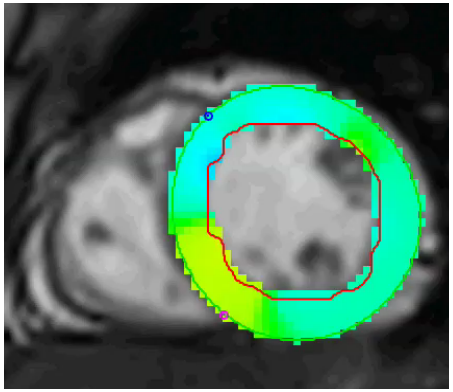
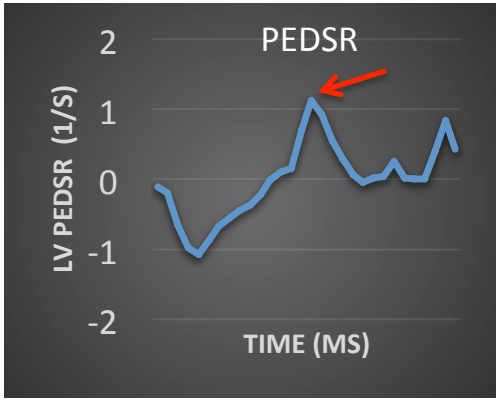
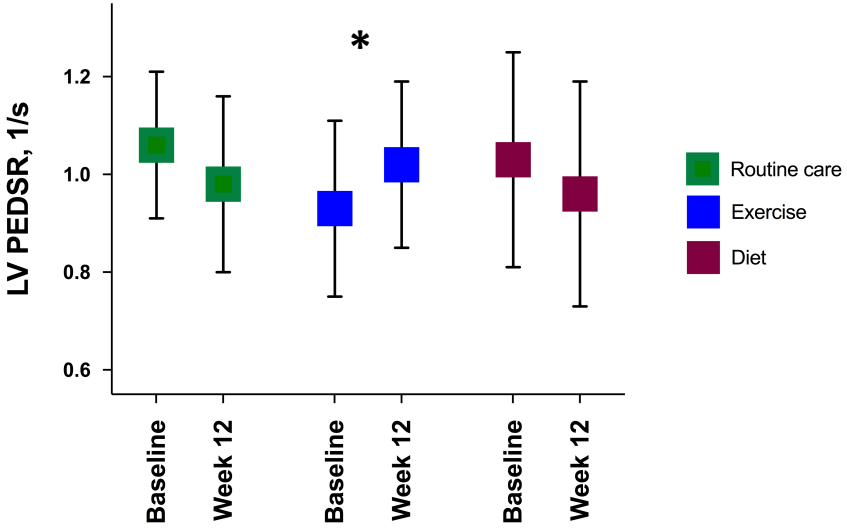
American Diabetes Association. Diabetes Care

Effects of low-energy diet or exercise on cardiovascular function in working-age adults with type 2 diabetes: a prospective, randomized, open-label, blinded endpoint trial

Journal:	*Diabetes Care*
Manuscript ID	DC20-0129
Manuscript Type:	Original Article: Cardiovascular and Metabolic Risk
Date Submitted by the Author:	19-Jan-2020
Complete List of Authors:	Gulsin, Gaurav; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Swarbrick, Daniel; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Athithan, Lavanya; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Brady, Emer; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Henson, Joseph; University of Leicester and the Leicester NIHR Biomedical Research Centre, Leicester Diabetes Centre Baldry, Emma; University of Leicester and the Leicester NIHR Biomedical Research Centre, Leicester Diabetes Centre Argyridou, Stavroula; University of Leicester and the Leicester NIHR Biomedical Research Centre, Leicester Diabetes Centre Jaicim, Nishal; University of Leicester Clinical Trials Unit Squire, Gareth; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Walters, Yvette; University of Leicester Clinical Trials Unit Marsh, Anna-Marie; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences McAdam, John; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Parke, Kelly; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences Biglands, John; Leeds NIHR Biomedical Research Centre Yates, Thomas; University of Leicester and the Leicester NIHR Biomedical Research Centre, Diabetes Research Centre Khunti, Kamlesh; University of Leicester, Leicester Diabetes Centre Davies, Melanie; University Hosptials of Leicester, Leicester Royal Infirmary, Dept. Diabetes McCann, Gerry; University of Leicester and the Leicester NIHR Biomedical Research Centre, Cardiovascular Sciences




PEDSR
LV PEDSR (1/S)
2
1
0
-1
-2
TIME (MS)


LV PEDSR, 1/s
1.2
1.0
0.8
0.6
*
Baseline
Week 12
Baseline
Week 12
Baseline
Week 12
Routine care
Exercise
Diet

Effects of low-energy diet or exercise on cardiovascular function in working-age adults with type 2 diabetes: a prospective, randomized, open-label, blinded endpoint trial

Running title: Effects of diet or exercise in type 2 diabetes

Gaurav S Gulsin MRCP[a], Daniel J Swarbrick MRCP[a], Lavanya Athithan MRCP[a], Emer M Brady PhD[a], Joseph Henson PhD[b], Emma Baldry PhD[b], Stavroula Argyridou MSc[b], Nishal B Jaicim PhD[c], Gareth Squire MBChB[a], Yvette Walters BSc[c], Anna-Marie Marsh PhD[a], John McAdam MSc[a], Kelly S Parke BSc[a], John D Biglands PhD[d], Thomas Yates PhD[b], Kamlesh Khunti MD[b], Melanie J Davies MD[b] and Gerry P McCann MD[a]

a. Department of Cardiovascular Sciences, University of Leicester and the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre.
b. Diabetes Research Centre, University of Leicester and the NIHR Leicester Biomedical Research Centre.
c. Leicester Clinical Trials Unit, University of Leicester.
d. NIHR Leeds Biomedical Research Centre.

Correspondence to: Dr Gaurav S Gulsin. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester LE39QP, UK. Tel: +44 (0)116 258 3038. Email: gg149@leicester.ac.uk.

Word count: 3,989

Number of tables: 3

Number of figures: 1

Abstract

Objective

To confirm the presence of subclinical cardiovascular dysfunction in working-age adults with type 2 diabetes (T2D) and determine if this is improved by a low-energy meal replacement diet (MRP) or exercise training.

Research design and Methods

Prospective, randomized, open-label, blinded-endpoint trial with nested case-control study. Asymptomatic younger adults with T2D were randomized 1:1:1 to a 12-week intervention of: 1) routine care; 2) supervised aerobic exercise training or 3) a low-energy (≈810kcal/day) MRP. Participants underwent echocardiography, cardiopulmonary exercise testing and cardiac magnetic resonance imaging (CMR) at baseline and 12-weeks. The primary outcome was change in left ventricular (LV) peak early diastolic strain rate (PEDSR), measured by CMR. Healthy volunteers were enrolled for baseline case-control comparison.

Results

Eighty-seven participants with T2D (age 51±7y, HbA1c 7.3±1.1%) and 36 matched controls were included. At baseline, those with T2D had evidence of diastolic dysfunction (PEDSR 1.01±0.19 vs. 1.10±0.16s^{-1}, p=0.02) compared with controls. Seventy-six participants completed the trial (30 routine care, 22 exercise, and 24 MRP). The MRP arm lost 13kg in weight, improved blood pressure, glycemia, LV mass/volume and aortic stiffness. The exercise arm had negligible weight loss but increased exercise capacity. PEDSR increased in the exercise arm versus routine care (β=0.132, p=0.002), but did not improve with the MRP (β=0.016, p=0.731).

