External insulin pump treatment in the day-to-day management of diabetes: benefits and future prospective

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Abstract

The aim of diabetes treatment is to achieve tight glucose control to avoid the development of chronic diabetes complications while reducing the frequency of hypoglycaemic episodes. The main clinical indications of pump therapy in type 1 diabetes are persistently elevated HbA1c in spite of the best attempts of intensified insulin therapy with multiple daily injections (MDI) and/or frequent, disabling or severe hypoglycaemia. Several trials have demonstrated the superiority of continuous subcutaneous insulin infusion (CSII) over MDI, and highlighted the benefits of using short-acting insulin analogues. However, new MDI regimens with long-acting insulin analogues challenge insulin pump therapy in some indications, thus indicating the need for precise selection of those patients who will benefit the most from CSII. In type 2 diabetes, pump therapy may be an invaluable tool in selected patients characterized by chronic elevation of HbA1c, obesity and high insulin requirements. In addition, in any case, specific education, training and ongoing evaluation of the benefit/risk ratio of the treatment are mandatory. Furthermore, there is continuing progress in the development of pump and catheter features, and insulin kinetics can still be improved. These technical advances are part of the work in progress towards developing closed-loop systems.

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Keywords: External insulin pump; Intensive insulin therapy; HbA1c; Glycaemic control; Diabetes; Review

1. Introduction

The goal of type 1 diabetes treatment is to achieve tight glucose control to avoid chronic diabetes complications while limiting the frequency of hypoglycaemic episodes in day-to-day life. Over the past few decades, considerable efforts have been made to improve the tools of treatment. The development of continuous subcutaneous insulin infusion (CSII) and, more recently, short-acting insulin analogues with advantageous pharmacokinetic properties constitute important advances in the treatment of diabetes.

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CSII using external insulin pumps was first introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in type 1 diabetes patients [1] through more physiological insulinization than achieved with multiple daily injections (MDI). The exclusive use of soluble short-acting insulin, infused subcutaneously at the same site for 2 or 3 days, reduces the variability of insulin absorption compared with long-acting insulins. CSII also allows greater flexibility of insulin infusion, thanks to the ability to program several basal rates and to adjust meal-time boluses when required. It is noteworthy that the modern intensified insulin regimens, whether delivered by CSII or MDI, all require the implementation of frequent blood glucose self-monitoring, dietary advice and structured diabetes education to improve glycaemic control. Under these conditions, CSII has proven superior to MDI in terms of HbA₁c, hypoglycaemic episodes, glucose variability and quality of life in those selected patients who fail to obtain good glycaemic control in spite of an intensified MDI regimen. These findings have also led to the validation by the French Health Authority of insulin pump treatment in patients who fail to obtain good glycaemic control with MDI [2], and to the recent publication of French recommendations for the use of CSII in type 1 and type 2 diabetes patients [3].

2. Benefits of CSII in type 1 diabetes

2.1. HbA₁c

Several studies have confirmed the superiority of CSII over MDI in terms of HbA₁c [4-7]. In the Diabetes Control and Complications Trial (DCCT) [8], HbA₁c levels in the intensive-treatment group were significantly lower with CSII than with MDI (ranging from -0.2% to -0.4%). However, because the patients who were randomly assigned to receive intensive treatment in the DCCT could choose between CSII and MDI (they were not randomly allocated to the type of intensive therapy), the results could be biased. Nevertheless, two recent meta-analyses of trials have compared CSII and MDI regimens, involving 600 and 1547 patients, respectively [9,10], and have reported an overall benefit of CSII over MDI, with a reduction of HbA₁c in the range of 0.4–0.5% that was associated with a reduction in insulin requirements. A recent Cochrane review reported a lower mean difference of 0.3% [11], but included studies of very short duration and early trials from the 1980s, when pumps were less reliable and less technically sophisticated.

