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Multiple Daily Injections OR Insulin Pump Therapy: Choosing the Best Option for Your Patient—An Evidence-based Approach

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Abstract Achieving optimal glucose control with minimal hypoglycemia and minimizing the impact of diabetes on quality of life are the aims of management of type 1 diabetes. The main therapeutic options for patients include multiple daily injections (MDI) and continuous subcutaneous insulin therapy (CSII). It is important to differentiate fixed dose MDI with more flexible use, based on carbohydrate counting and structured education programmes, often termed functional insulin therapy (FIT), shown to deliver better outcomes. A significant proportion of patients can achieve optimal glucose control with either therapy, and for those who are unable to achieve desired glucose control with MDI, there is a large body of observational data showing CSII enables them to reduce HbA1c and hypoglycemia, with associated improvements in diabetes-related quality of life. However, in many healthcare systems, guidelines restrict the use of CSII on the basis of cost, with only 20–35 % of patients with type 1 diabetes across Europe using CSII. Although data support improved glucose control and quality of life with CSII, we must recognize that insulin pump therapy is not for everyone and has some downsides such as being attached to a device or issues with cannulas. When we sit down with our patients, we have a responsibility to support those patients with the therapeutic strategy that is best suited to them. In this paper, we review some of the literature that informs this decision-making, highlighting areas where CSII offers clear benefits and also some areas where it may not be appropriate.

Keywords Type 1 diabetes · Continuous subcutaneous insulin infusion · Multiple daily injections · Hypoglycemia · Insulin pump therapy

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Introduction

In treating patients with type 1 diabetes, we aim to mimic as closely as possible physiological replacement of insulin with the aim of maintaining glucose as close to the normal range as possible without inducing an unacceptable degree of hypoglycemia. The landmark DCCT [1] and subsequent EDIC studies [2] demonstrated significant reductions in micro- and macrovascular complications with achieving these aims. The DCCT study in particular showed the superiority of an intensive approach using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) over the "conventional" twice daily mixed insulin regime.

Most patients with type 1 diabetes are now offered multiple daily injections as a standard of care, using rapid-acting insulin analogues to cover meal-time insulin requirements and longer-acting insulin to replace basal insulin. CSII using insulin pumps delivers rapid-acting insulin as a continuous infusion, allowing greater flexibility with the rate of basal delivery and allowing frequent boluses without the need for repeated injections. This offers the opportunity to replace insulin in a more physiological profile.

When we sit down with our patients, we have a responsibility to support that individual patient with the therapeutic

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strategy that is most appropriate for them. In this paper, we review some of the literature that informs this decision-making, highlighting areas where CSII offers clear benefits and also some areas where it may not be appropriate.

Multiple Daily Injections

Since the demonstration of its benefits in the DCCT study, MDI has been the standard of care for patients with type 1 diabetes. However, in that study, MDI was associated with a threefold greater risk of severe hypoglycemia requiring third party assistance [3]. MDI has advanced notably since then with the advent of insulin pens, rapid-acting insulin analogues and improved patient education. The German Diabetes Teaching and Treatment Program (DTTP), later adapted in the UK as the Dose Adjustment For Normal Eating [DAFNE] programme, demonstrated that teaching patients more flexible use of insulin using principles of adult education can achieve improved glucose control with reductions rather than increase in hypoglycemia [4, 5•]. This flexible regimen, incorporating carbohydrate counting, and adjustments for exercise and ill health has been termed "functional insulin therapy (FIT)" to differentiate it from the more traditional "fixed-dose" multiple daily injection regimen. Audit data from the British and German groups demonstrate sustained reductions in HBA1c between 0.3 and 0.6 %, with reductions of up to 70 % in rates of severe hypoglycemia [4]. In the UK, of the 40 % patients who reported impaired awareness of hypoglycemia at enrolment in DAFNE; in a year, almost half reported restoration of awareness [6]. There is also a marked improvement in a number of measures of quality of life.

