first is another genetically modified basal insulin known as insulin detemir (detemir). The prolonged duration of action of insulin detemir is due to increased self-association and albumin binding resulting from acylation of the amino acid B29 with a ^{14}C fatty acid [14]. Studies have shown that insulin detemir may have less intrasubject variability compared with glargine and NPH [15-17]. However, it should be noted that detemir has been administered twice daily in many of the clinical trials [15-20].

Exenatide is a glucagon-like peptide-1 (GLP-1) analogue for use in Type 2 diabetes in addition to oral glucose-lowering drugs and can be prescribed prior to commencing insulin therapy. A head-to-head study with glargine suggests that exenatide is as effective as insulin in improving glycaemic control, but is associated with weight loss rather than weight gain; however, its use is associated with increased gastrointestinal side effects and dropout [21].

3. Introduction to the insulin analogue

Glargine was first launched in Germany in 2000, followed shortly by availability in the UK and US. Glargine is a basal (long-acting) insulin analogue that has been genetically modified to produce a near 24-h, relatively flat profile in most people, with little variability in subcutaneous absorption [22,23]. It may be administered as part of a basal-bolus regimen in combination with soluble insulin or rapid-acting insulin analogues and is also suitable for use in combination with oral glucose-lowering drugs in Type 2 diabetes. The clear solution is injected once daily, usually in the evening, but may be injected before breakfast or the evening meal. Glargine should not be mixed with other insulins, as there is a risk of precipitation. Glargine is available in vials for use with syringes and in 3-ml cartridges to be used with the Autopen 24® (Owen Mumford) or Optipen Pro® (Sanofi-Aventis) pens or the disposable insulin injection pen, OptiSet® (Sanofi-Aventis). The

Medicines and Healthcare Regulatory Agency (MHRA) issued an alert in January 2005 regarding the Optipen Pro-1® (Sanofi-Aventis), as there were concerns about the dosage button failing to engage at the end of an injection, increasing the risk of insulin overdosage. However, this was a technical problem that was rare in practice.

4. Chemistry

Glargine is produced by genetic modification using a nonpathogenic laboratory strain of *Escherichia coli* as the production organism. Glargine differs from human insulin at position A21, where the amino acid asparagine is replaced by glycine, and at the C-terminus of the B chain due to the addition of two arginine molecules. The chemical structure is 21^A-Gly^B_a-30^B_b-L-Arg-human insulin, the molecular weight is 6063 Da and the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆. The amino acid sequence of the compound is shown in Figure 1.

5. Pharmacodynamics and pharmacokinetics

Genetic modifications to human insulin allow glargine to have low aqueous solubility at neutral pH by shifting the isoelectric point. Therefore, it is completely soluble in the injection solution, which has a pH of 4. Following injection into subcutaneous tissue, the acidic solution is neutralised, and as the hexameric structure breaks down into monomers, microprecipitates of glargine are formed and slowly released. The addition of zinc delays absorption further. This leads to the relatively peak-free 24-h profile of glargine, enabling its once-daily subcutaneous administration, usually in the abdomen or thighs.

A significantly lower area under the glucose infusion rate curve (AUC) has been demonstrated with glargine compared with NPH in the 4 h following administration (1.02 versus 1.48 g/kg, $p < 0.01$), although over 30 h, AUC values were similar [24].

Glargine is similar to regular human insulin in its binding to and activation of human insulin receptors in rat fibroblasts [25]. In *in vitro* studies, glargine activates IGF-1 receptor signalling to the same extent as native insulin, although it binds with a slightly higher affinity [26]. Tumourigenesis of rat mammary gland was not observed after 12 months of treatment with 40 IU/kg/day of glargine [27].

Human clinical studies have shown that intravenous glargine and human insulin lower glucose concentrations to a similar degree. The onset of action of subcutaneous glargine was slower than NPH human insulin and ultralente in euglycaemic clamp studies (1.5 ± 0.3 h versus 0.8 ± 0.2 h versus 1 ± 0.2 h, respectively, $p < 0.05$) [22]. The duration of action was longer with glargine and ultralente (22 ± 4 h and 20 ± 6 h) compared with NPH insulin (14 ± 3 h). Glargine also demonstrated a flat concentration/action profile, similar to that obtained with CSII, as shown in Figure 2 [27]. Interindividual variability was lower with glargine than with NPH or ultralente [22,23,28].

In summary, the structural modifications in glargine have resulted in a basal insulin with a nearly 24-h profile with no pronounced peak and little absorption or interindividual variability when compared with other long-acting insulins, such as human NPH or ultralente.

6. Efficacy and safety of insulin glargine in Type 1 diabetes

6.1 Insulin glargine versus neutral protamine Hagedorn insulin in a basal-bolus regimen

A basal-bolus regimen usually consists of at least four injections daily. The basal component may be given as once- or twice-daily NPH, glargine or detemir, with short-acting soluble or analogue insulin administered before the three main meals of the day. The aim of such a regimen is to mimic some aspects of the normal endogenous pattern of insulin secretion.

A number of randomised controlled trials (RCTs) published in peer-reviewed journals have compared glargine with NPH in Type 1 diabetes as part of a basal-bolus regimen [29-37]. The main outcomes of these studies are shown in Table 1. Two studies were only 4 weeks in duration and used regular soluble insulin as the prandial insulin [29,30]. Three of these studies did not demonstrate statistically significant differences in HbA_{1c} between glargine and NPH at the end of the study [29,31,32]. In these studies, mean change in HbA_{1c} was -0.16 to 0.4% with glargine and -0.21 to 0.4% with NPH. In another study conducted in 333 patients with Type 1 diabetes, there was a significant HbA_{1c} reduction with glargine (-0.14%) compared with NPH ($p = 0.030$) [30].

In a trial of 121 patients with Type 1 diabetes, subjects were randomised to 12 months of treatment with either four-times daily NPH or once-daily glargine along with lispro at mealtimes. At the end of the study, subjects in the glargine arm had lower HbA_{1c} (7.1 versus 6.7%, $p < 0.05$) compared with NPH [34].

A randomised, crossover (16 weeks per treatment arm) study of 28 adolescents (mean age 14.8 years) with Type 1 diabetes receiving basal-bolus therapy with either glargine and insulin lispro or NPH and soluble human insulin showed no significant difference in HbA_{1c} levels (8.7 versus 9.1%, $p = 0.13$) between the two treatment groups [35].

The efficacy of four-times daily NPH has been compared with once-daily glargine in a basal-bolus regimen in 51 patients with Type 1 diabetes in a 3-month randomised study [33]. The simpler glargine regimen was associated with a greater decrease in HbA_{1c} and a lower frequency of hypoglycaemia compared with NPH ($p < 0.05$ for both). However, the HbA_{1c} assay was not aligned to the Diabetes Control and Complications Trial at the time and was therefore difficult to compare with other studies. Plasma insulin concentrations were more stable with glargine than with NPH at night and before meals ($p < 0.05$).

A nonrandomised, retrospective study of 196 subjects compared those on basal-bolus therapy with glargine or NPH and

Insulin glargine

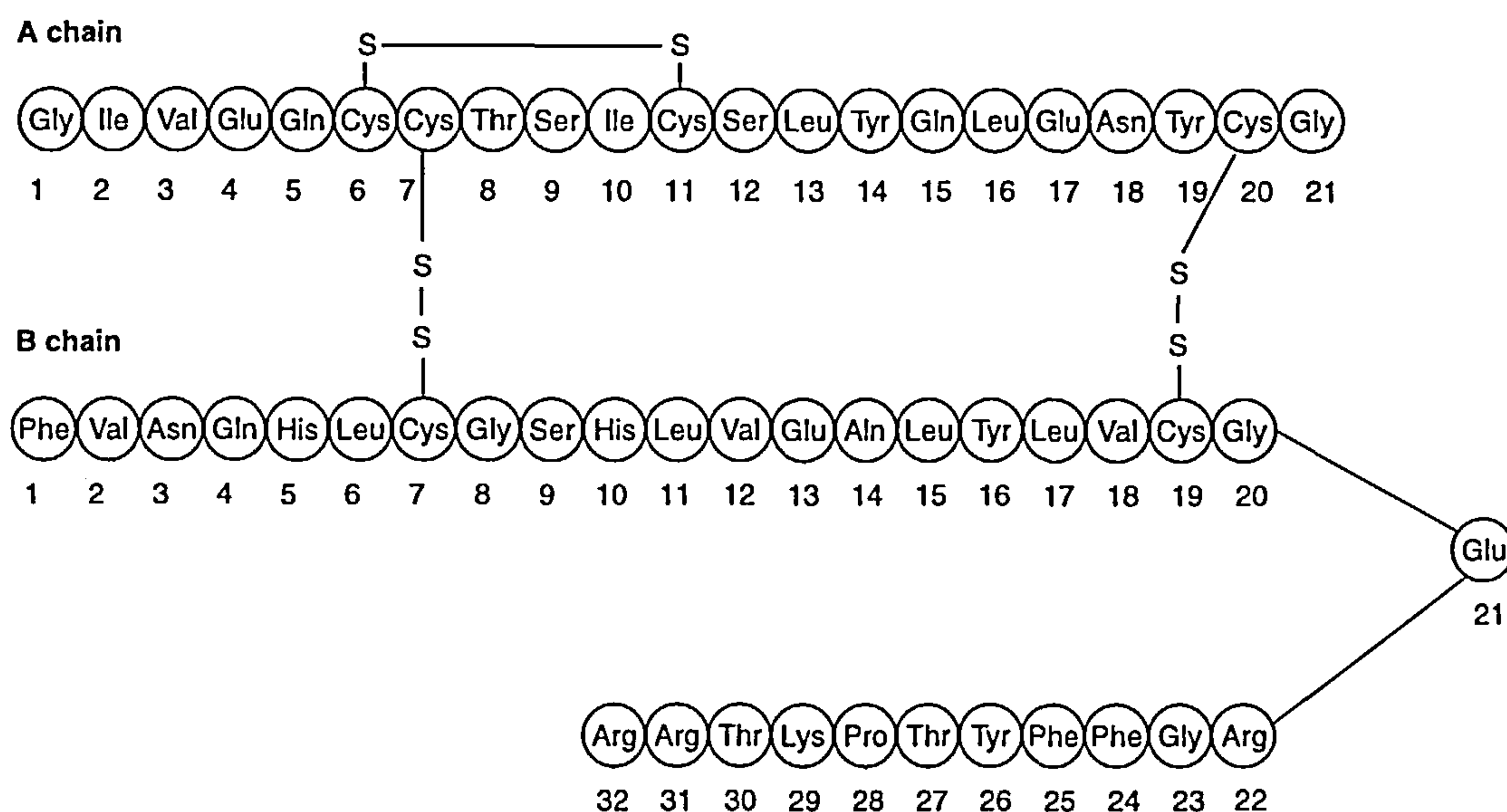


Figure 1. The amino acid sequence of insulin glargine.

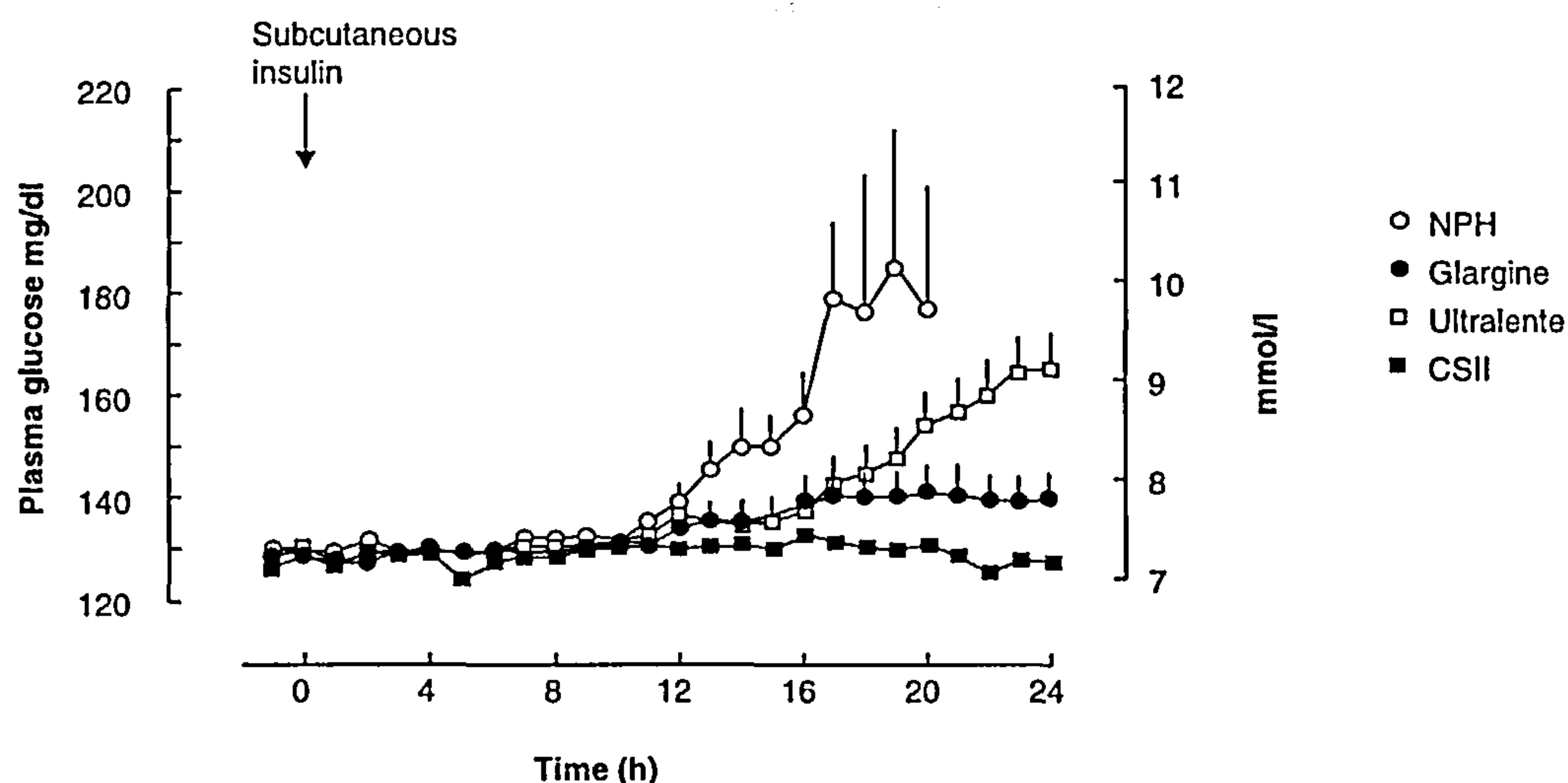


Figure 2. Pharmacodynamics of insulin glargine compared with NPH, ultralente and CSII. n = 20 Type 1 diabetic patients. Mean \pm s.e.m.

Reproduced with permission from LEPORE M, PAMPANELLI S, FANELLI C et al.: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin and Ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* (2000) 49:2142-2148. CSII: Continuous subcutaneous insulin; NPH: Neutral protamine Hagedorn.

found that there was no change in HbA_{1c} after ~ 13 months of therapy [38]. However, severe hypoglycaemic events were significantly lower with glargine versus NPH (0.5 versus 1.2 episodes/patient-year; $p = 0.04$).

The timing of the glargine dose is recommended before bedtime, usually ~ 22.00 h, by the manufacturers. It has been shown to be safe and effective when given before

breakfast, dinner or at bedtime [39]. However, the injection can be given at lunch or dinner to avoid hyperglycaemia in the early part of the night [40]. If necessary, the dose can be split into twice-daily injections. A nonrandomised, prospective clinical study showed that splitting the dose was necessary in 25% of 82 Type 1 diabetic subjects to achieve adequate control [41].

Table 1. Randomised controlled trials of insulin glargine in the treatment of Type 1 diabetes.

Study	Design	HbA _{1c}	Blood glucose	Hypoglycaemia	Other comments
Rosenstock <i>et al.</i> , 2000 [29]	4-week RCT; n = 256; glargine [30] or [80] once daily vs NPH once or twice daily in basal-bolus regimen; soluble insulin at mealtimes	No significant difference at study end between glargine or NPH (-0.4% for all)	Mean FBG lower with glargine vs twice-daily NPH, but not once daily (-1.5 vs -1.8 vs -0.3 mmol/l, glargine [30] vs glargine [80] vs NPH, respectively)	More hypoglycaemia with glargine [30] and [80] vs NPH (97.6 and 100% vs 93.2%, respectively, p = 0.03)	Median basal insulin dose of glargine similar to NPH once-daily prestudy regimen, but 6–7 U lower than twice-daily NPH prestudy regimen; no clinically meaningful change in weight
Pieber <i>et al.</i> , 2000 [30]	4-week RCT; n = 333; glargine [30] or [80] once daily vs NPH once or twice daily; soluble insulin at mealtimes	Mean HbA _{1c} lower with glargine (-0.14%, p = 0.030) at study end	Mean change in FPG from baseline was lower with glargine (-1.88 mmol/l; p = 0.0005)	Nocturnal hypoglycaemia frequency lower with glargine (36 vs 55% p = 0.0037), but only with NPH once daily	Short study duration
Raskin <i>et al.</i> , 2000 [31]	16-week RCT; n = 619; glargine once daily vs NPH twice daily in basal-bolus regimen; lispro at mealtimes	No significant difference in HbA _{1c}	Greater decrease in mean FBG with glargine vs NPH insulin at study end (-2.33 vs -0.69 mmol/l, p = 0.0001)	No differences in symptomatic hypoglycaemia, including nocturnal, observed	Less weight gain with glargine (0.12 vs 0.54 kg, p = 0.034); injection-site pain more with glargine (6.1 vs 0.3%)
Ratner <i>et al.</i> , 2000 [32]	28-week RCT; n = 534; bedtime glargine once daily or NPH once or twice daily with mealtime soluble insulin; target FPG 4.4–6.7 mmol/l	No significant difference in HbA _{1c}	Greater decrease in median FPG with glargine vs NPH insulin at study end (-1.67 vs -0.33 mmol/l, p = 0.0145)	Less nocturnal hypoglycaemia with glargine (18.2 vs 27.1%, p = 0.0116); all symptomatic (p < 0.05) and severe (p = 0.0117) hypoglycaemia also lower with glargine	Total glargine dose unchanged over study period, whereas insulin doses in NPH regimen increased slightly
Rossetti <i>et al.</i> , 2003 [33]	12-week RCT; n = 51; NPH four times daily vs once-daily evening glargine vs once-daily bedtime glargine; lispro at mealtimes	No change in HbA _{1c} with NPH insulin; decrease in HbA _{1c} with dinnertime and bedtime glargine at study end (p < 0.04 vs NPH)	Mean daily BG lower with dinnertime and bedtime glargine vs NPH insulin (7.5 and 7.4 vs 8.3 mmol/l, p < 0.05)	Less nocturnal hypoglycaemia with glargine (1.7 vs 2.0 vs 3.6 episodes/patient-month, p < 0.05); no difference between dinnertime and bedtime glargine	No difference in insulin dose at study end between glargine or NPH
Porcellati <i>et al.</i> , 2004 [34]	52-week RCT; n = 121; glargine once daily vs NPH four times daily; lispro at mealtimes	Mean HbA _{1c} lower with glargine vs NPH (6.7 vs 7.1%, p < 0.05)	Mean daily BG lower with glargine vs NPH (7.6 vs 8.1 mmol/l)	Less nocturnal hypoglycaemia with glargine vs NPH (1.2 vs 3.2 episodes/patient-month, p < 0.05)	No difference in total insulin dose at study end (0.67 vs 0.63 U/kg/day); no differences in body weight change at study end

BG: Blood glucose; CSII: Continuous subcutaneous insulin infusion; FBG: Fasting blood glucose; FPG: fasting plasma glucose; Hb: Haemoglobin; NPH: Neutral protamine Hagedorn; NS: Not significant; RCT: Randomised controlled trial; SMBG: Self-monitoring of blood glucose.

Table 1. Randomised controlled trials of insulin glargine in the treatment of Type 1 diabetes.

Study	Design	HbA _{1c}	Blood glucose	Hypoglycaemia	Other comments
Home <i>et al.</i> , 2005 [36]	28-week RCT; n = 585; bedtime glargine or bedtime or twice-daily NPH; soluble human insulin at mealtimes	No significant difference in HbA _{1c} decrease between glargine and NPH insulin	Similar reduction in FBG unless more than once-daily basal insulin injection prior to study (glargine vs NPH, -1.38 vs -0.72 mmol/l, respectively, p < 0.01)	No differences in hypoglycaemia	Basal insulin change with glargine -1.0 IU/day at study end (no change with NPH); change in weight not documented
Fulcher <i>et al.</i> , 2005 [37]	30-week RCT; n = 125; bedtime glargine or NPH; lispro at mealtimes	Mean HbA _{1c} lower with glargine vs NPH (8.3 vs 9.1%); treatment benefit of glargine 0.53%, p < 0.01	Mean FBG at end point lower with glargine (7.9 vs 9.0 mmol/l)	Less moderate (p = 0.04) or severe (p = 0.02) nocturnal hypoglycaemia with glargine	Mean bolus dose was similar in the glargine vs NPH groups (35.1 vs 34.1 IU/day); no significant difference in weight change (+1.97 vs +2.34 kg, p < 0.05)
Hirsch <i>et al.</i> , 2005 [45]	5-week crossover RCT; n = 100; bedtime glargine + mealtime aspart vs CSII with aspart	Mean fructosamine lower with CSII (difference: -11.8 µmol/l, p = 0.0001) HbA _{1c} similar at study end	No difference between mean 8-point SMBG profiles	Similar incidence in daily minor hypoglycemia between treatments; however, fewer nocturnal minor hypoglycaemia with CSII (110 vs 155 episodes, p = 0.002) and fewer daytime minor hypoglycaemia with glargine (232 vs 333 episodes; p < 0.001)	Slightly lower insulin dose with CSII (NS); short study duration

BG: Blood glucose; CSII: Continuous subcutaneous insulin infusion; FBG: Fasting blood glucose; FPG: fasting plasma glucose; Hb: Haemoglobin; NPH: Neutral protamine Hagedorn; NS: Not significant; RCT: Randomised controlled trial; SMBG: Self-monitoring of blood glucose.

6.1.1 Fasting plasma glucose and fasting blood glucose

Although the data regarding improved HbA_{1c} levels are somewhat equivocal, significant differences in fasting plasma glucose (FPG) or fasting blood glucose (FBG) levels have been observed with glargine in most studies (see Table 1) [29,31-33]. For example, in a 4-week study of 256 patients, glargine demonstrated greater efficacy versus NPH in lowering FPG (adjusted mean FPG of 9.2 versus 11.3 mmol/l; difference: -2.2 mmol/l; p = 0.0001). This clinically meaningful effect on FPG was observed as early as week 1 [29]. The FPG levels of patients in the NPH group only improved if they were using a once-daily regimen. Two other studies demonstrated greater decreases in FPG with glargine when compared with NPH [31,32].

6.1.2 Insulin dose

Most studies did not show significant differences in insulin dose between glargine and NPH at the end of the study [29,32-34,37].

One study demonstrated that in patients previously treated with once-daily NPH, mean glargine dose increased at study

end by 2 U/day, whereas NPH decreased by 0.5 U/day (glargine versus NPH, p < 0.005) [30]. A similar increase in dose was seen in a second study, in which doses of glargine and NPH both increased by 1.8 U/day for patients previously treated with once-daily NPH, but the changes were nonsignificant [31]. In comparison, a third study described decreased doses of glargine, but increased doses of NPH [29]. However, in this study, the actual values were not given.

These changes in insulin dose are of relatively little clinical significance and inevitably a consequence of insulin use.

In patients previously treated with twice-daily NPH, more substantial decreases (between 4 and 7 U/day) in glargine dose were observed compared with increased doses of NPH (between 0.7 and 1.0 U/day) [30,31].

6.1.3 Patient satisfaction

In a randomised, controlled European study of 517 patients with Type 1 diabetes, assessment using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Well-Being Questionnaire (W-BQ) showed that glargine was associated

with significantly improved treatment satisfaction and general well-being when compared with NPH [42]. There was also a lower perceived frequency of hypoglycaemia with glargine although there was no difference in psychological well-being.

6.2 Insulin glargine versus continuous subcutaneous insulin infusion

The gold standard of insulin therapy is CSII because it provides physiological insulin replacement. Studies have shown that CSII results in equivalent or better glycaemic control than multiple daily injection (MDI) therapy with either glargine or other long-acting insulins [43-46]. Several of these studies were conducted prior to the availability of glargine [43-45]. However, the benefits of CSII have to be counterbalanced with problems such as cost, need for a high level of professional support and pump failure.

A randomised, multi-centre, crossover study of 100 patients, 10 weeks in duration compared CSII using aspart with MDI consisting of bedtime glargine and mealtime aspart [46]. All patients underwent a 1-week run-in period with CSII using aspart initially. As the study duration was short, fructosamine was used to assess efficacy; this was significantly lower with CSII than with MDI using glargine ($p = 0.0001$). Glucose exposure was also lower with CSII, as measured by AUC. Overall, the number of daily minor hypoglycaemic episodes was similar with both regimens, although nocturnal minor hypoglycaemia (110 versus 155 episodes, $p = 0.002$) and daytime minor hypoglycaemia episodes with glargine (232 versus 333 episodes; $p < 0.001$) were less frequent than with CSII.

6.3 Safety

6.3.1 Hypoglycaemia

Hypoglycaemia is the most common side effect associated with insulin therapy. Several studies have demonstrated that the use of glargine in Type 1 diabetes is associated with a reduction in nocturnal hypoglycaemia compared with NPH [30,32].

In a study of 534 patients with Type 1 diabetes, the percentage of patients reporting at least one episode of symptomatic, nocturnal or severe hypoglycaemia, confirmed by a blood glucose level of < 2 mmol/l, was significantly lower in those treated with glargine compared with those on NPH [32]. A 4-week, randomised, multi-centre study in 333 patients showed that although the overall frequency of hypoglycaemia was similar between glargine and NPH-treated patients, fewer nocturnal hypoglycaemic episodes occurred with glargine versus NPH (36 versus 55%, $p = 0.0037$). However, this effect on nocturnal hypoglycaemia was only significant versus once daily, and not twice daily, NPH [30].

Another longer study (16 weeks) did not show any differences in hypoglycaemia, including nocturnal hypoglycaemia, between NPH and glargine [31]. Nocturnal hypoglycaemia was shown to occur more frequently if glargine was injected at dinner or bedtime compared with breakfast (71.9, 77.5 and 59.5%, respectively, $p = 0.005$) [39]. One study showed that

thresholds and maximal responses of plasma adrenaline and symptom responses improved with glargine more than NPH and this may account for the observed differences in hypoglycaemia rate [34].

6.3.2 Weight change

Effect on body weight has varied with studies and some trials did not report their results. A 16-week study of glargine or NPH in a basal-bolus regimen showed that weight gain was 0.12 kg with glargine and 0.54 kg with NPH ($p = 0.034$) [31]; likewise, a 30-week study showed that glargine resulted in weight gain of 1.97 kg compared with 2.34 kg with NPH ($p < 0.05$) [37]. Other studies have shown no significant differences in weight gain between glargine and NPH at the end of the study [29,34,38]. These changes in weight are probably of little clinical significance.

6.3.3 Injection-site pain

Glargine has been associated with more injection-site pain than NPH [31,32]. However, these episodes were mild and transient in nature and did not usually result in the discontinuation of glargine.

6.3.4 Antibody titres

No significant changes in antibody titres for insulin or *E. coli* have been observed [29-31].

6.4 Summary of effects of insulin glargine in Type 1 diabetes

- Glargine results in at least equivalent glycaemic control, as measured by HbA_{1c}, when compared with NPH in a basal-bolus regimen
- FPG and FBG tend to be lower with glargine treatment
- Glargine is superior to once-daily NPH in reducing nocturnal hypoglycaemia, but not when compared with twice-daily NPH
- There is less weight gain and greater patient satisfaction with glargine compared with NPH

7. Efficacy and safety in Type 2 diabetes

Although the initial management of Type 2 diabetes is concentrated around lifestyle management and oral glucose-lowering drugs, insulin therapy is indicated with progressive deterioration in β -cell function. There is accumulating evidence that insulin should be commenced earlier in Type 2 diabetes to achieve tighter glycaemic control [47], as risk of complications are reduced by 37% with every 1% fall in HbA_{1c} [6]. This places an increasing burden on healthcare systems and professionals, which is coupled with the enormous rise in the number of worldwide cases. Previously, Type 2 patients on insulin have remained on suboptimal doses and have been insufficiently titrated to achieve treatment targets [7]. Glycaemic goals (HbA_{1c} $\leq 6.5\%$) were not achieved by two thirds of European patients with Type 2 diabetes [48].

With limited evidence in the literature, there is no consensus as to the optimal insulin therapy for patients with Type 2 diabetes. Current options include premixed insulins, basal-bolus regimens, NPH or long-acting analogues administered once or twice daily and a combination of basal insulin with oral glucose-lowering agents.

7.1 Basal insulin and oral glucose-lowering drugs

In theory, basal insulin supplementation, for example with glargine, insulin detemir or NPH, offers the advantage of a simple once or twice-daily injection regimen, which is easier to add to current oral glucose-lowering drugs.

The low injection and monitoring frequency may increase patient compliance and acceptance. In addition, constant supplementation may allow overnight β -cell rest with recovery of prandial secretory capacity.

The disadvantages of basal insulin supplementation are that it does not address the key secretory defect (loss of first-phase insulin secretion) observed in Type 2 diabetes, and provides inadequate cover of postprandial glucose excursions. As titration is often against FPG, this removes the focus from postprandial control. However, as glycaemic control deteriorates, FPG is of greater consequence than postprandial glucose [49]. Finally, questions arise as to the sustainability of this regimen and subsequent options for therapy.

Table 2 illustrates the various trials conducted to compare glargine as a basal insulin versus NPH in Type 2 diabetes.

In the Treat-to-Target trial, 756 subjects with Type 2 diabetes and inadequate control ($\text{HbA}_{1c} > 7.5\%$) on one or two oral agents were randomised either to continue these agents or to commence once-daily bedtime glargine or NPH [50]. Although at study end point, HbA_{1c} was similar (6.96 versus 6.97%, glargine versus NPH) and in both groups $\sim 60\%$ of subjects reached $\text{HbA}_{1c} < 7\%$, in the glargine arm this was achieved without documented nocturnal hypoglycaemia in 25% more patients.

In the LANMET (LANTUS® plus metformin) study [51], 110 insulin-naïve patients with Type 2 diabetes with $\text{HbA}_{1c} > 8\%$ on oral agents were randomised to receive 36 weeks of treatment with bedtime glargine with metformin or bedtime NPH with metformin. Patients self-adjusted their insulin, aiming for FPG levels of 4.0–5.5 mmol/l in both groups. At study end, there was no significant difference between the groups for HbA_{1c} (7.14 versus 7.16%, glargine versus NPH) or insulin doses, but there was a significant reduction in symptomatic hypoglycaemia in the first 12 weeks with glargine and FPG values were lower.

In another randomised study, 426 patients with poor glycaemic control on oral glucose-lowering agents were allocated to 12 months treatment with either bedtime glargine or bedtime NPH with continued oral glucose-lowering drugs [52]. At study end, mean HbA_{1c} was 7.5% with glargine and 7.6% with NPH and there was a significant improvement with both basal insulins. In addition, there was an improvement in post-

dinner glucose concentrations with glargine compared with NPH (9.9 ± 0.2 versus 10.7 ± 0.3 mmol/l; $p < 0.02$).

In a further multinational, open-label, randomised study, 624 patients with Type 2 diabetes who were poorly controlled on oral glucose-lowering agents were commenced on morning or bedtime glargine plus morning glimepiride [53]. No differences were observed in nocturnal hypoglycaemia rate, regardless of time of glargine administration with -1.7% HbA_{1c} reduction in the morning versus -1.6% with bedtime glargine.