As all of the trials included in these meta-analyses were performed with human regular insulin, except one study that used insulin lispro [12], it was necessary to investigate whether the introduction of short-acting insulin analogues would modify the relative performances of CSII and MDI. In fact, with either CSII or MDI, the optimal meal-time insulin is a short-acting insulin analogue, as this exhibits pharmacodynamic advantages over human regular insulin, including faster absorption, earlier onset and shorter duration of action. Several randomized controlled trials have shown that CSII with short-acting insulin analogues is more efficient for postprandial glycaemia and HbA₁c concentrations than CSII with human regular insulin [13-15] (Table 1). A meta-analysis also concluded that the use of insulin analogues in pump therapy results in a modest (0.26%), but significant, reduction in HbA₁c compared with soluble insulin [16]. The pharmacokinetic properties of short-acting insulin analogues are certainly responsible for this slight superiority, thanks to improvements in postprandial glucose levels and stability. However, the efficacy of CSII vs MDI therapy has been evaluated in only a limited number of randomized controlled trials in which rapid-acting analogues were used for both regimens, with two out of three concluding the superiority of CSII [14,17,18] (Table 2). A pooled analysis of the three studies suggested that CSII is associated with better glycaemic control, particularly in patients with initially suboptimal control [19]. The magnitude of the effect of CSII compared with MDI on glycaemic control was similar to the previous findings of trials using human regular insulin, with the difference in HbA₁c concentrations between CSII and MDI being ~0.35%. Also, the relative benefit of CSII over MDI was found to increase with higher baseline HbA₁c levels (Fig. 1) [20]. In addition,

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Study design</th>
<th>Patients (n) and type of insulin</th>
<th>Difference in HbA₁c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinman et al., 1997 [13]</td>
<td>Double-blind crossover</td>
<td>30 CSII with lispro/Humulin</td>
<td>-0.34%</td>
</tr>
<tr>
<td>Melki et al., 1998 [14]</td>
<td>Open crossover</td>
<td>39 CSII with lispro/Actrapid</td>
<td>-0.53%</td>
</tr>
<tr>
<td>Renner et al., 1999 [15]</td>
<td>Open crossover</td>
<td>113 CSII with lispro/Humulin</td>
<td>-0.13%</td>
</tr>
</tbody>
</table>

![Fig 1. Predicted relative benefits of CSII over MDI in lowering HbA₁c according to baseline HbA₁c (adapted from [20]).](image-url)
the results obtained with CSII were superior to those achieved with MDI whatever the level of baseline HbA1c.

### 2.2. Hypoglycaemia

As the definition and reporting of hypoglycaemia are different in different trials, it is not easy to make any direct comparisons. However, based on the available data, it appears that CSII use was associated with a decrease in the frequency of mild hypoglycaemic episodes [10], and this was probably related to the lower variability of blood glucose concentrations, as measured by the standard deviation (SD) [9]. In patients prone to severe hypoglycaemia, the use of CSII resulted in a large and sustained reduction in such episodes [21]. In addition, a meta-analysis of randomized controlled trials and observational studies, conducted with CSII and short-acting insulin analogues in patients with severe hypoglycaemia at baseline, showed that severe hypoglycaemia was reduced by a mean of about 75% by CSII treatment compared with MDI in adults as well as in children [22].

### 2.3. Blood glucose variability

In patients failing to obtain good glycaemic control with MDI, high glycaemic variability was frequently associated with both high HbA1c levels and frequent hypoglycaemic episodes, thus preventing tight insulin adjustments because of the difficulty of predicting blood glucose fluctuations and the fear of having even more frequent hypoglycaemia. The improvement in control achieved by CSII appears to be related to both HbA1c and blood glucose variability with MDI. Indeed, pump therapy was most effective in those least controlled with MDI [23]. CSII reduced both the within-day and day-to-day variability, as determined by the mean amplitude of glycaemic excursions (MAGE) [24], and the SD of mean blood glucose [14,17], probably thanks to better predictability and reproducibility of insulin absorption.

### 3. CSII vs long-acting analogues

Reported improvements in glucose control with MDI using only analogues raised the question of whether CSII was truly an unchallenged “gold-standard” treatment. Therefore, comparison of CSII and MDI using both rapid- and long-acting insulin analogues is clearly of great interest, although few randomized controlled studies have assessed the issue (Table 3).

The first randomized study performed in adults showed similar glucose improvements with the two options [25]. However, it should be noted that the baseline HbA1c in the study was not excessively high (7.7% for CSII and 7.8% for MDI).

### Table 2

Superiority of continuous subcutaneous insulin infusion (CSII) using short-acting insulin analogues over multiple daily insulin injections (MDI) using short-acting insulin analogues.