The use of rapid-acting insulin analogues has been associated with better post-prandial glucose control, and long-acting basal insulins have reduced overnight hypoglycemia [7, 8]. The Hypo-Ana study shows that using an analogue-based regimen reduces severe hypoglycemia in patients with impaired awareness of hypoglycemia [9].

The recent evolution of automated bolus calculators for MDI, available for a while with insulin pumps, may also help patients perform the often complex calculations required for FIT. Data suggest that despite being taught how to adjust insulin, many patients underestimate insulin doses, and that for a number of patients, the health numeracy required to perform these calculations and adjustments becomes a barrier. Early results from the use of bolus calculators suggest reduced insulin errors and fear of hypoglycemia [10, 11]. Even in younger patients with type 1 diabetes (9–16 years) on MDI, the use of automated bolus calculators is associated with improved Hba1c and reduced glycemic variability [12], while a similar study in an older group reported better treatment satisfaction [13].

There are some important limitations of MDI that must be considered: patients who use either very small doses, such as children or those who are very insulin-sensitive, as accuracy and practicality limits the use of very small doses may struggle with MDI through currently available pens. Similarly, in patients on very large doses, the use of CSII may be beneficial from a pharmacodynamic perspective, as basal insulin delivered through continuous infusion works better than a large subcutaneous depot. MDI also becomes difficult to manage in those with very a flexible lifestyle, who eat frequently, requiring a large number of injections of rapid-acting insulin or those who do a lot of sport or shift work with differing requirements of basal insulin.

Insulin Pump Therapy

Insulin pump therapy was introduced over 30 years ago [14, 15], and it is somewhat surprising to see how poor the penetrance has been for this treatment. Indeed, across Europe, less than 30 % of patients with type 1 diabetes are using insulin pumps, although the use in the USA is higher [15]. The main advantage of insulin pumps is the extra flexibility they offer, allowing the patient to alter basal insulin in response to changes in requirements due to exercise, alcohol, illness or the dawn phenomenon. Most pumps offer on-board automated bolus calculators and allow frequent boluses for snacks or corrections through the day. They also allow for "advanced" bolus options, allowing meal-time bolus insulin to be delivered over a longer period to cover more slowly absorbed meals. In addition, increased flexibility and well-being in patients using CSII may increase adherence to intensified therapy [16].

The evidence for CSII starts with the DCCT trial, in which half the patients in the intensive treatment arm were allocated insulin pump therapy [17]. A short randomized crossover trial demonstrated increased glucose in target but was too short to report HbA1c levels [18]. Other small randomized controlled trials (RCTs) failed to show a benefit of CSII over a glargine-based MDI regimen [19]. In a meta-analysis of 12 RCTs comparing the use of CSII compared to MDI in type 1 diabetes, Pickup et al. found that CSII use was associated with a better glycemic control and reduced insulin requirements [20•]. Subsequently in 2010, a Cochrane review of 23 RCTs, Misso et al. analysed data from 976 participants randomized to either CSII or MDI therapy and concluded that though small, there was a statistically significant improvement in HbA1c with CSII with additional benefit of fewer severe hypoglycemias and better quality of life [21]. In contrast, a 2012 meta-analysis from Yeh et al. found no benefit in terms of hypoglycemia for CSII over MDI, although quality of life scores seemed to be better for CSII in children and adults [22]. There is certainly far more data in the paediatric age group than in adults.

It is worth noting that many of the studies included in these meta-analyses were done before the introduction of modern analogue basal insulins and were mostly small and of short

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duration. Many of the studies were performed in children, where pumps may offer other advantages over injections such as enabling greater parental control and allowing more boluses. The amount of education given was also not controlled between groups and may have influenced outcomes. There are no published studies comparing CSII with FIT. However, before we interpret this paucity of data as suggesting there is no benefit of CSII, we should consider the large body of observational data demonstrating sustained benefit of CSII over a number of years [23, 24]. In particular, when we consider patients with problematic hypoglycemia at baseline, insulin pumps offer significant and sustained reduction in rates of hypoglycemia [20•].