Conclusions

In asymptomatic working-age adults with T2D, exercise training improved diastolic function. Despite beneficial effects of weight loss on glycemic control, concentric LV remodelling and aortic stiffness, a low-energy MRP did not improve diastolic function.

Abbreviations

CMR=cardiovascular magnetic resonance

HOMA-IR=homeostatic model assessment-insulin resistance

LV=left ventricle

MRP=meal replacement plan

NICE=National Institute for Health and Care Excellence

NIHR=National Institute for Health Research

PEDSR=peak early diastolic strain rate

T2D=type 2 diabetes mellitus

The likelihood of developing cardiovascular disease is markedly increased in younger adults with type 2 diabetes mellitus (T2D), who have the highest lifetime risk(1). The United Kingdom National Diabetes Audit 2015-16, which includes data on over 2.7 million people with diabetes, found that heart failure is the commonest cardiovascular complication of type 2 diabetes (T2D) and a major cause of premature mortality(2). This is especially the case in younger adults with T2D, where the risk of heart failure development is four- to five-fold higher than matched controls(1). Importantly, undiagnosed heart failure is highly prevalent (present in up to one third) in people with T2D(3). We have previously demonstrated evidence of subclinical diastolic impairment in young adults (mean age 32 years) with T2D, despite their young age and relatively short duration of disease(4).

Whilst the risk of atherosclerotic cardiovascular disease can be mitigated by strict risk factor management in T2D, this has little to no effect on the excess risk of heart failure(5). Therefore, the development of effective therapies to prevent and treat heart failure in people with T2D represents an important unmet need in this population.

Reversal of T2D can be achieved with weight loss, accomplished either by bariatric surgery(6) or via a low-energy meal replacement plan diet (MRP)(7). Exercise training also leads to modest but sustained improvements in glycemic control, improvements in insulin resistance, and improved cardiovascular fitness, even in the absence of accompanying weight loss(8,9). Whether weight loss or exercise training can improve subclinical cardiac dysfunction in people with T2D remains to be established. There have been no randomized controlled trials assessing cardiac function with a MRP and the results of trials in exercise training have been inconsistent(10).

The aims of this study were: (1) to confirm the presence and nature of subclinical cardiovascular dysfunction in working-age adults with T2D, and (2) to determine if diastolic function can be improved by either a low-energy MRP or a supervised aerobic exercise programme, compared to routine care.

Research design and Methods

Study design

The rationale and study design and conduct, including details of participant recruitment and planned analyses, have been published previously(11). In brief, this was a single-centre prospective, randomized, open-label, blinded-endpoint trial with a nested case-control study, at the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. Ethical approval was granted by the National Research Ethics Service (15/WM/0222). The trial is registered at https://clinicaltrials.gov (unique identifier: NCT02590822).

Participants

Eligible participants were aged 18 to 65 years, with established T2D (duration ≥3 months) diagnosed before age 60 years and BMI >30kg/m^2 (or >27kg/m^2 if South Asian or Black ethnicity). Key exclusion criteria were T2D duration >12 years, current treatment with >3 glucose-lowering medications or insulin, history, signs or symptoms of cardiovascular disease (including coronary artery disease, stroke, transient ischemic attack, peripheral artery disease or heart failure), weight loss >5kg in the preceding six months, and inability to exercise or undertake the MRP. A list of the complete study inclusion and exclusion criteria is provided in the protocol(11). Healthy volunteers free of T2D, obesity, hypertension, or prevalent cardiovascular disease were recruited for baseline case-control comparison. All participants provided written informed consent.

Participants with T2D underwent two main study assessment visits, at baseline and 12 weeks (see below). Control subjects underwent the same assessments, but at baseline only.

Randomization and blinding

Subjects with T2D were randomised at the end of the baseline visit in a 1:1:1 ratio, using an independent online computerised randomization system incorporating concealed allocation (Sealed Envelope®) to one of three arms: 1) routine care as per National Institute for Health and Care Excellence (NICE) guidance(12), 2) a supervised aerobic exercise programme or 3) a low-energy (≈810kcal/day) MRP diet. Randomization was stratified by sex and baseline glucose-lowering therapy (any glucagon-like peptide-1 agonist, dipeptidyl peptidase-IV inhibitor or sodium glucose cotransporter 2 inhibitor versus none of these agents). The nature of the trial interventions prevented blinding of allocation.

Assessments

Demographics, medical history and anthropometric measures were collected at the assessment visits. A fasting blood sample was collected to obtain a biochemical profile for diabetes control, liver and kidney function, lipid profile, adiposity, insulin and C-peptide. Insulin resistance was estimated using the homeostatic model assessment-insulin resistance method (HOMA-IR)(13). Participants in the MRP arm with a fasting glucose of <7.0mmol/L or HbA1c <6.5% without taking any hypoglycemic agent post-intervention were considered to have remission of T2D(14).

Cardiovascular magnetic resonance imaging

Comprehensive cardiovascular magnetic resonance (CMR) scanning was performed on a 1.5T field strength scanner (Siemens Aera, Erlangen, Germany) using a standardised protocol(11). CMR images were analysed offline blinded to all patient details and treatment group. Cardiac chamber volumes, function and strain were assessed by a single experienced observer (G.S.G) using cmr42 version 5 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

Transthoracic echocardiography

Transthoracic echocardiography was performed and interpreted by two accredited operators (A-M.M and J.M.) using an iE33 system with S5-1 transducer (Philips Medical Systems, Best, The Netherlands). Images were acquired and reported as per American Society of Echocardiography guidelines(15). Early diastolic transmitral flow velocities (E) and early diastolic mitral annular velocities (e') to estimate LV filling pressures were assessed by Doppler echocardiography per current recommendations(16).

Cardiopulmonary exercise testing

A symptom-limited incremental cardiopulmonary exercise test was performed on a stationary electromagnetically braked cycle ergometer (eBike, General Electric Healthcare, Bedford, UK) with expired gas analysis (Ganshorn PowerCube, General Electric Healthcare, Bedford, UK) to determine peak oxygen consumption (VO_2)(17).

Trial interventions

Routine care

Standard lifestyle advice was provided in a single coaching interview at week 0, along with signposting to freely available NHS resources in accordance with NICE guidance(12). Optimisation of blood pressure and glucose-lowering medications was undertaken by a study clinician at baseline in accordance with NICE guidance(12).

Supervised exercise programme

Participants attended thrice weekly, supervised moderate-intensity aerobic exercise sessions. Exercise sessions consisted of a warm-up, stimulus and cool-down phase. The stimulus phase included walking and/or lower extremity cycling. Exercise intensity was titrated to ≈60% baseline peak VO_2 and heart rate. The total exercise duration was gradually increased to achieve a target of 50 minutes per session. Objective (heart rate monitoring) and subjective (Borg Rate of Perceived Exertion

Scale) measures were used to evaluate the response to exercise sessions and to adjust exercise intensity in accordance with increasing fitness levels throughout the intervention period. Compliance was assessed by attendance at the supervised exercise sessions. Participants who attended less than two-thirds of the exercise sessions were considered non-compliant and excluded from the study. Participants were asked to maintain their usual dietary intake.

Low energy MRP diet

The low-energy MRP comprised an average of ≈810kcal/day (30% protein, 50% carbohydrate and 20% fat) (Cambridge Weight Plan®). Participants were asked to discontinue all glucose-lowering therapies following randomization to avoid hypoglycemia. Antihypertensive medications were stopped on the day of commencement. Blood pressure and glucose were monitored throughout the study by a study clinician. Participants were advised to maintain their usual daily activities while on the diet and asked not to initiate any additional physical activity for the duration of the intervention. The diet was discontinued and a maintenance diet introduced once 50% excess body weight had been lost, or by 12 weeks, whichever came first. Those participants who did not achieve a loss of >2% body weight at week 1 and 4% at week 3 were considered non-compliant and were excluded from the study.