Several studies have shown that targets of $\text{HbA}_{1c} < 7\%$ and $\text{FPG} < 5.5$ mmol/l can be achieved in more patients when structured titration algorithms are applied [50,51,54].

A retrospective analysis of 46 patients over 30 months with suboptimal glycaemic control showed a significant decrease in HbA_{1c} with glargine added to oral agents (-0.96% , $p < 0.001$) compared with prandial insulin and oral agents [55]. The study was conducted with close clinical supervision and education support.

7.2 Insulin glargine versus premixed insulins

A premixed formulation that consists of both basal and prandial insulin, addresses some of the key secretory defects in Type 2 diabetes while providing 24-h supplementation and a simple convenient injection schedule. Conversely, premixed regimens are relatively inflexible with their limited prandial:bolus ratios and the lack of individualisation. They can be difficult to intensify, as hypoglycaemia and weight gain occur. The theoretical advantages may only be observed with analogue-based formulations. Patients may also be unaware and unappreciative of the basal and prandial concept.

Therefore, the dilemma in choosing between basal and premixed regimens is based on the following considerations: the role of oral glucose-lowering agents; conventional versus analogue insulins; side effects of hypoglycaemia and weight gain; titration schedules; and, finally, the protocol for intensifying therapy. Studies comparing premixed insulins with glargine as a basal insulin are shown in Table 3.

A 24-week study randomised 371 insulin-naïve patients with poor glycaemic control to receive either once-daily morning glargine plus glimepiride and metformin, or premixed insulin (30% regular, 70% NPH) twice daily without oral glucose-lowering agents [56]. This study found that glargine plus oral glucose-lowering agents achieved a greater reduction in mean HbA_{1c} (-1.64 versus -1.31% , $p = 0.0003$) and more patients reached target $\text{HbA}_{1c} \leq 7.0\%$ without confirmed nocturnal hypoglycaemia compared with premixed insulin (45.5 versus 28.6%, $p = 0.0013$). A greater decrease in FBG was also seen in the glargine arm. However, it should be noted that, in this study, oral glucose-lowering drugs were discontinued on starting premixed insulin and a conventional rather than rapid-acting insulin analogue was used.

A 28-week study of 233 insulin-naïve subjects compared a twice-daily premixed insulin regimen containing the rapid-acting analogue aspart (BIAsp 70/30) with bedtime glargine [57]. In contrast to the previous study, metformin

Table 2. Randomised controlled trials of glargine versus NPH in combination with oral agents in Type 2 diabetes.

Study	Design	HbA _{1c}	Plasma glucose	Hypoglycaemia	Other comments
Riddle <i>et al.</i> , 2003 [50]	24-week RCT; n = 7560; prestudy oral agents plus bedtime glargine or NPH once daily using algorithm with target FPG ≤ 5.5 mmol/l	Mean end study HbA _{1c} similar (6.96 vs 6.97%, glargine vs NPH, respectively)	Mean end study FPG similar (6.5 vs 6.7 mmol/l, glargine vs NPH, respectively)	Less nocturnal hypoglycaemia when HbA _{1c} ≤ 7% attained with glargine (33.2 vs 26.7%, p < 0.05)	Mean insulin dose higher with glargine (47.2 IU vs 41.8 IU; p < 0.005) at study end; similar weight gain over study period (3.0 vs 2.8 kg, glargine vs NPH)
Yki-Jarvinen <i>et al.</i> , 2006 [51]	36-week RCT; n = 110; previously on oral glucose-lowering drugs; randomised to metformin and once-daily bedtime glargine or once- or twice-daily bedtime NPH	Mean end study HbA _{1c} similar (7.14 vs 7.16%, glargine vs NPH, respectively, p > 0.05); no difference in those reaching target HbA _{1c} < 7%	Similar improvements in FPG between the groups; pre-dinner glucose levels higher with NPH (10.1 vs 8.6 mmol/l, p = 0.002)	Less symptomatic hypoglycaemia with glargine in first 12 weeks (4.1 vs 9.0 episodes/patient-year, p < 0.05)	Insulin doses similar (68 vs 70 IU/day, glargine vs NPH)
Yki-Jarvinen <i>et al.</i> , 2000 [52]	52-week RCT; n = 426; once-daily glargine or NPH added to prestudy OHA; target FBG 6.7 mmol/l	Mean end study HbA _{1c} similar (7.75 vs 7.60%, glargine vs NPH, respectively) in those reaching target FBG	Lower postdinner glucose (9.9 vs 10.7 mmol/l, p < 0.02)	Less nocturnal hypoglycaemia with glargine (9.9 vs 24.0%, p < 0.001)	Similar mean insulin dose (23 vs 21 U/day, glargine vs NPH); similar weight gain (2.57 vs 2.34 kg, glargine vs NPH)
Massi Benedetti <i>et al.</i> , 2003 [62]	52-week RCT; n = 570; once daily glargine or NPH added to prestudy OHA	Decrease in HbA _{1c} similar for glargine and NPH (-0.46% vs -0.38%; p = 0.415)		Less nocturnal hypoglycaemia with glargine (12 vs 24%, p = 0.002)	
Fritsche <i>et al.</i> , 2003 [63]	24-week RCT; n = 695; randomised to morning or bedtime glargine, or bedtime NPH plus glimepiride; target FBG < 5.56 mmol/l	Mean HbA _{1c} improved most with morning glargine (-1.24%) vs bedtime glargine (-0.96%) and NPH (-0.84%)	FBG improved similarly in all three groups at end point (7.0, 6.8 and 6.9 mmol/l, morning glargine, bedtime glargine and NPH, respectively)	Less nocturnal hypoglycaemia with morning and bedtime glargine compared with NPH (17, 23 and 38%, respectively, p < 0.001)	Insulin doses increased over study period; mean end point insulin dose 40 IU (morning glargine), 39 IU (bedtime glargine), 37 IU (bedtime NPH)

FPG: Fasting plasma glucose, Hb: Haemoglobin; NPH: neutral protamine Hagedorn; NS not significant; OHA: Oral glucose-lowering drugs; RCT: Randomised controlled trial.

and/or pioglitazone was continued in both arms, although insulin secretagogues were discontinued. At study end, mean HbA_{1c} was lower in the twice-daily premixed insulin group, although there was no difference in FPG. However, less minor hypoglycaemia, lower mean insulin dosage and less weight gain were observed with glargine at the end of the study.

The importance of effective treatment algorithms is increasingly recognised. Few studies have evaluated the role of titration algorithms in optimising glycaemic control. A recent study of two different glargine treatment algorithms being used in the ATLANTUS trial (A Trial Comparing LAN-TUS® + Metformin versus NPH) demonstrated that a simple subject-administered titration algorithm was more effective at improving glycaemic control than physician-managed titration (Table 4) [58]. They were based on the two successful, but

different algorithms, which had been used in the Treat-to-Target Trial [50] and the Yki-Jarvinen trial [52].

7.3 Insulin glargine as a basal-bolus regimen in Type 2 diabetes

Table 5 shows the two studies comparing glargine and NPH as part of a basal-bolus regimen [57,60]. No differences were noted in HbA_{1c} or FBG, but there was less hypoglycaemia with glargine.

7.4 Continuous subcutaneous insulin compared with insulin glargine in Type 2 diabetes

A study of 107 subjects ≥ 60 years of age showed that in Type 2 diabetes, comparable glycaemic control with good safety and patient satisfaction was achieved with both CSII and basal-bolus therapy using glargine as the basal insulin [61].

Table 3. Randomised controlled trials of glargine versus premixed insulin in Type 2 diabetes.

Study	Design	HbA _{1c}	Plasma glucose	Hypoglycaemia	Other comments
Janka <i>et al.</i> , 2005 [56]	24-week RCT; n = 371; previously insulin naive; randomised to once-daily morning glargine plus OHA or premixed 30% regular/70% NPH insulin twice daily	Mean HbA _{1c} decrease greater with glargine + OHA (-1.64 vs -1.31%, p = 0.0003)	FBG decrease greater with glargine + OHA (adjusted mean difference: -0.9 mmol/l, p < 0.0001)	Fewer confirmed hypoglycaemic episodes with glargine + OHA (mean 4.07 vs 9.87/patient-year, p < 0.0001)	Mean insulin dose ~ 50% less with glargine + OHA (64.5 vs 28.2 IU); similar weight gain with glargine + OHA and premixed insulin (1.4 vs 2.1 kg, NS)
Raskin <i>et al.</i> , 2005 [59]	28-week RCT; n = 233; previously insulin naive; randomised to BAsp 70/30 twice daily or bedtime glargine; continued on metformin and/or pioglitazone	Mean HbA _{1c} lower in BAsp 70/30 vs glargine (6.91 vs 7.41%, p < 0.01)	No difference in FPG at end of study	Less minor hypoglycaemia with glargine (0.7 vs 3.4 episodes/patient-year, p < 0.05)	Lower mean insulin dose with glargine (51.3 vs 78.5 units/day); mean body weight increased in both glargine vs BAsp groups (3.5 vs 5.4 kg; p < 0.01)

BAsp: Blood aspartame; FPG: Fasting plasma glucose; NPH: Neutral protamine Hagedorn; NS: Not significant; OHA: Oral glucose-lowering drugs; RCT: Randomised controlled trial.

Table 4. Comparison of two different algorithms for titration of insulin glargine on glycaemic control.

Mean FBG (previous 3 consecutive days)	Increase in daily basal insulin glargine dose (IU)	
	Algorithm 1; n = 2493; physician-led insulin dose titration; insulin doses adjusted on a weekly basis during practice visits or through telephone contact	Algorithm 2; n = 2468; patients' self-adjusted insulin dose; insulin dosage self-adjusted every 3 days; dose adjustments reviewed at clinical visits or over the telephone
≥ 5.5 and < 6.7 mmol/l	0 – 2 (at the discretion of the investigator)	0 – 2 (at the discretion of the investigator)
≥ 6.7 and < 7.8 mmol/l	2	2
≥ 7.8 and < 10 mmol/l	4	2
≥ 10 mmol/l	6–8	2

Information from the ATLANTUS study [58].

Target FBG ≤ 5.5 mmol/l.

FBG: Fasting blood glucose.

After 12 months, HbA_{1c} was 6.6% with CSII and 6.4% with basal–bolus therapy. Severe hypoglycaemia rates were low with both regimens and there was no difference in weight gain. However, in practice, CSII is infrequently used in the management of most patients with Type 2 diabetes.

7.5 Insulin dose

In one study in which insulin-naive patients were enrolled, average doses of insulin at study end were 23 U/day for those on glargine and 21 U/day on NPH [52]. In another study, slightly more insulin was used by both glargine and NPH at study end by patients previously treated with once-daily NPH [58]. In the same study, patients who had been on more than once-daily basal insulin pretrial used less insulin with glargine (reduced by ~ 4.4 U/day compared with the baseline dose), whereas in patients on NPH, the insulin dose was similar at

study end compared with baseline. In the Treat-to-Target trial [50], mean daily dosages at end point were 47.2 IU for glargine and 41.8 IU for NPH (p < 0.005). In the LANMET study, mean insulin doses were 68 ± 5 and 70 ± 6 IU/day (0.69 ± 0.05 and 0.66 ± 0.04 IU kg/day, nonsignificant, glargine versus NPH) [51].

7.6 Safety

7.6.1 Hypoglycaemia

Despite the necessity for a 'treat-to-target' strategy, one of the greatest barriers to intensification of insulin replacement in Type 2 diabetes has been the fear of increased hypoglycaemia. The use of intermediate-acting evening or bedtime NPH as basal supplementation is associated with nocturnal hypoglycaemia on account of plasma insulin peaks, which are then followed by high fasting glucose levels. The advent of basal

Table 5. Randomised controlled trials of glargine as part of basal-bolus therapy in Type 2 diabetes.

Study	Design	HbA _{1c}	Plasma glucose	Hypoglycaemia	Other comments
Rosenstock et al., 2001 [57]	28-week RCT; n = 518; previously on NPH ± prandial insulin; randomised to once-daily glargine or once- or twice-daily NPH and prandial insulin	Similar improvements in HbA _{1c} for glargine (-0.41%) and NPH (-0.59%)	Similar improvements in FBG between the groups; 29.6% on glargine and 27.1% on NPH achieved FBG < 6.7 mmol/l by study end	Less nocturnal hypoglycaemia with glargine (26.5 vs 35.5%, p = 0.014)	Median total daily insulin dose same with glargine and NPH (0.75 IU/kg) Less weight gain with glargine (0.4 vs 1.4 kg, p = 0.0007)
Fonseca et al., 2004 [60]	28-week RCT; n = 100; bedtime glargine or NPH regular insulin preprandial	Similar reductions in HbA _{1c} at study end with glargine and NPH (-0.41 vs -0.46%)	Similar reductions in FBG at study end with glargine and NPH (-22.0 mg/dl for both)	Less overall confirmed hypoglycaemia with glargine vs NPH (17.3 vs 31.3%, p < 0.005)	Similar basal doses at study end for glargine vs NPH (36.4 IU vs 30.2 IU)

FBG: Fasting blood glucose; FPG: Fasting plasma glucose; Hb: Haemoglobin; NPH neutral protamine Hagedorn; RCT: Randomised controlled trial.

insulins, such as glargine, theoretically should reduce the risk of daytime and, especially, nocturnal hypoglycaemia.

The Treat-to-Target Trial [50] assessed the ability of glargine to improve glycaemic control in patients with Type 2 diabetes who were failing on oral glucose-lowering agents. In this 24-week trial, 756 patients were randomised to receive glargine or NPH in addition to pre-existing oral agents. The study involved systematically titrating bedtime insulin to a target FPG ≤ 5.5 mmol/l (100 mg/dl); most patients (~ 60%) achieved an HbA_{1c} level ≤ 7% in both groups. However, almost 25% more patients in the glargine group achieved this level of control without experiencing an episode of nocturnal hypoglycaemia. This ability to improve the likelihood of reaching glycaemic targets without increasing the risk of hypoglycaemia was also demonstrated in a 1-year trial of similar design [52]. In a comparison of glargine plus oral agents and a premixed 30% regular/70% NPH formulation alone, patients in the glargine arm had fewer confirmed episodes of hypoglycaemia (mean 4.07 versus 9.87/patient-year, p < 0.0001) [56].

Several other individual trials have consistently demonstrated a reduction in overall and/or nocturnal hypoglycaemia with glargine [50,51,52,61,62,63].

A recent meta-analysis comparing glargine with human NPH in Type 2 diabetes found a reduced risk of hypoglycaemia with glargine [57]. With the exception of one study 52 weeks in duration, the other studies were between 24 and 28 weeks. The advantage of this meta-analysis was that > 2000 subjects with Type 2 diabetes were in the pooled cohort. A target HbA_{1c} of ≤ 7.0% was achieved in an equivalent proportion of patients on glargine or NPH (30.8 versus 32.1%). However, a significant reduction of hypoglycaemia risk was associated with glargine when compared with NPH. In particular, the risk of moderate and severe nocturnal hypoglycaemia were reduced by 46% (p = 0.04) and 59% (p = 0.02), respectively, with glargine. The reduction in nocturnal hypoglycaemia seen with glargine is most likely due to its smooth time-action profile.

7.6.2 Weight Change

Weight gain was similar when bedtime glargine or NPH were added to oral agents [52] and averaged 2.57 ± 0.23 kg in the glargine group and 2.34 ± 0.23 kg in the NPH group. In the Treat-to-Target trial, a similar level of weight gain was observed (3.0 versus 2.8 kg, glargine versus NPH) [50]. In another study, mean weight gain was 1.4 ± 3.4 kg when glargine was added to oral medication and 2.1 ± 4.2 kg with premixed twice-daily insulin (p = 0.09) [56]. When subjects were randomised to prandial regular insulin along with once daily glargine or once- or twice-daily NPH, less weight gain was seen with glargine (0.4 versus 1.4 kg, p = 0.0007) [57].

7.6.3 Antibody titres

Insulin antibodies were less prevalent with glargine than NPH [52].

7.7 Summary of benefits in Type 2 diabetes

- Glargine results in better glycaemic control without nocturnal hypoglycaemia when compared with conventional insulins such as NPH
- Glargine can result in lower FPG and FBG levels
- Hypoglycaemia, especially nocturnal, is seen less frequently with glargine than with conventional insulin
- Patient satisfaction is greater with glargine than with NPH
- Targets of HbA_{1c} < 7% and FPG < 5.5 mmol/l can be achieved in more patients when structured titration algorithms are applied
- Weight gain is equivalent or less compared with NPH
- The insulin injection can be given either in the morning or evening

8. Treatment satisfaction

Diabetes affects a patient's quality of life and well-being, with the greatest negative impact occurring in the freedom to eat as

desired [65]. Validated questionnaires in both Types of diabetes have shown that glargine is associated with greater patient satisfaction compared with NPH [42,66]. The DTSQ and W-BQ was used in 517 patients from 10 European countries with Type 1 diabetes who were randomised to either bedtime glargine or once- or more than once-daily NPH along with regular human insulin before meals [42]. The questionnaires were completed four times during the course of the study. At all time points, including end point, treatment satisfaction improved with glargine and deteriorated slightly with NPH. In particular, perceived frequency of hyperglycaemia and hypoglycaemia were better with glargine insulin. However, there were no differences in psychological well-being between glargine and NPH, with mean scores improving in both.

9. Special populations

9.1 Pregnant women

At present, glargine, similar to other insulins, is not licensed for use in pregnancy. Animal studies have shown that there does not seem to be any harm to the fetus from administration of glargine in pregnancy [67]. There have been several case reports in the literature of glargine being given safely to pregnant women in the first trimester, although in some cases it was subsequently discontinued and replaced by NPH [68-70].

9.2 Children

The use of glargine is licensed in children 6 years of age and older. In a 16-week, randomised, crossover study, 28 adolescents received either bedtime glargine plus lispro preprandially or bedtime NPH plus regular human insulin preprandially [35]. The combination of glargine and lispro was associated with lower fasting blood glucose levels compared with the NPH regimen. Nocturnal hypoglycaemia was found to be 43% lower with glargine and lispro compared with NPH and regular insulin. No significant differences in HbA_{1c} were found at the end of the study. A prospective study in 80 children and adolescents aged 2 – 19 years showed an improvement in HbA_{1c}, FBG and severe hypoglycaemia after 6 months' treatment with glargine [71]. Other prospective non-randomised studies have found that 6 months of glargine therapy resulted in less severe hypoglycaemia in children > 6 years of age compared with NPH [72].

9.3 Elderly/renal and hepatic impairment

The use of glargine in these populations has not been associated with problems, but must be monitored carefully because, as with any insulin regimen, they can be sensitive to relatively low doses of insulin and are at greater risk of hypoglycaemia.

9.4 Diabetic retinopathy

Early concerns regarding the mitogenic potential of glargine (through its increased affinity for IGF-1 receptor) and increased risk of retinopathy remain unconfirmed. Only one study has shown significant deterioration in vision as a conse-

quence of glargine use and the current consensus is that glargine does not cause ocular adverse effects [73].

10. Cost implications

A systematic review of glargine has compared the cost utility of glargine with NPH [74]. Using an amended School of Health and Related Research (ScHARR) model, this estimated that the base-case cost per quality-adjusted life year (QALY) was UK£3496 – 4978 in Type 1 diabetes and £32,508 – 43,411 in Type 2 diabetes. The cost per QALY ratio was dependent on the method of administration; that is, insulin pen, vial or cartridge. The review concluded that, based on these figures, glargine ranged from cost-effective to non-cost-effective, but that cost-effectiveness was highly dependent on amount of utility associated with reducing the fear of hypoglycaemia in both Types of diabetes. The long-term cost implications based on reduction of microvascular and macrovascular complications remains to be evaluated.

11. Expert opinion

The advent of glargine as a long-acting insulin with no pronounced peak and a 24-h time-action profile, which can provide a basal supply of insulin in both Type 1 and Type 2 diabetes, has been greeted enthusiastically. It provides at least equivalent glycaemic control when compared with NPH and premixed formulations, as well as in comparison with CSII in a basal-bolus combination. In addition, it seems to be associated with lower FPG and FBG levels, as well as significantly lower rates of nocturnal hypoglycaemia. Balanced against these advantages are the increased costs of glargine as part of a basal-bolus regimen, the inability to mix it with other insulins and increased injection-site pain. It is licenced for use as a once-daily insulin at bedtime. For convenience, and sometimes greater efficacy, this dose can be given before breakfast or the evening meal or even split into a twice-daily dose. The ability to vary the timing of the single dose may be particularly useful in young people.

There is clear evidence that in a basal-bolus regimen, glargine provides a more physiological supply of basal insulin, but improvements in glycaemic control are associated with increased expense. Glargine is ~ 60% more expensive than conventional insulins such as NPH. However, the reduction in hypoglycaemia, especially nocturnal, provides the opportunity to titrate to optimal doses, thereby increasing the potential for further glycaemic improvement. Glargine is a useful addition to the current therapeutic armamentarium for diabetes.

Conflicts of interest

MJ Davies has received funds for research, honoraria for speaking at meetings and has served on Advisory Boards for Sanofi-Aventis and Novo Nordisk. S Chatterjee and JR Tringham have no conflicts of interest to declare.

Bibliography

1. ZIMMET P, ALBERTI KG, SHAW J: Global and societal implications of the diabetes epidemic. *Nature* (2001) 414(6865):782-787.
2. DIABETES UK, ALL-PARTY PARLIAMENTARY GROUP, HANSARD SOCIETY: Report: State of the Nations 2005 – Progress made on the national diabetes frameworks (2005).
3. DEPARTMENT OF HEALTH: Report: National Service Framework for Diabetes. (2001).
4. DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* (1993) 329:977-986.
5. WRITING TEAM FOR THE DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS RESEARCH GROUP: Effect of intensive therapy on the microvascular complications of Type 1 diabetes mellitus. *JAMA* (2002) 287(19):2563-2569.
6. STRATTON IM, ADLER AI, ANDREW H *et al.*: Association of glycaemia with macrovascular and microvascular complications of Type 2 diabetes (UKPDS 35): prospective observational study. *Br. Med. J.* (2000) 321:405-412.
7. UK PROSPECTIVE DIABETES STUDY (UKPDS) GROUP: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet* (1998) 352:837-853.
8. DEPARTMENT OF HEALTH: Report: National Diabetes Audit – key findings about the quality of care for people with diabetes in England (2005).
9. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE: Report: clinical guidelines for Type 2 diabetes – management of blood glucose (2002).
10. BARNETT A: A review of basal insulins. *Diabet. Med.* (2003) 20:873-885.
11. *Diabetes atlas executive summary, 2nd edn.* International Diabetes Federation (2003).
12. CRUICKSHANKS KJ, LAPORTE RE, DORMAN JS *et al.*: The epidemiology of insulin-dependent diabetes mellitus: etiology and prognosis. In: *Coping With Juvenile Diabetes*. Ahmed PI, Ahmed N, (Eds). Charles C Thomas, Springfield, IL (1985):332-357.
13. KARVONEN M, VIK-KARJANDER M, MOLTCHANOVA E: Incidence of childhood Type 1 diabetes worldwide. *Diabetes Care* (2000) 23:1516-1526.
14. HEINEMANN L, SINHA K, WEYER C, LOFTAGER M, HIRSCHBERGER S, HEISE T: Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. *Diabet. Med.* (1999) 16:332-338.
15. PIEBER TR, DRAEGER E, KRISTENSEN A, GRILL V: Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir versus morning plus bedtime NPH insulin. *Diabet. Med.* (2005) 22:850-857.
16. HEISE T, NOSEK L, RONN BB *et al.*: Lower within-subject variability of insulin detemir in comparison to nph insulin and insulin glargine in people with Type 1 diabetes. *Diabetes* (2004) 53:1614-1620.
17. HAAK T, TIENGO A, DRAEGER E, SUNTUM M, WALDHAUSL W: Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with Type 2 diabetes. *Diabetes Obes. Metab.* (2005) 7:56-64.
18. DE LEEUW I, VAGUE P, SELAM JL *et al.*: Insulin detemir used in basal-bolus therapy in people with Type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab* (2005) 7:73-82.
19. STANDL E, LANG H, ROBERTS A: The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of Type 1 diabetes. *Diabetes Technol. Ther.* (2004) 6:579-588.
20. VAGUE P, SELAM JL, SKEIE S *et al.*: Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with Type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* (2003) 26:590-596.
21. HEINE RJ, VAN GAAL LE, JOHNS D *et al.*: Exenatide versus insulin glargine in patients with suboptimally controlled Type 2 diabetes. *Ann. Intern. Med.* (2005) 143:559-569.
22. LEPORE M, PAMPANELLI S, FANELLI C *et al.*: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin and Ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* (2000) 49:2142-2148.
23. SCHOLTZ HE, PRETORIUS SG, WESSELS DH, BECKER RH: Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. *Diabetologia* (2005) 48(10):1988-1995
24. HEINEMANN L, LINKESCHOVA R, RAVE K, HOPESCH B, HEISE T: Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* (2000) 23(5):644-649
25. BERTI L, KELLERER M, BOSSENMAIER B, SEFFER E, SEIPKE G, HARING HU: The long acting human insulin analog HOE 901: characteristics of insulin signalling in comparison to Asp(B10) and regular insulin. *Horm. Metab. Res.* (1998) 30(3):123-129
26. BAHR M, KOLTER T, SEIPKE G *et al.*: Growth promoting and metabolic activity of the human insulin analogue [Gly(A21),Arg(B31),Arg(B32)]insulin (HOE901) in muscle cells. *Eur. J. Pharmacol.* (1997) 320:259-265.
27. SEIPKE G, BERCHTHOLD H, GEISEN K *et al.*: HOE901 – a new insulin with prolonged action. *Diabetes* (1999) 48(Suppl. 1):25.
28. COATES PA, MUKHERJEE S, LUZIO S *et al.*: Pharmacokinetics of a long-acting human insulin analogue (HOE901) in healthy subjects. *Diabetes* (1995) 44(Suppl. 1):130A.
29. ROSENSTOCK J, PARK G, ZIMMERMAN J, US INSULIN GLARGINE (HOE): Basal insulin glargine (HOE 901) versus NPH insulin in patients with Type 1 diabetes on multiple daily insulin regimens. US Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. *Diabetes Care* (2000) 23:1137-1142.

30. PIEBER TR, EUGENE-JOLCHINE I, DEROBERT E *et al*: Efficacy and safety of HOE 901 versus NPH insulin in patients with Type 1 diabetes. *Diabetes Care* (2000) 23:157-162.
31. RASKIN P, KLAFF L, BERGENSTAL R, HALLE J-P, DONLEY D, MECCA T: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with Type 1 diabetes. *Diabetes Care* (2000) 23:1666-1671.
32. RATNER RE, HIRSCH IB, NEIFING JL, GARG SK, MECCA TE, WILSON CA: Less hypoglycaemia with insulin Glargine in intensive insulin therapy for Type 1 diabetes. US study group of insulin Glargine in Type 1 diabetes. *Diabetes Care* (2000) 23:639-643.
33. ROSSETTI P, PAMPANELLI S, FANELLI C *et al*: Intensive replacement of basal insulin in patients with Type 1 diabetes given rapid-acting insulin analog at mealtime. *Diabetes Care* (2003) 26:1490-1496.
34. PORCELLATI F, ROSSETTI P, PAMPANELLI S *et al*: Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet. Med.* (2004) 21:1213-1220.
35. MURPHY NP, KEANE SM, ONG KK *et al*: Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with Type 1 diabetes on intensive insulin regimens. *Diabetes Care* (2003) 26:799-804.
36. HOME PD, ROSSKAMP R, FORJANIC-KLAPPROTH J, DRESSLER A: A randomized multicentre trial of insulin glargine compared with NPH insulin in people with Type 1 diabetes. *Diabetes Metab. Res. Rev.* (2005) 21(6):545-553.
37. FULCHER GR, GILBERT RE, YUE DK: Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern. Med. J.* (2005) 35(9):536-542.
38. GARG SK, PAUL JM, KARSTEN JI *et al*: Reduced severe hypoglycaemia with insulin glargine in intensively treated adults with Type 1 diabetes. *Diabetes Technol. Ther.* (2004) 6:589-595.
39. HAMANN A, MATTHAEI S, ROSAK C *et al*: A randomised clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with Type 1 diabetes. *Diabetes Care* (2003) 26:1738-1744.
40. ASHWELL SG, GEBBIE J, HOME PD: Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. *Diabet. Med.* (2006) 23:46-52.
41. ALBRIGHT ES, DESMOND R, BELL DS: Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in Type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* (2004) 27:632-633.
42. WITTHAUS E, STEWART J, BRADLEY C: Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. *Diabet. Med.* (2001) 18:619-625.
43. TSUI E, BARNIE A, ROSS S, PARKES R, ZINMANN B: Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily injection. *Diabetes Care* (2001) 24:1722-1727.
44. HANAIRE-BROUTIN H, MELKI V, BESSIERES-LACOMBE S *et al*: Study Group for the Development of Pump Therapy in Diabetes: comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in Type 1 diabetic patients on intensified treatment. *Diabetes Care* (2000) 23:1232-1235.
45. DEVRIES JH, SNOEK FJ, KONSTENSE PJ *et al*: A randomized trial of continuous subcutaneous injection therapy in Type 1 diabetes for patients with long-standing poor glycaemic control. *Diabetes Care* (2002) 25:2074-2080.
46. HIRSCH IB, BODE BW, GARG S *et al*: Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in Type 1 diabetic patients previously treated with CSII. *Diabetes Care* (2005) 28:533-538.
47. RIDDLE M: Timely addition of insulin to oral therapy for Type 2 diabetes. *Diabetes Care* (2002) 25:395-396.
48. LIEBL L, MATA M, ESCHWEGE E: Evaluation of risk factors for the development of complications in Type 2 diabetes in Europe. *Diabetologia* (2002) 45:S23-S28.
49. MONNIER L, LAPINSKI H, COLETTE C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of Type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* (2003) 26:881-885.
50. RIDDLE M, ROSENSTOCK J, GERICH J: The treat-to-target trial: randomised addition of glargine of human NPH insulin to oral therapy of Type 2 diabetic patients. *Diabetes Care* (2003) 26:3080-3086.
51. YKI-JARVINEN H, KAUPPINEN-MAKELIN R, THIKKAINEN M *et al*: Insulin glargine or NPH combined with metformin in Type 2 diabetes: the LANMET study. *Diabetologia* (2006) 49:442-451.
52. YKI-JARVINEN H, DRESSLER A, ZIEMAN M, HOE 901/3002 STUDY GROUP: Less nocturnal hypoglycaemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in Type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care* (2000) 23:1130-1136.
53. STANDL E, MAXEINER S, RAPTIS S *et al*: Good glycaemic control with flexibility in timing of basal insulin supply. *Diabetes Care* (2005) 28:419-420.
54. GERSTEIN HC, YALE JF, HARRIS SB, ISSA M, STEWART JA, DEMPSEY EA: Randomized trial of early glargine use to achieve optimal a1c levels in insulin naive people with Type 2 diabetes. *Diabetes* (2005) 54(Suppl. 1):A67-A68 Abstract.
55. SCHREIBER SA, RUSSMANN A: The effects of insulin glargine treatment and an educational programme on glycaemic control in Type 2 diabetes patients in clinical practice. *Curr. Med. Res. Opin.* (2006) 22:335-341.
56. JANKA HU, PLEWE G, RIDDLE MC, KLIEBE-FRISCHE C, SCHWEITZER MA, YKI-JARVINEN H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for Type 2 diabetes. *Diabetes Care* (2005) 28:254-259.
57. ROSENSTOCK J, SCHWARTZ SL, CLARK CM *et al*: Basal insulin therapy in Type 2 diabetes: 28 week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* (2001) 24:631-636.
58. DAVIES MJ, STORMS F, SHUTLER S *et al*: Improvement of glycaemic control in

- subjects with poorly controlled Type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* (2005) 28:1282-1288.
59. RASKIN P, ALLEN E, HOLLANDER P *et al.*: Initiating insulin therapy in Type 2 diabetes. *Diabetes Care* (2005) 28:260-265.
 60. FONSECA V, BELL DS, BERGER S, THOMSON S, MECCA TE: A comparison of bedtime insulin glargine with bedtime neutral protamine hagedorn insulin in patients with Type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study. *Am. J. Med. Sci* (2004) 328(5):274-280.
 61. HERMAN WH, ILAG LL, JOHNSON SL *et al.*: A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with Type 2 diabetes. *Diabetes Care* (2005) 28:1568-1573.
 62. MASSI BENEDETTI M, HUMBURG E, DRESSLER A, ZIEMEN M: A one year randomised multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with Type 2 diabetes. *Horm. Metab. Res.* (2003) 3:189-196.
 63. FRITSCH A, SCHWEITZER M, HARING HU, THE 4001 STUDY GROUP: Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin or bedtime insulin glargine in patients with Type 2 diabetes: a randomised controlled trial. *Ann. Intern. Med.* (2003) 138:952-959.
 64. ROSENSTOCK J, DAILEY G, MASSI-BENEDETTI M *et al.*: Reduced hypoglycaemia risk with insulin glargine. *Diabetes Care* (2005) 28:950-955.
 65. BRADLEY C, SPEIGHT J: Patient perceptions of diabetes and diabetes therapy: assessing quality of life. *Diabetes Metab. Res Rev* (2002) 18(Suppl. 3):S64-S69.
 66. WITTHAUS E, STEWART J, BRADLEY C: Improved psychological outcomes after initiation of insulin treatment in patients with Type 2 diabetes. *Diabetologia* (2000) 43(Suppl. 1):A205.
 67. HOFMANN T, HORSTMANN G, STAMMBERGER I: Evaluation of the reproductive toxicity and embryotoxicity of insulin glargine (LANTUS) in rats and rabbits. *Int. J. Toxicol.* (2002) 21:181-189.
 68. DEVLIN JT, HOTHERSALL L, WILKIS JL: Use of insulin glargine during pregnancy in a Type 1 diabetic woman. (Letter). *Diabetes Care* (2002) 25:1095-1096.
 69. HOLSTEIN A, PLASCHKE A, EGBERTS EH: Use of insulin glargine during embryogenesis in a pregnant woman with Type 1 diabetes. *Diabet. Med.* (2003) 20:779-780.
 70. DI CIANNI G, VOLPE L, LENCIONI C *et al.*: Use of insulin glargine during the first weeks of pregnancy in five Type 1 diabetic women. *Diabetes Care.* (2005) 4:982-983.
 71. COLINO E, LOPEZ-CAPAPE M, GOLMAYO L, ALVAREZ MA, ALONSO M, BARRIO R: Therapy with insulin glargine (Lantus) in toddlers, children and adolescents with Type 1 diabetes. *Diabetes Res. Clin. Pract.* (2005) 70(1):1-7.
 72. DIXON B, PETER CHASE H, BURDICK J *et al.*: Use of insulin glargine in children under age 6 with Type 1 diabetes. *Pediatr. Diabetes* (2005) 6(3):150-154.
 73. BOLLI GB, OWENS DR: Insulin glargine. *Lancet* (2000) 356:443-445.
 74. WARREN E, WEATHERLEY-JONES E, CHILCOTT J, BEVERLEY C: Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. *Health Technol. Assess.* (2004) 8(45):1-57.