Interestingly, in a 2×2 factorial RCT comparing insulin pump with MDI and continuous with conventional glucose self-monitoring (HypoCOMPaSS) performed exclusively in patients with impaired awareness of hypoglycemia found similar reductions in rates of severe hypoglycemia in patients using CSII, CGM or sensor-augmented pumps as in those using SMBG and MDI [25]. Authors concluded that with frequent contact and education, good glycemic control can be achieved with prevention of symptomatic hypoglycemia, restoring hypoglycemia unawareness, without worsening metabolic control [25].

Insulin pump therapy is however not for everyone. A number of patients are reluctant to be connected to a device 24×7, and many do not like the cannulas or tubing as they can often get caught in clothing. Cannula occlusions, which are a frequent cause of unexplained high glucose readings, can also be particularly problematic for some patients and can even lead to ketoacidosis [26, 27]. The reasons for occlusions are unclear, and it is speculated that a complex interaction occurs between the plastic in the infusion set and the insulin formulation [28]. These are more common when the infusion set is left in situ beyond 3 days. Some patients also have trouble with local skin reactions, which may be to teflon or materials used in catheters [29].

Some newer pumps such as the OmniPod and Tandem pumps consist of re-usable or disposable units with integrated cannulas or very short tubes. Often called "patch-pumps", they are attractive to many as they do away with the long cumbersome tubing and are becoming increasingly popular. They do however sometimes pose their own problems around placement and size.

A key concern in patients using CSII is around the frequency of capillary glucose monitoring. In patients not performing capillary monitoring, CSII may present a higher risk of diabetic ketoacidosis than MDI, as there is no subcutaneous depot of basal insulin, which means that in the absence of frequent capillary glucose testing, a cannula occlusion may go undetected and lead to rapid decompensation. Indeed, some of the early experience with CSII were affected by a higher incidence of DKA, although this is not confirmed in subsequent papers [30•], and increased education and healthcare professional input associated with initiation of CSII at most centres may also be a contributory factor. Other potential issues include infections at infusion sites and pump malfunctions. In a recent survey of 640 new pumps from four different manufacturers, 36 % were reported to have had a defect of some sort including 16 % which had to be replaced [31]. The T1D Exchange Clinic Registry data suggests 4.4 % of patients discontinued insulin pump therapy, with a variety of reasons cited, the most common being comfort.

Some Special Circumstances

CSII Versus MDI in the Paediatric Population

CSII is far more widely used in paediatric patients than in adult patients. The early use of CSII leads to better and sustained glycemic control. Especially in very young children with small insulin requirements, and when food intake is variable, being able to programme the basal rates and give small boluses allows better glucose control [32]. The T1D Exchange Clinic Registry also found lower Hb1c levels in those using CSII [33]. This may be a marker for more engaged patients and indeed more engaged clinicians. Uptake of CSII is lower in those with lower socio-economic and educational status.

CSII used in pre-school children has particular benefits—allowing altering basal rates in response to activity and delivering boluses without the need for repeated injections [34]. Registry data from Europe and the USA show better metabolic control with fewer episodes of severe hypoglycemia with CSII [30•, 35].

CSII Versus MDI in Pregnancy

Given the very tight glycemic targets recommended in pregnancy, CSII certainly offers practical benefits in pregnancy, and a number of international guidelines recommend the use of CSII during pregnancy in type 1 diabetes. However, the Cochrane review and recent systematic reviews found no differences in maternal or foetal outcomes or in glucose control between MDI and CSII in pregnancy [36, 37]. With modern pumps, it is easier for women to perform frequent boluses and use new techniques such as "super-boluses" where the basal insulin delivery is temporarily suspended to allow a larger bolus to be delivered without increasing the risk of late hypoglycemia.