Outcomes

The primary outcome was a measure of diastolic function: change in left ventricular peak early diastolic strain rate (LV PEDSR, an index of the speed of myocardial relaxation), measured by CMR, from baseline to 12 weeks, in the two intervention arms (MRP diet and exercise) compared to routine care. Key secondary outcomes were change in echocardiographic measures of diastolic function (E/A ratio and E/e'). Additional secondary outcomes were CMR measures of cardiac structure and function

(LV mass and volumes, global longitudinal strain) myocardial perfusion reserve, aortic stiffness (distensibility) and peak oxygen consumption(11).

Power calculation

The trial sample size calculation was determined according to published pilot data from our group(4). To detect a between-group difference in PEDSR of $0.2s^{-1}$ post-interventions, at least 21 participants with T2D completing each of the three trial arms were needed to provide 80% power, at alpha=0.025 (to allow for two primary comparisons, i.e. MRP vs. routine care and exercise vs. routine care). Assuming a maximum dropout rate of 30%, we targeted recruitment of 30 patients per group at baseline.

Statistical analysis

Statistical analyses were performed by an independent trial statistician (NBJ) at the Leicester Clinical Trials Unit. Normality was assessed using histograms, the Shapiro-Wilk test and Q-Q plots. Continuous data are expressed as mean (± standard deviation), if normally distributed or median (25-75% interquartile range) if not. At baseline, patients and control groups were compared by independent *t*-tests or Mann-Whitney tests as appropriate. Categorical variables were compared using the Chi-squared test or Fisher's exact test as appropriate. For the analysis of the primary outcome, each intervention was compared with the routine care arm using linear regression adjusted for stratification factors (sex and baseline glucose lowering therapy) and baseline PEDSR. The treatment effect was presented as a point estimate, confidence interval and p-value. Changes in the key secondary outcomes (E/A ratio and E/e') were also assessed using linear regression with the same stratification factors as the primary outcome. Given the large number of additional secondary outcomes, formal statistical testing was not undertaken on these parameters but changes between baseline and follow-up are presented with 95% confidence intervals.

Statistical analysis was done using Stata software, version 15 (StataCorp LLC, Texas, USA).

Results

The trial profile displayed in supplementary figure 1. Between November 2015 and May 2018, 260 patients were screened, of whom 93 consented and enrolled. Three were found to be ineligible after consent and 90 subjects were randomized: 30 to routine care, 31 to the supervised exercise programme and 29 to the MRP diet. Three of these participants (two in the exercise arm and one in the MRP arm) were found to be ineligible after laboratory test results became available and did not undertake the intervention. A total of 76 patients with T2D completed the trial (30 in the routine care arm, 22 in the exercise arm and 24 in the MRP arm). Reasons for discontinuation are shown in supplementary figure 1. Thirty-nine healthy volunteers were enrolled for baseline case-control comparison. Three of these were subsequently excluded (one due to the presence of obesity and two who were unable to undergo CMR scanning due to claustrophobia). A total of 36 healthy volunteers were therefore included in case-control comparisons.

Baseline characteristics

The baseline demographic characteristics of subjects with T2D and controls are shown in table 1. Mean age of participants with T2D was 50.5±6.5 years, mean body mass index was 36.6±5.5 kg/m^2, mean duration of diabetes was 5.4±3.2 years, 41% were women, and 37% were from a minority ethnic group. The control group were similar for age, sex and ethnicity, but had lower overall body weight and body mass index. Among those with T2D, 43% had a history of smoking and 52% had a history of hypertension. None of the control subjects had a history of hypertension or dyslipidemia. Antihypertensive and lipid-lowering medication use was therefore higher in those with T2D compared to controls.

Fasting blood test results are displayed in table 1. Both T2Ds and healthy controls had similar renal function. Subjects with T2D had higher overall glycated

hemoglobin (7.3±1.0 vs. 5.4±0.2%, p<0.001), lower total cholesterol (4.6±1.0 vs. 5.7±0.8mmol/L, p<0.001) and LDL cholesterol (2.4±0.8 vs. 3.3±0.8mmol/L, p<0.001) than controls, respectively. Adiponectin levels were significantly lower and leptin levels significantly higher (both p<0.001) in T2Ds versus controls. Fasting C-peptide and insulin levels were significantly higher (both p<0.001) in T2Ds compared with controls. Similarly, overall HOMA-IR was higher in T2Ds versus controls (9.2 [6.2 – 13.5] vs. 1.6 [1.1 – 2.5], respectively, p<0.001). B-natriuretic peptide levels were significantly lower in the T2D group compared to controls (10.6 [4.5 – 17.9] vs. 16.0 [8.7 – 22.6] ng/L, respectively, p=0.048).

Cardiovascular differences between T2Ds and controls

Baseline CMR imaging, cardiopulmonary exercise testing, and echocardiography data comparing T2Ds and controls are displayed in table 1. Left ventricular PEDSR was significantly lower in T2Ds compared to controls (1.01±0.19 vs. 1.10±0.16, p=0.02). Subjects with T2D also had smaller indexed LV volumes, higher LV ejection fraction, and higher LV mass than controls. In those with T2D, there was increased concentric LV remodelling (LV mass:volume 0.82±0.12 vs. 0.71±0.10g/mL, p<0.001) and lower mean aortic distensibility (4.16±2.05 vs. 6.56±2.02mmHg^{-1}x10^{-3}, p<0.001) than controls. There were no significant differences in indexed LV mass or global longitudinal strain between groups. Myocardial perfusion reserve was lower in T2Ds compared with controls.

Complete echocardiographic transmitral flow velocities were measurable in 84 subjects with T2D and all 36 controls. Mean E/A ratio was significantly lower in the T2D group compared with controls (0.95±0.21 vs. 1.21±0.25, p<0.001). Mitral annular velocities were measureable in 78 individuals with T2D and all 36 controls.

Overall, average E/e' was higher in those with T2D compared to the control group (8.1 [6.2 – 9.6] vs. 62. [5.0 – 7.8], p<0.001) (table 1).

All measures of cardiorespiratory fitness (maximum workload achieved, absolute and body-weight corrected peak oxygen uptake) were lower in the T2Ds versus controls (table 1).

Prospective, randomised, open-label, blinded-endpoint trial

The baseline demographic characteristics and prescribed diabetes and anti-hypertensive medications of participants stratified by treatment arm in the trial are shown in supplementary table 1. The three groups were well balanced.

Changes in bio-anthropometric measures, physical activity and cardiorespiratory fitness indices with interventions

Changes from baseline to 12 weeks in anthropometric measures, biochemical parameters, and cardiorespiratory fitness in subjects who completed the study are shown in table 2.

In the routine care arm, body weight remained stable and there were no significant changes in body composition measures (body mass index and waist-to-hip ratio). Markers of insulin resistance and glycemic control remained similar from baseline to 12 weeks. Mean systolic blood pressure dropped by 7mmHg, driven by a guideline-directed increase in the doses of existing prescribed antihypertensive medications. Cardiopulmonary fitness did not change by the end of the trial period.

In the exercise programme arm there were small non-significant reductions in body weight (median weight loss 1.6kg) and body mass index (median reduction 0.8kg/m^2). There was no significant change in glycemic control, insulin resistance or blood pressure. Although there was no significant change in peak oxygen uptake by week 12, subjects' total exercise duration and maximum workload achieved did increase (by 1.2 mins and 22 Watts, respectively).

