Insulin Pump for Type 2 Diabetes

Use and misuse of continuous subcutaneous insulin infusion in type 2 diabetes

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Progressive hyperglycemia in type 2 diabetes results from a progressive β-cell failure together with a state of insulin resistance (1). Insulin deficiency worsens with the natural progression of type 2 diabetes, explaining the escape from oral antihyperglycemic agents and the need for exogenous insulin therapy (2).

The use of external pumps in patients with type 2 diabetes is a recent practice compared with that in type 1 diabetes, and its use is still debated. In only a few countries, such as in France and Israel, continuous subcutaneous insulin infusion (CSII) using an external pump is an alternative in type 2 diabetes that the health authorities have allowed for reimbursement. The rationale for using pump therapy was first suggested by its use in case reports of type 2 diabetes with extreme insulin resistance and poor glycemic control (3–6). In such patients, insulin was administered transiently by intravenous insulin infusion allowing lower mean glucose level despite a 40% reduction of insulin requirements. The sequential use of 4-week intravenous insulin infusion followed by 1-year CSII in a group of patients with type 2 diabetes patients poorly controlled despite very high insulin requirements allowed a dramatic reduction of HbA1c (−3%, −9 mmol/mol), while insulin requirements were reduced by one-third. Such beneficial effects of CSII were attributed to increased insulin sensitivity assessed by the hyperinsulinemic-euglycemic clamp study (7). These observations raised the question as to whether insulin continuous administration by a pump device gives an advantage compared with the conventional approach of insulin intensification by multiple daily injections (MDIs). The evidence base is still under debate and will be discussed in this review.

Is CSII effective for the intensification of insulin therapy in type 2 diabetes?

Very few randomized controlled studies have looked at the comparative effectiveness of CSII versus MDI (8–11) (Table 1). Two parallel-group studies performed over 6 and 12 months, respectively, included moderately obese type 2 diabetic patients with a mean age range of 55–66 years. Their baseline HbA1c values were moderately high (8%, 64 mmol/mol, and 8.4%, 68 mmol/mol) despite an insulin therapy with at least one daily injection with or without oral antihyperglycemic agents (8,9). Treatment intensification strategies in these studies compared CSII with a basal/bolus (NPH or a long-acting analog, respectively, plus a rapid-acting analog) and resulted in HbA1c lowering of the same magnitude with both MDI and CSII treatments, although the magnitude of HbA1c lowering in both arms was much greater in one study (approximately by −0.5 vs. −1.6%) (8,9).

In contrast to these results, two randomized crossover studies with small numbers of subjects have shown an advantage of CSII in comparison with MDI. In these studies, obese type 2 diabetic patients were successively treated by CSII and MDI for periods of 12 and 18 weeks, respectively (10,11). In these studies, intensification was offered in patients failing to respond to two or more insulin injections per day (NPH or premixed NPH plus rapid-acting analog). Interestingly, these subjects exhibited a baseline HbA1c >9% (75 mmol/mol) despite high insulin requirements (≥1 units/kg/day). For insulin intensification, a rapid-acting analog was used in CSII in both studies, and NPH plus a rapid-acting analog (10) or regular human insulin (11) was used in MDI basal bolus regimens. In these two studies, CSII was more effective than MDI for lowering HbA1c (−1.2 vs. −0.45%, P < 0.03, and −0.8 vs. 0.4%, P < 0.01, respectively). Continuous glucose monitoring was performed in both studies, showing a significant reduction of glucose area under curve with CSII in comparison with MDI (10,11). What may explain such discrepancy observed between the crossover studies compared with the parallel-group studies? Given the heterogeneity of the type 2 diabetic population, it can be difficult to ascertain the potential confounding variables for each study. Nevertheless, there were several differences seen in the selection criteria: β-cell failure and insulin resistance were likely more severe in the crossover studies as evidenced by the higher baseline HbA1c level, the higher baseline insulin requirement, and the higher number of insulin injections in comparison with the parallel-group studies. The uses of NPH in three of these four studies (8,10,11) and regular insulin in one of the crossover studies (11) instead of the rapid- and long-acting analogs are also limiting factors for establishing a comparison between the MDI versus CSII regimens.