Websites

101. National institute for health and clinical EXCELLENCE (2002) Report: Final Appraisal Determination. Long-acting insulin analogues for the treatment of diabetes – insulin glargine. Issue Date: October 2002

Affiliation

Sudesna Chatterjee¹ MRCP,
Jennifer R Tringham¹ MRCP &
Melanie J Davies^{1,2} MD, FRCP

[†]Author for correspondence

¹Clinical Research Fellow, Diabetes Research Unit, University Hospitals of Leicester, UK

²Professor of Diabetic Medicine, Department of Cardiovascular Sciences, University of Leicester, Diabetes Research Unit, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, LE1 5WW, UK

Tel: +44 (0)116 2586481;

Fax: +44 (0)116 2585344;

E-mail: melanie.davies@uhl-tr.nhs.uk

▼Nateglinide and ▼repaglinide for type 2 diabetes?

BNF 6.1.2.3

▼Nateglinide (Starlix – Novartis) and ▼repaglinide (NovoNorm – Novo Nordisk) are two of a new class of orally active antidiabetic drugs, the meglitinides. They have a rapid-onset and short-lasting stimulating effect on insulin secretion. Both are licensed for combination therapy with metformin in patients with type 2 diabetes mellitus who are inadequately controlled by maximally tolerated doses of metformin alone. In addition, repaglinide is licensed for use as monotherapy in patients with type 2 diabetes whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Here we discuss whether repaglinide and nateglinide offer worthwhile advantages in the management of patients with type 2 diabetes.

Background

Key features in the pathogenesis of type 2 diabetes include insulin resistance and beta cell dysfunction (such that insulin secretion is compromised). Antidiabetic drugs that reduce insulin resistance include metformin and the thiazolidinediones, ▼rosiglitazone and ▼pioglitazone. Like the sulphonylureas, nateglinide and repaglinide stimulate insulin secretion, and work by closing ATP-dependent potassium channels in the beta cell membrane. However, they have a more rapid onset, and shorter duration, of action than do the sulphonylureas.

In type 2 diabetes, elevated serum concentrations of both fasting and post-prandial glucose correlate with adverse cardiovascular outcomes.¹ In theory, therefore, treatment that affects post-prandial as well as fasting glucose concentrations could improve overall glycaemic control,² and might reduce cardiovascular risk. Early promotional material for nateglinide implied that it could reduce such risk and mortality through its specific ability^{3,4} to lower post-prandial glucose concentrations. However, the drug company withdrew the advertising when it was revealed that there were no data to support this claim.⁵

Nateglinide

Nateglinide (pronounced na-*te*-gli-nide) is a novel amino acid derived from D-phenylalanine. Oral bioavailability is around 70%, and plasma concentrations generally peak in under 1 hour.⁶ Following an oral dose of nateglinide, the insulinotropic response to a meal occurs within the first 15 minutes, and insulin concentrations return to baseline by around 2 hours.⁶ The elimination half-life of nateglinide is around 1.5 hours, with the drug extensively metabolised by the liver.⁶ Most (83%) of the drug and its metabolites are excreted in urine.⁶ The two main metabolites are 5–6 times and 3 times less potent than nateglinide, respectively.⁶

Dosage

The company recommends a starting dose of 60mg nateglinide three times daily, taken up to 30 minutes before meals. The dose should subsequently be adjusted according to response (e.g. assessed by periodic measurement of serum concentration of glycosylated haemoglobin; HbA_{1c}), with the maximum dose being 180mg three times daily. If a meal is to be missed, the dose should be omitted.

Clinical efficacy

In a 24-week double-blind randomised controlled trial, 701 patients with type 2 diabetes for at least 3 months (HbA_{1c} concentrations of 6.8–11%) were assigned to one of four treatments: placebo; nateglinide monotherapy (120mg three times daily before meals); metformin monotherapy (500mg three times daily at the start of meals); or nateglinide plus metformin (same regimens as with the monotherapies).⁷ By 24 weeks, both HbA_{1c} (the primary outcome measure) and fasting plasma glucose concentrations had increased from baseline with placebo but had decreased with all active treatments, and particularly with the combination (by -1.4% and -2.4mmol/L vs. -0.5% and -0.7mmol/L with nateglinide, and -0.8% and -1.6mmol/L with metformin). The decrease was greater with metformin alone than with nateglinide alone (0.3% difference in the HbA_{1c} concentrations; $p<0.01$).

Another 24-week double-blind randomised controlled trial evaluated the effect of adding either nateglinide (60mg or 120mg three times daily) or placebo to metformin (1g twice daily) in 467 patients with type 2 diabetes (HbA_{1c} concentrations of 6.8–11%) stabilised on 1.5g or more of metformin daily for at least 4 weeks.⁸ There was a greater reduction from baseline in HbA_{1c} concentration (the primary outcome measure) in the metformin plus nateglinide groups (-0.51% and -0.82% with 60mg and 120mg nateglinide, respectively vs. -0.08% with metformin plus placebo). Patients in the nateglinide plus metformin-treated group were more likely to develop symptomatic hypoglycaemia than were patients on placebo plus metformin (3.1% vs. 0.7%). Also, there was a significant mean weight gain of 0.9kg with the higher dose of nateglinide plus metformin compared with metformin alone.

We know of no published studies comparing nateglinide plus metformin with a sulphonylurea plus metformin.

Unwanted effects and precautions

In a double-blind randomised controlled trial involving 289 patients with type 2 diabetes given nateglinide 30mg, 60mg, 120mg or 180mg three times daily or matched placebo, more patients in the pooled nateglinide group experienced unwanted effects (about 49% vs. 35% with placebo) and these mainly reflected the symptoms of hypoglycaemia, such as sweating, tremor, dizziness and weakness.⁴ Rare unwanted effects with nateglinide have included hypersensitivity reactions such as rash, itching and urticaria, and mild, transient elevations in liver enzymes that have rarely led to discontinuation of therapy.⁶

As with other insulin secretagogues, nateglinide will temporarily need to be replaced with insulin therapy if glycaemic control is lost because of fever, trauma, infection or surgery. The company recommends that nateglinide be "used with caution" in patients with "moderate hepatic impairment" and avoided in those with "severe hepatic impairment".⁶ The drug is contraindicated during pregnancy and breast-feeding. It is not licensed for patients under 18 years of age. In-vitro data suggest the drug is predominantly metabolised by CYP2C9, but in-vivo studies have not shown clinically significant

interactions between nateglinide and drugs metabolised by CYP2C9 or CYP3A4.⁶

Repaglinide

Repaglinide (pronounced re-*pa*-gli-nide) is a derivative of carbamoylmethyl benzoic acid. Oral bioavailability of repaglinide is around 63% and plasma concentrations peak within 1 hour of administration.⁹ Following an oral dose of repaglinide, the insulinotropic response to a meal occurs within 30 minutes, and insulin concentrations return to fasting levels within 4–6 hours.⁹ The drug's elimination half-life is around 1 hour.⁹ Repaglinide is mainly metabolised in the liver, with its metabolites excreted primarily in bile.⁹ Less than 8% of the administered dose is excreted in urine, primarily as metabolites.⁹

Dosage

The company recommends a starting dose of 500µg repaglinide to be taken no more than 30 minutes before a main meal. A dose of 1mg may be needed in patients who were previously on another oral antidiabetic agent. The dose of repaglinide should be adjusted at intervals of 1–2 weeks according to response (e.g. assessed by self-monitoring of blood and/or urinary glucose). The recommended maximum single dose is 4mg, and the total daily dose 16mg. If a meal is to be missed, the dose should be omitted. Clinical trials suggest that patients can vary their meal (and dosing) times from the conventional three times a day to two or four times a day without loss of glycaemic control.^{10,11}

Clinical efficacy

A 4-month double-blind randomised controlled trial compared repaglinide alone (500µg three times daily, increased stepwise to 1mg, 2mg and 4mg), metformin alone (pre-study dose of 1–3g daily) and repaglinide plus metformin (dosage as with the monotherapies) in 83 patients with type 2 diabetes who had been on metformin alone for more than 6 months without achieving adequate control.¹² In the combined-therapy group, HbA_{1c} concentration fell from baseline by 1.4% ($p=0.0016$) and fasting plasma glucose by 2.2mmol/L ($p=0.0003$). No significant changes were seen in HbA_{1c} or fasting plasma glucose concentrations in patients switched to repaglinide or in those remaining on metformin alone. Patients taking repaglinide alone or the combined regimen gained weight (2.4kg and 3kg, respectively; $p<0.05$), while weight remained stable in patients taking metformin alone.

A 1-year double-blind randomised controlled trial involving 424 patients with type 2 diabetes compared repaglinide (1.5mg, 3mg, 6mg or 12mg daily in three divided doses) with glibenclamide (1.75mg, 3.5mg or 7mg before breakfast, or 7mg before breakfast plus 3.5mg before dinner).¹³ There were no significant differences between the two drugs in terms of efficacy (primary outcome measures were changes in HbA_{1c} and fasting plasma glucose concentrations) or frequency of unwanted effects, including hypoglycaemia.

Another 1-year double-blind randomised controlled trial, involving 576 patients with type 2 diabetes for at least 6 months who had been treated with dietary measures,

exercise or oral antidiabetic drugs, compared repaglinide (starting dose 500µg three times daily before meals, adjusted as necessary to 1mg, 2mg or 4mg doses) with glibenclamide (2.5mg daily before breakfast, increased as necessary to 5mg, 10mg or 15mg).¹⁴ Changes from baseline in HbA_{1c} and fasting plasma glucose concentrations were similar with the two drugs, as were insulin and lipid profiles, changes in body weight, incidence of hypoglycaemia and overall safety.

A 1-year double-blind randomised controlled trial compared repaglinide (500µg, 1mg, 2mg or 4mg with meals) with that of glipizide (5mg, 7.5mg, 10mg or 15mg daily) in 256 patients with type 2 diabetes who had been treated with diet or oral antidiabetic drugs.¹⁵ At 1 year, HbA_{1c} concentrations in the repaglinide group had not changed from baseline, while there had been a gradual increase in HbA_{1c} concentrations in the glipizide group (0.78%; $p<0.05$). Fasting blood glucose concentrations increased by 0.5mmol/L with repaglinide and by 1.3mmol/L with glipizide ($p<0.05$) over the study period. The number of patients experiencing minor hypoglycaemia was similar with both drugs. No patient experienced a major hypoglycaemic event.

Unwanted effects and precautions

Unwanted effects with repaglinide are rare (less than 1 in 1,000 patients) and include hypoglycaemia, abdominal pain, constipation, diarrhoea, nausea, vomiting, visual disturbances, hypersensitivity reactions such as itching and rashes, and mild, transient elevations in liver enzymes that have rarely led to discontinuation of therapy.⁹ In 1-year follow-up studies, the unwanted-effects profile of repaglinide was similar to that of glibenclamide, with hypoglycaemia being the most frequently reported problem.^{13,14}

As with other insulin secretagogues, repaglinide will temporarily need to be replaced with insulin therapy if glycaemic control is lost because of fever, trauma, infection or surgery. Repaglinide is contraindicated in patients with "severe hepatic function disorders", in children under 12 years old, and during pregnancy and breast-feeding.⁹ The company does not recommend using repaglinide in patients younger than 18 years or older than 75 years.

Repaglinide undergoes hepatic metabolism into inactive substances by CYP2C8 and CYP3A4,¹⁶ and so should be used with caution when co-administered with inducers or inhibitors of these enzymes. When repaglinide and gemfibrozil are taken concomitantly, the blood glucose-lowering effect of repaglinide may be markedly enhanced and prolonged.¹⁶ The company has received five spontaneous reports of serious hypoglycaemic episodes in patients taking repaglinide plus gemfibrozil and recommends that this combination is not used.

Approximate drug costs* for 1 year's treatment

Drug	Daily dose	Cost
▼nateglinide	180–540mg	£257–£293
▼repaglinide	1.5–16mg	£147–£397
glibenclamide	5–15mg	£16–£48
gliclazide	40–320mg	£17–£135
metformin	1–3g	£20–£60
tolbutamide	500mg–2g	£14–£57

* Based on information in *Drug Tariff and Chemist & Druggist*.

Conclusion

▼Nateglinide and ▼repaglinide are orally active, fast-acting insulin secretagogues, with a similar mode of action to sulphonylureas. Repaglinide is no more effective than metformin or glibenclamide in terms of lowering serum HbA_{1c} concentrations, and is more expensive. Also, data are needed on whether, like metformin and glibenclamide, repaglinide has preventative effects on the complications of diabetes. The drug may have a limited place in patients with irregular meal times where glycaemic control has proved difficult with conventional therapy. Nateglinide is only licensed for use in combination with metformin, a combination that needs to be compared with metformin plus a sulphonylurea in randomised controlled trials before its use can be recommended.

Both repaglinide and nateglinide appear to lower post-prandial glucose concentrations, but whether this effect is clinically beneficial in terms of cardiovascular outcomes is not known.

[M=meta-analysis; R=randomised controlled trial]

1. Hanefeld M et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 1996; 39: 1577–83.
2. Bastyr III EJ et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}. *Diabetes Care* 2000; 23: 1236–41.
3. Hollander PA et al. Importance of early insulin secretion. Comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care* 2001; 24: 983–8.
4. Hanefeld M et al. Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycaemia. *Diabetes Care* 2000; 23: 202–7.
5. Ferriman A. Novartis breached code after doctors say it "invented" a disease. *BMJ* 2002; 325: 1379.
6. *Starlix*. Summary of product characteristics, UK. Novartis Europharm Limited, July 2002.
7. Horton ES et al. Nateglinide alone and in combination with metformin improves glycaemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; 23: 1660–5.
8. Marre M et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab* 2002; 4: 177–86.
9. *NovoNorm*. Summary of product characteristics, Denmark. Novo Nordisk A/S, September 2002.
10. Moses RG et al. Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naïve type 2 diabetes. *Diabetes Care* 2001; 24: 11–5.
11. Landgraf R et al. Prandial glucose regulation with repaglinide: its clinical and lifestyle impact in a large cohort of patients with type 2 diabetes. *Int J Obes* 2000; 24: S38–44.
12. Moses R et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 1999; 22: 119–24.
13. Woffenbuttel BH, Langraf R on behalf of the Dutch and German repaglinide study group. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 1999; 22: 463–7.
14. Marbury T et al. Repaglinide versus glyburide: a one-year comparison trial. *Diabetes Res Clin Pract* 1999; 43: 155–66.
15. Madsbad S et al. Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1-year multicentre study. *Diabetes Med* 2001; 18: 395–401.
16. Niemi M et al. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia* 2003; 46: 347–51.

Meglitinides: Basic Aspects and Clinical Uses

M.J. Davies and Sudesna Chatterjee

in

International Textbook of Diabetes Mellitus, Third Edition

Editors-in-Chief

R A DeFronzo, E Ferrannini, H Keen and P Zimmet

1

© John Wiley & Sons, Ltd., Chichester, 2004

Meglitinides: Basic Aspects and Clinical Uses

M.J. Davies and Sudesna Chatterjee

Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester

INTRODUCTION

General Background

Type 2 diabetes mellitus (T2DM) is one of the commonest chronic diseases in the world and the number of new cases continues to rise inexorably. It is estimated that the worldwide prevalence of all types of diabetes will rise from 100 million in 1994 to 220 million in 2010 [1]. The majority of cases will be of T2DM, especially in developing countries. Adolescents and even children are becoming more susceptible to this chronic condition, which is related to lifestyle factors such as obesity and reduced activity levels. In the United States, there has been a fivefold increase in the number of new patients with T2DM and approximately \$100 billion of health care costs are currently spent annually on diabetes management [2]. The bulk of this cost is related to hospitalization and management of complications such as cardiovascular disease and nephropathy. There is a significant increase in mortality in patients with T2DM, particularly from cardiovascular causes. The need for agents that will provide effective control of glucose metabolism and lessen the development of macrovascular and microvascular complications is therefore a high priority.

Type 2 Diabetes and Glycemic Control

The United Kingdom Prospective Diabetes Study (UKPDS), a landmark study and the largest of its kind to date, looked at more than 5000 patients with T2DM who were followed for up to 20 years [3]. The aim of this study was to clarify whether more intensive management of glycemic control in T2DM lessened microvascular and macrovascular complications. In addition, various modes of therapy namely sulfonylureas, metformin, insulin, and

latterly acarbose were also compared. This study clearly demonstrated that improved glycemic control resulted in fewer complications. For example a 0.9% reduction in glycosylated haemoglobin (HbA_{1c}) resulted in the benefits shown in Table 1.

However, despite showing initial improvement in HbA_{1c} with intensive treatment, glycemic control deteriorated progressively with time (Figure 1).

The key metabolic defects characterizing T2DM are β -cell dysfunction and insulin resistance. β -Cell dysfunction is progressive and leads to a rise in HbA_{1c}, necessitating management with higher doses and combinations of oral hypoglycemic agents (OHAs) and insulin. UKPDS showed that 3 years into the study about 50% of patients required combination therapy, and by 9 years this figure rose to 75%. The need for agents capable of sustaining improved glycemic control and maintaining or improving β -cell function has become clear from the findings of UKPDS.

Current Therapies

Since the 1950s, the biguanides and sulfonylureas have formed the mainstay of treatment of T2DM. Metformin, the only biguanide in routine clinical practice, targets insulin resistance probably by suppressing hepatic glucose output and possibly by reducing peripheral glucose uptake and utilization. It may have other mechanisms of actions that are not completely understood. UKPDS showed that metformin was effective in lowering HbA_{1c}, and in particular was the only agent to confer cardiovascular benefits. However, like sulfonylureas and insulin, metformin did not maintain good glycemic control. Metformin is also associated with significant gastrointestinal side effects (resulting in around 10% of patients being unable to

Table 1 Effect of 1% reduction in HbA_{1c} on complications of type 2 diabetes*

An intensive vs. conventional glucose control policy, which achieved a median HbA _{1c} of 7.0% vs 7.9% (Δ = 0.9%) over 10 years, reduced risk by:		
12%	Any diabetes-related endpoint	$p = 0.029$
16%	Myocardial infarction	$p = 0.52$
25%	Microvascular disease	$p = 0.0099$
21%	Retinopathy at 12 years	$p = 0.015$
33%	Albuminuria at 12 years	$p = 0.000054$

* From reference 3.

tolerate therapy), however it may only rarely cause lactic acidosis.

The sulfonylureas such as gliclazide and glibenclamide (glyburide) are insulin secretagogues that bind to the sulfonylurea receptor of the pancreatic β -cell, promoting closure of ATP-dependent potassium channels. They are effective at improving glycemic control but are associated with weight gain and increased risk of hypoglycemia. The incidence of severe episodes of hypoglycemia with sulfonylurea therapy is approximately 0.2/1000 patient-years. About 20–25% of patients with T2DM are initially unresponsive to the sulfonylureas, and secondary failure of these agents occurs in 5–10% of individuals on an annual basis.

α -Glucosidase inhibitors such as acarbose are used either as monotherapy or in combination with metformin and sulfonylureas to reduce carbohydrate absorption from the small intestine. UKPDS showed that acarbose was less efficacious in lowering HbA_{1c} compared to other agents. The study to prevent non-insulin-dependent diabetes mellitus (STOP-NIDDM) trial showed that acarbose can delay progression to T2DM in impaired glucose tolerance (IGT) by 32% [4]. Although acarbose is not associated with any serious adverse effects, unfortunately many subjects have to discontinue the drug because of unpleasant gastroin-

testinal side effects. In the STOP-NIDDM trial, 31% of subjects had to discontinue the drug because of its side effects.

A summary of the characteristics of these oral hypoglycemic agents is given in Table 2.

New Therapeutic Options

Thiazolidinediones

More recent oral hypoglycemic agents include the thiazolidinediones or peroxisome proliferator-activated receptor γ (PPAR- γ) agonists, which enhance the effects of endogenous insulin on target organs, mainly skeletal muscle, liver, and adipose tissue. The first of these to be launched was troglitazone but had to be withdrawn because of hepatotoxicity. Rosiglitazone and pioglitazone are currently available and appear to have no such effects on the liver. They target insulin resistance, which is a major component of the metabolic syndrome. They potentially have other benefits (reduce cardiovascular risk) and these areas continue to be explored (see under Thiazolidinediones).

Meglitinides

A new class of drugs known as the meglitinides have recently been launched on the international market. These agents have been developed to improve early-phase insulin secretion, which is one of the earliest pathophysiological manifestations of T2DM. They are derived from the meglitinide portion of sulfonylureas. Currently available drugs of this group are repaglinide and nateglinide. Another meglitinide known as mitiglinide is still in clinical trials. Repaglinide is derived from the non-sulfonylurea moiety of glibenclamide whereas nateglinide is derived from an amino acid. The meglitinides are rapid-acting insulin secretagogues (also known as prandial glucose regulators) that have a fast onset and short duration of action resulting in more physiological secretion of insulin from the β -cell. The mechanism of action of the meglitinides is glucose-dependent and this has important implications for lessening the risk of hypoglycemia.

This chapter will begin by discussing the pathophysiology of T2DM and the importance of postprandial hyperglycemia (PPH). The mechanism of action and pharmacokinetics of repaglinide and nateglinide will then be described, followed by a review of their clinical use both as monotherapy and in combination with other agents.

PATHOPHYSIOLOGY OF T2DM

General Introduction

T2DM is a complex heterogeneous condition characterized by abnormalities of both insulin action (resistance) and secretion. The relative contribution of these

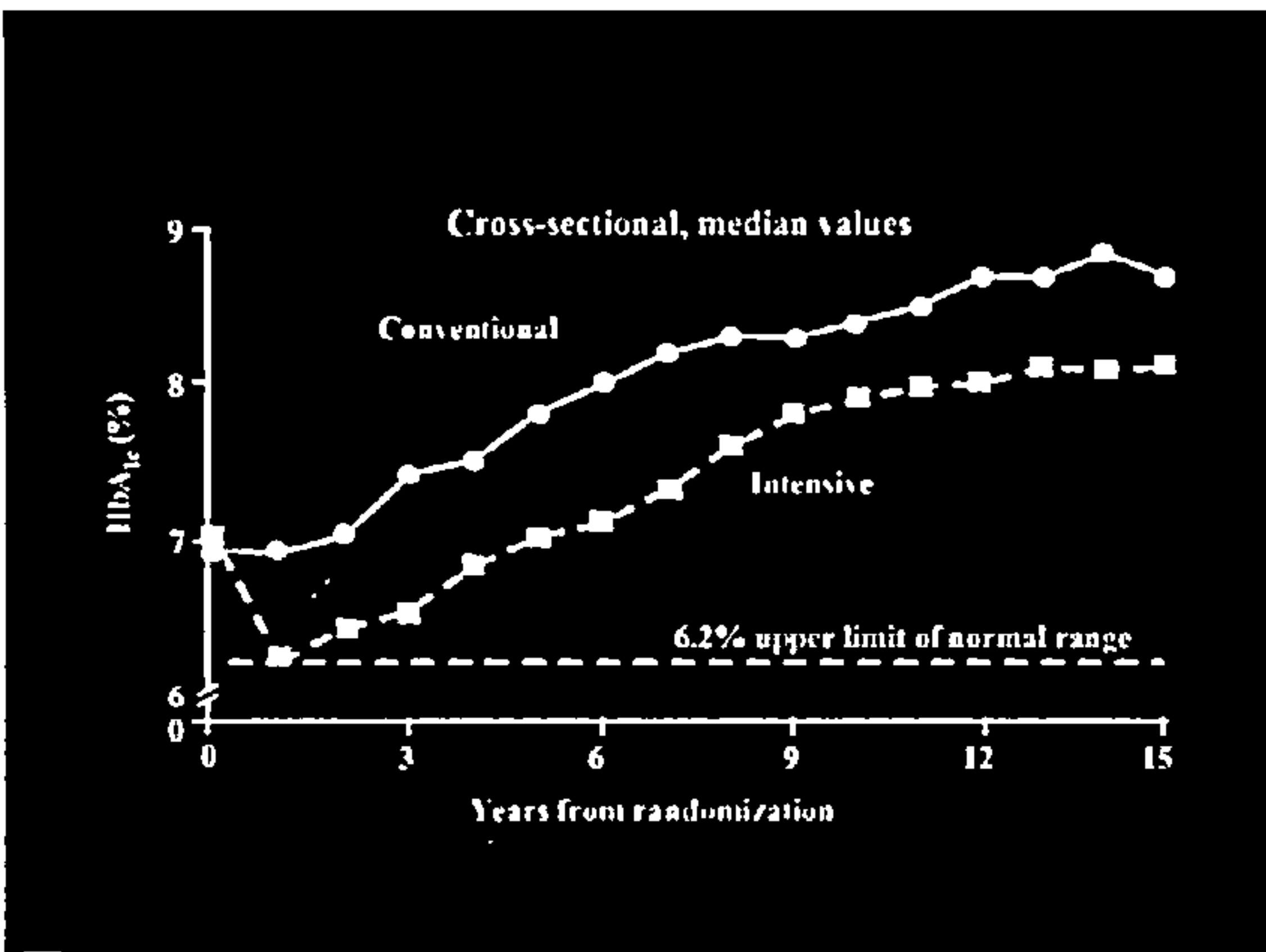


Figure 1 Progressive decline in glycemic control regardless of treatment intensity (from reference 3)

Table 2 Characteristics of current oral hypoglycemic agents

	Sulfonylureas	Biguanides	α -glucosidase inhibitors
Fasting plasma glucose	\downarrow 3–4 mmol/l	\downarrow 3–4 mmol/l	\downarrow 1–1.7 mmol/l
HbA _{1c}	\downarrow 1–2%	\downarrow 1–2%	\downarrow 0.2–1.0%
Triglycerides	—	(\downarrow)	—
LDL cholesterol	—	(\downarrow)	—
HDL cholesterol	—	(\uparrow)	—
Body weight	(\uparrow)	—	—
Plasma insulin	(\uparrow)	(\downarrow)	—
Side effects	Hypoglycemia	Gastrointestinal Lactic acidosis	Gastrointestinal

abnormalities may vary between populations, as exemplified by the Pima Indians of Arizona and Pacific Islanders of Nauru who are severely insulin resistant, compared to other populations such as White Caucasians. A number of factors appear to predispose to insulin resistance. A genetic contribution is likely although as yet specific genes remain unidentified. Obesity and insulin resistance are significantly related and central adiposity is of particular importance. A low-calorie, low-fat diet enhances insulin sensitivity possibly by promoting weight loss. Exercise has also been shown to increase insulin sensitivity.

β -Cell Dysfunction

The importance of β -cell dysfunction is increasingly recognized although earlier work has concentrated mainly on insulin resistance as the primary abnormality in T2DM. It is not clear which pathological condition develops first. It has been suggested that insulin resistance leads to relative

insulin deficiency, whereas β -cell exhaustion means that insufficient insulin is produced to overcome the degree of insulin resistance. The combination of insulin resistance and insufficient insulin secretion lowers glucose uptake in insulin-sensitive tissues and reduces the suppression of hepatic glucose output.

The normal secretion of insulin is divided into two phases. Following an acute secretagogue challenge, there is an initial early-phase insulin response that peaks at 3–5 min and is complete by 10 min. This is followed by a late-phase insulin response that typically lasts for 2–3 h with a slow sustained rise in circulating insulin levels (Figure 2).

This dual-phase insulin response ensures normal glucose tolerance and primes tissues, especially the liver, to glucose levels. Early-phase insulin secretion also leads to a reduction in hepatic glucose output. Reduced suppression of hepatic glucose output exaggerates postchallenge hyperglycemia, promoting late hyperinsulinemia.