In the MRP arm, median weight loss was 13.6kg, body mass index fell by 4.8kg/m^2, and mean systolic blood pressure dropped by 13mmHg, despite a reduction in the number and/or dose of anti-hypertensives taken. Median HbA1c decreased by 0.75% (7.5mmol/mol), with 20 (83%) participants achieving T2D remission. There was a non-significant trend for adiponectin to increase and median leptin decreased by 9,873pg/mL, median HOMA-IR decreased by 6 units, and median brain natriuretic peptide increased by 3.5ng/L. There was a small increase in peak oxygen uptake when corrected for body weight (1.9mL/kg/min), but not in absolute peak oxygen uptake. Other measures of cardiorespiratory fitness did not change.

Primary and key secondary cardiac outcomes

Changes in the primary endpoint from baseline to 12 weeks are displayed in figure 1. For the primary outcome measure, participants in the supervised exercise programme arm demonstrated a significant improvement in PEDSR compared to those in the routine care arm of the trial (β=0.132, 97.5% CI 0.038 to 0.225, p=0.002). No improvement in PEDSR was observed in participants in the MRP arm versus those in the routine care arm of the trial (β=0.016, 97.5% CI -0.075 to 0.106, p=0.731).

Average E/e' and early diastolic to late filling ratio (E/A) ratio could be obtained in 63 (83%) and 70 (92%) of participants who completed the trial, respectively. E/A ratio and non-invasive assessment of filling pressure (E/e') tended to improve in both intervention arms, but these changes were not statistically significant compared to the routine care arm: average E/e' in the exercise arm of the trial versus the routine care arm at 12 weeks β=-0.459, 95% CI -1.452 to 0.534, p=0.355, and E/A ratio β=0.028, 95% CI -0.086 to 0.142, p=0.621. Similarly, there was no difference in average E/e' in the MRP arm versus routine care at 12 weeks

(β=-0.060, 95% CI -1.099 to 0.978, p=0.907), or E/A ratio (β=0.036, 95% CI -0.090 to 0.161, p=0.568).

Key secondary cardiac imaging endpoints at baseline and 12 weeks in the three trial arms are displayed in table 3. In the routine care arm and the exercise arm there were negligible changes in most cardiac parameters. In the MRP arm there was a trend towards a reduction in LV mass (mean reduction 5.6grams) and indexed LV end diastolic volume increased by 5mL/m^2, with a corresponding significant reduction in concentric LV remodelling (mean change -0.03g/mL, 95% CI -0.06 to -0.01). Aortic distensibility increased by 0.90$mmHg^{-1}x10^{-3}$ (95% CI 0.38 to 1.41). With regards to systolic function there was a significant lowering of ejection fraction (-1.32%, 95% CI -0.27 to -2.37) in the MRP arm. There were no significant changes in myocardial perfusion reserve in any group.

Discussion

This is the first randomized controlled trial to compare the effects on cardiac structure and function of a low-energy diet versus an aerobic exercise programme or routine care in working-age adults with T2D. Compared with controls, individuals with T2D had reduced diastolic function, increased concentric LV remodelling, reduced myocardial perfusion, and increased aortic stiffening, consistent with asymptomatic stage B heart failure(18). A 12-week supervised aerobic exercise training programme led to favourable improvements in diastolic function in the absence of any major effects on LV remodelling, perfusion or aortic stiffening. Despite beneficial effects observed on glycometabolic profile, blood pressure, aortic stiffness and concentric LV remodelling, a low-energy MRP diet did not lead to improved diastolic function.

Our T2D cohort may already have stage B heart failure(18), with clear evidence of reduced diastolic function by both CMR and echocardiographic measures. Diastolic dysfunction and concentric LV remodelling are typically the earliest manifestations of diabetic cardiomyopathy, and likely precursors to the onset of clinical heart failure(19). Our results suggest that supervised aerobic exercise training may improve the earliest functional consequence of T2D on the myocardium. Subjects with T2D had markedly lower aerobic exercise capacity compared to controls at baseline, and beneficial effects on diastolic function were observed even when only accompanied by small improvements in fitness.

Several studies have assessed the effects of various exercise interventions on diastolic function in people with T2D, predominantly using echocardiography(10). In general, these have shown that exercise training has favourable effects on diastolic function, although with inconsistent results, likely due to differences in study populations, modes of exercise intervention, and various measures of diastolic

function being employed. Although we did not see any significant improvement in echocardiographic measures of diastolic function, resting measures may not have adequate sensitivity(20). This is especially true in a population who have obesity, such as ours; with a higher likelihood of poor echocardiographic windows. Almost 20% of our patients did not have sufficient windows for accurate measurement of diastolic function by echocardiography.

The mechanism of benefit of aerobic exercise on diastolic function in our cohort is unclear. We did not observe significant improvements in myocardial perfusion or cardiac remodelling with exercise, although the study was not powered to detect these outcomes. It is posited that exercise interventions cause improvements in myocyte calcium handling, mitochondrial function, inflammation and energy metabolism(10,21,22), which are linked to impaired cardiac contraction and relaxation(23). We were not able to assess these parameters in the current study, but given the lack of improvement in cardiac energetics following 12-weeks of high intensity interval training in a previous study in people with T2D(24), it seems this mechanism is unlikely to explain the benefit observed in diastolic function.

The ability to achieve remission of T2D by weight loss with administration of low-energy MRP diet was convincingly demonstrated in the DiRECT trial(7). However, improvements in cardiac function after weight loss in T2D have not been studied in a randomised controlled trial setting previously. Administration of a low-energy MRP diet in our patients led to dramatic improvements in body weight, blood pressure and resting heart rate, fasting triglycerides, HbA1c, and markers of insulin resistance, mirroring the findings of the DiRECT trial(7). We also observed similar rates of remission of T2D to those in the DiRECT trial. However PEDSR did not change after MRP and we observed a reduction in LV ejection fraction with a small

rise in brain natriuretic peptide levels. It is recognised that obesity is associated with increased sympathetic activity, which may result in hyperdynamic LV function(25). This is supported by our finding that LV ejection fraction was higher at baseline in those with T2D compared to healthy weight controls. The observed reduction in ejection fraction in the MRP arm may, therefore, reflect normalisation of hyperdynamic LV function with weight loss. Furthermore, obesity and T2D are both known to lower brain natriuretic peptide levels and its increase in the MRP arm of the trial is also likely to be a consequence of the weight loss(26,27).

Our interpretation is that diastolic dysfunction may be irreversible with improvements in glycometabolic derangements alone. Supporting evidence includes data from interventional trials that have not shown reductions in heart failure risk with strict glycemic control(28). Although diastolic function did not improve, we did observe modest changes in cardiac remodelling and aortic distensibility in the MRP arm of the trial. Given that LV hypertrophy and smaller LV volumes are typically seen in diabetic cardiomyopathy (which was confirmed by our case-control analysis) and are associated with poorer cardiovascular outcomes(29,30), these changes may indicate favourable long-term effects of the dietary restriction or weight loss on the structural manifestations of heart failure in T2D. Furthermore, we have previously shown that aortic stiffening is an independent determinant of concentric LV remodelling(31) and the observed increase in aortic distensibility with MRP suggests that weight loss may ameliorate vascular stiffness in T2D and could prompt reverse cardiac remodelling. It is possible that the best approach for improving stage B heart failure in people with T2D is a combination of exercise and dietary restriction to achieve weight loss, given the different effects of these interventions on diastolic function and cardiac remodelling in our study. Further trials are needed to assess the

cardiovascular effects of combined exercise with dietary restriction and weight loss in people with T2D and for longer durations.