The Role of Sensor-Augmented Pumps Continuous glucose monitoring (CGM) systems measure glucose in the interstitial fluid, providing people with diabetes not only ongoing information on the absolute glucose values but also trends of glucose. Most systems also have alarms that can alert patients to impending high or low glucose values, allowing the patient to

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intervene early and keep their glucose values within target range. Pumps that integrate with CGM systems are called sensor-augmented pumps (SAP). A number of large randomized trials have demonstrated significant improvements in HbA1c with these systems, without any increase in hypoglycemia [38, 39]. The latest generation of SAP devices can suspend insulin delivery automatically if sensor glucose values are predicted to drop below pre-determined thresholds. These systems can reduce the duration of nocturnal hypoglycemia [40] and may help reduce severe hypoglycemia in patients with impaired awareness of hypoglycemia [41, 42].

Access to CGM and SAP is variable across different health systems, and there is a significant drop-off rate amongst those using CGM even when this is fully funded. This may be related to the relative inaccuracy of current generation sensors, alarm fatigue and, in many cases, cost. In a meta-analysis of six RCTs, Pickup et al. reported that a greater benefit was achieved with the use of CGM-based system in patients with higher Hba1c at baseline and with regular use [43].

Use of CSII in Type 2 DM The recent OPTIMISE study, a multicentre RCT, demonstrated that in overweight patients with suboptimal control despite high [>0.7 units/kg] daily insulin requirements, CSII resulted in significantly better glycemic control than further attempts at optimizing MDI. There was a 0.7 % reduction in HBA1c with 20 % lower use of insulin in the CSII arm compared to the MDI arm which showed no improvement in HBA1c despite an increase in total daily insulin over the 6-month study [44••]. This opens up the question of benefits of CSII in patients with type 2 diabetes. Some studies show patients on multiple injections prefer CSII [45], and there may be a role for those who are failing to achieve targets despite efforts at optimizing MDI. The OPTIMISE trial suggests that this benefit can be achieved without using many of the complex features of the pump, such as multiple basal rates, flexible boluses and carbohydrate counting, and may be related to more stable kinetics of basal insulin when infused continuously.

Conclusions

MDI and CSII are both valid treatments for people with type 1 diabetes, and as shown by the T1D Exchange database, patients using either therapy are able to achieve excellent diabetes control. It must be emphasized that by MDI here, we really mean flexible insulin therapy, based on carbohydrate counting and active adjustment of insulin doses. However, a proportion of patients will be unable to achieve these glucose targets using injections alone. In these patients, there are clear benefits from using insulin pump therapy. There are certain categories of patients, such as those with very high or very low insulin doses, those with a strong dawn phenomenon and those with problematic hypoglycemia, in whom there is strong observational data for benefit with CSII, where MDI is likely to prove difficult. The difficulty many of us face is seeing patients who have acceptable levels of glucose control but would like to use CSII. While the benefits in terms of health-related quality of life may be viable, often funding for CSII based on clinical improvement is difficult to demonstrate, especially if they are already doing well at the expense of health-related quality of life. We often face a dilemma between patient choice and health system economics. We also need to have realistic expectations of what CSII can offer. When faced with the patient in front of us, we need to provide the full picture, including not only benefits but also downsides such as tubing, being attached to a device and cannula, or device failures. The fact that a disproportionate number of healthcare professionals with type 1 diabetes chose CSII over MDI points to the subtle intangible benefits of CSII over MDI. There is a similar conundrum with CGM, which stands to benefit a large proportion of patients but is not available for many. As the technology advances, we hope we will be able to offer their advantages to a wider group of patients, with less intrusion and greater accuracy. Until we have the tools to understand the wider impact of the use of these technologies on productivity and well-being, over and above the crude measures provided by HBA1c and severe hypoglycemia, it is likely that their use will be restricted to a limited few.

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Compliance with Ethics Guidelines

Conflict of Interest Mamta Joshi declares that she has no conflict of interest.

Pratik Choudhary has received speaker fees and travel support and participated in advisory boards for manufacturers of insulin and insulin pumps (Lilly, Sanofi, Novo Nordisk, Medtronic, Roche, Johnson and Johnson).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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