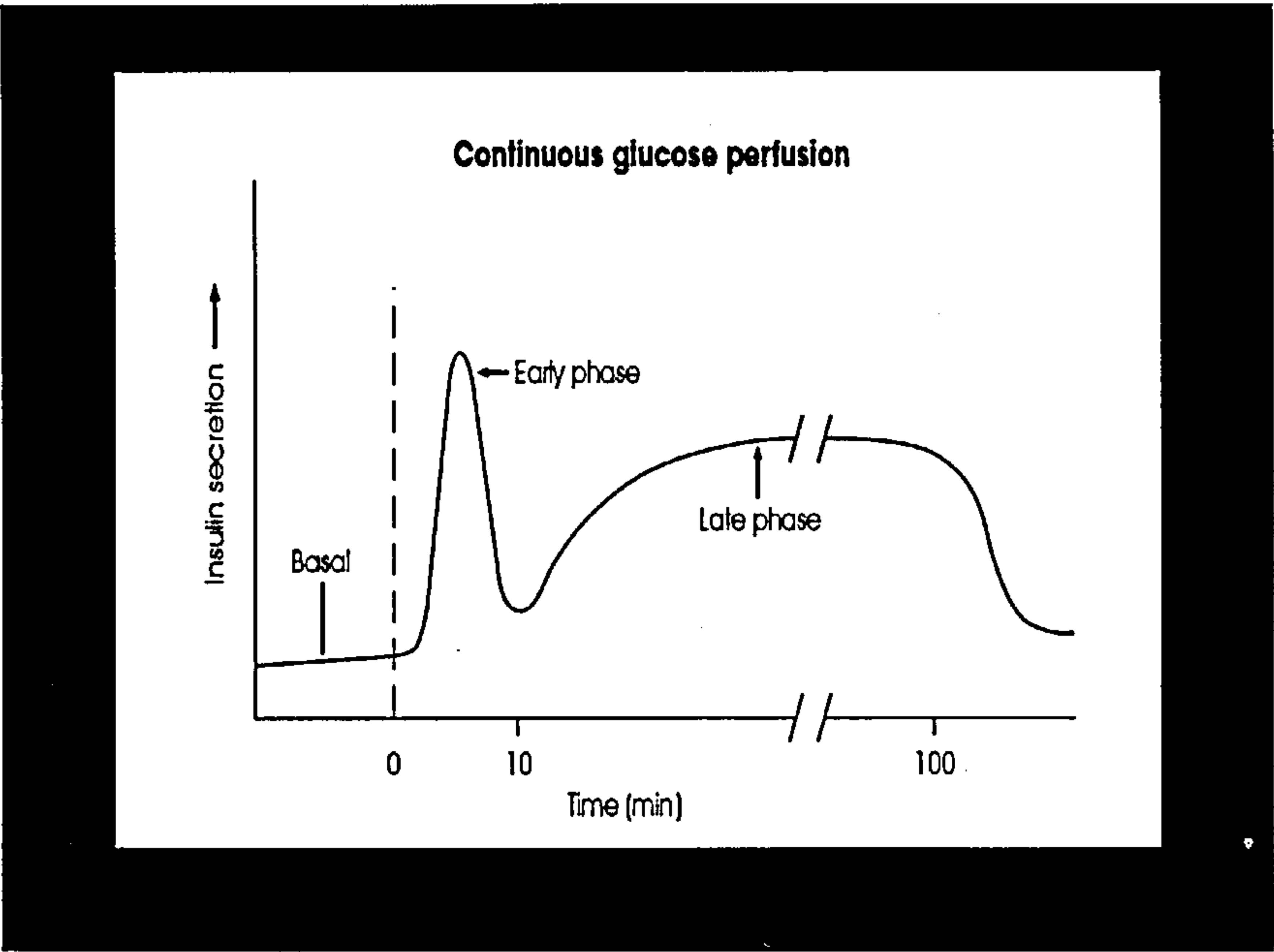


Figure 2 Physiological secretion of insulin. (Reproduced by permission of Elsevier)

Insulin secretion in the basal fasting state is pulsatile, occurring every 10–14 min with a slower superimposed cycle of secretion every 105–120 min. Biological activity is greater when insulin is secreted in a pulsatile fashion as opposed to continuous infusion. One of the earliest changes in the pathogenesis of T2DM is loss of the normal oscillatory pattern of insulin secretion.

Early-Phase Insulin Secretion

Loss or reduction of early-phase insulin secretion occurs early in subjects with T2DM and even in those with IGT (Figure 3).

Reduced early-phase insulin secretion has been discovered to be the most reliable predictor of subsequent development of T2DM even in the Pima Indians (Figure 4).

Insulin secretion is controlled by the membrane potential of the β -cell. This is dependent on the activity of ATP-sensitive K^+ (K_{ATP}) channels in the plasma membrane. When there is an increase in the cytoplasmic ATP/ADP ratio, membrane depolarization occurs with opening of the voltage-gated Ca^{2+} channels, and the cytoplasmic Ca^{2+} rises. This leads to stimulation of Ca^{2+} -dependent exocytosis of the insulin-containing granules. These K_{ATP} channels are the site of action for both sulfonylureas and meglitinides.

Deterioration of β -Cell Function

UKPDS identified that β -cell function worsened from approximately 53% at diagnosis of diabetes to around 28%

after 6 years of follow-up. Deterioration in blood glucose control was correlated with increasing loss of β -cell function. Extrapolation of these data suggests that β -cell dysfunction may have commenced about 12 years before T2DM was clinically diagnosed (Figure 5a).

In the past it has been suggested that sulfonylureas might increase β -cell demise. UKPDS showed that the rate of loss of β -cell function was similar regardless of body mass index or the type of therapy used to improve glycemic control (Figure 5b).

However, the sulfonylureas undergo prolonged binding with the β -cell receptor, leading to hyperinsulinemia and the potential for subsequent β -cell failure.

Significance of Postprandial Hyperglycemia

In today’s westernized societies, little time while awake is spent in the fasting state. Patients with established T2DM have fasting and postprandial hyperglycemia both of which increase HbA_{1c} levels. At the present time, HbA_{1c} is considered the gold standard for monitoring and assessing long-term glycemic control. Some studies have shown that postprandial plasma glucose is a better predictor of glycemic control than is fasting plasma glucose. In one study, 66 patients with T2DM were asked to provide a glycemic profile consisting of plasma glucose measurements at prebreakfast, pre-lunch, postlunch (2 h), and extended postlunch (4 h) intervals between 8 a.m. and 5 p.m. [8]. Sixty-six percent of these patients were on combination therapy with

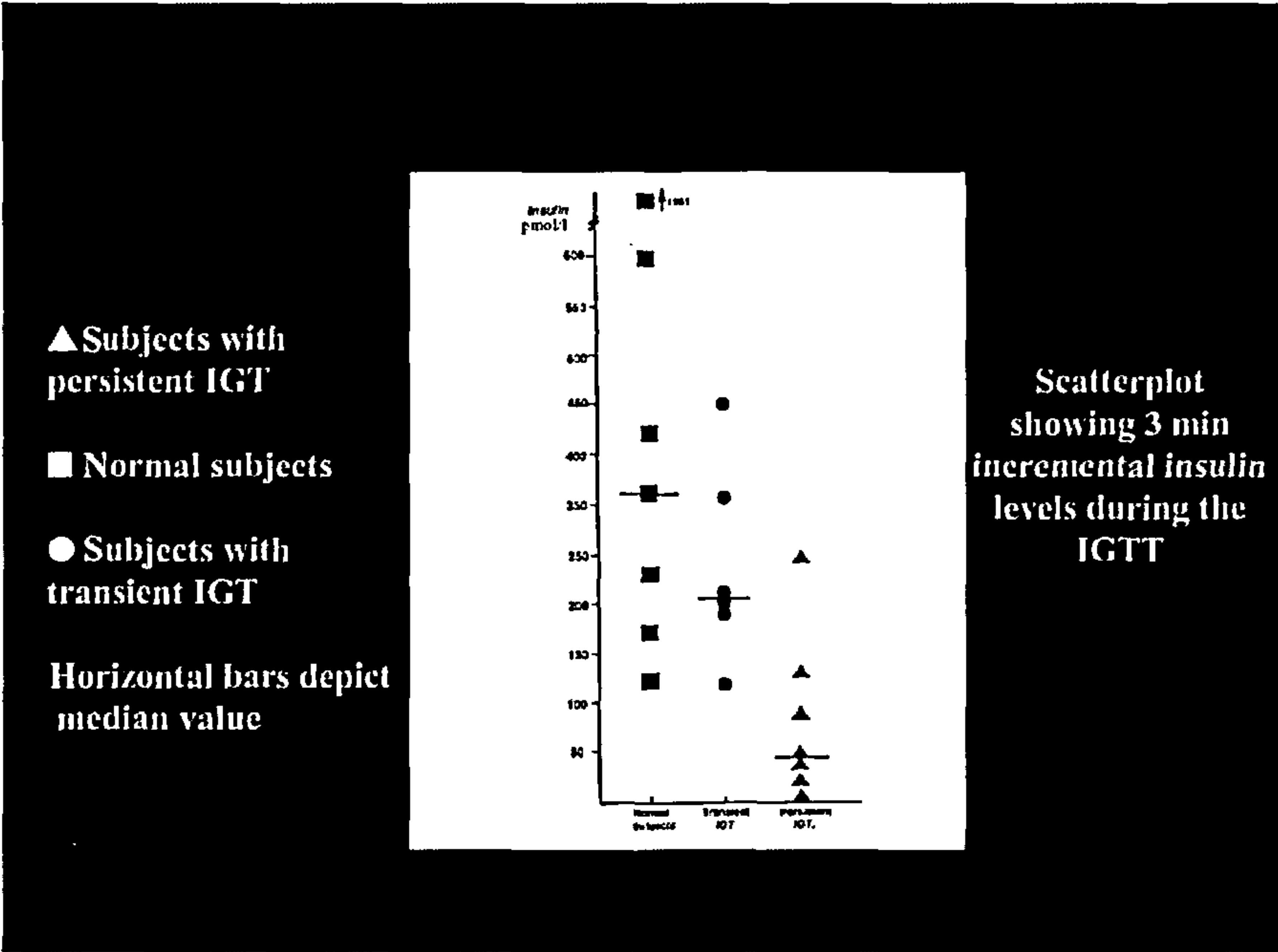


Figure 3 Loss of early-phase insulin secretion early in disease process (reproduced with permission from reference 5)

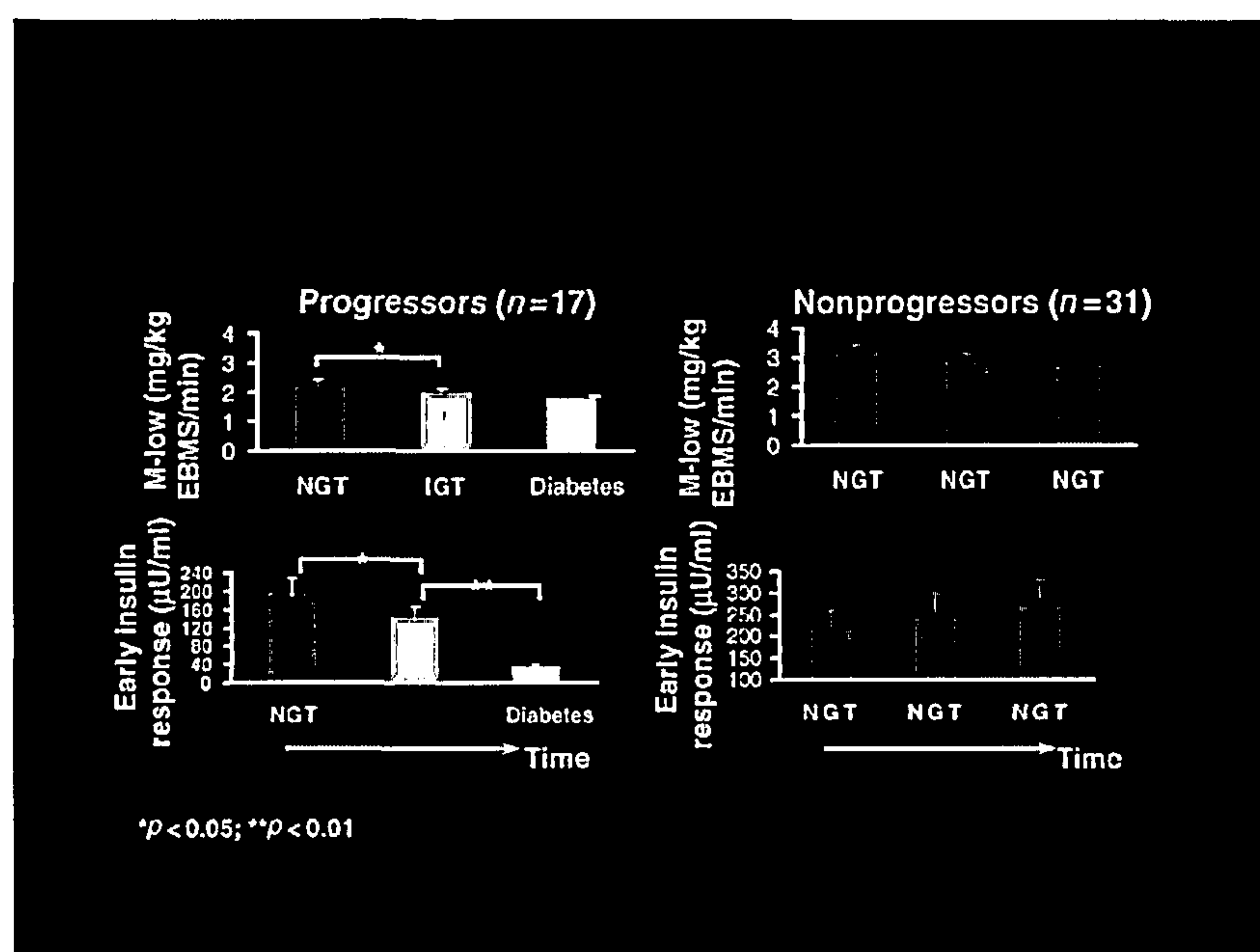


Figure 4 Natural history of type 2 diabetes in Pima Indians (NGT = normal glucose tolerance) (reproduced with permission from reference 6)

sulfonylureas and metformin. None were on insulin therapy. The results showed that extended postlunch plasma glucose was lower than prebreakfast plasma glucose in patients demonstrating good glycemic control ($HbA_{1c} \leq 7.0\%$). In addition, postlunch and extended postlunch plasma glucose demonstrated better sensitivity, specificity, and positive predictive value in predicting poor glycemic control than did prebreakfast or prelunch plasma glucose.

The extent of PPH was identified by a study in 218 patients with T2DM, aged between 40 and 74 years, and who were not on insulin [9]. This data was obtained from the Third National Health and Nutrition Examination Survey (NHANES III) conducted between 1988 and 1994 in the United States. In this cross-sectional analysis, PPH was determined by 2-h plasma glucose of > 11 mmol/l after an oral glucose challenge. In patients on sulfonylurea therapy with $HbA_{1c} > 7\%$, PPH was present in 99% of cases. Even in those with $HbA_{1c} < 7\%$, PPH occurred in 39%. In the subgroup of patients taking sulfonylureas and with $HbA_{1c} < 7\%$, PPH was prevalent in 63%.

Association of Postprandial Hyperglycemia to Adverse Outcomes

In recent years, the American Diabetes Association (ADA) has moved away from the use of a postchallenge glucose or oral glucose tolerance test in favor of the exclusive use of fasting glucose in diagnosing diabetes. This has raised some concern with respect to the importance of postchal-

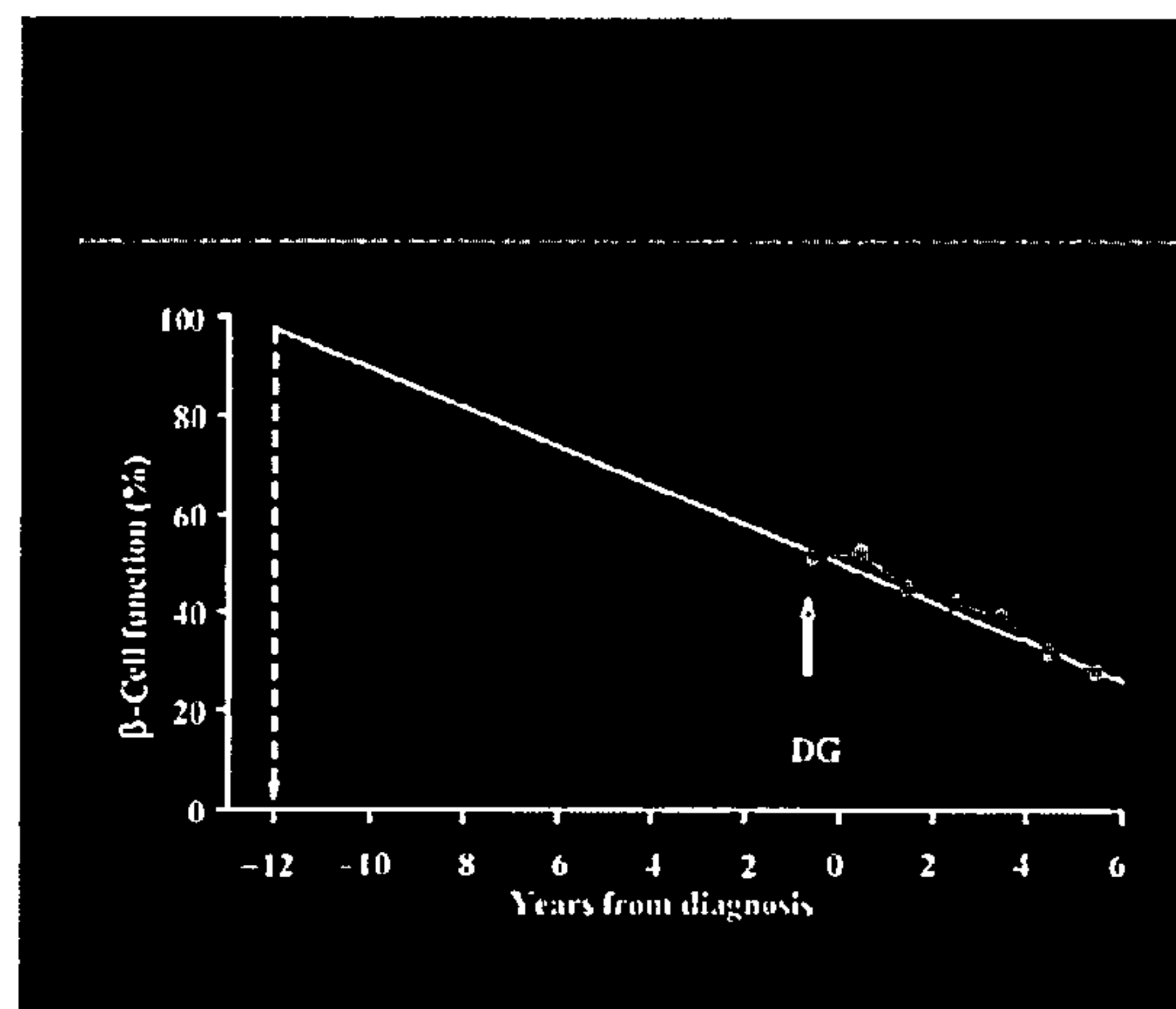
lenge or postprandial hyperglycemia and its relationship to both diagnosis of T2DM and cardiovascular outcomes across the spectrum of glucose intolerance.

In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) the relationship between fasting and postchallenge glucose to mortality and morbidity was analyzed in more than 25 000 subjects [9]. This large study identified that postchallenge glucose was more sensitive than fasting glucose at predicting risk of all-cause mortality.

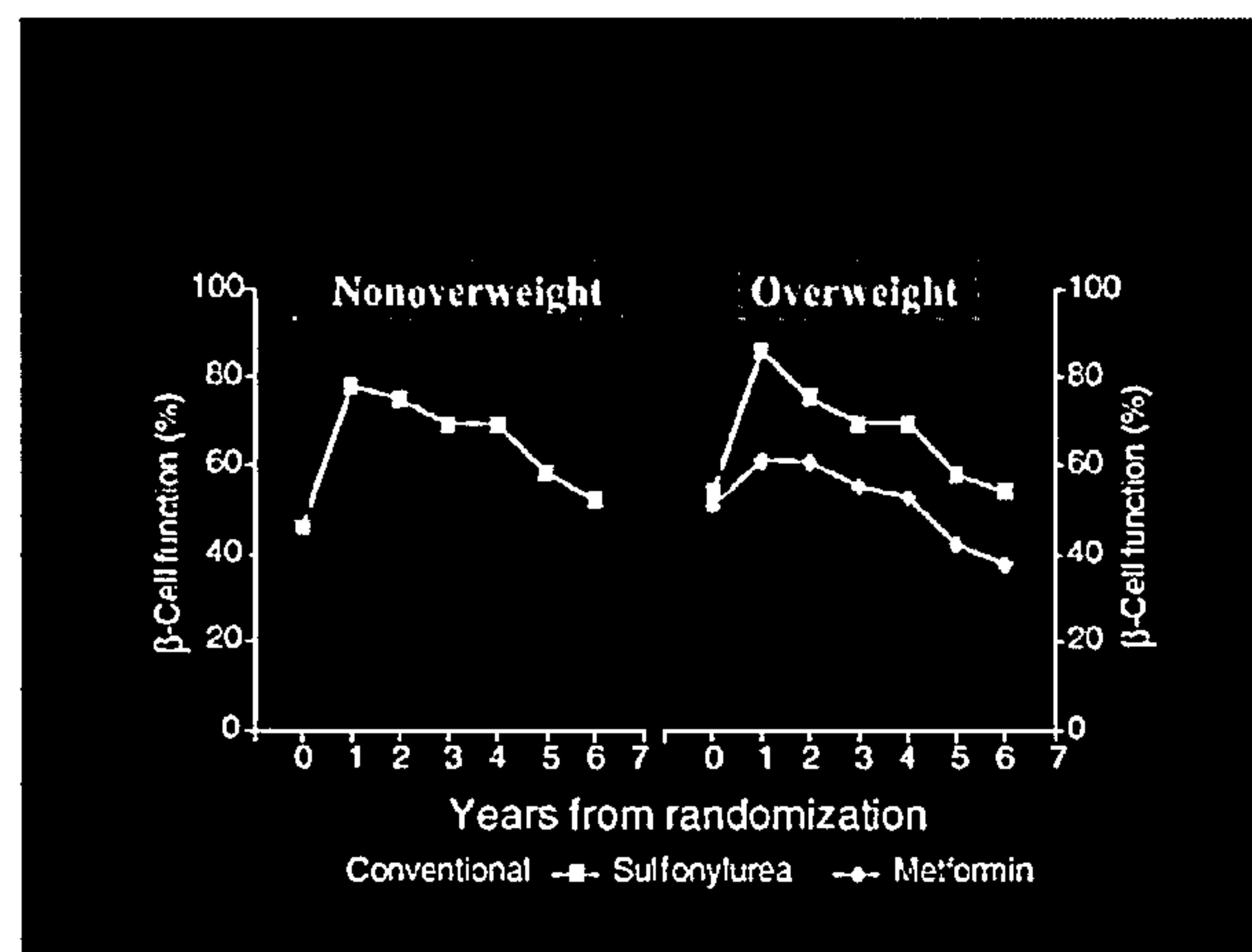
Several other large epidemiological studies have provided data suggesting a link between postchallenge hyperglycemia and adverse cardiovascular outcomes that are consistent with the findings of DECODE (Table 3).

Potential Pathological Associations with Postprandial Hyperglycemia

In theory, there are a number of reasons for the association of adverse cardiovascular outcomes with PPH. PPH is linked to several deleterious pathological effects. PPH is associated with the production of increased free radicals with subsequent oxidative stress [15]. Other effects include increased insulin resistance and glucose auto-oxidation with decreased early-phase insulin secretion. In addition, there is increased blood coagulation and high density lipoprotein-cholesterol (HDL-C) catabolism. Free fatty acids and triglyceride-rich lipoproteins and low density lipoprotein (LDL) removal are reduced. Effects on the arterial wall include decreased fibrinolysis, disturbed



(a)



(b)

Figure 5 (a) Extrapolation of the time of deterioration of β -cell dysfunction (DG = diagnosis) (reproduced with permission from reference 6). (b) Progressive loss of β -cell function with different agents (from reference 7)

endothelial function with reduction in nitric oxide release, and reduced plaque stability (Figure 6).

The importance of circulating inflammatory markers such as cytokines and their role in the pathogenesis of vascular disease in T2DM is gradually emerging. A prospective study has found that the risk of development of T2DM in apparently healthy middle-aged women correlated with two circulating markers of systemic inflammation, namely C-reactive protein and the cytokine interleukin 6 (IL-6) [16]. Tumour necrosis factor α (TNF- α) has also been linked with the insulin resistance syndrome and clinically overt T2DM. Another recently published study has shown that subjects with IGT had higher fasting plasma IL-6 and TNF- α levels than did control subjects. Interleukin-18 (IL-18), which has been implicated in plaque destabilization, was also measured and its levels rose along with IL-6 and TNF- α in the control subjects but not in the subjects

with IGT. Cytokine levels were affected more by oscillatory than continuous hyperglycemia, which correlates with postprandial glucose excursions. The different pattern of cytokine secretion with PPH may be of clinical relevance, since vascular risk increases with increased cytokine circulation, such as IL-6 and TNF- α [17].

Despite the wealth of epidemiological studies to date, none have investigated the direct relationship of PPH to cardiovascular outcomes. As a result, the link between PPH and adverse cardiovascular events remains an interesting hypothesis.

Postprandial Monitoring in Clinical Practice: Is it Justified?

Only one study to date has shown that monitoring and targeting postprandial blood glucose levels improves

Table 3 Association between postprandial glucose values and the risk of cardiovascular heart disease (CHD) across the spectrum of glucose tolerance

Study	Characteristics	Cardiovascular outcomes
DECODE Study Group [10]	18 408 men 7316 women 13 European centers 28-year follow-up	All-cause mortality is more related to 2-h postmeal glucose than fasting plasma glucose
Whitehall, Paris Prospective, and Helsinki Policeman Studies [11]	17 285 men 44–55 years 20-year follow-up	Men in upper 2.5% of 2-h postmeal glucose distribution had significantly higher CHD mortality
Hoorn Study [12]	2363 subjects 50–75 years 8-year follow-up	High plasma glucose levels especially 2-h postload glucose concentrations and to a lesser extent HbA _{1c} values indicate a risk of CHD mortality
Diabetes Intervention Study [13]	1139 subjects with type 2 diabetes 30–55 years 11-year follow-up	1-h postbreakfast blood glucose but not fasting blood glucose was associated with higher rates of myocardial infarction and death
Honolulu Heart Program [14]	6005 men 45–70 years 12-year follow-up	CHD incidence and mortality increase stepwise with increasing 1-h postchallenge glucose

outcomes. In a randomized study of 66 women with gestational diabetes, two glucose monitoring protocols were used to achieve glycemic control. In one group, the women were asked to perform preprandial monitoring before meals and at bedtime. The other group was assigned to capillary blood glucose monitoring before breakfast (fasting) and 1 h after each meal. This study showed that in the postprandial monitoring group, the mean change in HbA_{1c} was greater and there was less macrosomia. Also in this group, rate of neonatal hypoglycemia was reduced and infants were less often delivered by caesarean section due to cephalopelvic disproportion. There

was also a fivefold reduction in HbA_{1c} (3% vs. 0.6%) [18].

The ADA has published a consensus statement with regard to which individuals should monitor postprandial glucose levels [19]. The recommendation includes all women with gestational diabetes. In addition, postprandial glucose monitoring should be carried out by patients who

- achieve preprandial targets but whose HbA_{1c} remains suboptimal
- are on treatments that specifically target PPH
- experience PPH.

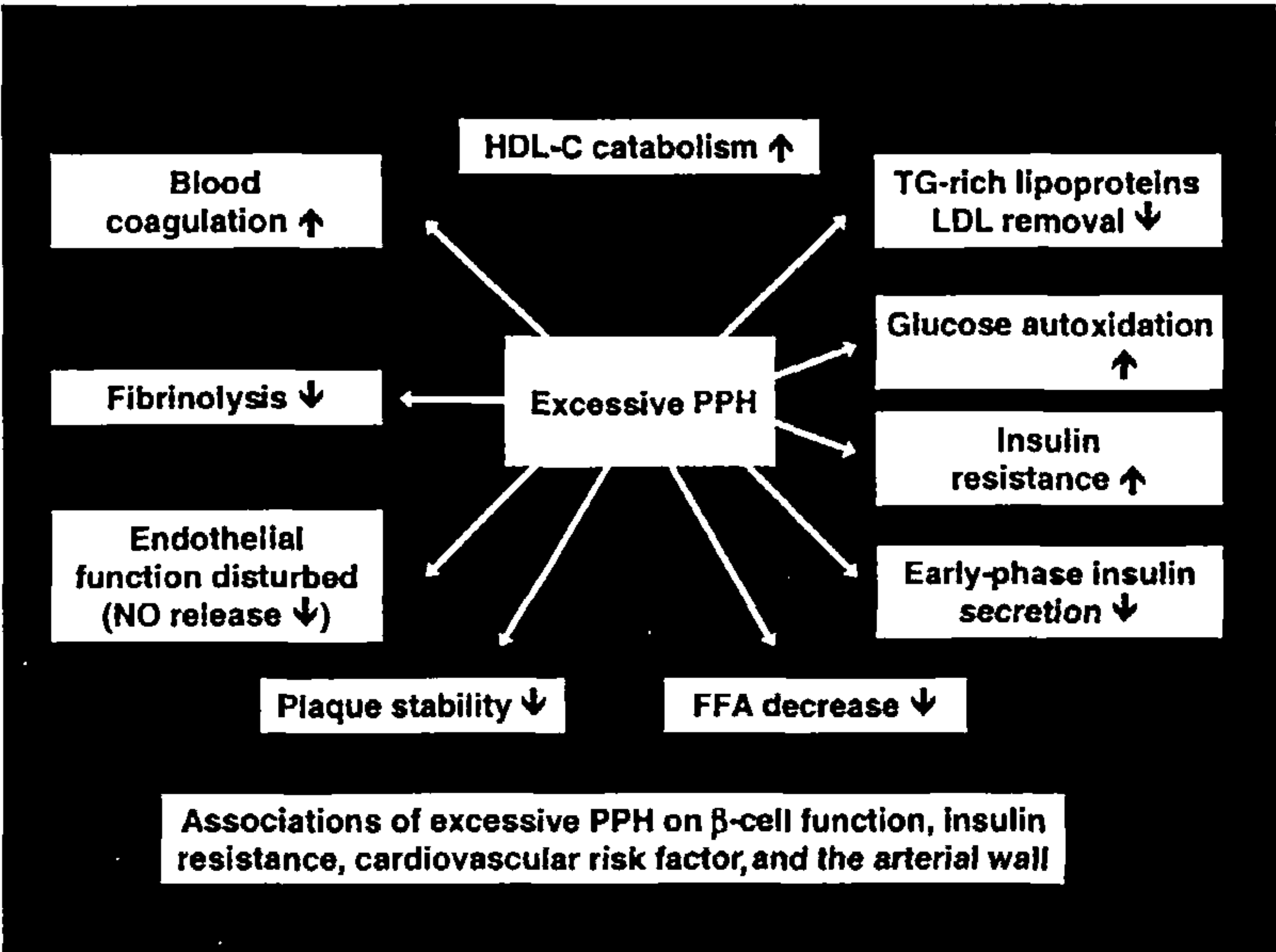


Figure 6 Pathological associations with postprandial hyperglycemia. (Reproduced by permission of the American Diabetes Association)

Table 4 Predominant targets of currently available hypoglycemic therapies

Target fasting plasma glucose	Target postprandial hyperglycemia
Sulfonylureas	Acarbose
Metformin	Meglitinides
Isophane and insulin glargine	Short-acting insulin analogues
Thiazolidinediones	

Current drug therapies in the management of T2DM can be divided into those that predominantly target fasting plasma glucose or PPH (Table 4).

Meglitinide—Basic Aspects

Chemical Structure of the Meglitinides

More than 20 years ago, the insulinotropic and antidiabetic properties of the non-sulfonylurea moiety of glibenclamide were identified. This chemical structure was subsequently referred to as meglitinide.

Repaglinide is an acylaminobenzoic acid derived from the non-sulfonylurea moiety of glibenclamide. It has a molecular formula of $C_{27}H_{36}N_2O_4$ and a molecular mass of 452.6 Da. Nateglinide is distinct from the sulfonylureas and is chemically derived from an amino acid. It consists of an acylamino moiety and D-phenylalanine. The structures of these compounds are shown in Figure 7.

Mechanism of Action of Repaglinide

Repaglinide (Novonorm, Prandin, Novo Nordisk) was the first meglitinide to be commercially available. It was launched in 1998.

Repaglinide is structurally different from the sulfonylurea group although it binds to a specific site of the sulfonylurea receptor on the pancreatic β -cell. This site is distinct from the sulfonylurea binding site. Binding with this site closes the K_{ATP}^+ channel and this initiates insulin secretion (Figure 8).