Key strengths our trial were the randomization of participants to interventions with blinded analyses and the comprehensive cardio-metabolic phenotyping that subjects underwent. Although the younger, working-age population in this study have the highest lifetime risk of heart failure, they are under-represented in large-scale cardiovascular outcomes trials of T2D, and no studies have demonstrated effective therapies to prevent or treat heart failure in this group.

Our trial also has some limitations, including the unblinded design, with ascertainment bias eliminated as far as possible with blinding of all imaging parameters, and the short duration of follow-up. The exclusion criteria were set to maximise the probability of remission of T2D with the MRP and therefore the results are not generalizable to the entire population with T2D. The effects of sustained weight loss on cardiac structure and function were not assessed, nor the possibility that de-training could lead to worsening of diastolic function in those who undertook the supervised exercise arm of the trial. Although we achieved the necessary statistical power for our trial, the relatively high rate of non-compliance (19%) with the supervised exercise intervention may hinder its real-world application.

Conclusions

In working-age adults with T2D and obesity without prevalent cardiovascular disease, there is already evidence of subclinical diastolic dysfunction, concentric LV remodelling and aortic stiffening. A 12-week supervised aerobic exercise training programme led to improvements in LV diastolic function without major effects on cardiac remodelling, weight loss, blood pressure, or glycemic control. Conversely, a

low-energy MRP diet led to improvements in glycometabolic profiles, concentric LV remodelling and aortic stiffness, but did not improve measures of diastolic function.

Acknowledgements

Author contributions

GPM, EMB, EB, MJD, TY, KK and DJS contributed to the design of the study. GSG, DJS and LA recruited study participants, supervised assessment visits and clinical reviews. EB and SA initiated and oversaw administration of the MRP diet. JH supervised the exercise training sessions. GSG provided clinical oversight of trial participants. YW oversaw trial management. AMM and JM performed the echocardiograms and cardiopulmonary exercise testing. GSG, KP, GS, AMM, JM, MJH and JDB analysed the data. NBJ performed the statistical analyses. GSG drafted the report, which was critically revised by GPM, EMB, EB, MJD, TY and KK. All authors have read and approved the final version.

Statements of assistance

We thank Susan Mackness (NIHR Leicester Biomedical Research Centre) for research nurse support; Joanne Wormleighton (University Hospitals of Leicester NHS Trust) for support with CMR protocol design and scanning; Yvonne Doherty for support with participant health behaviour coaching; independent members of the trial steering committee (Professor Roy Taylor (Chair), Newcastle University; Professor Sven Plein, University of Leeds; Professor Richard Holt, University of Southampton); and the trial participants. We acknowledge support from the NIHR Leicester Biomedical Research Centre, NIHR Leicester Clinical Research Facility and the NIHR Collaboration in Leadership Applied Health Research and Care East Midlands. We are also grateful to Cambridge Weight Plan® for provision of the low-energy MRP diet.

Funding

This study was funded by the NIHR through a career development fellowship (G McCann, CDF 2014-07-045). Cambridge Weight Plan® provided the dietary supplements free of charge, but were not involved in the conduct of the study, analysis or interpretation of the data, or writing of the report.

Author comments

This work was presented at the American Heart Association Annual Scientific Sessions 2019 (Philadelphia, USA) in the Lifestyle and Cardiometabolic Health Early Career Investigator Competition, where GSG was awarded first prize. The abstract is published in the conference proceedings(32).

Conflicts of interest

None.

References

1. Sattar N, Rawshani A, Franzen S et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks Findings From the Swedish National Diabetes Registry. Circulation 2019.
2. Partnership HQI. National Diabetes Audit, 2015-2016. NHS Digital: NHS Digital, 2017.
3. Boonman-de Winter LJ, Rutten FH, Cramer MJ et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia 2012;55:2154-62.
4. Khan JN, Wilmot EG, Leggate M et al. Subclinical diastolic dysfunction in young adults with Type 2 diabetes mellitus: a multiparametric contrast-enhanced cardiovascular magnetic resonance pilot study assessing potential mechanisms. Eur Heart J Cardiovasc Imaging 2014;15:1263-9.
5. Rawshani A, Rawshani A, Franzen S et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018;379:633-644.
6. Meijer RI, van Wagensveld BA, Siegert CE, Eringa EC, Serne EH, Smulders YM. Bariatric surgery as a novel treatment for type 2 diabetes mellitus: a systematic review. Arch Surg 2011;146:744-50.
7. Lean ME, Leslie WS, Barnes AC et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2017.
8. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. Jama 2001;286:1218-27.
9. Colberg SR, Sigal RJ, Yardley JE et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016;39:2065-2079.
10. Verboven M, Van Ryckeghem L, Belkhouribchia J et al. Effect of Exercise Intervention on Cardiac Function in Type 2 Diabetes Mellitus: A Systematic Review. Sports Med 2019;49:255-268.
11. Gulsin GS, Brady EM, Swarbrick DJ et al. Rationale, design and study protocol of the randomised controlled trial: Diabetes Interventional Assessment of Slimming or Training tO Lessen Inconspicuous Cardiovascular Dysfunction (the DIASTOLIC study). BMJ Open 2019;9:e023207.
12. Excellence NIfHaC. NICE guideline [NG28] Type 2 diabetes in adults: management. NICE, 2015.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
14. Nagi D, Hambling C, Taylor R. Remission of Type 2 Diabetes: A Position Statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). 2019.
15. Picard MH, Adams D, Bierig SM et al. American Society of Echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011;24:1-10.

16. Nagueh SF, Smiseth OA, Appleton CP et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-1360.
17. Wasserman K. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications: Lippincott Williams & Wilkins, 2005.
18. Hunt SA, Abraham WT, Chin MH et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-235.
19. Gulsin GS, Athithan L, McCann GP. Diabetic cardiomyopathy: prevalence, determinants and potential treatments. Ther Adv Endocrinol Metab 2019;10:2042018819834869.
20. Nauta JF, Hummel YM, van der Meer P, Lam CSP, Voors AA, van Melle JP. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. Eur J Heart Fail 2018.
21. Levelt E, Rodgers CT, Clarke WT et al. Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. Eur Heart J 2016;37:3461-3469.
22. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985) 2005;98:1154-62.
23. Phan TT, Abozguia K, Nallur Shivu G et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol 2009;54:402-9.
24. Cassidy S, Thoma C, Hallsworth K et al. High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. Diabetologia 2016;59:56-66.
25. Packer M. Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart Failure in People With Obesity. Circulation 2018;137:1614-1631.
26. Wang TJ, Larson MG, Levy D et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594-600.
27. Baldassarre S, Fragapani S, Panero A et al. NTproBNP in insulin-resistance mediated conditions: overweight/obesity, metabolic syndrome and diabetes. The population-based Casale Monferrato Study. Cardiovasc Diabetol 2017;16:119.
28. Castagno D, Baird-Gunning J, Jhund PS et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients:

evidence from a 37,229 patient meta-analysis. Am Heart J 2011;162:938-948 e2.
29. Gjesdal O, Bluemke DA, Lima JA. Cardiac remodeling at the population level--risk factors, screening, and outcomes. Nat Rev Cardiol 2011;8:673-85.
30. Bluemke DA, Kronmal RA, Lima JA et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;52:2148-55.
31. Gulsin GS, Swarbrick DJ, Hunt WH et al. Relation of Aortic Stiffness to Left Ventricular Remodeling in Younger Adults With Type 2 Diabetes. Diabetes 2018;67:1395-1400.
32. Gulsin GS, Swarbrick DJ, Athithan L et al. Abstract 10122: A Randomized Trial of Exercise versus Low-energy Meal Replacement Diet to Improve Cardiac Dysfunction in Working-Age Adults With Type 2 Diabetes. Circulation 2019;140:A10122-A10122.