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Study design</th>
<th>Patients (n)</th>
<th>Difference in HbA1c</th>
<th>Hypoglycaemic episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanaire-Broutin et al., 2000 [12]</td>
<td>Crossover</td>
<td>41 MDI/CSII</td>
<td>-0.35%</td>
<td>NS</td>
</tr>
<tr>
<td>Tsui et al., 2001 [18]</td>
<td>Parallel</td>
<td>13 CSII, 14 MDI</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DeVries et al., 2002 [17]</td>
<td>Parallel</td>
<td>39 CSII, 40 MDI</td>
<td>-0.84%</td>
<td>+0.96/patient/week</td>
</tr>
<tr>
<td>Retnakaran et al., 2004 [19]</td>
<td>Pooled analysis</td>
<td>139 MDI/CSII</td>
<td>-0.35%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant

### Table 3

Randomized controlled trials of continuous subcutaneous insulin infusion (CSII) using fast-acting insulin analogues vs multiple daily insulin injections (MDI) using fast- and long-acting insulin analogues in type 1 diabetes patients.

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Study description</th>
<th>Insulin used for MDI</th>
<th>Insulin used for CSII</th>
<th>HbA1c at end of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolli et al., 2004 [25]</td>
<td>n = 57 (adults), 6 months, randomized</td>
<td>Glargine + lispro</td>
<td>Lispro</td>
<td>CSII: 7.0% NS MDI: 7.2% <em>(P &lt; 0.05)</em></td>
</tr>
<tr>
<td>Hirsch et al., 2005 [27]</td>
<td>n = 100 (adults), 10 weeks, randomized (crossover)</td>
<td>Glargine + lispro</td>
<td>Aspart</td>
<td>CSII: 7.1%* NS MDI: 7.3% <em>(NS)</em></td>
</tr>
<tr>
<td>Doyle et al., 2004 [26]</td>
<td>n = 32 (children), 16 weeks, randomized</td>
<td>Glargine + aspart</td>
<td>Aspart</td>
<td>CSII: 7.2 NS MDI: 8.1 <em>(P &lt; 0.05)</em></td>
</tr>
</tbody>
</table>

*Significant reduction in fructosamine; NS: not significant.
regimen, many type 2 diabetes patients eventually require insulin treatment. With bedtime insulin injection has then to be implemented. With bedtime insulin injection, oral antidiabetic agents (OADs) fails to maintain long-term optimal diabetes control in most patients, and insulin treatment is the defect progresses, the combination of lifestyle changes and insulin resistance and a progressive defect in islet beta-cell function. As the defect progresses, the combination of lifestyle changes and oral antidiabetic agents (OADs) fails to maintain long-term optimal diabetes control in most patients, and insulin treatment has then to be implemented. With bedtime insulin injection combined with OADs commonly used as the first insulin regimen, many type 2 diabetes patients eventually require MDI therapy to maintain blood glucose control. However, even if intensive insulin therapy can improve glycaemic control in obese type 2 diabetes patients, it often comes at the cost of high insulin doses that, in turn, may lead to further marked weight gain. In the worst-case scenario, patients gain weight while their glycaemic control remains suboptimal in spite of increasing insulin doses. Also, regimens using short- and long-acting insulin analogues are not superior to human insulin-based regimens in terms of HbA1c and insulin doses required, although they can result in a trend towards less hypoglycaemia and weight gain. For these reasons, it may be useful to consider the potential indications for insulin pump therapy in type 2 diabetes.

4. Benefits of CSII in type 2 diabetes

CSII is now widely used in type 1 diabetes patients, but its development as a treatment of type 2 diabetes is a much more recent area of research and remains a subject of debate. Type 2 diabetes is associated with insulin resistance and a progressive defect in islet beta-cell function. As the defect progresses, the combination of lifestyle changes and oral antidiabetic agents (OADs) fails to maintain long-term optimal diabetes control in most patients, and insulin treatment has then to be implemented. With bedtime insulin injection combined with OADs commonly used as the first insulin regimen, many type 2 diabetes patients eventually require MDI therapy to maintain blood glucose control. However, the potential benefits of CSII over MDI; however, the MDI regimens used as comparators were not analogue-based basal-bolus regimens.

4.1. HbA1c

Several authors have reported positive experiences with CSII in small cohorts of severely obese type 2 diabetes patients with poor glycaemic control (HbA1c 10-12%) in spite of intensified insulin therapy using high insulin dosages (1.5-5.0 U/kg) [37,38]. Interestingly, in these particularly insulin-resistant patients, both HbA1c and insulin requirements were decreased with CSII [39].