The conclusions that can be drawn from the available randomized controlled studies are limited by their paucity and the small size of the sample population studied. A prospective trial involving the
### Table 1: Randomized controlled studies comparing CSII with MDI in type 2 diabetic patients

| First author, year (ref.) | Design | n, BMI (kg/m²), diabetes duration | Antidiabetes treatment before CSII | Insulin requirement before CSII (units/kg/day) | Baseline A1C (%) for CSII vs. MDI | Final A1C (%) for CSII vs. MDI | Weight difference (kg) for CSII vs. MDI (units/kg) | Type of insulin average insulin requirement | CGM data | Nonsevere hypoglycemia frequency (%) |
|---------------------------|--------|----------------------------------|-----------------------------------|---------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-----------|----------------------------------|
| Raskin et al., 2003 (8)   | Randomized parallel CSII vs. MDI, 24 weeks | n = 127, BMI 32, 12–14 years | Insulin + OHA insulin only | 0.69 vs. 0.75 | 8.2 vs. 8 | 7.6 vs. 7.5 (NS) | 1.7 vs. 0.8 (NS), 0.6 vs. 0.7 (NS) | MDI/Aspart + NPH, CSII/Aspart | NA | 54 vs. 59 (NS) |
| Herman et al., 2005 (9)   | Randomized parallel CSII vs. MDI, 48 weeks | n = 98, BMI 32, 15–17 years | Insulin + OHA insulin only | NA | 8.4 vs. 8.1 | 6.6 vs. 6.4 (NS) | 2.1 vs. 2.6 (NS) | MDI/Lispro + glargine, CSII/Lispro 108 units/day | NA | 81 vs. 90 (NS) |
| Wainstein et al., 2005 (11) | Randomized crossover CSII vs. MDI, 2 × 18 weeks* | n = 29, BMI 30–45, NA | 2–3 daily injections | >1 | 10.2 and 10.3 (groups 1 and 2)* | −0.4 vs. 0.8 (P < 0.01) | −0.04 vs. 0.09 CSII/Lispro, MDI/regular + NPH metformin, both groups −15 vs. 20 units/day | Hyperglycemia, AUC CSII < MDI | 6 vs. 20 (NS) |
| Berthe et al., 2007 (10)  | Randomized crossover CSII vs. MDI, 2 × 12 weeks* | n = 17, BMI 33.7, 16.8 years | 2 daily injections | 1 | 9 | −1.3 vs. −0.4 (P < 0.03)* | No change in both groups | CSII/Lispro, MDI/Lispro + NPH ×3, 1 unit/kg/day, stable in both groups | Hyperglycemia, AUC 41 vs. 47%, CSII < MDI, no difference in hypoglycemia AUC |

OHA, oral hypoglycemic agents. *Patients were randomized to begin with CSII or MDI (respectively, groups 1 and 2).
In type 2 diabetic patients with suboptimal glycemic control despite very high insulin requirements, the use of the concentrated insulin preparation U-500 (500 IU/mL) may be offered. Its use in a CSII regimen was evaluated in a retrospective study and allowed a significant reduction of HbA1c (−1.23%, P < 0.001) and the percentage of time spent in the normoglycemic target range (+70%) (20). A recent meta-analysis confirmed such results and reported an increase in patient satisfaction and in cost savings (21).