Tables

Table 1. Baseline bio-anthropometrics, cardiac MRI, cardiopulmonary exercise testing and echocardiographic data in subjects with T2D versus controls.

	T2D (n=87)	CONTROLS (n=36)	*P*-value
DEMOGRAPHICS			
Age, years	50.5±6.5	48.6±6.2	0.15
Sex, n (%)			
Male	51 (59)	19 (53)	0.552
Female	36 (41)	17 (47)	
Ethnic origin, n (%)			
Caucasian	55 (63)	25 (69)	0.51
Black or other minority ethnicity	32 (37)	11 (31)	
ANTHROPOMETRICS			
Height, cm	168±10	169±9	0.54
Weight, kg	103.3±16.7	70.4±10.8	**<0.001**
Body mass index, kg/m^2	36.6±5.5	24.5±2.4	**<0.001**
Systolic blood pressure, mmHg	140±15	121±13	**<0.001**
Diastolic blood pressure, mmHg	87±8	76±7	**<0.001**
Heart rate, beats/min	74±10	62±10	**<0.001**
MEDICAL HISTORY			
Diabetes duration, months	56 (32 – 94)	N/A	N/A
Smoking history, n (%)	39 (45)	9 (25)	<0.001
Hypertension, n (%)	44 (51)	0 (0)	<0.001
Dyslipidemia, n (%)	56 (64)	0 (0)	<0.001
MEDICATIONS			
ACE inhibitor, n (%)	28 (32)	0 (0)	<0.001
ARB, n (%)	11 (13)	0 (0)	0.025
Beta blocker, n (%)	6 (7)	0 (0)	0.106
Calcium channel blocker, n (%)	19 (22)	0 (0)	0.002
Statin, n (%)	58 (67)	0 (0)	<0.001
Metformin, n (%)	82 (94)	N/A	N/A
Sulfonylurea, n (%)	13 (15)	N/A	N/A
DPP-IV inhibitor, n (%)	17 (20)	N/A	N/A
SGLT2 inhibitor, n (%)	10 (11)	N/A	N/A
GLP-1 receptor agonist, n (%)	10 (11)	N/A	N/A
FASTING BLOOD TESTS			
Urea, mmol/L	5.4±1.2	5.2±1.4	0.59
Creatinine, mmol/L	76±15	79±12	0.332
Estimated GFR, mL/min	90 (80 - 90)	85 (78 - 90)	0.122
Glucose, mmol/L	7.6 (6.6 - 10.1)	5.0 (4.6 - 5.2)	**<0.001**
HbA1c, %	7.3±1.0	5.4±0.2	**<0.001**
HbA1c, mmol/mol	56±11	35±3	**<0.001**
Total cholesterol, mmol/L	4.6±1.0	5.7±0.8	**<0.001**
Triglycerides, mmol/L	1.88 (1.18 - 2.74)	0.98 (0.72 - 1.54)	**<0.001**
HDL, mmol/L	1.2 (1.0 - 1.4)	1.7 (1.6 - 2.0)	**<0.001**
LDL, mmol/L	2.4±0.8	3.3±0.8	**<0.001**
Cholesterol:HDL	3.9±0.9	3.3±0.8	**<0.001**

Hemoglobin, g/L	144±16	141±14	0.279
Adiponectin, ng/L	3460 (2550 - 5652)	9514 (4820 - 14589)	**<0.001**
Leptin, pg/L	18911 (9821 - 34115)	4811 (2400 - 9818)	**<0.001**
C-peptide, ng/L	2591 (1865 - 3371)	969 (743 - 1199)	**<0.001**
Insulin, miu/L	26.5 (18.8 - 35.8)	7.4 (4.9 - 10.4)	**<0.001**
HOMA-IR	9.2 (6.2 - 13.5)	1.6 (1.1 - 2.5)	**<0.001**
B-natriuretic peptide, ng/L	10.6 (4.5 - 17.9)	16.0 (8.7 - 22.6)	**0.048**
CARDIAC MRI			
LV EDVi, mL/m^2	67±10	83±19	**<0.001**
LV EF, %	68±7	65±5	**0.016**
LV mass, g	121±25	107±32	**0.011**
LV mass index, g/m^2	55±9	58±14	**0.133**
LV mass:volume, g/mL	0.82±0.12	0.71±0.10	**<0.001**
LV global longitudinal strain, %	−16.9±2.6	−17.6±1.5	0.179
LV PEDSR, s^{-1}	1.01±0.19	1.10±0.16	**0.02**
Myocardial perfusion reserve	3.02±0.98	3.98±1.01	**<0.001**
Aortic distensibility, mmHg^{-1}x10^{-3}	4.16±2.05	6.56±2.02	**<0.001**
ECHOCARDIOGRAPHY			
E/A ratio	0.95±0.21	1.21±0.25	**<0.001**
Average E/e'	8.1 (6.2 - 9.6)	6.2 (5.0 - 7.8)	**<0.001**
CARDIOPULMONARY EXERCISE TESTING			
Maximum workload achieved, W	125±47	173±67	**<0.001**
Peak V_{O_2}, mL/kg/min	16.6±4.1	27.5±8.2	**<0.001**
Peak V_{O_2}, L/min	1.70±0.46	1.96±0.73	**0.019**

Data are n (%), mean±SD, or median (IQR). Abbreviations: ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; GLP-1=glucagon-like peptide-1; DPP-IV=dipeptidyl peptidase-IV; SGLT2=sodium glucose cotransporter-2; HOMA-IR=homeostatic model assessment of insulin resistance, LV=left ventricle; EDVi=end-diastolic volume indexed to body surface area; EF=ejection fraction; PEDSR=peak early diastolic strain rate.

Table 2. Bio-anthropometric measures at baseline, 12 weeks and change from baseline to 12 weeks in the three trial arms.