More recently, four randomized controlled trials compared the potential benefits of CSII vs MDI in insulin-requiring type 2 diabetes patients (Table 4). The trial by Raskin et al. [40] compared CSII using aspart insulin with MDI using premeal aspart and one or two injections of isophane as basal insulin. The improvement in HbA1c after 24 weeks was similar in the two groups. In older type 2 diabetes patients (mean age: 66 years), the trial by Herman et al. [41] compared CSII using lispro insulin vs MDI with glargine and lispro. HbA1c decreased significantly and similarly in both groups, reaching an optimal level after 1 year. In both these studies, most of the patients were receiving insulin at baseline, but not in an intensified regimen, and HbA1c levels were moderately elevated (8.2%). Thus, it was to be expected that MDI would be more effective than the baseline treatment in these patients. In these populations, therefore, CSII was as effective as, but not superior to, MDI in terms of overall glycaemic control.

Two other studies, each with a crossover design, showed significant improvements in glycaemic control with CSII compared with MDI. The trial by Wainstein et al. [42], conducted in 40 obese type 2 diabetes patients with poor glycaemic control (HbA1c 10.2%), showed the superiority of CSII with lispro insulin vs MDI with isophane insulin and human regular insulin in the control of HbA1c levels. The trial by Berthe et al. [43] included 17 patients in poor glycaemic control, treated with two daily injections of premixed insulin (isophane 70/human regular 30), who were allocated to either CSII using lispro insulin or premixed insulin given three times daily. Glycaemic control was improved with both treatments, but to a greater extent with CSII. These two studies indicate the benefits of CSII over MDI; however, the MDI regimens used as comparators were not analogue-based basal-bolus regimens.
4.2. Hypoglycaemia and weight gain

Three of the four above-mentioned randomized studies showed the superiority of CSII over MDI in terms of glycaemic variability, and in particular postprandial glycaemic excursions, as assessed by continuous glucose monitoring [43]. In all these studies, mild hypoglycaemic episodes were reported at the same (low) rates with MDI and CSII. Insulin dosages increased slightly and similarly with both MDI and CSII in all of the studies, and reached around 1 U/kg. There was also no difference between CSII and MDI in weight gain, which was moderate and in parallel with the improvement in HbA1c.

Table 4

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Patients (n)</th>
<th>Diabetes duration (years)</th>
<th>Baseline HbA1c</th>
<th>Type of insulin</th>
<th>OADs</th>
<th>Study description</th>
<th>HbA1c</th>
<th>Insulin doses (U/day)</th>
<th>Hypoglycaemic events</th>
<th>Weight change (kg)</th>
<th>Quality of life</th>
<th>Improved P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin et al., 2003 [40]</td>
<td>132</td>
<td>12.5</td>
<td>8%</td>
<td>CSII: aspart</td>
<td>MDI: 1 or 2 NPH + 3 aspart</td>
<td>No</td>
<td>Parallel-group, 6 months</td>
<td>NS, CSII: 7.6±1.22%</td>
<td>NS, CSII: 0.7 U/kg</td>
<td>NS, CSII: +0.8/month</td>
<td>NS, CSII: +1.7</td>
<td>NS, CSII: +0.9</td>
</tr>
<tr>
<td>Herman et al., 2005 [41]</td>
<td>107</td>
<td>16</td>
<td>8.3%</td>
<td>CSII: lispro</td>
<td>MDI: glargine +3 lispro</td>
<td>No</td>
<td>Parallel-group, 12 months</td>
<td>NS, CSII: 6.6±0.8%</td>
<td>NS, CSII: 108±62</td>
<td>NS, CSII: 1.08</td>
<td>NS, CSII: +2.1</td>
<td>NS, CSII: +2.6</td>
</tr>
<tr>
<td>Wainstein et al., 2005 [42]</td>
<td>40</td>
<td>NA</td>
<td>10.2%</td>
<td>CSII: lispro</td>
<td>MDI: 1 NPH +3 human regular</td>
<td>Metformin</td>
<td>Crossover, two periods of 4.5 months</td>
<td>P = 0.007</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Berthe et al., 2007 [43]</td>
<td>17</td>
<td>17</td>
<td>9%</td>
<td>CSII: lispro</td>
<td>MDI: 3 premixed (lispro–NPH 50/50)</td>
<td>No</td>
<td>Crossover, two periods of 3 months</td>
<td>P &lt; 0.03, CSII: 7.7±0.8%</td>
<td>NS, CSII: 1 U/kg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