It has been proposed that insulin-secreting cells have two or three distinct binding sites for glibenclamide and repaglinide with differing affinities for each drug [21]. It would appear that there are some common and some distinct cellular mechanisms of action between repaglinide and glibenclamide.

Repaglinide increases cytoplasmic Ca^{2+} concentration in β -TC3 insulinoma cells. Unlike glibenclamide, repaglinide does not enhance exocytosis in voltage-clamped β -cells or stimulate insulin secretion from β -TC3 insulinoma cells in the absence of glucose. Additionally, repaglinide has no direct biosynthetic activity and is not taken up by the β -cell despite its lipophilic nature. Repaglinide is five times more potent at stimulating insulin secretion than is glibenclamide. Repaglinide does not stimulate insulin secretion in the complete absence of glucose and its action is usually confined to intermediate concentrations of glucose. These characteristics may account for the reduced risk of hypoglycemia seen with repaglinide in contrast to the sulfonylureas.

A recently published randomized controlled open-label study of 46 patients with T2DM evaluated the effect of repaglinide on insulin secretion and oxidative stress as measured by reduced serum antioxidants and superoxide dismutase [22]. This study showed that first-phase insulin secretion was significantly increased in the repaglinide group, which is already well-established. More interestingly, a significant increase in total serum antioxidant

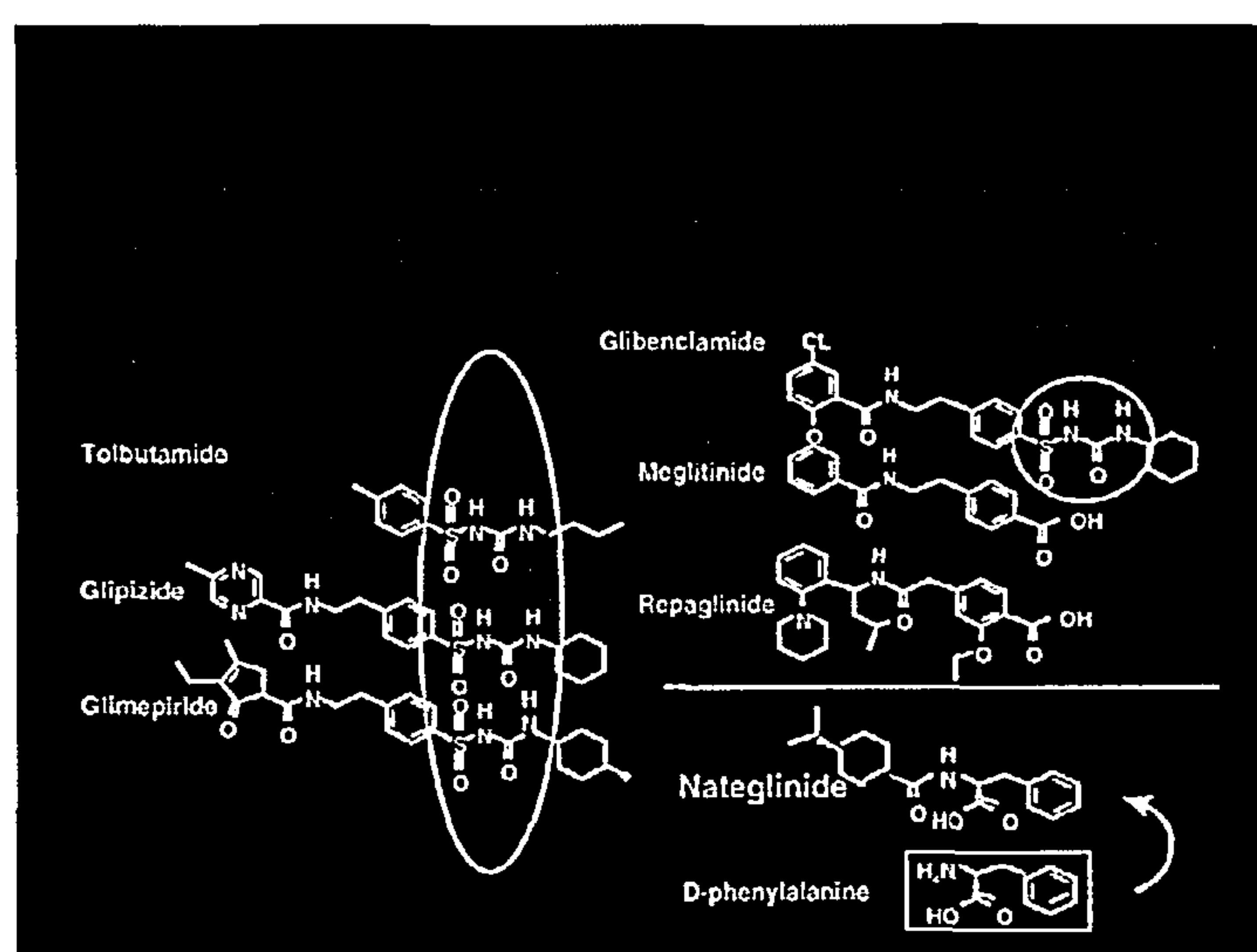


Figure 7 Chemical structures of the meglitinides

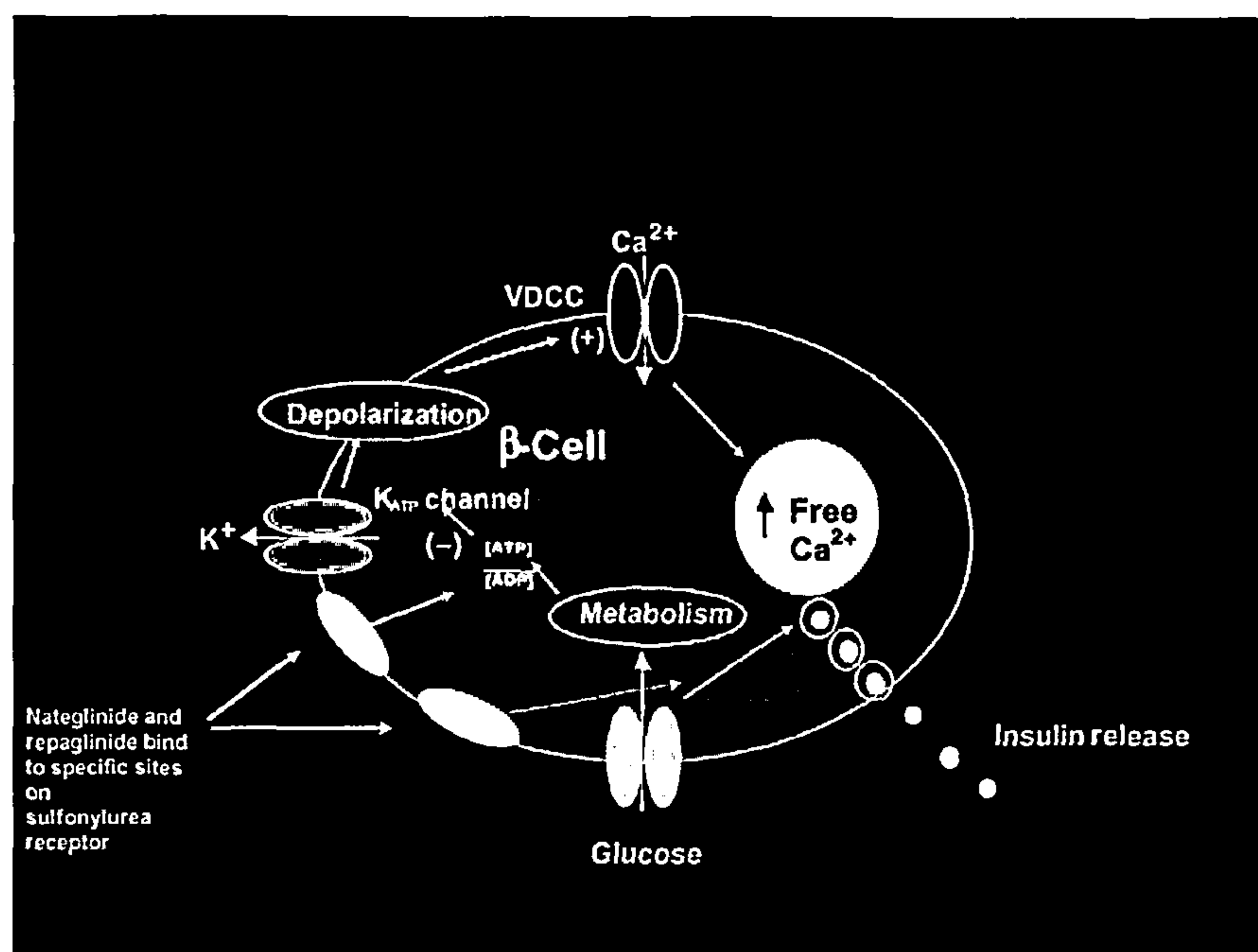


Figure 8 Mechanism of action of meglitinides at level of pancreatic β -cell (from reference 20)

capacity ($p < 0.05$) and serum superoxide dismutase ($p < 0.0004$) was discovered in the repaglinide group.

The S-enantiomer of repaglinide is the pharmacologically active part of the racemic molecule. In the rat model, this enantiomer has more than 100 times greater hypoglycemic potency than the R-enantiomer. Clinically available repaglinide is about 98% pure for the S-enantiomer.

Mechanism of Action of Nateglinide

Nateglinide (StarlixTM, Novartis) is derived from D-phenylalanine and has no sulfonylurea moiety. It is biochemically and pharmacologically distinct from other hypoglycemic agents. Its mechanism of action is similar to that of repaglinide, involving inhibition of pancreatic β -cell K_{ATP} -sensitive channels (Figure 8). Studies have shown that nateglinide has significantly faster association/dissociation kinetics in the pancreatic β -cell, which results in a more rapid and transient increase in early-phase insulin secretion in normal healthy volunteers compared to that with [23] repaglinide (Figure 9).

Kinetic information from experiments on rat pancreatic cells has shown that time to 50% maximal inhibition was 4.1 min for nateglinide and 12 min for repaglinide. Time to 50% relief of inhibition was 35 min for nateglinide compared to 175 min for repaglinide. Overall insulin exposure is much less with nateglinide, and plasma insulin concentrations return to baseline 2 h after oral administration of the drug.

Isolated rat islet experiments have shown that there is 16-fold enhancement of nateglinide-induced inhibition of K_{ATP}^+ current when the glucose concentration is raised from 3 to 16 mmol/l. Repaglinide potency is increased fourfold whereas glibenclamide potency is reduced under the same conditions. These observations may explain the low incidence of mild and severe hypoglycemia reported in clinical trials with nateglinide.

Pharmacokinetics of the Meglitinides

Pharmacokinetics of Repaglinide Repaglinide is rapidly absorbed after oral administration and appears in the bloodstream within 15 min. Maximum plasma levels (C_{max}) are reached within 30–60 min of oral administration of a 2 mg tablet of repaglinide. This occurs in healthy volunteers and in those with T2DM. Notably repaglinide does not accumulate with repeated dosing and has a rapid elimination half-life of approximately 1 h. These factors potentially lessen the risk of hypoglycemia. C_{max} and area under the curve (AUC) increase in a dose-dependent manner in healthy subjects and in those with T2DM. The absolute bioavailability of a 2 mg tablet of repaglinide is 62.5%, which is slightly affected by meal composition. In particular, a high fat meal decreases AUC and C_{max} from fasting levels by 20 and 12.4% respectively. Repaglinide is highly bound to plasma proteins in the circulation [25].

AUC and C_{max} are greater in elderly patients with T2DM. Mean half-life is slightly longer but elimination is

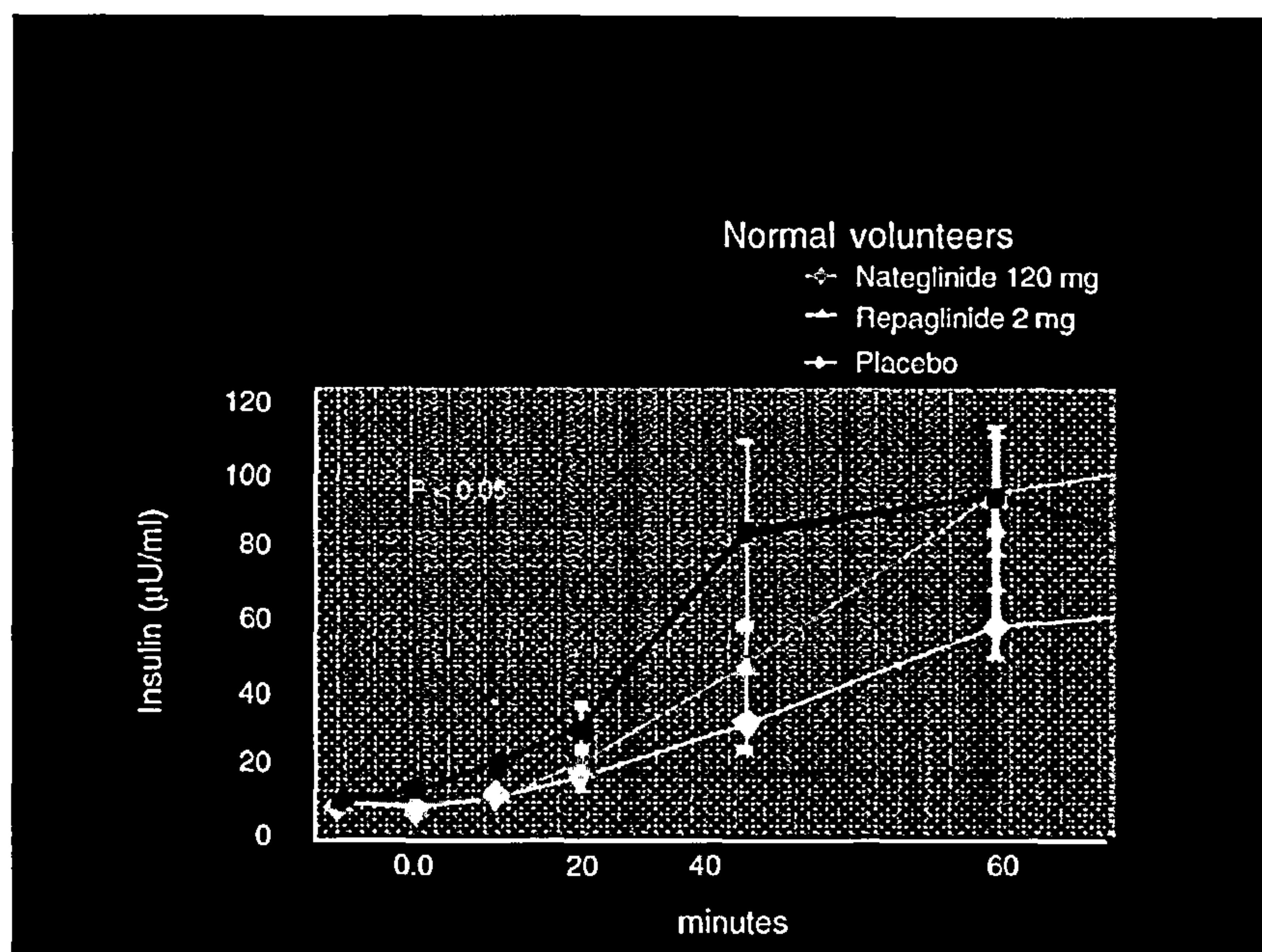


Figure 9 Comparison of repaglinide and nateglinide with placebo on early-phase insulin secretion (reproduced with permission from reference 24)

still rapid in elderly patients. Repaglinide is well-tolerated in the elderly, and dosage adjustment in this group is not necessary.

Approximately 98% of repaglinide is metabolized after oral administration with the remaining 2% excreted unchanged. Repaglinide undergoes hepatic metabolism by the CYP3A4 isoform of the P450 cytochrome enzyme and is mainly excreted via bile. AUC and C_{max} of repaglinide are increased in patients with moderate or severe hepatic impairment. In these patients half-life of the drug is prolonged compared to that in healthy volunteers (14.7 vs. 0.6–0.7 h).

Only 6% is excreted by the kidneys, and repaglinide is thus licensed for use in mild to moderate renal dysfunction. In severe renal impairment the plasma half-life of repaglinide is increased from 1.5 to 3.6 h and it is therefore not recommended in this situation.

Theoretically any compound inhibiting or inducing CYP3A4 isoenzyme might affect the metabolism of repaglinide. Ketoconazole and erythromycin both inhibit CYP3A4 but do not appear to cause clinically relevant changes in repaglinide plasma concentration.

Rifampicin, carbamazepine, and barbiturates induce CYP3A4 and may increase the metabolism of repaglinide. Higher doses of repaglinide would therefore be needed to maintain adequate plasma concentrations and an effective hypoglycemic effect.

Pharmacokinetics of Nateglinide Nateglinide has 75% systemic bioavailability and is mostly unaffected by first-

pass hepatic metabolism. Only 10% is metabolized and excreted by the kidneys. Nateglinide and its metabolites are rapidly eliminated with a half-life of 1.5 h. Ninety-nine percent of nateglinide is bound to plasma proteins.

The CYP2C9 and CYP3A4 isoenzymes are thought to be involved in hepatic breakdown of nateglinide. No interactions between nateglinide and warfarin, diclofenac, or digoxin have been reported. A study of the pharmacokinetic profile and bioavailability of nateglinide in subjects with biopsy-proven hepatic cirrhosis compared to healthy individuals showed no statistically significant or clinically relevant differences between the two groups. Thus, nateglinide may be used without dose adjustment in patients with mild to moderate hepatic cirrhosis.

A recent open-label, two-center, controlled study of 40 subjects investigated the pharmacokinetics and safety of nateglinide in renal disease [26]. Patients with impaired renal function and those with renal failure on hemodialysis were compared with age-, sex-, height-, and weight-matched healthy controls. Plasma nateglinide concentrations increased rapidly in all subjects and there was no statistically significant difference in C_{max} or AUC between the groups. Nateglinide was eliminated rapidly in all groups ($t_{1/2} = 1.9$ –2.8 h) with no correlation between the level of renal function and systemic exposure. The extent of renal excretion of nateglinide was low in healthy subjects (11%) and diabetic patients with renal impairment (3%). These data suggest that use of nateglinide may be safe in patients with impaired renal function.

CLINICAL USE OF THE MEGLITINIDES

Clinical Use of Repaglinide

Repaglinide is licensed as monotherapy in the treatment of T2DM and may be prescribed in combination with metformin when metformin alone is inadequate. It may also be used in combination with the thiazolidinediones. It is licensed for use between 18 and 75 years.

Repaglinide is usually given 15–30 min before meals up to three times daily at a starting dose of 500 µg. An initial dose of 1 mg can be used if the patient was previously on another oral hypoglycemic agent. The maximal single dose is 4 mg with a total daily dose of 16 mg. It is recommended that dose adjustments be made at intervals of 1–2 weeks according to response. In comparison to sulfonylureas, repaglinide is more expensive.

Repaglinide as Monotherapy

Studies have shown that repaglinide is effective at lowering HbA_{1c} when used as monotherapy in comparison with placebo-controlled trials (Table 5).

A multicenter, double-blind, randomized, placebo-controlled, parallel group study of 408 patients with T2DM assessed the safety and efficacy of repaglinide when used in a flexible mealtime dosing regimen [26]. Patients who were considered poorly controlled by diet were randomly assigned to receive either repaglinide 0.5 mg at mealtimes or placebo. The prandial dose of repaglinide was doubled to 1 mg after 4 weeks if fasting plasma glucose exceeded 7.8 mmol/l. This trial showed a reduction in HbA_{1c} of 1.14% from baseline ($p < 0.001$) and fasting plasma glucose of 1.8 mmol/l ($p < 0.001$). Nine patients (four on repaglinide and five on placebo) were withdrawn from the trial because of a deterioration of $\geq 1\%$ in HbA_{1c}. No significant increase in body weight occurred. Hypoglycemia was the most frequent adverse event but did not appear related to meal pattern. Minor hypoglycemia occurred in 18% with 0.5 mg/meal of repaglinide and 11%

with 1 mg/meal compared to placebo (3%). One percent reported a total of four major hypoglycemic events but none required hospitalization or intravenous glucose or glucagon.

Repaglinide in “Head-to-Head” Studies with Sulfonylureas

The efficacy and safety of repaglinide compared to glipizide was investigated in 256 patients with T2DM in a double-blind, multicenter, parallel-group trial (Table 6) [29]. Patients were randomized to receive either repaglinide 1–4 mg at mealtimes up to three times daily or glipizide 5–15 mg daily and were followed up for 12 months. HbA_{1c} fell by 1.5% in the repaglinide group and 0.3% in the glipizide group ($p < 0.05$ between groups) in those patients who were oral hyperglycemic agent (OHA)-naive. HbA_{1c} increased by 0.5% in the repaglinide group and 0.9% in the glipizide group in patients who were previously treated with OHAs ($p < 0.05$). Fasting blood glucose decreased with repaglinide but increased with glipizide. There were no major hypoglycemic episodes in either group. Minor hypoglycemia was equivalent in both groups (15% with repaglinide, 19% with glipizide).

Repaglinide in Combination with Metformin

The combination of metformin with repaglinide has been shown to be more effective than is repaglinide or metformin monotherapy. In a randomized study of 83 patients (Table 7) with T2DM, the combination group showed a significant reduction in HbA_{1c} of 1.4% and a fall in fasting plasma glucose of 2.2 mmol/l [31]. The mean weight gain in this group was 3 kg.

A much larger uncontrolled prospective study of 5985 patients with T2DM demonstrated the practical advantages of being able to dose flexibly with repaglinide in the everyday clinical setting [32]. The use of repaglinide as a prandial glucose regulator to be taken at the same time as a main meal was explored. The major subgroups in

Table 5 Studies of repaglinide as monotherapy

Study	Intervention	Outcomes	Adverse effects
Moses et al. [27] Double-blind, randomized, placebo-controlled; 408 T2DM	Repaglinide 0.5–1 mg or placebo, preprandially for 16 weeks	HbA _{1c} ↓ 1.14% ($p < 0.001$) FPG ↓ 1.8 mmol/l ($p < 0.001$)	Hypoglycemia Repaglinide 17% Placebo 3% Weight No significant difference ($p = 0.49$) between groups
Van Gaal et al. [28] Double-blind, randomized, placebo-controlled, parallel group; 25 T2DM sulfonylurea-naïve	Repaglinide 0.5–4 mg bd; follow-up 10 weeks	HbA _{1c} ↓ 2.3% ($p = 0.018$) FPG ↓ 3.9 mmol/l PBG ↓ 6.2 mmol/l ($p < 0.001$)	Hypoglycemia Repaglinide 15 patients Placebo 20 patients (NS) Weight Repaglinide ↑ 2.1 kg ($p < 0.01$) Placebo ↓ 0.8 kg (NS)

Note: T2DM = type 2 diabetes mellitus; FPG = fasting plasma glucose; PBG = plasma blood glucose; NS = non significant.

Table 6 Summary of trials of repaglinide versus sulfonylureas

Study	Intervention	Outcomes	Adverse effects
Madsbad et al. [29] Double-blind, randomized, parallel-group, multicentre; 256 T2DM	Repaglinide 1–4 mg, premeals or glipizide 5–15 mg, daily; follow-up for 1 year	HbA _{1c} Repaglinide (mean baseline HbA _{1c} 7.3%) Therapy-naïve ↓ 1.5% Previous therapy ↑ 0.5% Glipizide (mean baseline HbA _{1c} 7.2%) Therapy-naïve ↓ 0.3% Previous therapy ↑ 0.9% FPG Repaglinide ↓ 2.4 mmol/l Glipizide ↑ 1.0 mmol/l <i>p</i> < 0.05 for all groups	Hypoglycemia No major events Minor hypoglycemia Repaglinide 15% Glipizide 19% Weight Repaglinide ↓ 0.7 kg Glipizide ↓ 0.9 kg (NS)
Marbury et al. [30] Double-blind, randomized, parallel-group, multicentre; 576 T2DM	Repaglinide 0.5–4 mg three times, preprandially or Glyburide 2.5–15 mg, daily; follow-up for 1 year	HbA _{1c} Repaglinide Therapy-naïve ↓ 1.3% Previous therapy ↑ 0.3% (<i>p</i> < 0.05) Glyburide Therapy-naïve ↓ 1.1% Previous therapy ↑ 0.3% (<i>p</i> < 0.05)	Hypoglycemia Repaglinide 15% Glyburide 19% Weight Repaglinide ↓ 0.22 kg Glyburide ↑ 0.05 kg (NS)

this study were 2091 therapy-naïve patients, 2180 patients who had switched to repaglinide from another oral hypoglycemic agent, usually a sulfonylurea, and 1530 combination therapy (with metformin) patients. Overall mean HbA_{1c} decreased from 8.6 to 7.4% with reduction in fasting blood glucose from 10.2 to 7.4 mmol/l. Preprandial and 2-h postprandial blood glucose concentrations were also reduced. Body weight decreased slightly by 1.2 kg. Only 49 episodes of hypoglycemia were reported, the majority of which were mild, and in general, adverse drug reactions were rare. Psychosocial benefits were also identified and 80% of patients indicated a sense of relief at being able to miss meals. The need to take snacks for fear of hypoglycemia was also reduced.

Repaglinide in Combination with Insulin

The addition of repaglinide to insulin therapy has been investigated. Repaglinide in combination with bedtime NPH insulin was associated with lowering of HbA_{1c} to 1.68% over a 14-week period [33]. A statistically nonsignificant deterioration in HbA_{1c} was observed in a study comparing insulin combination with either metformin, or repaglinide. However, the additive effect of bedtime isophane insulin, metformin, and premeal repaglinide has been shown to significantly reduce HbA_{1c} and also lower the actual dose of subcutaneous insulin required, compared with the combination of twice daily insulin and metformin [34].

Table 7 Repaglinide in combination with metformin

Study	Intervention	Outcomes	Adverse effects	Comments
Moses et al. [31] Multicentre, double-blind, randomized; 83 T2DM	Metformin alone (1–3 g/d) or repaglinide alone (0.5–4 mg thrice daily) or metformin and repaglinide for 3 months	HbA _{1c} ↓ 1.4% (<i>p</i> = 0.0016) FPG ↓ 2.2 mmol/l (<i>p</i> = 0.0003) No significant difference in HbA _{1c} or FPG in either monotherapy group	Hypoglycemia Metformin 0% patients Repaglinide 10.7% patients Combination 33.3% patients Weight gain Repaglinide 2.4 ± 0.5 kg Combination 3.0 ± 0.5 kg Diarrhoea Headache	
Landgraf et al. [32] Uncontrolled prospective, 5985 T2DM; 2091 therapy naïve, 2180 other OHA → repaglinide, 1530 combination with metformin	Prandial flexible dosing with repaglinide 0.5–2 mg/meal, Mean follow-up 46 days	Mean HbA _{1c} ↓ 1.2% (<i>p</i> = 0.0001) Mean FPG ↓ 2.8 mmol/l (<i>p</i> = 0.0001) Mean 2-h PG ↓ 3.7 mmol/l (<i>p</i> = 0.0001)	Hypoglycemia 38 mild 11 severe Weight ↓ 1.2 ± 2.7 kg	Fewer snacks on repaglinide Patients able to miss meals

Repaglinide in Combination with Other Agents

The combination of repaglinide with troglitazone (now withdrawn following hepatotoxicity) was investigated in 256 patients with T2DM inadequately controlled by monotherapy. In this multicenter open-label clinical trial, there was a fall of 1.7% in HbA_{1c} in the combination group. Repaglinide was also shown to be more effective as monotherapy compared to troglitazone (−0.8% vs. −0.4%, *p* < 0.05). It will be interesting to examine the results of current trials comparing and combining the use of repaglinide with either pioglitazone or rosiglitazone.

Clinical Use of Nateglinide

In the United Kingdom and Europe, nateglinide may be used in combination with metformin when metformin alone is inadequate. It is not licensed for use in the pediatric age group (below 18 years). It is more expensive than other oral hypoglycemic agents such as the sulfonylureas.

Several studies have reported the efficacy of nateglinide either as monotherapy or in combination with other oral hypoglycemic agents such as metformin or troglitazone. A number of trials have compared nateglinide with other sulfonylureas and there are some early reports comparing it with repaglinide.

The starting dose of nateglinide is usually 60 mg three times daily taken within 30 min of a main meal. The dose should subsequently be adjusted according to response, with a maximal dose of 180 mg three times daily.

Nateglinide as Monotherapy

As has been reported with other insulin secretagogues, nateglinide has a glucose-dependent action. A study in 24 patients with T2DM observed significantly greater insulin secretion when nateglinide was taken with a meal compared to when it was taken while fasting.

In a randomized, double-blind, placebo-controlled, multicenter study consisting of 289 patients with T2DM, patients were randomized to receive either nateglinide at doses of 30, 60, 120, or 180 mg, or placebo, before three main meals for 12 weeks (Table 8) [35]. Baseline HbA_{1c}

was 8.3–8.5% across all groups. This trial showed a modest although statistically significant reduction of 0.45–0.64% in HbA_{1c} at study endpoint with nateglinide at doses of 60 mg upwards compared with placebo. In the 120-mg-nateglinide group only, the mean level of fasting plasma glucose was significantly reduced. Following a liquid meal challenge, the administration of nateglinide resulted in rapid onset of prandial insulin secretion with high insulin levels present 15 min postdose and maximal plasma concentrations observed 30–60 min postdose. This demonstrates the rapid action and short duration of nateglinide therapy. Nateglinide was well-tolerated. Mild symptoms suggestive of hypoglycemia were reported in the pooled nateglinide group although most of these were not confirmed biochemically.

Nateglinide in “Head-to-Head” Studies with Sulfonylureas

Nateglinide reduces postmeal glucose excursions more effectively than does glyburide (glibenclamide) as shown by a double-blind, placebo-controlled, parallel group study of 8 weeks’ duration in 152 patients with T2DM (Table 9) [36]. Nateglinide 120 mg before meals was compared with glyburide 10 mg four times daily. It was shown that nateglinide primarily reduced mealtime glucose excursion (as measured by AUC) whereas glibenclamide reduced fasting glucose levels. Nateglinide did not increase fasting insulin levels and increased only the early insulin response to a liquid meal. This represents a more physiological release of insulin than that for glibenclamide. In patients with T2DM, nateglinide monotherapy for 12 weeks resulted in a dose-dependent reduction in HbA_{1c} and a very low risk of hypoglycemia (Figure 10).

A recently published small, double-blind study compared the efficacy of acute premeal administration of glipizide with nateglinide in 20 patients with T2DM. Patients were randomly assigned to glipizide monotherapy, nateglinide monotherapy, a combination of glipizide and nateglinide, or placebo. This study demonstrated that there was equal efficacy in controlling postbreakfast hyperglycemia with glipizide and nateglinide, in contrast to previous studies comparing these agents. It was suggested that this was due to administration of glipizide

Table 8 Nateglinide as monotherapy

Study	Intervention	Outcomes	Adverse effects
Hanefeld et al. [35] Randomized; double-blind, placebo-controlled, multicenter; 289 T2DM	Nateglinide (thrice daily), 30 mg (<i>n</i> = 51) or 60 mg (<i>n</i> = 63) or 120 mg (<i>n</i> = 63) or 180 mg (<i>n</i> = 57) or placebo; 12-week follow-up	HbA _{1c} 60 mg ↓ 0.45% 120 mg ↓ 0.62% 180 mg ↓ 0.64% (<i>p</i> < 0.05) FPG 120 mg ↓ 1.14 mmol/l (<i>p</i> < 0.01)	Mild symptoms suggestive of hypoglycemia confirmed in 1.3% Weight 120 mg ↑ 0.72 kg

Table 9 Summary of studies of nateglinide versus sulfonylureas

Study	Intervention	Outcomes	Adverse effects
Hollander et al. [36] Double-blind, randomized, placebo-controlled, multicentre; 152 T2DM	Nateglinide 120 mg tds or glyburide 5–10 mg qds or placebo; follow-up 8 weeks	AUC Nateglinide ↓ −4.94 mmol/h/l Glyburide ↓ 2.71 mmol/h/l ($p < 0.05$) FPG Nateglinide ↓ 1.0 mmol/h/l Glyburide ↓ 2.9 mmol/h/l ($p < 0.001$)	Hypoglycemia Symptomatic Nateglinide 12 events Glyburide 53 events Placebo 2 events Confirmed Nateglinide 3 events Glyburide 14 events Placebo 1 event
Carroll et al. [37] Double-blind, randomized, placebo-controlled; 20 T2DM	Nateglinide 120 mg, premeal or Glipizide 10 mg, premeal or Nateglinide 120 mg + Glipizide 10 mg, premeal or placebo; follow-up 4 h	PPG excursion Glipizide + nateglinide 4.1 mmol/l Nateglinide 4.2 mmol/l ($p = 0.001$) Glipizide 4.3 mmol/l Placebo 6.1 mmol/l AUC Nateglinide + glipizide 5.6 mmol/h/l Nateglinide 9.7 mmol/h/l Glipizide 6.9 mmol/h/l Placebo 14 mmol/h/l	Hypoglycemia confirmed Glipizide 3 events Nateglinide + glipizide 3 events

30 min (rather than 10 min) before the meal. The combination of nateglinide and glipizide resulted in increased early insulin secretion compared with nateglinide alone but did not significantly change the postprandial glucose profile compared with monotherapy with either agent.