	Routine care (n=30)			Exercise (n=22)			MRP (n=24)		
	Baseline	**Week 12**	**Median change (95% CI)**	**Baseline**	**Week 12**	**Median change (95% CI)**	**Baseline**	**Week 12**	**Median change (95% CI)**
Anthropometrics									
Weight (kg)	102·6 (14·9)	100·4 (14·5)	-1.05 (-3.16, -0.01)	99·2 (16·3)	97·8 (16·6)	-1.55 (-2.51, -0.48)	106·7 (16·2)	93·0 (15·0)	-13.55 (-15.53, -11.90)
Body mass index (kg/m2)	35·0 (33·0 - 40·7)	34·5 (32·0 - 41·0)	-0.25 (-1.00, 0.00)	33·0 (31·8 - 35·0)	33·0 (31·0 - 34·7)	-0.75 (-1.00, -0.09)	35·2 (33·5 - 40·3)	30·3 (28·1 - 35·5)	-4.75 (-5.17, -4.00)
Systolic BP (mmHg)	137·8 (12·7)	130·8 (14·4)	-7.07 (-10.60, -3.54)*	135·5 (16·9)	133·0 (14·3)	-2.45 (-8.94, 4.03)*	145·9 (15·9)	132·9 (18·0)	-13.00 (-21.60, -4.40)*
Diastolic BP (mmHg)	85·3 (7·3)	83·5 (10·2)	-1.83 (-4.65, 0.99)*	87·2 (8·2)	86·7 (8·5)	-0.55 (-4.08, 2.98)*	91·1 (7·4)	86·5 (9·1)	-4.67 (-9.50, 0.17)*
Heart rate (bpm)	76·3 (7·5)	73·3 (9·6)	-3.03 (-6.06, -0.01)*	75·0 (12·7)	73·4 (9·6)	-1.55 (-4.94, 1.85)*	73·1 (8·6)	67·8 (9·8)	-5.29 (-8.55, -2.03)*
Fasting bloods									
HbA1c (mmol/mol)	56·3 (10·1)	55·2 (11·6)	-0.50 (-6.00, 1.00)	57·8 (12·1)	56·6 (12·3)	-1.00 (-3.07, 1.07)	54·8 (11·9)	44·4 (7·6)	-7.50 (-13.34, -5.00)
HbA1c (%)	7·3 (0·9)	7·2 (1·1)	0.00 (-0.59, 0.10)	7·4 (1·1)	7·3 (1·1)	-0.10 (-0.31, 0.20)	7·2 (1·1)	6·2 (0·7)	-0.75 (-1.23, -0.40)
Glucose (mmol/L)	7·3 (6·7 - 9·1)	7·6 (6·3 - 9·0)	-0.19 (-0.97, 0.60)*	8·2 (7·2 - 10·1)	7·7 (6·4 - 9·0)	-0.82 (-1.59, -0.05)*	7·1 (6·4 - 10·0)	6·3 (5·2 - 7·3)	-1.89 (-2.78, -1.00)*
Insulin (miu/L)	21·5 (14·4 - 28·7)	18·5 (11·2 - 32·5)	0.07 (-5.83, 5.96)*	26·2 (19·2 - 35·4)	20·0 (14·3 - 41·4)	-3.79 (-9.92, 2.34)*	29·2 (25·1 - 38·1)	16·2 (11·7 - 19·0)	-16.15 (-21.89, -10.40)*
HOMA-IR	7·8 (4·7 - 9·3)	6·6 (3·3 - 11·7)	-0.81 (-2.07, 2.03)	9·8 (6·6 - 14·3)	6·5 (4·5 - 13·8)	-2.91 (-4.98, 0.39)	10·3 (8·0 - 13·6)	4·3 (3·0 - 6·0)	-5.98 (-9.48, -3.44)
Adiponectin (ng/mL)	4121·3 (3090·1 - 7550·2)	4006·9 (2417·5 - 6865·8)	17.81 (-795.87, 515.42)	3043·2 (2435·4 - 4169·0)	2767·5 (2186·9 - 3495·9)	-354.54 (-815.60, 256.48)	3714·4 (2546·3 - 4681·7)	4764·1 (3158·4 - 6159·5)	774.33 (-98.58, 2,784.91)
Leptin (pg/mL)	19606·6 (9617·2 - 34115·0)	18112·9 (8544·5 - 27105·2)	-2,035.80 (-4,300.81, -559.33)	16831·1 (11403·0 - 23753·9)	12691·9 (10098·3 - 21983·9)	-526.05 (-2,736.59, 2,248.05)	19294·6 (9808·7 - 51040·7)	6413·1 (3337·4 - 20558·8)	-9,873.31 (-13,360.80, -5,803.63)
BNP (ng/L)	9·4 (4·4 - 15·7)	8·3 (4·8 – 14·4)	0.00 (-1.43, 2.89)	7·4 (2·7 - 18·0)	7·5 (3·5 - 16·4)	1.05 (-3.91, 4.26)	10·8 (5·0 - 15·1)	13·6 (5·0 - 24·3)	3.45 (0.73, 8.61)
Cardiopulmonary exercise testing									
Peak VO_2 (mL/Kg/min)	16·7 (3·7)	16·2 (4·1)	-0.54 (-1.55, 0.47)*	17·2 (4·5)	18·2 (4·9)	0.97 (-0.46, 2.40)*	16·4 (4·5)	18·3 (5·5)	1.93 (0.64, 3.23)*

Peak VO2 (L/min)	1·72 (0·48)	1·63 (0·51)	-0.09 (-0.18, 0.01)*	1·67 (0·50)	1·73 (0·52)	0.06 (-0.08, 0.20)*	1·72 (0·45)	1·67 (0·46)	-0.05 (-0.16, 0.06)*
Total exercise duration (mins:secs)	11·3 (2·2)	11·1 (2·2)	-0.15 (-0.60, 0.25)	10·6 (2·3)	11·8 (3·1)	1.20 (0.17, 2.07)	11·4 (2·2)	11·2 (1·7)	-0.37 (-0.62, 0.47)
Maximum workload (W)	123·0 (41·9)	122·0 (47·3)	-2.50 (-8.74, 3.00)	123·2 (47·1)	141·3 (54·9)	22.00 (5.81, 32.00)	132·5 (56·4)	132·3 (50·1)	-3.50 (-9.34, 10.01)

Data are n (%), median (IQR) or mean (SD), and median change (95% confidence interval). *Data are mean change (95% confidence interval). BP=blood pressure. RAAS=renin angiotensin aldosterone system. GLP-1=glucagon-like peptide-1. DPP-IV=dipeptidyl peptidase-IV. SGLT-2=sodium glucose cotransporter-2. HOMA-IR=homeostatic model assessment of insulin resistance. BNP=brain natriuretic peptide.

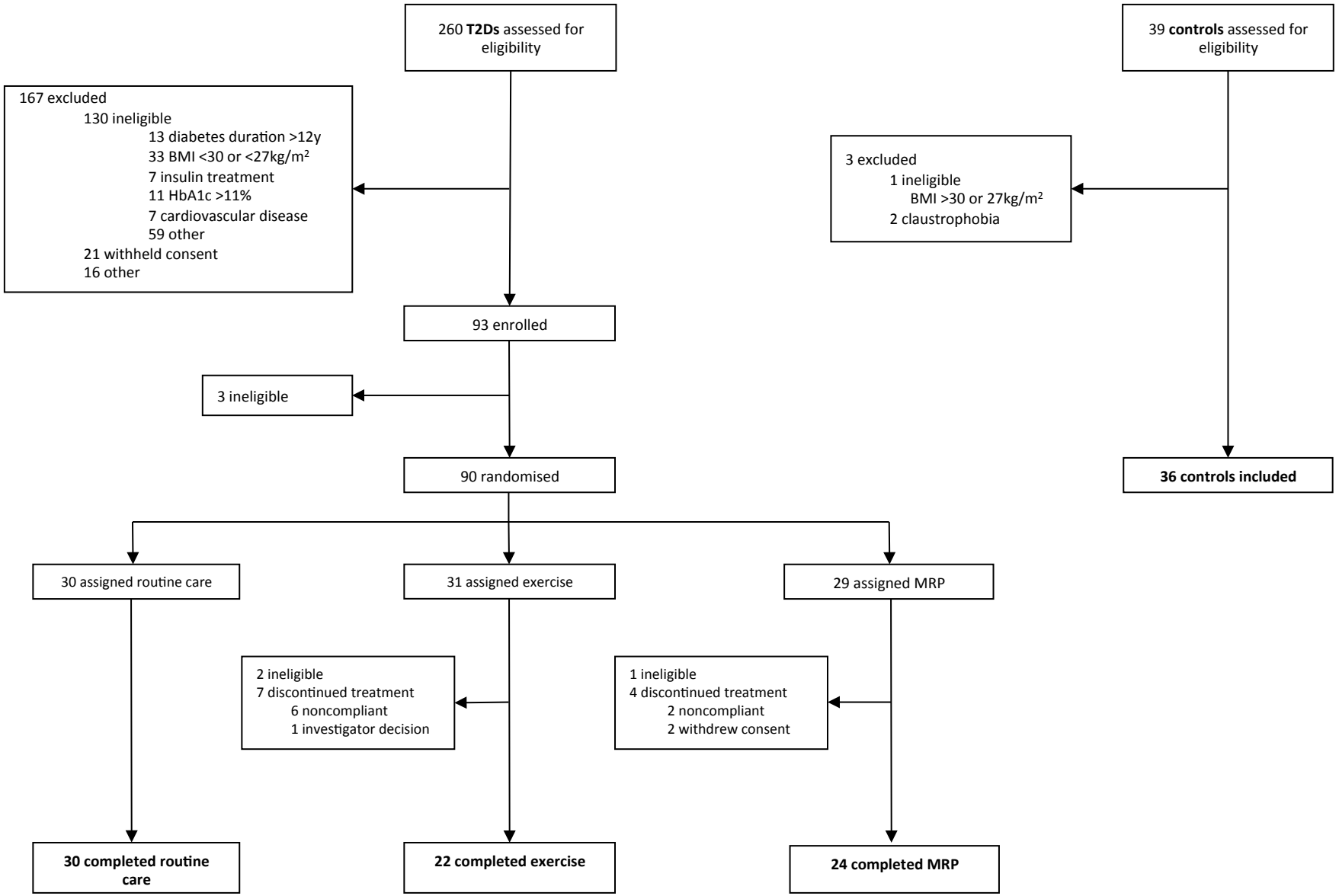
Table 3. Cardiac magnetic resonance imaging and echocardiography data at baseline and 12 weeks in the three trial arms.