OADs: oral antidiabetic drugs; NPH: neutral protamine Hagedorn; NS: not significant; NA: not applicable

5. CSII in type 2 diabetes in the long term

Several studies in type 2 diabetes report improvement in patients’ satisfaction and quality of life with insulin pump therapy. This was particularly well documented in the study by Raskin et al. [40] (Fig. 2). The CSII-treated subjects showed significant improvement in overall treatment satisfaction, flexibility, ease of use, and patient burden compared to the MDI-treated group. The beneficial effects of pump therapy on HbA1c were maintained in the long term [41]. The study by Herman et al. [41] also demonstrated that CSII is effective in the management of type 2 diabetes, with a significant decrease in HbA1c (-1.2% after 3 years). Metformin treatment was used with the intensification of insulin therapy throughout the study to achieve glycemic control. Most of the excess weight reported was gained during the first year of treatment. The results of these studies are encouraging and suggest that pump therapy, especially when combined with intensive insulin therapy, is both feasible and effective in the long term.

5.1. Quality of life

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their quality of life. At the end of the 3 year study period, 92% of the patients chose to continue with the pump therapy, thus confirming the good tolerability of the pump and the improved quality of life in the long term in patients with type 2 diabetes. For these reasons, in type 2 diabetes, pump therapy may be a valuable tool, especially for those patients with chronically inadequate glycaemic control, obesity and high insulin requirements despite an intensified and accurately adjusted MDI regimen.

6. Insulin pump treatment: do we need more?

6.1. Pump and catheter features

Today’s insulin pumps are highly reliable and easy to use in daily life, at least as regards their basic functions. They have become smaller and more discreet but, also, in some ways, more complex, as many new technological features are now embedded in the pumps, including the different ways of infusing boluses, different patterns of basal rates for different days and reminders for boluses. Bolus calculators are particularly useful for helping patients to adjust their prandial doses. The capability to download data already exists, and may well be accompanied by automatic analysis of these data and by expert advice for treatment adjustment.

However, whereas catheters have considerably improved over the past few years, the technical aspects of pump and catheter handling remain an obstacle for some patients. Filling the pump reservoir, priming the catheter and inserting the needle require precision, skill and time; however, patch pumps should bring about important improvements in this field. Also, avoidance of the catheter and automatic needle insertion/retraction are attractive features that should reduce the discomfort of pump therapy for activities such as showering, sports participation and swimming.

6.2. Insulin

The use of short-acting insulin analogues has considerably improved the day-to-day management of diabetes, particularly in patients using CSII. However, the subcutaneous site introduces delays in insulin kinetics, with the onset of insulin action still too slow and the duration of action still too long to mimick physiological postprandial insulin secretion. Nevertheless, attempts are being made to improve insulin kinetics either by modifying its formulation to reduce the time between insulin injection and its onset of action or by introducing other compounds, such as hyaluronidase, to accelerate the onset on insulin action and reduce its duration.

6.3. Sensor-augmented pumps

Pumps that display continuous glucose monitoring are already available (for example, the Medtronic Paradigm® Veo and the Animas® Vibe). Indeed, not only the actual glucose level, but also the alarms and trends displays can all help the patient to modify his insulin doses. These pumps may also be expected to adapt their calculators to the individual needs of the patient and to not only give advice in real time, but also on the basis of several days’ worth of glucose profiles. Such improvements are the next steps towards a closed-loop insulin delivery system.

7. Conclusion

Despite the remarkable improvements in diabetes management thanks to the introduction of insulin analogues, a significant number of patients still cannot achieve their target HbA1c levels without experiencing disabling or severe hypoglycaemia. In such patients, pump therapy provides convenient and flexible insulin delivery while improving their glycaemic control and stability, and quality of life. In addition, efforts are being made to further improve insulin kinetics, and to develop user-friendly monitors and miniaturized insulin pumps. Appropriate teaching and training programmes are necessary, however, to achieve all of the benefits afforded by these technical improvements. Furthermore, considerable work is now in progress to develop algorithms for the automated regulation of glycaemia.

Conflicts of interest statement

H. Hanaire has participated on the boards and in conferences for Medtronic, Eli Lilly, Novo Nordisk and Sanofi-Aventis.
References