Despite some data that suggest that there may be benefits, there are no large- or medium-term data of head-to-

head studies between nateglinide and sulfonylureas looking at weight gain, hypoglycemia, or glycemic control.

Nateglinide in Combination with Metformin

The efficacy of nateglinide in combination with metformin was demonstrated in a randomized double-blind study of 701 patients with T2DM (Table 10) [38].

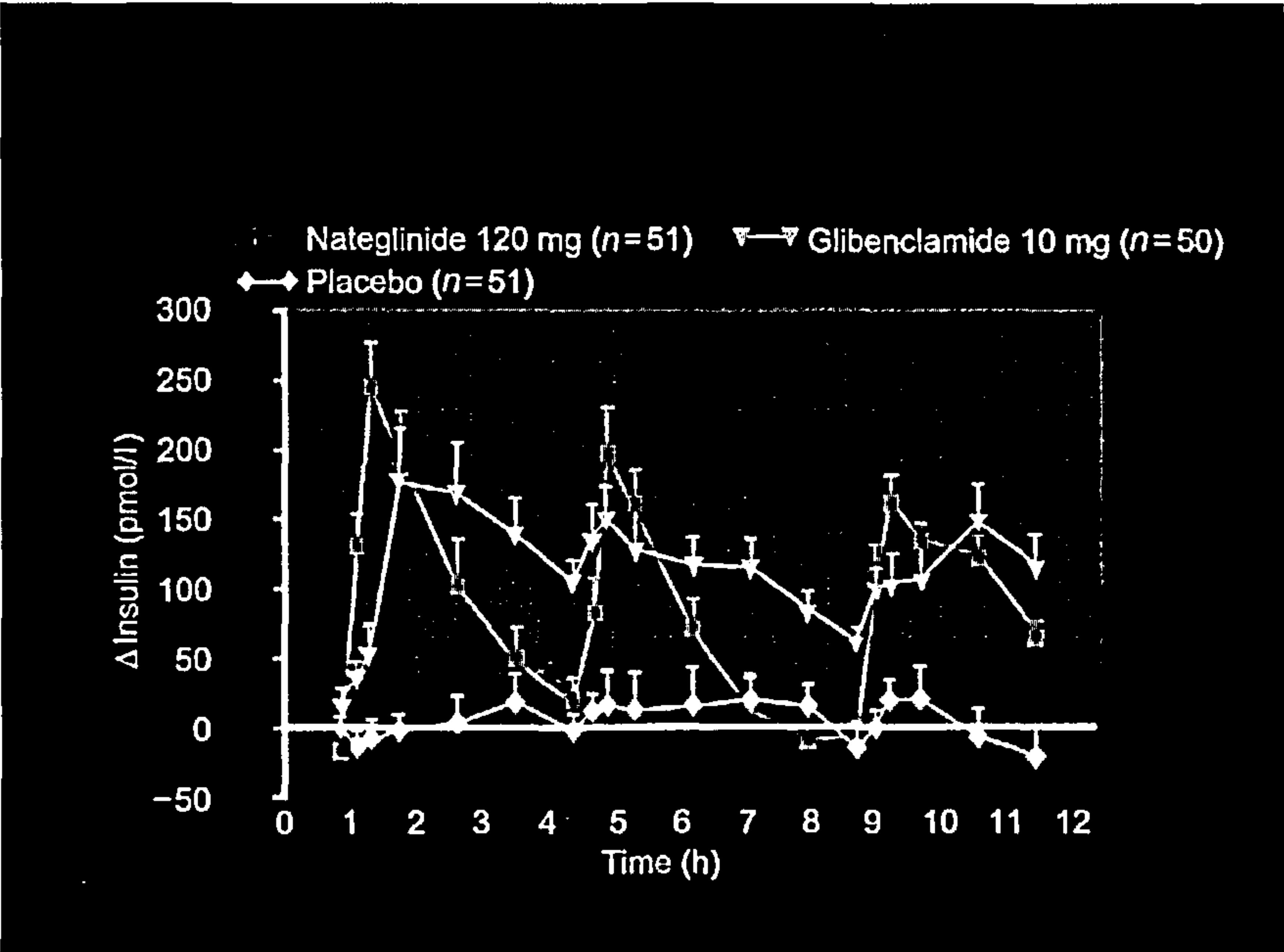


Figure 10 Comparison of nateglinide with glipenclamide and placebo. (Reproduced by permission of the American Diabetes Association [35])

Table 10 Nateglinide in combination with metformin

Study	Intervention	Outcomes	Adverse effects	Comments
Horton et al. [38] Randomized, double-blind, placebo-controlled; 701 T2DM	Nateglinide 120 mg tds or Metformin 500 mg tds or Combination therapy or placebo	HbA _{1c}	Hypoglycemia	
		Nateglinide	No severe episodes	
		↓ 0.5%	Confirmed episodes	
		Metformin	Nateglinide 3 patients	
		↓ 0.8%	Metformin 1 patients	
		Placebo	Combination 5 patients	
		↑ 0.5%		
		(<i>p</i> ≤ 0.0001)		
		Combination ↓ 1.4% (<i>p</i> ≤ 0.01)		
		FPG		
Marre et al. [39] Randomized, double-blind, placebo-controlled, parallel-group, multi-center; 467 T2DM on metformin	Nateglinide 60 mg tds or nateglinide 120 mg tds or placebo, Added to metformin 1 g bd; 24-week follow-up	Nateglinide	Metformin + placebo 3.9%	Greater reduction in HbA _{1c} for combination with both nateglinide doses if baseline HbA _{1c} >9.5%
		↓ 0.36% (<i>p</i> = 0.003)	Nateglinide 60 mg 8.4%	
		Nateglinide 120 mg + metformin	Nateglinide 120 mg 15.6%	
		↓ 0.59% (<i>p</i> < 0.001)	Weight	
			Nateglinide 120 mg ↑ 0.9 kg	
			(<i>p</i> < 0.001)	

Patients were assigned to four different groups, namely placebo, nateglinide monotherapy metformin monotherapy, or a combination of nateglinide and metformin. After 24 weeks of therapy, HbA_{1c} and fasting plasma glucose was lowered by 1.9% and 2.4 mmol/l respectively in the combination group, which showed the greatest effect. This study also showed that nateglinide decreased mealtime glucose excursions after a liquid meal challenge, whereas metformin mainly had an effect on fasting plasma glucose.

In a multicenter, double-blind, parallel group trial, 467 metformin-treated patients were randomized to treatment with 60 mg or 120 mg nateglinide or placebo before three meals [39]. This was in combination with 1 g metformin twice daily for 24 weeks. The results showed a significant reduction in HbA_{1c} with nateglinide at either dose (−0.36%, *p* = 0.003; −0.59%, *p* < 0.001, respectively) compared with metformin alone. Hypoglycemic symptoms were more likely to occur if HbA_{1c} was less than 8% at baseline. Weight gain in the nateglinide 120 mg plus metformin group was 0.9 kg. There was no change in plasma lipids.

Nateglinide in Combination with Other Agents

A double-blind, randomized, multicenter study has compared the effects of monotherapy using nateglinide, the thiazolidinedione troglitazone, and the combination of these two agents on HbA_{1c} in patients with T2DM in-

adequately controlled by diet alone [40]. Monotherapy with nateglinide after 16 weeks resulted in 0.6% reduction in HbA_{1c} compared with 0.8% in the troglitazone monotherapy group. Combination therapy with nateglinide and troglitazone resulted in an even greater improvement of 1.7% in HbA_{1c}. Longer follow-up studies investigating the combination of nateglinide with either pioglitazone or rosiglitazone are needed.

Nateglinide and Impaired Glucose Tolerance

The Pharmacokinetics of nateglinide make it an ideal agent to address the loss of early-phase insulin secretion seen in IGT. Studies are underway to explore the effect of nateglinide in IGT.

A recently published multicenter, double-blind, randomized, parallel-group, fixed-dose study of 8 weeks' duration in 288 patients with IGT has assessed the effects of various doses of nateglinide and associated adverse events, including hypoglycemia. Patients received nateglinide (30, 60, and 120 mg) or placebo before main meals, and response to standardized meal challenges was recorded. The study showed that nateglinide increased early insulin response to a meal and reduced prandial glucose excursions in a dose-dependent manner with no significant effect on fasting plasma glucose or fasting insulin levels. Apart from hypoglycemia (28 cases in nateglinide group and 1 in placebo group), the overall incidence of adverse events was low. The study concluded that nateglinide was

safe and effective in reducing PPH in subjects with IGT and recommended that the lower doses (30 mg and 60 mg) would be suitable for investigation in longer term studies.

A large, multicenter, randomized, double-blind, placebo-controlled trial known as NAVIGATOR is currently in progress. This has set out to explore the efficacy of nateglinide in combination with valsartan on glycemic control and cardiovascular outcomes in individuals with IGT. This 7-year study of 10 000 subjects with IGT is the largest ever diabetes prevention study and should provide data about whether targeting PPH will improve cardiovascular outcomes. By design, one third of patients recruited to the study have established cardiovascular disease, which should provide sufficient power to look at cardiovascular outcomes.

Safety of Meglitinides

Trials have shown that the safety of meglitinides is comparable with other oral hypoglycemic agents such as the sulfonylureas. Three large 1-year studies indicated that repaglinide has an adverse event profile similar to that of glibenclamide. The most common side effect is hypoglycemia but this is usually mild. The incidence of serious hypoglycemia was 0.6% with repaglinide and 1% with sulfonylureas. From pooled data from Phase III studies, the proportion of patients presenting with hypoglycemia was 16% for repaglinide, compared with 20% for glibenclamide, 19% for glipizide, and 15% for gliclazide.

In long-term clinical trials, incidence of serious adverse events was low with repaglinide (10%) and similar to the incidence reported with sulfonylureas (11.6%).

Similarly for nateglinide, studies have shown that the commonest adverse event is symptoms suggestive of mild hypoglycemia. A study of 152 patients showed that symptomatic hypoglycemia occurred in 12 patients randomized to nateglinide and 53 patients on glyburide. Confirmed hypoglycemia was documented in 3 patients on nateglinide and 14 patients on glyburide. Other studies suggest that the incidence of hypoglycemia is similar for both sulfonylureas and nateglinide.

Respiratory disorders are the next most frequently reported adverse events in long-term clinical trials, namely upper respiratory tract infection (10%), rhinitis (7%), and bronchitis (6%). However the incidence and severity of these events was similar in patients treated with sulfonylureas and most were not drug related.

Other reported side effects are hypersensitivity reactions, increased liver enzymes, gastrointestinal symptoms, and headache. These have been reported with similar incidence to placebo. Combination therapy does not appear to result in more adverse events compared to monotherapy.

According to national drug formulary guidelines (British National Formulary), in the presence of fever,

trauma, infection, or surgery, the meglitinides should be substituted by insulin therapy. The risk of hypoglycemia is increased in patients with adrenal or pituitary insufficiency, in malnourished individuals, and in the elderly.

SUMMARY

The meglitinides offer an opportunity to target specifically the PPH that occurs commonly in patients with type 2 diabetes [41, 42]. Their rapid onset and short duration of action leads to more "physiological" release of insulin and partially restores the pattern of postprandial insulin secretion that is defective in type 2 diabetes mellitus. This potentially allows tighter glycemic control while reducing the risk of hypoglycemia. As prandial glucose regulators they allow flexible dosing such that a tablet need only be taken before a patient has a meal. Repaglinide in particular has been shown to reduce HbA_{1c} and is well-tolerated by patients both as monotherapy and in combination with other agents. It appears to have some advantages from head-to-head studies with sulfonylureas. Nateglinide appears to produce a faster early-phase insulin response that gives it the potential to produce less hypoglycemia, but randomized controlled trials in comparison with sulfonylureas are lacking. Both agents are more expensive than sulfonylureas. Formal data regarding cost-effectiveness are not currently available. However, their flexible administration may be of benefit in certain subgroups such as shift-workers and those with flexible lifestyles. Efficacy in early diabetes and impaired glucose tolerance is currently being investigated. The ability to flexibly dose with these agents makes them useful in patients with flexible lifestyles. Macrovascular and microvascular outcome data for the meglitinides are awaited.

REFERENCES

1. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med* 1997; 14 (suppl 5): 1-85.
2. Takiya L, Chawla S. Therapeutic options for the management of type 2 diabetes. *Am J Manag Care* 2002; 8 (11): 1009-23.
3. The UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas compared with conventional treatment and risks of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-53.
4. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* June 2002; 359 (9323): 2072-7.
5. Davies MJ, Rajman G, Grenfell A, Gray IP, Day JL, Males CN. Loss of the first phase insulin response to intravenous

- glucose in subjects with persistent impaired glucose tolerance. *Diabet Med* 1994; 11: 432–6.
6. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes Mellitus. *J Clin Invest* 1999; 104: 789–94.
 7. The UKPDS group. UKPDS 16. Overview of 6 years therapy of Type II diabetes: a progressive disease. *Diabetes* 1995; 44: 1249–58.
 8. Avignon A, Radauceanu A, Monnier L. Non-fasting glucose is a better marker of diabetes control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 1997; 20: 1822–6.
 9. Erlinger TP, Brancati FL. Postchallenge hyperglycaemia in a national sample of US adults with type 2 diabetes. *Diabetes Care* 2001; 24: 1734–8.
 10. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999; 354: 617–21.
 11. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 1998; 21 (3): 360–7.
 12. de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 1999; 42 (8): 926–31.
 13. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: The Diabetes Intervention Study (DIS), 11-year follow-up. *Diabetologia* 1996; 39: 1577–83.
 14. Donahue RP, Abbot RD, Reed DM, Yano K. Post-challenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. *Diabetes* 1987; 36: 689–92.
 15. Ceriello A. The emerging role of post prandial hyperglycaemic spikes in the pathogenesis of diabetic complications. *Diabet Med* 1998; 15: 188–93.
 16. Pradhan AD, Manson JAE, Rifai N, et al. C-reactive protein, interleukin-6, and risk of developing T2DM. *JAMA* 2001; 286: 327–34.
 17. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycaemia in humans—role of oxidative stress. *Circulation* 2002; 106: 2067–72.
 18. De Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 1995; 333: 1239–41.
 19. American Diabetes Association. Postprandial blood glucose. *Diabetes Care* 2001; 24: 775–8.
 20. Hu S, Wang S, Fanelli B, Bell PA, Dunning BE, Geisse S, Schmitz R, Boettcher BR. Pancreatic B-cell K-ATP channel activity and membrane-binding studies with nateglinide: a comparison with sulfonylureas and repaglinide. *J Pharmacol Exp Ther* 2000; 293: 444–52.
 21. Fuhlendorff J, Rorsman P, Kofod H, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. *Diabetes* 1998; 47: 345–51.
 22. Tankova T, Koev D, Dakovska L, Kirilov G. The effect of repaglinide on insulin secretion and oxidative stress in type 2 diabetic patients. *Diabetes Res Clin Pract* 2003; 59: 43–9.
 23. Hu S, Wang S, Dunning BE. Glucose-dependent and glucose-sensitising insulinotropic effect of nateglinide: a comparison to sulfonylureas and repaglinide. *Int J Exp Diabetes Res* 2001; 2 (1): 63–72.
 24. Kalbag J, Hirschberg Y, Mcleod JF, Garrefta S, Lassetes K. Comparison of Mealtime glucose regulation by nateglinide and repaglinide in healthy subjects. *Diabetes* 1999 (suppl 1): Abstract 106.
 25. Massi-Benedetti M, Damsbo P. Pharmacology and clinical experience with repaglinide. *Exp Opin Invest Drugs* 2000; 9 (4): 885–98.
 26. Devineni D, Walter YH, Smith HT, Lee JS, Prasad P, McLeod JF. Pharmacokinetics of nateglinide in renally impaired diabetic patients. *J Clin Pharmacol* 2003; 43 (2): 163–70.
 27. Moses RG, Gomis R, Frandsen KB, et al. Flexible meal-related dosing with repaglinide facilitates glycaemic control in therapy-naïve type 2 diabetes. *Diabetes Care* 2001; 24: 11–5.
 28. Van Gaal LF, Van Acker KL, De Leeuw IH. Repaglinide improves blood glucose control in sulphonylurea-naïve type 2 diabetes. *Diab Res Clin Pract* 2001; 53: 141–8.
 29. Madsbad S, Kilhovd B, Lager I, et al. Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1 year multicenter study. *Diabet Med* 2001; 18: 395–401.
 30. Marbury T, Huang WC, Strange P, Lebovitz H. Repaglinide versus glyburide: a one year comparison trial. *Diab Res Clin Pract* 1999; 43: 155–66.
 31. Moses R, Siobodniuk R, Boyages S, Colagiuri S, et al. Effect of repaglinide addition to metformin monotherapy on glycaemic control in patients with type 2 diabetes. *Diabetes Care* 1999; 22 (1): 119–24.
 32. Landgraf R, Frank M, Bauer C, Dieken ML. Prandial glucose regulation with repaglinide: it's clinical and lifestyle impact in a large cohort of patients with type 2 diabetes. *Int J Obes Relat Metab Disord* 2000; 24 (suppl 3): 38–44.
 33. Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized controlled trial. *Ann Intern Med* 1999; 130: 389–96.
 34. Davies MJ, Johnston V, Howe J, et al. Comparison of combination regimes of insulin, repaglinide and metformin in type 2 diabetes: an interim analysis. *Diabet Med* 2001; 18 (suppl 2): A44.
 35. Hanefeld M, Bouter KP, Dickinson S, Guitard C. Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycaemia. *Diabetes Care* 2000; 23: 202–7.
 36. Hollander P, Schwartz SL, Gatlin MR, et al. Nateglinide but not glyburide, selectively enhances early insulin release and more effectively controls post-meal glucose excursions with less insulin exposure. *Diabetes* 2000; 49: 449.
 37. Carroll F, Izard A, Riboni K, Burge MR, et al. Control of postprandial hyperglycaemia. Optimal use of short-acting insulin secretagogues. *Diabetes Care* 2002; 25: 2147–52.
 38. Horton E, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves

- glycaemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; 23: 1660–5.
39. Marre M, Van Gaal L, Usadel K-H, Ball M, Whatmough I, Guitard C. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes. *Diabetes Obes Metab* 2002; 4: 177–86.
40. Rosenstock J, Shen SG, Gatlin MR, Foley JE. Combination therapy with nateglinide and a thiazolidinedione improves glycemic control in type 2 diabetes. *Diabetes Care* 2002; 25: 1529–33.
41. Davies MJ. Insulin secretagogues. *Curr Med Res Opin* 2002; 18 (suppl 1): S22–30.
42. Dornhorst A. Insulinotropic meglitinides analogues. *Lancet* 2001; 358: 1709–16.

21 had end-stage renal failure treated with CAPD. This is the largest study of young people with diabetes undertaken in New Zealand. The results confirm the difficulty of achieving good glycaemic control in children and young adults. Microvascular complications are common, particularly in those of long duration.

A94

A 10 year outcomes following screening for type 2 diabetes and impaired glucose tolerance in White Europeans and South Asians in Leicestershire

S CHATTERJEE*, NT RAYMOND[†], H BLACKLEDGE*, K KHUNTI[‡] and MJ DAVIES*

*Diabetes Research Unit, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, UK, [†]Warwick Medical School, University of Warwick, Coventry, UK, [‡]Department of Public Health, University Hospitals of Leicester NHS Trust, Leicester, UK, [§]Department of General Practice, University of Leicester Medical School, Leicester, UK

UKPDS confirmed that delayed diagnosis of T2DM results in development and progression of undetected complications. A national screening programme has not yet been recommended. In 1993–4, 9896 subjects (63% South Asian) in Leicestershire were screened for diabetes and IGT using self-testing for post-prandial glycosuria and 75g OGTT. Ten-year all-cause mortality and complications outcome data in those with known diabetes (KDM), screened diabetes (SDM), IGT or normal were analysed. All-cause mortality in the KDM group was 17.6% vs 15.3% in SDM, 4% screened IGT and 7.6% screened normal. Acute MI occurred in 12% KDM, 3.3% SDM, 4% IGT and 7.6% normal; CABG in 12% KDM, 3.3% SDM, 4% IGT and 1.9% normal; renal failure in 8.1% KDM, 4.9% SDM, 0% IGT and 2.9% normal. Amputation only occurred with known diabetes (0.3%). Odds ratios (95% CI) in KDM/SDM for all-cause mortality were 1.2 (0.6–2.5), MI 2.7 (0.8–8.8), CABG 1.9 (0.4–8.1), and renal failure 1.7

(0.5–5.6). South Asians were younger across all groups and had fewer events. Odds ratios showed increased but non-significant outcomes with KDM. Lead and length time biases affect the findings of our study, which does not clearly show that screening leads to better outcomes in the first decade.

A95

Maternal and ethnic differences in GDM pregnancies used to predictor future diabetes development

MD OLDFIELD, P DONLEY, L WALWYN and R GREGORY

Leicester General Hospital, Leicester, UK

Background: Gestational diabetes (GDM) identifies women at increased risk of future diabetes (DM). The influence of ethnicity was examined in the multiethnic Leicestershire population.

Methods: 310 women with previous GDM (62% Indian, 38% Caucasian) who delivered at the Leicester General Hospital between 1980 and 2002 were invited to attend for reassessment of their glucose tolerance.

Results: Data was available for 40% of the cohort. After a follow-up of 67 ± 52.3 months, 64 had developed diabetes (59 diagnosed prior to follow-up and 5 who attended screening); an overall prevalence of 20.6% (original cohort). DM was more frequent and occurred earlier in Indian women (47 vs 83 months, $P < 0.01$). In both groups increasing age, weight and measures of adverse pregnancy hyperglycaemia including the need for insulin treatment were associated with diabetes. Fasting glucose, HbA1c and insulin-treatment predicted diabetes development most strongly in Caucasian women (OR 6.9, 14.1, 23.4, $P < 0.01$), whereas family history, HbA1c and insulin treatment were more predictive in women from the Indian subcontinent (OR 9.0, 5.9, 2.7, $P < 0.01$).

Conclusion: Previous GDM is a significant risk factor for future diabetes. In particular women of Indian origin requiring insulin during pregnancy appear to be at the greatest risk and should be screened yearly.

Clinical care orals: Management of Type 2 diabetes

A96

The effect of Atorvastatin therapy on C-reactive protein in patients with Type 2 Diabetes Mellitus and no prior history of cardiovascular disease, in the Collaborative Atorvastatin Diabetes Study (CARDS)

SS SOEDAMAH-MUTHU*, HM COLHOUN*, DJ BETTERIDGE[†], PN DURRINGTON[‡], GA HITMAN[§], HAW NEIL[§], SJ LIVINGSTONE* and JH FULLER*

*Department of Epidemiology and Public-Health, University College London, London, UK, [†]University College London and Middlesex School of Medicine, London, UK, [‡]University of Manchester, Department of Medicine, Manchester Royal Infirmary, Manchester, UK, [§]Barts and the London Queen Mary's School of Medicine and Dentistry, University of London, London, UK, [¶]University of Oxford, Oxford, UK

Aim: To examine the effect of atorvastatin on CRP in type 2 diabetic patients with no history of cardiovascular disease.

Methods: Baseline and two-year follow-up concentrations of CRP were measured in 650 patients with type 2 diabetes, randomized to placebo ($n = 313$) or atorvastatin 10 mg ($n = 337$). These patients were a random sub-sample from the Collaborative Atorvastatin Diabetes Study (CARDS).

Results: The two treatment groups were well balanced for age (61 years), sex, and cardiovascular risk factors. In both groups CRP rose during the follow-up as to be expected from the rise in BMI through time. In the placebo group CRP rose during the follow-up by 0.63 mg/L [interquartile

range (IQR): $-0.02, 2.40$] for median within-person-change. In the atorvastatin group this rise through time was significantly less (0.25, IQR: $-0.56, 1.18$, median within-person-change, $P < 0.0001$). The increase in CRP was reduced by 34% in the atorvastatin compared to placebo group (95%CI: 19–46%), $P < 0.0001$ and was independent of age, sex, centre, diabetes duration, current smoking, race, change in BMI, HbA1c, LDL-cholesterol, and concomitant medication.

Conclusions: Atorvastatin slows down the increase in CRP in type 2 diabetic patients compared to placebo, independently of the change in LDL-cholesterol, BMI, HbA1c and concomitant medication, indicating anti-inflammatory effects. On behalf of the CARDS investigators.

A97

Is intensive medical management in patients with type 2 diabetes and nephropathy cost effective?

N JOSS*, C BROWN*, C FERGUSON*, K PATERSON[†], A WALKER[‡] and M BOULTON-JONES*

*Renal Unit, [†]Diabetic Unit, Glasgow Royal Infirmary, Glasgow, UK,

[‡]Department of Statistics, Glasgow University, Glasgow, UK

A 2-year randomised controlled study assessed the effect of intensive management on the rate of decline of renal function in patients with type 2 diabetes. The intensive group (IG $n = 47$) had a mean of 19 clinic visits over 2 years, spent a total of 496 days in hospital and progressed at a rate

complication of insulin treatment which counteracts some of its benefits. Our study shows that this problem is not abolished by metformin, and that more effective treatment strategies are badly needed. Risk stratification will allow these to be targeted more effectively.

P92

Insulatard vs. glargine: efficacy in combination with insulin aspart in Type 1 diabetes mellitus (GLASS study)

S. Chatterjee, T. Rengarajan, M. O. Akinsola, I. G. Lawrence, P. G. McNally and M. J. Davies

Diabetes Research Unit, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, UK

Our aim was to compare efficacy of once-daily Glargine with twice-daily Insulatard, in combination with prandial insulin Aspart, on HbA_{1c}, hypoglycaemia, lipids, weight, and patient satisfaction (DTSQ and ADDQoL). GLASS (GLargine and ASpart Study) is a single centre 36-week open-label, randomized crossover study. After 4-weeks' run-in, patients were randomized to either basal insulin for 16 weeks before crossing over. Inclusion criteria were males or females with Type 1 diabetes for at least 1 year, age 18–75 years, and HbA_{1c} 6–11%. 55 T1DM patients were recruited and 37 have completed the study. 31(84%) of those completing the study have stated a preference for continuing Glargine. 3 patients withdrew after the first arm of the study on Glargine as they did not want to switch back to Insulatard. Mean HbA_{1c} decreased on Glargine from 8.6% to 8.4% ($P < 0.05$). With Insulatard, mean HbA_{1c} increased from 8.4% to 8.7% ($P < 0.05$). There was a 0.5% difference between insulin therapies ($P < 0.05$). There were no significant differences in change in mean weight, lipid profile or hypoglycaemia (mild, severe or nocturnal) between insulin therapies. Patient satisfaction was better with Glargine than with Insulatard.

P93

Age and HbA_{1c} at initiation of insulin therapy in Type 2 diabetes

H. Whitty, M. McKay, A. McCallum, R. S. Gray and J. D. Walker

Medical Unit, St John's Hospital, Livingston, UK

Good glycaemic control in patients with Type 2 diabetes (T2) reduces the progression of microvascular complications and is of particular benefit to those patients anticipating prolonged duration of diabetes vis. the younger patients. We retrospectively surveyed our clinic to ascertain whether Primary Care Physicians (PCP) and Diabetes Clinic Doctors (DCD) referred younger patients with T2 for insulin therapy at a lower HbA_{1c} level compared with older patients. The last 200 consecutive patients with a prior diagnosis of T2 commenced on insulin in our unit were studied. Median (range) age was 60 (32–90) years; duration of diagnosed T2 8 (1–20) years and 55% were male. Median HbA_{1c} prior to insulin therapy was 10.0 (7.7–14.7)%. We classified patients as being young (Y)(51(32–60) years, $n = 104$) or older (O)(67(61–90) years, $n = 96$). HbA_{1c} at initiation of insulin therapy was not different in the Y (10.0 (8.0–14.3)%) or O (10.0 (7.7–14.7)%) groups. The correlation between age and HbA_{1c} at initiation of insulin was 0.08 (NS). There were no differences between patients referred by PCP ($n = 87$) or DCD ($n = 113$). Thus, age is not influencing the decisions of clinicians to commence insulin therapy in T2, which appears to be based on HbA_{1c} alone. We conclude that younger patients are not being referred for insulin therapy at an earlier stage than older patients.

P94

Experience with insulin glargine in routine diabetes practice

C. Lunken, J. W. Stephens, D. Gable and S. J. Hurel

Department of Diabetes & Endocrinology, UCL Hospitals, London, UK

The long acting insulin analogue glargine (Lantus), provides a more predictable supply of basal insulin than NPH injected once/twice a day. Studies have shown efficacy in reducing nocturnal hypoglycaemia and high fasting glucose. There have been six multicentre trials in the use of insulin glargine in Type 1 and five in Type 2 diabetes without documented improvement in HbA_{1c} compared with NPH. We audited the use of glargine in our clinic. The indications for prescribing and efficacy both in terms of improvement of symptoms and glycaemic control were examined. Of a total of 70 patients, 37 were initiated to improve control, 11 for nocturnal hypoglycaemia, 7 for nocturnal hypoglycaemia and fasting hyperglycaemia, 6 for daytime hypoglycaemia, 4 for high fasting glucose. A further 2 were keen to start and 3 were changed from monotard/ultratard. Overall, HbA_{1c} improved by 0.7%. There was a 1.0% reduction in those with fasting hyperglycaemia, 0.8% in those commenced to improve control, 0.3% in those with nocturnal hypoglycaemia and 0.9% in those with daytime hypoglycaemia. All patients switched to glargine because of nocturnal hypoglycaemia reported reduced symptoms. Overall 18 patients reported an improvement in wellbeing. In clinical practice glargine improves wellbeing, nocturnal hypos and also HbA_{1c}.

P95

Earning pump therapy in Type 1 diabetes: not NICE

J. Everett, E. Jenkins, D. A. Cavan and D. Kerr

BDEC, Royal Bournemouth Hospital, Bournemouth, UK

The National Institute for Clinical Excellence (NICE) have suggested that insulin pump therapy should only be considered for patients unable to maintain an HbA_{1c} of less than 7.5% without disabling hypoglycaemia. However, prior to NICE, 27 individuals with Type 1 diabetes (10 men, age 38 ± 13 years, duration of diabetes 21 ± 16 years) started pump therapy for the following reasons: Presence of progressive microvascular complications ($n = 6$); Brittle diabetes ($n = 4$); Difficult to heal diabetic foot ulcers ($n = 3$). In this group HbA_{1c} fell from 9.8 to 8.0% (1.7(1.1–2.2)%, $P < 0.0001$), mean (95%CI), associated with a reduction in total insulin dose (from 59 to 38 units, $P = 0.001$) and no increase in weight. Before starting pump therapy 13 had hypoglycaemia unawareness all of whom had a return of warning symptoms by 3 months. The other patients did not suffer from recurrent severe hypoglycaemia but may have eschewed tight glycaemic control because of fear of hypoglycaemia. Therefore, NICE guidelines for initiating insulin pump therapy may be unduly restrictive. Furthermore we do not believe that patients with suboptimal glycaemic control need to 'earn' the pump by suffering recurrent, severe hypoglycaemia.