	Routine care (n=30)			Exercise (n=22)			MRP (n=24)		
	Baseline	**Week 12**	**Mean change (95% CI)**	**Baseline**	**Week 12**	**Mean change (95% CI)**	**Baseline**	**Week 12**	**Mean change (95% CI)**
Cardiovascular magnetic resonance imaging									
LV PEDSR (s^{-1})	1·06 (0·15)	0·98 (0·18)	-0.07 (-0.13, -0.02)	0·92 (0·20)	1·02 (0·17)*	0.10 (0.04, 0.16)	1·00 (0·21)	0·96 (0·23)	-0.05 (-0.13, 0.03)
LV global longitudinal strain (%)	-17·4 (2·2)	-16·8 (1·8)	0.63 (-0.16, 1.41)	-16·3 (2·9)	-16·1 (2·5)	0.23 (-0.79, 1.25)	-16·6 (2·9)	-16·0 (1·8)	0.61 (-0.51, 1.72)
LV mass (g)	116·1 (22·8)	117·0 (24·2)	0.90 (-2.93 to 4.73)	123·1 (21·9)	122·0 (20·9)	-1.15 (-6.73, 4.44)	131·2 (26·9)	125·6 (27·0)	-5.56 (-11.53 to 0.40)
LV mass/volume	0·82 (0·77 - 0·86)	0·83 (0·77 - 0·92)	0.02 (-0.01, 0.05)	0·86 (0·75 - 0·91)	0·85 (0·76 - 0·88)	-0.02 (-0.06, 0.02)	0·80 (0·74 - 0·91)	0·79 (0·72 - 0·87)	-0.03 (-0.06 to -0.01)
LV EDV (mL)	133·9 (125·3 - 148·8)	128·7 (117·4 - 149·6)	-0.37 (-4.75, 4.00)	147·2 (129·3 - 161·3)	145·1 (132·0 - 159·7)	2.45 (-4.36, 9.27)	172·5 (131·7 - 180·7)	172·3 (116·3 - 188·9)	-0.15 (-5.90 to 5.60)
LV EDVi (mL/m^2)	63·3 (58·1 - 67·8)	61·5 (56·3 - 69·0)	0.46 (-1.79, 2.72)	67·4 (62·0 - 70·6)	66·1 (62·9 - 72·4)	1.50 (-1.53, 4.52)	71·6 (59·9 - 78·4)	77·9 (64·3 - 87·5)	4.97 (2.22 to 7.73)
LV EF (%)	67·6 (5·4)	66·2 (5·3)	-1.42 (-3.76, 0.92)	66·8 (7·9)	66·0 (6·2)	-0.79 (-3.78, 2.20)	69·8 (7·4)	65·2 (6·1)	-4.54 (-6.89 to -2.18)
Myocardial perfusion reserve	2·7 (0·8)	3·2 (1·1)	0.49 (-0.03, 1.00)	3·3 (0·9)	3·4 (1·2)	0.10 (-0.54, 0.75)	3·0 (1·1)	3·2 (0·9)	0.18 (-0.44, 0.79)
Aortic distensibility ($mmHg^{-1}x10^{-3}$)	3.7 (2.9 – 5.5)	4·8 (3·0 – 5·8)	0.51 (-0.20, 1.21)	3.3 (2·7 – 5·7)	3·8 (2·9 - 4·6)	0.55 (-0.87, 1.97)	3·2 (2·3 – 4·3)	4·2 (3·1 – 6·1)	0.90 (0.38, 1.41)
Echocardiography									
Average E/e'	8·0 (6·5 – 9·7)	8·6 (7·1 – 9·3)	0.18 (-0.49, 0.85)	8·8 (7·0 – 10·6)	8·1 (6·8 – 9·3)	-0.70 (-1.78, 0.39)	10·1 (7·5 - 11·0)	8·5 (7·6 – 9·7)	-0.67 (-1.83, 0.48)
Average E/A	1·00 (0·21)	1·01 (0·25)	0.01 (-0.06, 0.09)	0·94 (0·19)	1·00 (0·21)	0.06 (-0.03, 0.15)	0·92 (0·20)	0·99 (0·23)	0.07 (-0.03, 0.17)

Data are mean (SD) or median (IQR), and mean (95% confidence interval). MRP=meal replacement plan. LV=left ventricle. PEDSR=peak early diastolic strain rate. BSA=body surface. EDV=end diastolic volume. EDVi=end diastolic volume indexed to body surface area. ESV=end systolic volume. ESVi=end systolic volume indexed to body surface area. EF=ejection fraction.

Figure legends

Figure 1. Box plots displaying change in left ventricular peak early diastolic strain rate (LV PEDSR) from baseline to 12 weeks in the three trial arms. *denotes statistical significance.



Supplementary Figure 1. Trial profile. Abbreviations: T2D=type 2 diabetes mellitus; MRP=meal replacement plan.

Supplementary table 1. Baseline characteristics of prospective, randomized, open-label, blinded-endpoint trial participants stratified by treatment arm.

	Routine care (n=30)	Exercise (n=31)	MRP (n=29)
Age, years	50·7±6·4	50·5±7·2	49·7±6·3
Sex			
Male	18 (60%)	18 (58%)	17 (59%)
Female	12 (40%)	13 (42%)	12 (41%)
Ethnic origin			
Caucasian	18 (60%)	22 (71%)	16 (55%)
Black or other minority ethnicity	12 (40%)	9 (29%)	13 (45%)
Weight, Kg	102.6±14.9	102.8±18.3	104.6±16.9
Body mass index, Kg/m²	36.7±4.8	36.0±5.8	37.2±6.1
Systolic BP, mmHg	138±13	138±18	144±18
Diastolic BP, mmHg	85±7	88±10	90±9
Medications			
RAAS inhibitor	15 (50%)	11 (35%)	15 (52%)
Other antihypertensive(s)	9 (30%)	8 (26%)	11 (38%)
Statin	21 (70%)	20 (65%)	19 (66%)
Metformin	30 (100%)	29 (94%)	25 (86%)
Sulphonylurea	6 (20%)	6 (19%)	2 (7%)
GLP-1 agonist	3 (10%)	4 (13%)	3 (10%)
DPP-IV inhibitor	7 (23%)	6 (19%)	5 (17%)
SGLT-2 inhibitor	4 (13%)	3 (10%)	4 (14%)
Fasting blood tests			
Glucose, mmol/L	8.2±2.3	8.9±2.4	8.1±2.5
HbA1c, %	7.3±0.9	7.6±1.3	7.2±1.1