P96

An achievable endpoint in insulin treatment: reduction of hypoglycaemia

Y. P. Samarasinghe, E. Barden, N. Munro, C. McIntosh, K. Shotliff and M. D. Feher

Beta Cell Diabetes Centre, Chelsea and Westminster Hospital, London, UK

Aims Assessing hypoglycaemia frequency following glargine therapy initiation.

Aim: To characterise adiponectin levels in prepubertal children and their relationship to BMI, adiposity and insulin resistance (HOMA-IR).

Methods: Participants: healthy children (111 boys, 83 girls) from the Early Bird Study measured at 5,6,7,8 years. Measures: adiponectin, HOMA-IR, BMI, adiposity (sum of 5 skin folds).

Results (1) Mean changes 5–8 years: BMI and % body fat rose (+ 5% and + 18%, both $P < 0.001$); HOMA-IR fell –4% ($P < 0.001$); adiponectin fell (boys 13.8–12.9–12.7–12.6 $\mu\text{g/ml}$), –9.1%, $P < 0.001$; girls (13.7–12.6–13.1–12.5 $\mu\text{g/ml}$), –8.7%, $P = 0.006$. (2) Associations: Adiponectin levels correlated strongly year-on-year ($r = 0.70$ – 0.80 , $P < 0.001$). Adiponectin did not correlate with BMI or adiposity at 5,6,7 or 8 years in boys, and only correlated with adiposity in girls at 8 years ($r = -0.23$, $P = 0.04$). Adiponectin correlated with HOMA-IR, independently of adiposity, in boys only at 5 years and 6 years ($r = -0.19$ and $r = -0.20$, both $P = 0.04$).

Conclusions: Adiponectin ranking was maintained with increasing age, and levels fell with rising adiposity, despite the falling HOMA-IR. Relationships of adiponectin with obesity, % body fat and HOMA-IR were weak and inconsistent. We found little evidence that circulating adiponectin mediates obesity-related IR in young children.

P88

Relationships between resting energy expenditure, adiponectin and changes in the body composition of young children – The EarlyBird Diabetes study

J Hosking, BS Metcalf, AN Jeffery, D Gardner, LD Voss and TJ Wilkin
Department of Endocrinology and Metabolism, Peninsula Medical School, Plymouth, UK

Background: Adiponectin is inversely related to adiposity and resting energy expenditure (REE) in adults, and thought to protect against diabetes by reducing insulin resistance. It may also protect against weight gain. Little is known of these associations in children.

Aim: To investigate the relationships between REE, adiponectin and weight gain in young children.

Methods: Adiponectin by ELISA, REE by indirect calorimetry and fat-free mass (FFM)/fat mass (FM) by DEXA measured in 156 children at age 6.9 ± 0.3 years, and repeated one year later.

Results: (1) REE of boys at 7 years was higher than that of girls independent of body composition (1134 kcal/day vs. 1096 kcal/day, $P = 0.04$) (2) Adiponectin and FM were higher in girls than in boys (12.9 $\mu\text{g/ml}$ vs. 11.6 $\mu\text{g/ml}$, $P = 0.02$ and 5.2 kg vs. 3.8 kg, $P = 0.003$) at 7 years. There were no correlations between adiponectin and REE independent of body composition (boys: $r = -0.06$, $P = 0.54$, girls: $r = -0.05$, $P = 0.64$). (3) There were no correlations between REE at 7 years and subsequent FFM (boys: $r = -0.10$, $P = 0.39$, girls: $r = -0.01$, $P = 0.92$) or FM gain (boys: $r = 0.18$, $P = 0.12$, girls: $r = 0.02$, $P = 0.85$) independent of initial FFM, FM or adiponectin.

Conclusion: Unlike in adults, REE and adiponectin were unrelated in 7 year-old children, and neither was associated with subsequent weight gain.

Clinical science posters – Screening

P89

Adipocytokines are associated with development of metabolic syndrome in subjects screened for Type 2 diabetes

S Chatterjee*, K Khunti†, NF Da Silva†, S Kumar†, PG McTernan†, N Taub† and MJ Davies*

*Diabetes Research Unit, University Hospitals of Leicester, Leicester, UK;

†Department of Health Sciences, University of Leicester, Leicester, UK;

‡Unit for Diabetes and Metabolism, University of Warwick Medical School, Coventry, UK

Adipose tissue secretes adiponectin, leptin, resistin and TNF α , which are associated with impaired glucose tolerance and Type 2 diabetes. Abnormal glucose tolerance is one of the criteria for metabolic syndrome (MS). We measured these adipocytokines in a cohort of 231 White

Europeans (WE) and South Asians (SA) from a diabetes screening programme and determined their association with MS. Using WHO, NCEP and IDF criteria respectively, MS prevalence in WE ($n = 118$, 32% Type 2 diabetes, 39% IGT, mean age 59.5 years, mean BMI 27.8 kg/m^2), was 58%, 38% and 57%, whereas in SA, ($n = 113$, 27% Type 2 diabetes, 43% IGT, mean age 52.7 years, mean BMI 26.8 kg/m^2), it was 44% ($P = 0.03$), 31% (NS) and 54% (NS) respectively. Leptin correlated with MS using all three definitions in WE females ($r = 0.30$ – 0.50 , $P < 0.05$) and in WE males using IDF criteria ($r = 0.33$, $P = 0.004$). In WE males, using IDF and NCEP, adiponectin negatively correlated with MS ($r = -0.44$ and -0.35 , $P = 0.03$ and 0.002). In SA males, resistin correlated with MS using NCEP ($r = 0.42$, $P = 0.017$). We conclude that adipocytokines are associated with Metabolic Syndrome and may be useful in screening for this condition in a multiethnic population.

Clinical care posters – Obesity

P261

Relationship of obesity to prevalence of the metabolic syndrome in a multi-ethnic population using NCEP-III and IDF definitions

K Khunti*, M Davies*, J Bowden*, J Tringham†, J Jarvis†, TC Skinner† and AM Farooqi*

*University of Leicester, Leicester, UK, †University Hospitals of Leicester, Leicester, UK, ‡University of Southampton, Southampton, UK

Aim: To estimate the prevalence of the metabolic syndrome (MS) in south Asian (SA) and white European (WE) populations using NCEP-III and IDF criteria and the association of MS risk factors with obesity.

Methods: We screened 3028 (28% SA) people aged 40–75 years using a 75 g OGTT in a mixed ethnic population with one conventional risk factor for diabetes.

Results: Prevalence of MS using NCEP and IDF definitions were 30.2% (28.7 in SA, 30.2% in WE), and 34.8% (33.8%, 34.4%) respectively. The mean number of risk factors increased with increasing waist circumference (WC) and BMI in both ethnic groups ($P < 0.001$ for lowest versus highest quintile of WC and BMI). For people with a WC of < 75 cm and > 120 cm (and BMI < 20 kg/m² and > 35 kg/m²), WE females had the highest number of risk factors (0.79 and 1.9 for WC, 0.86 and 1.93 for BMI) and SA men had the lowest mean number of risk factors (0.3 and 1.25 for WC and 0.24 and 1.02 for BMI).

Conclusion: The prevalence of MS is high in both SA and WE populations. WC should be routinely measured in primary care and those with high WC or BMI should be screened for MS.

P262

Bioimpedance, a simple and cheap measure of body fat composition, is a reliable measure for use in patients with diabetes in a multi-ethnic population

S Chatterjee*, MJ Davies*, F Al-Azzawi†, N Taub†, JR Tringham*, A Farooqi‡ and K Khunti†

*Diabetes Research Unit, University Hospitals of Leicester, Leicester, UK,

†Menopause Research Unit, University Hospitals of Leicester, Leicester, UK,

‡Department of Health Sciences, University of Leicester, UK, §East Leicester Medical Practice, Leicester, UK

Obesity predisposes to Type 2 diabetes but BMI underestimates ethnic differences. Bioelectrical impedance analysis (BIA) and skinfold thickness are simple methods of measuring body fat. We validated them against the gold standard of DEXA in White Europeans (WE) and South Asians (SA) with screen-detected T2DM. 20 WE (50% male, mean age

68.5 years, BMI 27.8 kg/m²) and 17 SA (41% male, mean age 55.9 years, BMI 26.6 kg/m²) with T2DM were recruited from a population-based screening programme. Using DEXA, BIA and skinfold thickness respectively, in WE, body fat composition was $37.0 \pm 1.5\%$ (mean \pm SEM), $34.9 \pm 1.6\%$, and $36.3 \pm 1.0\%$; and in SA, $40.1 \pm 2.0\%$, $34.0 \pm 2.9\%$, and $37.4 \pm 1.1\%$. Using Student's T test, there were no differences between ethnic groups for all three methods. In WE, both skinfolds and BIA correlated with DEXA ($r = 0.71$ and 0.84 , $P > 0.001$). In SA, only BIA correlated with DEXA ($r = 0.71$, $P = 0.048$). In both ethnic groups 90% limits of agreement between DEXA and skinfolds were -7.9% to 9.5% , and for DEXA and BIA -4.9% to 10.3% . DEXA showed differences between lean abdominal mass in WE and SA males (25.6 kg vs. 20.4 kg, $P = 0.01$) and females (20.1 kg vs. 16.5 kg, $P = 0.07$). We conclude that BIA is more useful than skinfold thickness for body fat estimation in different ethnicities.

P263

Marked improvements in insulin resistance after modest weight loss following bariatric surgery in morbidly obese subjects

RA Gandhi*, D Selvarajah*, C Emery*, R Ackroyd† and S Tesfaye*

*Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield, UK,

†Department of Surgery, Royal Hallamshire Hospital, Sheffield, UK

Bariatric surgery is proven to result in sustained weight loss and is increasingly used in the management of morbid obesity. The exact mechanism by which it improves glucose metabolism and insulin resistance, however, remains controversial. 9 subjects (8 females) were reviewed before and 1-month after bariatric surgery. Insulin resistance was measured using the HOMA2 model and body fat was estimated by bioelectrical impedance. Total weight (mean \pm SD) fell from 128.3 ± 19 kg to 115.8 ± 17.1 kg ($P < 0.001$) leading to an improvement in BMI from 46.5 ± 6.5 to 42.0 ± 5.8 ($P < 0.001$). Total body fat fell from 69.4 ± 14.7 kg to 56.9 ± 12.4 kg ($P < 0.001$). There was an improvement in the HOMA2 IR from 3.3 ± 0.9 to 2.0 ± 1.0 ($P < 0.005$) with the majority of this improvement due to a rise in HOMA2 %S from $33 \pm 12.5\%$ to $68 \pm 44.5\%$ ($P < 0.02$). This study clearly shows a rapid and significant improvement in insulin resistance in subjects following relatively modest weight loss and in whom BMI remains significantly elevated, suggesting that simple calorie restriction and weight loss is not the full explanation. The role that surgery plays in complex changes within the entero-insular axis and the release of various adipocytokines and whether there are differences between different surgical procedures or subject groups is currently under investigation.

Clinical care posters – Pregnancy

P264

Can CSII facilitate successful breastfeeding in women with Type 1 diabetes?

J Abayomi*, G Morrison†, T Purewal†, K Mcfadden* and L Wood*

*Liverpool Women's Hospital, Liverpool, UK, †Royal Liverpool University Hospital, Liverpool, UK

Introduction: Uptake of breastfeeding (BF) by Type 1 women is low despite health benefits for mother and child. Delays in milk production, 'let-down' and hypoglycaemia make BF and glycaemic control difficult to manage. Continuous subcutaneous insulin infusion (CSII) improves

glycaemic control and stability, and may facilitate successful BF. However, NICE recommends discontinuing CSII post-delivery.

Method: Six women with Type 1 diabetes, 5 primigravidas, average age 29.5 (range 26–32) years, diabetes duration 14.5 (7–26) years, CSII duration 12.6 (5–32) months, with a mean HbA1c and BMI at booking of 7.4% (6.9–8.0)% and 25.3 (22.5–34.0) respectively, utilised CSII whilst BF. Strategies included, reducing the basal rate, testing blood and correcting low sugars pre-feed and introducing snacks with reduced insulin carbohydrate-ratio (1 unit: 20 g).

Results: All women breast-fed, mean duration 17 (6–35) weeks. Mean HbA1c and BMI 3 months post delivery were 7.5 (6.9–8.0)% and 26.2

Age Adjusted Ethnic Differences in the Metabolic Syndrome and its Components

		N	Waist Cir	High TG	Low HDL	Diabetes	Hyper- tension	Metabolic Syn
Men	Turkey	228	61	37	42	9	31	30
	Sri Lanka	603	45	35	46	14	35	26
	Iran	358	50	28	38	4	25	22
	Pakistan	244	60	34	46	15	39	35
	Vietnam	244	14	32	18	8	24	10
Women	Turkey	196	58	24	44	10	19	22
	Sri Lanka	398	47	27	66	14	22	25
	Iran	238	29	20	41	3	14	11
	Pakistan	196	65	30	60	20	22	35
	Vietnam	291	5	16	34	5	17	6
Cut Offs			>90 cmM	>2.7 mmolM	<1.0 mmolM	self reported	>=135/ 85mmhg	
			>85 cmW	>2.2 mmolW	<1.3 mmolW	&Glucose & medi- >7.8M cation >7.6W		

Support: Norwegian Research Council

685

Comparison of biological variation of insulin resistance markers

B. I. Shand¹, P. A. Elder², R. S. Scott¹, J. A. Willis¹, J. G. Lewis², C. M. Frampton³;
¹Lipid and Diabetes Research Group, Christchurch Hospital, ²Steroid and Immunobiology Laboratory, Christchurch Hospital, ³Department of Medicine, Christchurch Hospital, Christchurch, New Zealand.

Background and Aims: Insulin resistance is a marker of incipient type 2 diabetes and is used routinely to identify individuals who are at increased risk of developing this disorder. It is important that biochemical markers used in clinical practice are relatively stable, reproducible and easily measured. We carried out a study to compare the biological variation of several established surrogate markers of insulin resistance in subjects with the metabolic syndrome and in healthy controls.
Material and Methods: Fasting blood samples were collected at baseline and 10, 20, 30 days later from 10 subjects with the metabolic syndrome (5 males, 5 females, mean age 39.3 ± 11.6 yr) and 10 age- and sex-matched healthy controls (mean age 38.0 ± 11.0 yr). The samples were used to determine plasma glucose, insulin, adiponectin and sex hormone binding globulin (SHBG) concentrations. The homeostasis assessment model [HOMA] % sensitivity index was then calculated using the HOMA/CIGMA computer model. A nested ANOVA was used to compare the data in the two groups and also to determine the percentage biological variation of all the indices over the 30 day study period. The results of these analyses are summarised below.

Results:

	Metabolic Syndrome Mean(SD) %Variation		Controls Mean(SD) %Variation	
Glucose (mmol/l)	5.4 (0.4)*	4.9%	5.1 (0.4)	4.3%
Insulin (pmol/l)	145 (116)*	24.6%	35 (18)	27.2%
HOMA (%S)	46 (24)*	27.0%	174 (122)	44.7%
Adiponectin (µg/ml)	3.7 (1.3)*	12.2%	6.3 (3.4)	18.8%
SHBG (nmol/l)	27.2 (13.3)*	10.1%	50.9 (32.0)	18.1%

* p <0.01 for difference between metabolic syndrome and control groups.

Conclusion: The nested ANOVA showed there were significant differences in all the indices between the two groups. This analysis also demonstrated relatively large variations over time in plasma insulin, adiponectin and SHBG levels and HOMA % sensitivity index. The biological variation in these indices was lower in the metabolic syndrome group than in the control group. In both groups, the percentage variation over time in plasma adiponectin and SHBG levels was considerably lower than that measured for insulin and HOMA (%S). These results demonstrate that plasma adiponectin and SHBG have less biological variation than other markers of insulin resistance and therefore may be more reliable for serial assessment of insulin function in normoglycaemic individuals.
This study was funded by the 2005 NovoNordisk New Zealand Diabetes Research Scheme.

686

Abnormalities of adiponectin and leptin in white European and South Asian subjects screened for impaired glucose tolerance and type 2 diabetes

S. Chatterjee¹, N. Fernandes Da Silva², P. McTernan², K. Khunti³, S. Kumar², M. J. Davies¹;
¹Diabetes Research Unit, University Hospitals of Leicester, ²Unit for Diabetes and Metabolism, University of Warwick Medical School, ³Division of General Practice, University of Leicester, United Kingdom.

Background and Aims: Accumulating evidence suggests that inflammation is the link between obesity, type 2 diabetes and cardiovascular disease. Inflammatory markers that have been implicated are CRP, TNFα and IL-6. In addition, adipose tissue produces a number of adipocytokines such as adiponectin, leptin and resistin, which have been correlated with risk of developing abnormal glucose tolerance and cardiovascular disease. The South Asian (SA) population is known to have 2–4 fold increase in CVD compared with White Europeans (WE) although the exact mechanisms for this remain unclear. We studied the levels of these circulating risk markers in a cohort of WE and SA subjects diagnosed with IGT or T2DM through screening and compared them with age and sex matched controls. We sought to determine the level of risk as determined by concentration of these markers in each ethnic group across the glucose intolerance spectrum.
Materials and Methods: 217 subjects (110 WE, 107 SA) were recruited following OGTT screening for diabetes in Leicestershire, UK, through the STAR study (LREC approved). 61 subjects had diabetes of which 34 were WE (53% male), age 62 ± 10y (mean ± SD), BMI 31.7 ± 4.8 kg/m², and 27 were SA (52% male), age 53 ± 11y, BMI 29.2 ± 5.5 kg/m². 92 subjects had IGT with 46 WE (46% male), age 60 ± 10y, BMI 29.7 ± 5.8 kg/m², and 46 SA (46% males), age 54 ± 10.6y, BMI 27.6 ± 4.3 kg/m². 64 were age and sex matched controls with 30 WE (53%), age 57 ± 11y, BMI 22.7 ± 1.5 kg/m², and 34 SA (47%), age 53 ± 11y, BMI 24.3 ± 2.9 kg/m². The samples were analysed using ELISA hsCRP assay and bioplex assays for determining adiponectin, leptin, resistin and TNFα.
Results: In both ethnic groups several inflammatory markers were altered in the IGT and diabetic states compared with controls. Leptin levels in both control groups were significantly different from each other (leptin: (Mean ± SEM) WE: 4.01 ± 1.14 ng/mL vs SA: 28.41 ± 7.99 ng/mL, p < 0.001). Leptin was also observed to increase progressively with IGT and T2DM in both SA and WE (p > 0.05 and p < 0.05 respectively), with a similar pattern noted with TNFα. Adiponectin significantly decreased in both ethnic groups with IGT and T2DM (p < 0.05 for both ethnic groups). There was no significant increase in resistin, hsCRP, and TNFα levels with glucose intolerance in either ethnic group.
Conclusion: Our study suggests that altered levels of adipocytokines are seen in SA prior to development of glucose intolerant states, whereas in WE, these markers change significantly only on developing IGT and T2DM. We hypothesise that adipocytokine levels such as leptin and adiponectin may represent important key metabolic markers to determine early pathogenic risk for T2DM related complications such as CVD in different ethnic groups.

insulin (n=32). Patients were initially titrated to target fasting blood glucose (FBG) levels ≥ 4.5 mmol/L and ≤ 7.2 mmol/L (≥ 80 mg/dL and ≤ 130 mg/dL) in the morning at 06:00–07:00 hours. Patients had no intake of any insulin or food between 22:00 hours and 12:00 hours the next day and blood glucose was determined at 01:00, 03:00 and 05:00 hours. If FBG levels were in the target range, blood glucose, non-esterified fatty acids (NEFA) and β -hydroxybutyrate (β -OHB) were determined hourly until 12:00 hours.

Results: At baseline, mean age (42.6 years), mean duration of diabetes (14.7 years), mean body mass index (25.6 kg/m^2) and mean levels of NEFA (0.5 mM), β -OHB (0.2 mM), HbA_{1c} (7.5%) and FBG (8.0 mmol/L [144.1 mg/dL]) were similar between the two treatment groups. At 22:00 hours, blood glucose levels were higher with insulin glargine versus NPH insulin (8.8 vs 7.2 mmol/L [158.2 vs 130.2 mg/dL]); however, from 22:00 to 12:00 hours the next day (the period of no insulin or food intake), blood glucose levels decreased with insulin glargine (-1.43 mmol/L [-25.8 mg/dL]) and increased with NPH insulin ($+0.5 \text{ mmol/L}$ [$+9.1 \text{ mg/dL}$]; $p=0.0284$). At 22:00 hours, NEFA levels were similar in both treatment groups, but were significantly lower with insulin glargine than NPH insulin from 07:00 to 12:00 hours. The β -OHB levels were also similar at 22:00 hours in both groups, but were significantly lower with insulin glargine versus NPH insulin from 07:00 hours (0.19 vs 0.37 mM) to 12:00 hours (0.37 vs 0.72 mM); in addition, the β -OHB levels with NPH insulin were above the normal range (0.03–0.30 mM).

Conclusion: In summary, insulin glargine provides significantly better control of blood glucose and lipometabolism compared with NPH insulin in patients with type 1 diabetes on intensified conventional insulin therapy who miss breakfast and their insulin injection in the morning. Insulin glargine may thus permit flexibility in the insulin regimen.

This study was supported by sanofi-aventis.

905

Introduction of insulin glargine to basal-bolus therapy improves metabolic control in patients with type 1 diabetes in everyday clinical practice

B. Donaubaue¹, K. Schneider², M. A. Schweitzer²;
¹Dr Donaubaue Practice, Oschatz, ²Aventis Pharma Deutschland GmbH – A company of sanofi-aventis group, Bad Soden, Germany.

Background and Aims: This study examined the effect of insulin glargine in basal-bolus therapy in type 1 diabetes patients with inadequate metabolic control in everyday practice.

Materials and Methods: In this 6-week, uncontrolled, observational study, 1942 patients with type 1 diabetes poorly controlled on their previous basal-bolus therapy (basal: 95.5% NPH insulin; 4.3% lente; 0.2% other; bolus: 43.5% human insulin; 29.7% insulin lispro; 23.3% insulin aspart; 3.5% other insulins) received insulin glargine (median time of application 20:00 hours) in combination with rapid-acting or regular human insulin. Dosing decisions were made at the physicians' discretion. The mean \pm standard deviation (SD) target fasting blood glucose (FBG) and HbA_{1c} levels set by the physicians were 6.3 ± 1.3 mmol/L and $6.6 \pm 0.6\%$, respectively, after 6 weeks' treatment. Data relating to changes in HbA_{1c} , FBG, postprandial blood glucose (BG) and insulin dose are presented here.

Results: At baseline, mean \pm SD age was 42.5 ± 14.8 years, the mean \pm SD duration of previous basal-bolus treatment was 2.5 ± 3.4 years, mean \pm SD HbA_{1c} was $8.0 \pm 1.3\%$, mean \pm SD FBG was 9.1 ± 2.5 mmol/L and mean \pm SD body mass index was $25.1 \pm 4.0 \text{ kg/m}^2$. Patients achieved target FBG levels 6 weeks after the change in basal insulin (Table). At baseline, the mean \pm SD bolus insulin dose was 32.6 ± 17.6 IU (5.9 ± 4.4 IU/bread exchange unit); after 6 weeks, the mean \pm SD bolus insulin dose was 24.5 ± 14.6 IU (5.8 ± 4.1 IU/bread exchange unit). A total of 40 adverse drug reactions were reported in 17 patients, 20 of which were hypoglycaemic events.

	FBG (mmol/L)	HbA _{1c} (%)	2-hour postprandial BG (mmol/L)	Insulin glargine dose (IU)
Baseline	9.1 \pm 2.5	8.0 \pm 1.3	9.4 \pm 2.6	20.9 \pm 9.5*
6 weeks	6.6 \pm 1.6	7.2 \pm 0.9	7.4 \pm 1.6	23.4 \pm 10.1

*Mean starting dose of insulin glargine

Conclusion: These results from everyday practice are consistent with data obtained in clinical trials and suggest that replacing the basal insulin in basal-bolus therapy with insulin glargine may contribute to achieving target glycaemic control in patients with type 1 diabetes.

This study was supported by sanofi-aventis.

906

Glargine vs insulatard: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes – the Glargine and Aspart Study (GLASS)

M. J. Davies, S. Chatterjee, T. Rengarajan, I. G. Lawrence, P. G. McNally; Diabetes Research Unit, University Hospitals of Leicester, United Kingdom.

Background and Aims: Recent trials show that the long-acting insulin analogue Glargine is as effective at improving glycaemic control as traditional basal insulins such as NPH, whilst resulting in less nocturnal hypoglycaemia. Previous studies used either regular soluble insulin or lispro as the meal-time insulin. We assessed the efficacy of insulin Glargine compared with NPH insulin when combined with the insulin analogue aspart in a 36 week cross-over trial.

Materials and Methods: GLASS is a randomised single centre open-label two-period crossover study comparing the effects on HbA_{1c} of the basal insulins Glargine and Insulatard combined with pre-prandial insulin Aspart. Inclusion criteria were T1DM subjects aged 18–75y with baseline HbA_{1c} 6–11% on insulin for at least 6 months. After four-week run-in, subjects were randomized to sixteen weeks' treatment with once-daily insulin Glargine or twice daily Insulatard, before crossing over to the other basal insulin for sixteen weeks. Insulin Aspart was continued as mealtime insulin for all patients throughout the study. Standardized local algorithm was used for both basal insulin groups and all underwent identical titration and visit schedules. The primary outcome measure was HbA_{1c} and secondary endpoints were fasting plasma glucose, weight change, incidence of hypoglycaemia and effects on lipid profile.

Results: 60 almost all White European patients (33 male, mean age \pm SD 42.7 ± 12.5 y, diabetes duration 17.9 ± 12 y) with T1DM were recruited. 53 completed the study. Baseline HbA_{1c} was 8.53%. After 16 weeks' treatment with Glargine HbA_{1c} was 8.05% and with Insulatard was 8.26% (mean difference 0.19%, 95% CI -0.36, -0.01). There was a significant difference between treatments ($p=0.04$). There was a highly significant difference between the insulins for change in fasting plasma glucose ($p=0.002$), with mean fasting glucose level 7.8 mmol/L after Glargine and 11.4 mmol/L after Insulatard. Mean (\pm SEM) basal insulin dose was 37 ± 2 IU/day of Glargine and 40 ± 3 IU/L/day of Insulatard ($p=NS$). After 16 weeks, Glargine dose was 41 ± 4 IU/L and Insulatard dose 36.7 ± 3 IU/L ($p=0.1$). There were no differences in minor hypoglycaemia ($p=0.63$), weight ($p=0.45$) or cholesterol ($p=0.18$) between groups. There was only one major hypoglycaemic event in each arm. Patient satisfaction was greater with Glargine and three patients dropped out of the study, as they did not wish to go back to Insulatard.

Variable	Glargine	Insulatard	Difference (Glargine- Insulatard)	95% Confidence Interval	p-value
HbA _{1c} (%)	8.07	8.26	-0.19	(-0.36, -0.01)	0.04
Fasting glucose (mmol/L)	8.42	11.42	-3.00	(-4.80, -1.20)	<.01
Incidence of hypos (%)	80.7% ¹	77.2% ²	1.21*	(0.56, 2.64)*	0.63
Weight (kg)	81.68	81.92	-0.24	(-0.87, 0.39)	0.45
Cholesterol (mmol/L)	4.74	4.84	-0.10	(-0.25, 0.05)	0.18
Triglyceride (mmol/L) (Geometric means)	0.82	0.80	1.02*	(0.93, 1.12)*	0.63

*Ratio

¹ 2 subjects with no data, percentage calculated using total in group (57)

² 3 subjects with no data, percentage calculated using total in group (57)

Conclusions: Our study shows a small but significant improvement in glycaemic control with insulin Glargine without adverse effects on hypoglycaemia rate, weight, lipids or patient satisfaction. We would suggest that Glargine combined with insulin aspart is a satisfactory basal bolus regimen in subjects with type 1 diabetes.

ADDQoL

This questionnaire asks about your quality of life and the effects of your diabetes on your quality of life. Your quality of life is how good or bad you feel your life to be.

Please shade the circle which best indicates your response on each scale.

There are no right or wrong answers; we just want to know how you feel about your life now.

I) **In general, my present quality of life is:**

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
excellent	very good	good	neither good nor bad	bad	very bad	extremely bad

For the next statement please consider the effects of your diabetes, its management and any complications you may have.

II) **If I did not have diabetes, my quality of life would be:**

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very much better	much better	a little better	the same	a little worse	much worse	very much worse

Please respond to the 18 more specific statements on the pages that follow.

For each statement, please consider the effects of your diabetes, its management and any complications you may have on the aspect of life described by the statement.

In each of the following boxes:

- a) shade a circle to show how diabetes affects this aspect of your life;
- b) shade a circle to show how important this aspect of your life is to your quality of life.

Some statements have a "not applicable" option. Please shade this "not applicable" circle if that aspect of life does not apply to you.

1a)	If I did not have diabetes, my working life and work-related opportunities would be:						<input type="radio"/> not applicable
	<input type="radio"/> very much better	<input type="radio"/> much better	<input type="radio"/> a little better	<input type="radio"/> the same	<input type="radio"/> a little worse	<input type="radio"/> much worse	
1b)	This aspect of my life is:						
	<input type="radio"/> very important	<input type="radio"/> important	<input type="radio"/> somewhat important	<input type="radio"/> not at all important			

2a)	If I did not have diabetes, my family life would be:						<input type="radio"/> not applicable
	<input type="radio"/> very much better	<input type="radio"/> much better	<input type="radio"/> a little better	<input type="radio"/> the same	<input type="radio"/> a little worse	<input type="radio"/> much worse	
2b)	This aspect of my life is:						
	<input type="radio"/> very important	<input type="radio"/> important	<input type="radio"/> somewhat important	<input type="radio"/> not at all important			

2a)	If I did not have diabetes, my family life would be:						<input type="radio"/> not applicable
	<input type="radio"/> very much better	<input type="radio"/> much better	<input type="radio"/> a little better	<input type="radio"/> the same	<input type="radio"/> a little worse	<input type="radio"/> much worse	
2b)	This aspect of my life is:						
	<input type="radio"/> very important	<input type="radio"/> important	<input type="radio"/> somewhat important	<input type="radio"/> not at all important			

4a)	If I did not have diabetes, my sex life would be:						<input type="radio"/> not applicable
	<input type="radio"/> very much better	<input type="radio"/> much better	<input type="radio"/> a little better	<input type="radio"/> the same	<input type="radio"/> a little worse	<input type="radio"/> much worse	
4b)	This aspect of my life is:						
	<input type="radio"/> very important	<input type="radio"/> important	<input type="radio"/> somewhat important	<input type="radio"/> not at all important			

5a)	If I did not have diabetes, my physical appearance would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much better	much better	a little better	the same	a little worse	much worse	very much worse
5b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
	very important	important	somewhat important	not at all important			

6a)	If I did not have diabetes, the things I could do physically would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased
6b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
	very important	important	somewhat important	not at all important			

7a)	If I did not have diabetes, my holidays or leisure activities would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much better	much better	a little better	the same	a little worse	much worse	very much worse
7b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
	very important	important	somewhat important	not at all important			

8a)	If I did not have diabetes, ease of travelling (local or long distance) would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much better	much better	a little better	the same	a little worse	much worse	very much worse
8b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
	very important	important	somewhat important	not at all important			

9a) If I did not have diabetes, my confidence in my ability to do things would be:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

9b) This aspect of my life is:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very important	important	somewhat important	not at all important

10a) If I did not have diabetes, my motivation to achieve things would be:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased

10b) This aspect of my life is:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very important	important	somewhat important	not at all important

11a) If I did not have diabetes, the way society at large reacts to me would be:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very much better	much better	a little better	the same	a little worse	much worse	very much worse

11b) This aspect of my life is:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very important	important	somewhat important	not at all important

12a) If I did not have diabetes, my worries about the future would be:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased

12b) This aspect of my life is:

<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
very important	important	somewhat important	not at all important

13a)	If I did not have diabetes, my finances would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much better	much better	a little better	the same	a little worse	much worse	very much worse
13b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very important	important		somewhat important		not at all important	

14a)	If I did not have diabetes, my need to depend on others for things I would like to do for myself would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much decreased	much decreased	a little decreased	the same	a little increased	much increased	very much increased
14b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very important	important		somewhat important		not at all important	

15a)	If I did not have diabetes, my living conditions would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much better	much better	a little better	the same	a little worse	much worse	very much worse
15b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very important	important		somewhat important		not at all important	

16a)	If I did not have diabetes, my freedom to eat as I wish would be:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very much increased	much increased	a little increased	the same	a little decreased	much decreased	very much decreased
16b)	This aspect of my life is:						
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	very important	important		somewhat important		not at all important	

17a) If I did not have diabetes, my enjoyment of food would be:

☐

very much increased

☐

much increased

☐

a little increased

☐

the same

☐

a little decreased

☐

much decreased

☐

very much decreased

17b) This aspect of my life is:

☐

very important

☐

important

☐

somewhat important

☐

not at all important

18a) If I did not have diabetes, my freedom to drink as I wish (e.g. sweetened hot and cold drinks, fruit juice, alcohol) would be:

☐

very much increased

☐

much increased

☐

a little increased

☐

the same

☐

a little decreased

☐

much decreased

☐

very much decreased

18b) This aspect of my life is:

☐

very important

☐

important

☐

somewhat important

☐

not at all important

If there are any other ways in which diabetes, its management and any complications affect your quality of life, please say what they are below:

The Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1.

How satisfied are you with your current treatment?

very satisfied

6

5

4

3

2

1

0

very dissatisfied
2.

How often have you felt that your blood sugars have been unacceptably high recently?

most of the time

6

5

4

3

2

1

0

none of the time
3.

How often have you felt that your blood sugars have been unacceptably low recently?

most of the time

6

5

4

3

2

1

0

none of the time
4.

How convenient have you been finding your treatment to be recently?

very convenient

6

5

4

3

2

1

0

very inconvenient
5.

How flexible have you been finding your treatment to be recently?

very flexible

6

5

4

3

2

1

0

very inflexible
6.

How satisfied are you with your understanding of your diabetes?

very satisfied

6

5

4

3

2

1

0

very dissatisfied
7.

Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment

6

5

4

3

2

1

0

No, I would definitely not recommend the treatment
8.

How satisfied would you be to continue with your present form of treatment?

very satisfied

6

5

4

3

2

1

0

very dissatisfied

Please make sure that you have circled one number on each of the scales.

The Diabetes Treatment Satisfaction Questionnaire (change): DTSQc

For the past few weeks/months you have been taking part in a diabetes treatment study. At the start of the study you may have had a change of treatment. Today we would like to know how your experience of your current treatment (including medication and diet) has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now
------------------------------	---	---	---	---	----	----	----	------------------------------

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now
------------------------------	---	---	---	---	----	----	----	------------------------------

4. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now
-----------------------------	---	---	---	---	----	----	----	-----------------------------

5. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now
---------------------------	---	---	---	---	----	----	----	---------------------------

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

7. How likely would you be to recommend your present treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now
---	---	---	---	---	----	----	----	---

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now
----------------------------	---	---	---	---	----	----	----	----------------------------

Please make sure that you have circled one number on each of the scales.

PATIENT INFORMATION SHEET

Insulatard versus Glargine - Efficacy in combination with Insulin Aspart, in Type 1 Diabetes Mellitus

GLASS - GLargine and ASpart Study

We would like to invite you to help the department of diabetes with a research project regarding the use of some new types of insulin called Glargine and Insulin Aspart in the treatment of people with insulin dependent (Type 1) diabetes.

What is the purpose of this study?

Previous research studies have proved that by controlling diabetes, long term complications such as eye and kidney disease can be significantly reduced. This can be done through intensive treatment regimens. One type of intensified insulin therapy is the administration of short acting insulin before main meals and intermediate/long acting insulin once or twice daily to cover the background insulin requirements. Both of these insulin's are usually injected 30 minutes before a meal to give them a chance to work. We want to look at one of our current insulins and 2 new insulins in combination with each other to see what effect they have on long term blood sugar levels, hypoglycaemia (low blood sugar) and fasting blood levels. We also want to look at the effect on blood fats such as cholesterol. The insulins we will be looking at will be:

- Insulin Aspart before each main meal plus Insulin Glargine before bedtime
- Insulin Aspart before each main meal plus twice daily Insulatard

What is Insulin Aspart?

Insulin Aspart is a new rapid acting insulin that is taken to cover glucose levels after your main meals. Insulin Aspart can be taken before, during or straight after meals. Insulin Aspart is used in combination with long acting insulins

What is Insulatard?

Insulatard is a long acting insulin which provides a background level of insulin to regulate blood sugar levels throughout the day. The action of Insulatard does not last for 24 hours, therefore usually 2 injections of Insulatard are needed to give 24 hour cover of background insulin.

What is Insulin Glargine?

Insulin Glargine is a new long acting insulin that gives a slow release of background insulin over a 24 hour period. This means that only one injection of insulin is needed

What will the study involve?

The study will involve taking both combinations of insulin. For 4 weeks you will receive Insulin Aspart 3 times a day and Insulatard twice a day. After this 4 weeks you will either continue taking insulin Aspart and Insulatard for a further 16 weeks or change over to take Insulin Aspart 3 times a day and insulin Glargine at bedtime for a further 16 weeks. This will be randomly chosen for you (a bit like tossing a coin). After 16 weeks you will then swap over to having the other treatment for 16 weeks. This means that patients taking Insulin Aspart and Insulatard for the first 16 weeks will swap over to Insulin Aspart and Glargine for the next 16 weeks and vice versa. The total length of the study will be 36 weeks.

If you decide to take part in the study we will ask you to come to the diabetes research clinic 7 times over the 36 week study period. The first visit will take approximately one hour with the following visits taking between half an hour to an hour. For most of these visits we will check your height, weight, blood pressure we will also take a small amount of blood (between one and one and a half teaspoons worth) for the following tests; long term blood glucose (HbA1c), fasting blood glucose and cholesterol. For these blood tests you will need to come to the clinic fasting. This means not having anything to eat or drink from midnight the night before your visit, although you may drink water if needed. We will also ask you to fill out a treatment satisfaction questionnaire. Before you come for 3 of the visits we will also take a 72 hour continuous blood glucose profile. This involves wearing a monitor for 72 hours which has a small needle that is attached under the skin. You would have to attend the hospital to have this attached before your clinic visits, this is a very simple, painless procedure and each visit should take no longer than one hour. This gives us a continuous reading of your blood sugar levels throughout the day and night.

What else will I have to do?

During the study, a diabetes specialist research nurse will keep in contact with you to adjust your insulin dose with you and monitor your blood sugar results. This will be around twice a week or more frequently if needed. We will ask you to do blood sugar readings at home and we will provide you with a new meter to do this. We will ask you to write down these results in a book that we will provide. We will also ask you to record in this book if you have any episodes of hypoglycaemia (low blood sugar).

Will there be any side effects?

Due to taking insulin, possible side effects include hypoglycaemia. Symptoms of having a low blood sugar include lack of energy, confusion, pounding heart, sweating, vomiting and headache. Severe cases of low blood sugar may lead to unconsciousness and in extreme cases, death. Data from trials with Glargine and Aspart suggest that there is a lower rate of hypoglycaemia (low blood sugar) compared to conventional insulin.

What if I am harmed by the study?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e compensation is only available if negligence occurs.

Will I benefit from taking part in the study?

This study will give a chance to see if insulin Glargine is suitable for you in controlling your blood sugars. If at the end of the study you and your doctor decide insulin Glargine are the best treatment for you, it may be possible to continue taking Glargine on an individual basis, despite Glargine being unavailable in the UK at the moment.

What happens if I do not wish to participate in this study or wish to withdraw from the study?

If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected

Who will see my medical records?

Only your consultant and other members of the research team will need to have access to your medical notes. All information will remain completely confidential. The results of the study may be published in a professional journal, but you will not be identified by name.

Will I receive payment for taking part in the study?

Although there is no payment for taking part in the study, travelling expenses will be reimbursed.

Thank you for taking the time to read this information sheet. If you require further information please do not hesitate to contact or on 0116 2587635.

PATIENT INFORMATION SHEET

A pilot study to look at the safety and efficacy of different combinations of nateglinide and pioglitazone early in patients with Type 2 diabetes

Short Title: PICNIC for early Type 2 Diabetes
(Pioglitazone In Combination with Nateglinide In Care for early Type 2 Diabetes)

We would like to invite you to participate in a research project using some new tablets for the treatment of people with type 2 diabetes. These tablets are called Pioglitazone and Nateglinide. This study is a randomized controlled trial.

What is Type 2 Diabetes?

Type 2 diabetes (also known as non-insulin dependent diabetes) is a disease where blood sugar levels (glucose) in the body become uncontrolled due to the pancreas not producing enough insulin and the body not responding to the insulin effectively. Patients who are diagnosed with type 2 diabetes are at risk of suffering with problems associated with the feet, eyes, heart, circulation and kidneys.

What is the purpose of this study?

Previous research studies have proved that by controlling diabetes, long term complications such as eye and kidney disease can be significantly reduced. This can be done through using different tablets in combination with each other. One of the treatment regimes that has been used for a long time in Leicester is the use of Gliclazide with Metformin. We want to look at the effect of 2 new types of tablets called Pioglitazone and Nateglinide to see what effect they have on long term sugar levels when compared with Gliclazide and Metformin.

We will also look at the rate of hypoglycaemia (low blood sugar) and fasting blood sugar levels. We also want to look at the effect on blood fats such as cholesterol.

What is Gliclazide and Metformin?

Gliclazide is a tablet for diabetes that increases the amount of insulin produced by the pancreas. Metformin works by making the body cells more sensitive to insulin, not by stimulating the pancreas. This combination of tablets is used commonly for type 2 diabetes.

What is Pioglitazone and Nateglinide?

Pioglitazone is a new tablet for diabetes that helps with reducing insulin resistance. Insulin resistance is common in type 2 diabetes. In diabetes the body is unable to use glucose properly for energy. Nateglinide mimics the pancreas's response to a meal by stimulating insulin only at meal times. The tablet is taken with meals

What will the study involve?

The study will involve taking either:

1. Metformin and Gliclazide
2. Pioglitazone and Nateglinide or
3. Nateglinide and Metformin
4. Metformin and Pioglitazone

This study is a randomised controlled trial, This means that the medication assigned to you will be randomly chosen (a bit like tossing a coin). The total length of the study will be 6 months.

If you decide to take part in the study we will ask you to come to the diabetes research clinic 4 times over the 6 month study period and we will also keep in touch with you by telephone. The first visit will take about one hour and the following visits between half an hour and one hour.

For most of these visits we will check your height, weight, blood pressure and we will also need to take a small amount of blood (between one to one and a half teaspoons worth) for the following tests; long term blood sugar (HbA1c), fasting blood sugar, cholesterol, kidney and liver blood tests.

For these blood tests you will need to come in fasting, this means that you should have nothing to eat or drink, although you can have water if needed, from midnight the night before your study visit. You will be given something to eat and drink as soon as the blood samples have been taken.

We will also ask you to fill out a questionnaire. The questionnaire will take approximately 10 minutes to complete. To start taking some of the study medication it is necessary to have a recent blood result to show how well your liver and kidneys are working. In most patients we will have a recent blood result and you will be able to start taking your medication at the first visit. In some people we do not have this information and we will need to wait until the blood results from the first visit have come back from the laboratory. If these blood results come back within the study range a research nurse will ring you approximately 2 days after your first visit to tell you to start taking the tablets.

Prior to visit 4 we would also like to randomly select (a bit like tossing a coin) 5 patients from each group to participate in a 72 hour continuous blood glucose profile. This involves wearing a monitor for 72 hours which has a small needle that is attached under the skin. You would have to attend the hospital

to have this attached before your clinic visit, this is a very simple, painless procedure and should take no longer than one hour. This gives us a continuous reading of your blood sugar levels throughout the day and night.

What else will I have to do?

We will ask you to do blood sugar readings at home and we will provide you with a new meter to do this. We will ask you to write down these results in a book that we will provide. We will also ask you to record in this book if you have any episodes of hypoglycaemia (low blood sugar).

Will there be any side effects?

Possible side effects include hypoglycaemia (low blood sugar). Symptoms of having a low blood sugar include lack of energy, confusion, pounding heart, sweating, vomiting and headache. Severe cases of low blood sugar may lead to unconsciousness and in extreme cases, death. Data from trials with all of the tablets being used in the study show low rates of hypoglycaemia (low blood sugar). At the start of the study you will be issued with contact telephone numbers to call for advice on hypoglycaemia. You will be asked to record any episodes of hypoglycaemia in your blood monitoring diary.

What if I am pregnant or Breast Feeding?

If you are pregnant or breast feeding you will not be able to take part in the trial. This is because the tablets being used in the trial are not licenced for use in pregnancy. If you become pregnant during the trial then you will be withdrawn from the study and your treatment will be reviewed by a consultant from the diabetes speciality. If you are a woman of child bearing age you will be asked to provide urine for a pregnancy test to be performed before you start taking any tablets. To take part in the study you have to be using adequate contraception.

What if I am harmed by the study?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e compensation is only available if negligence occurs.

What happens if I do not wish to participate in this study or wish to withdraw from the study?

If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected

Will information obtained in the study be confidential ?

Only your consultant and other members of the research team will need to have access to your medical notes. All information will remain completely

confidential. The results of the study may be published in a professional journal, but you will not be identified by name. Your GP will be informed of your participation in the trial, unless you state otherwise

Will I receive payment for taking part in the study?

Although there is no payment for taking part in the study, reasonable travelling expenses will be reimbursed.

Thank you for taking the time to read this information sheet. If you require further information please do not hesitate to contact the Diabetes Research Team on 0116 2587635.

PATIENT INFORMATION SHEET

Measurement of body fat composition using DEXA scanning in subjects screened for diabetes

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We know that having higher percentages of body fat compared to muscle increases the risk of developing diabetes and heart disease.

The purpose of this study is to measure body composition (the amount of fat, muscle and water in the body) in subjects who have been screened for diabetes. We will be using a method called dual-energy x-ray absorptiometry or DEXA scanning.

You will already have had other body measurements such as waist to hip ratio, skinfold thickness and bioelectrical impedance. DEXA scanning is a further way of measuring body composition in subjects who have been screened for diabetes. The results of DEXA scanning will be compared with these other methods. We will also compare White European subjects with South Asian subjects as there may be a difference depending on your ethnic background.

This study will be recruiting around 80 subjects over 6 months. Each subject will be invited to attend a single appointment at Leicester Royal Infirmary lasting about 1 hour during this six-month period.

Why have I been chosen?

You have been chosen for this study because you have participated in the STAR or ADDITION diabetes screening programmes during which you underwent various body measurements. These measurements will be compared with the DEXA scan result.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will be invited to attend an appointment for DEXA scanning at Leicester Royal Infirmary. This appointment will last approximately 1 hour. During this time, you will have an opportunity to discuss the procedure with the study investigators. We will obtain written consent from you. The scan, which is like an x-ray, will take about 10 minutes to perform.

Will I receive any payment for this study?

You will not be paid for taking part in the study.

However, we will pay for your travel expenses and parking.

What is the procedure that is being tested?

DEXA scanning is a commonly used x-ray procedure, which allows measurement of body fat, muscle and bone.

What are the possible disadvantages and risks of taking part?

The amount of x-ray radiation you will be exposed to is about one-fiftieth that of a standard chest x-ray. This radiation is not likely to harm you in any way.

The annual risk of a fatal accident in the home is more than three times as big as the risk from the exposure to radiation in this study.

What are the possible benefits of taking part?

This study will add information about your body composition. This will be useful in advising you to make certain lifestyle changes, which may reduce the amount of body fat you have. Such lifestyle changes are weight reduction, eating a healthy diet, and taking more exercise.

We will advise you of any required changes during and and/or after your visit.

What if I am harmed by the study?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential.

Information collected about you in this study will be stored in a computer database and protected by password. This information will be kept for up to five years before being destroyed.

Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Your GP will be notified of your participation in this study. We will check that you are happy for your GP to be notified when you give us your written consent.

What will happen to the results of the research study?

The results may be published in a professional journal but you will not be identified by name. All information will be kept completely confidential.

Who is organising and funding the research?

The study is being organised by the Diabetes Research Unit at Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. This trust is also partially funding the research.

Who has reviewed the study?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any

harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

Contact for Further Information

If you require any further information please do not hesitate to contact Dr S Chatterjee, Diabetes Research Registrar, in the Diabetes Research Unit, Tel No. (0116) 2047819.

Thank you for reading this information sheet.

Centre Number: :
Study Number:
Patient Identification Number for this trial:

Leicester Royal Infirmary

CONSENT FORM

Title of Project: Measurement of body fat composition using
DEXA scanning in subjects screened for diabetes

Name of Researcher: Dr S Chatterjee

Please initial box

1. I confirm that I have read and understand the information sheet dated 1/12/04, version 2, for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Diabetes Research Unit, Leicester Royal Infirmary, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

☐☐☐☐

Name of Patient
Signature

Date

Name of Person taking consent
Signature
(if different from researcher)

Date

Researcher
Signature

Date

**Insulatard versus Glargine - Efficacy in combination with Insulin Aspart, in
Type 1 Diabetes Mellitus**

GLASS - GLargine and ASpart Study

CONSENT FORM

This form should be read in conjunction with the patient information sheet

I agree to take part in the above study as described in the patient information sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant section of my medical records, but that all the information will be treated as confidential.

I understand that medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet and have had the opportunity to discuss the details with and ask any questions. The nature and purposes of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient: _____ Date: _____

Name of Patient (Block Capitals) _____

I confirm that I have explained the nature of the trial, as detailed in the Patient Information Sheet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Principle Investigator: _____ Date: _____

Name of Investigator (Block Capitals) _____

A pilot study to look at the safety and efficacy of different combinations of nateglinide and pioglitazone early in patients with Type 2 diabetes

Short Title: PICNIC for early Type 2 Diabetes

(Pioglitazone In Combination with Nateglinide In Care for early Type 2 Diabetes)

Lead Investigator: Dr M Davies, Consultant Diabetes and Endocrinology
Co Investigators: Dr P McNally, Consultant Diabetes and Endocrinology
Dr I Lawrence, Consultant Diabetes and Endocrinology

CONSENT FORM

This form should be read in conjunction with the patient information sheet, dated Version 5, 31st March 2004

I agree to take part in the above study as described in the patient information sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant section of my medical records, but that all the information will be treated as confidential.

I understand that medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet and have had the opportunity to discuss the details with _____ and ask any questions. The nature and purposes of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient: _____ Date: _____

Name of Patient (Block Capitals) _____

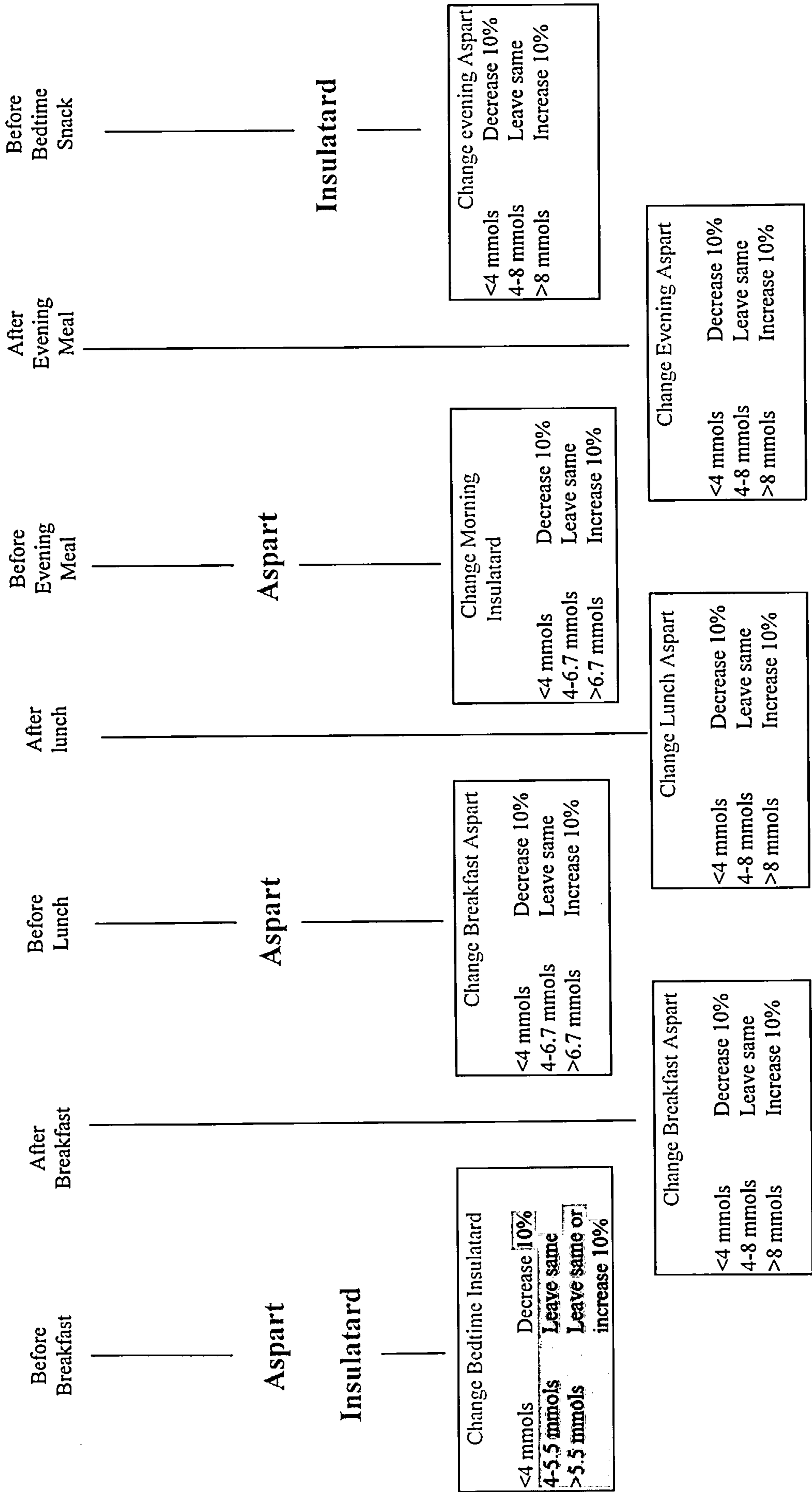
I confirm that I have explained the nature of the trial, as detailed in the Patient Information Sheet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Researcher taking consent: _____ Date: _____

Name of Researcher taking consent (Block Capitals) _____

Insulin Algorithm

Insulin Aspart TDS and Insulatard BD

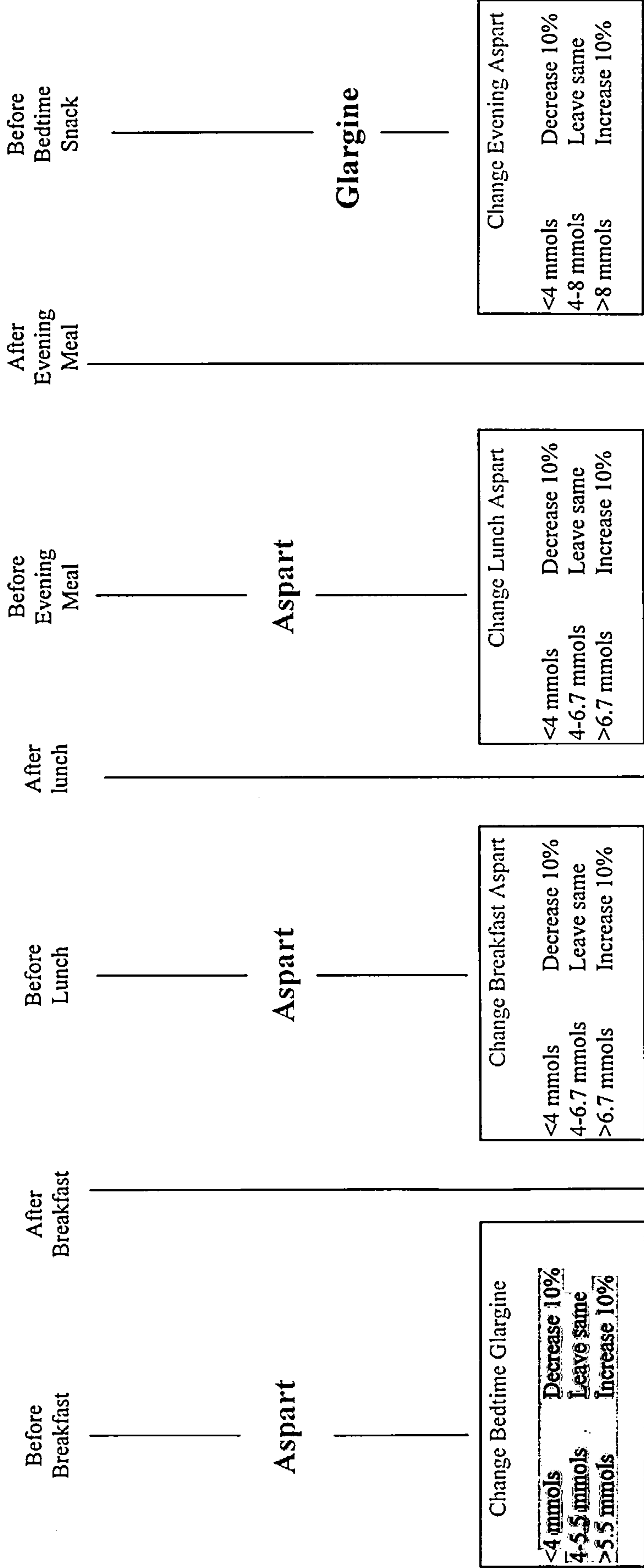


NB: Patients are asked to test once daily at different times of the day. If testing is at breakfast, lunch or evening meal, then testing should also be done before the meal and 120 minutes after the meal. Insulin will be changed 10% or no more than 6 units

When changing from twice daily Insulatard to Glargine once daily, the current basal insulin dose will be reduced by 20% and Mealtime Aspart will be increased by 2 units for each dose to compensate

Insulin Algorithm

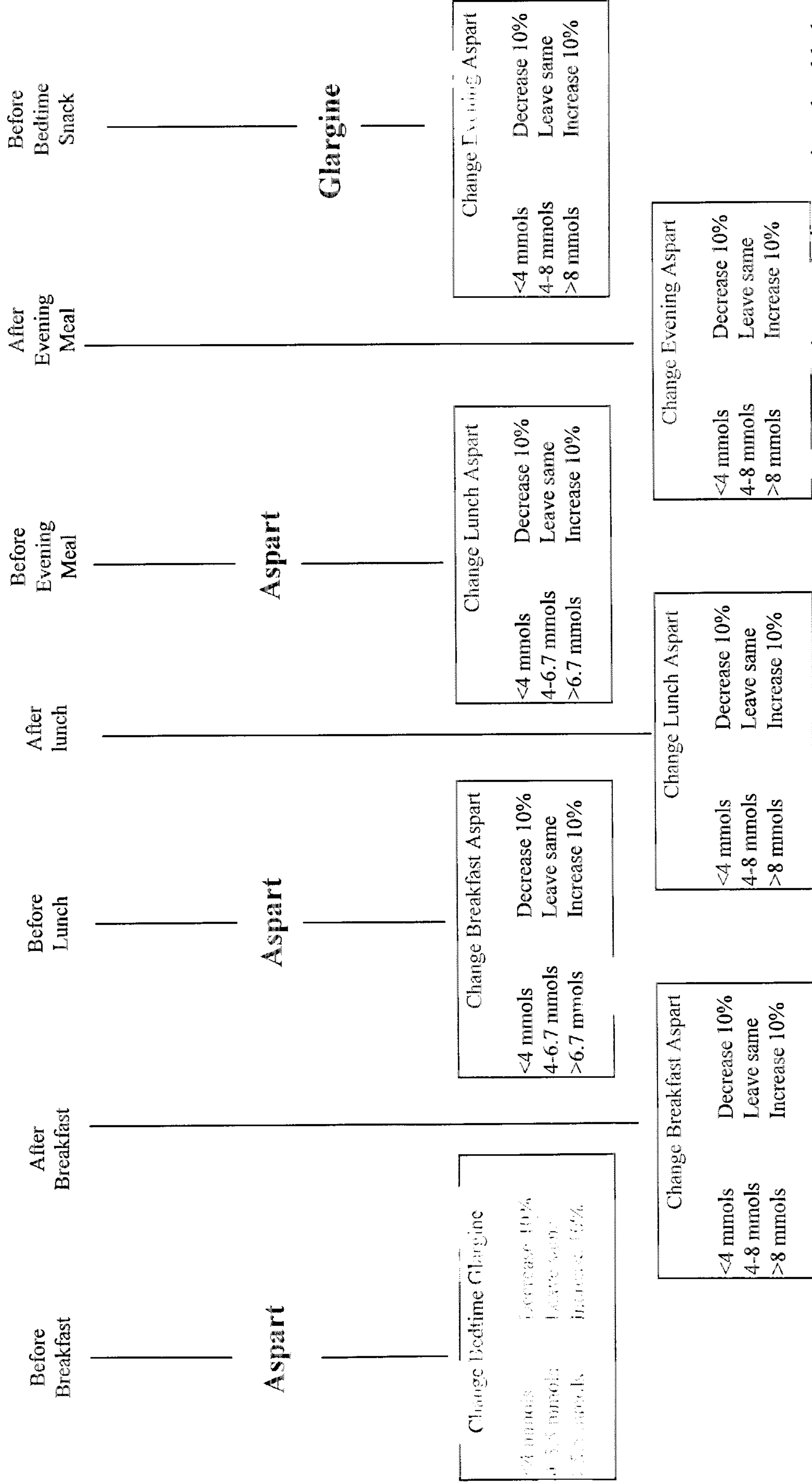
Insulin Aspart TDS and Glargine OD



NB: Patients are asked to test once daily at different times of the day. If testing is at breakfast, lunch or evening meal, then testing should also be done before the meal and 120 minutes after the meal. Increases made will be based on 10% or no more than 6 units

When changing from once daily Glargine, to twice daily insulatard the current basal insulin dose will be equal to the dose of insulatard at the end of the run-in period provided the Glargine dose at the end of the first treatment period is within 20% of the dose of insulatard at the end of the run-in period. If the dose of Glargine at the end of the first treatment period is greater than 120% of the dose of insulatard at the end of the run-in period, then patients will be commenced on a dose of insulatard that is between 80-90% of the current dose of Glargine (at the end of the first treatment period)

Insulin Algorithm
Insulin Aspart (ID) and Glargine OD



NB: Patients are asked to test once daily at different times of the day. If testing is at breakfast, lunch or evening meal, then testing should also be done before the meal and 120 minutes after the meal. Increases made will be based on 10% or no more than 6 units

When changing from once daily Glargine to twice daily insulin the current basal insulin dose will be divided by 2 to give the new basal dose

When changing from twice daily insulin to once daily Glargine the current basal insulin dose will be multiplied by 2 to give the new basal dose

When changing from once daily Glargine to twice daily insulin the current basal insulin dose will be divided by 2 to give the new basal dose

When changing from twice daily insulin to once daily Glargine the current basal insulin dose will be multiplied by 2 to give the new basal dose

When changing from once daily Glargine to twice daily insulin the current basal insulin dose will be divided by 2 to give the new basal dose