Is CSII beneficial or detrimental for weight maintenance in type 2 diabetic subjects?
Most prospective and observational studies evaluating CSII in type 2 diabetic patients were short-term studies, with ≤6 months’ duration (8,10,11,16,17) or 1 year’s duration (7,9). In the studies with ≤6 months’ duration, no weight change (10,11,17) or a 1.7–1.9 kg weight gain was observed (8,16). In 1-year duration studies, a weight gain of ~2 kg (P < 0.01) was observed in one (9), while no change occurred in the second (7). In the four randomized studies comparing CSII with MDI, no significant difference in weight change was observed between the two treatments (8–11). Three French retrospective studies gave data of weight variations for ≥2 years: one single center study showed a 4–6 kg weight gain after 6 year follow-up (P < 0.001), with a wide range in individual weight change (13).
The multicenter French study showed a nonsignificant weight gain (1.6 kg, \( P = 0.69 \)) after 2 years possibly related to the 25% decrease in insulin total daily dose after switching from MDI to CSII (15). In contrast, in one long-term study performed in 51 patients using CSII for at least 7 years, the mean weight gain of 10 kg \(( P < 0.001)\) can probably be explained by the twofold increase in the amount of insulin compared with the pre-CSII total daily dose (14). Intensification of insulin therapy by pump is usually accompanied by a moderate weight gain, which seems to correlate with the amount of insulin administered, and pump therapy probably does not provide any additional risk per se in comparison with MDI.

Does the switch from MDI to pump require a modification of the total amount of insulin administered to the type 2 diabetic patient?

Of 10 studies reporting total insulin requirement at the end of treatment, 7 reported no significant change in insulin doses in comparison with the period preceding CSII initiation \((8–11,13,16,17)\), while two reported that insulin dosage was lowered on CSII in comparison with MDI treatment \((7,15)\), and one had a twofold increase of insulin daily dose \((14)\). However, in the latter study baseline insulin doses were much lower \((0.42 \text{ units/kg/day})\) than in the other studies. A 1:1 dose switch from MDI to CSII is generally recommended and should not be associated with an increased risk of hypoglycemia in most cases. Because the actual insulin dose injected by the patient may be unknown and insulin dose actually absorbed may be uncertain, a careful blood glucose monitoring and insulin dose titration would be appropriate during the period of pump initiation.

What is the level of satisfaction and quality of life in type 2 diabetic patients on CSII?

In two randomized parallel-group studies, treatment satisfaction, diabetes impact, and diabetes satisfaction scores improved over time with both CSII and MDI treatments \((8,9)\). The satisfaction score did not differ between MDI and pump in the older population \((9)\), while the CSII group had greater improvement in overall treatment satisfaction compared with MDI in the younger population \((8)\). The 36-Item Short Form Health Survey \((SF-36)\) physical and mental composite score did not change significantly within and between groups in the older population \((9)\). When CSII and MDI were compared in a crossover fashion, the satisfaction subscores were comparable between CSII and MDI \((10)\). A multicenter observational study found after 1 year that health status evaluated in 61 patients on CSII was maintained in 75% and improved in 20% of the patients \((15)\). Another 3-year study found an improvement of quality of life stated by the Diabetes Quality of Life \((DQOL)\) and SF-36 questionnaires \((22)\).

Are hypoglycemia and other adverse events limitations in CSII use?

Hypoglycemia is a major outcome for evaluating the risk-to-benefit ratio of any antihyperglycemic treatment, and most studies have found a very low incidence of severe hypoglycemia in type 1 and type 2 diabetic patients using CSII \((23,24)\). A recent meta-analysis showed an advantage of CSII versus MDI with an odds ratio for severe hypoglycemia of 0.48 \((24)\). Data on the incidence of hypoglycemia in type 2 diabetics are scarce, but the two parallel-group studies, which lasted 6 and 12 months, respectively, showed very low incidence of severe hypoglycemia if any \((\text{no event in the study by Raskin et al.}[8]\) and 2.3% in that by Herman et al.[9]) In the former, a nonsignificant reduction \((0.8 \text{ vs. 1.2 per patient-month})\) was observed on CSII compared with MDI. Nocturnal hypoglycemia rate was similar for both treatment groups \((8)\). In the latter, the event rates per patient-year were 0.08 vs. 0.23 for CSII vs. MDI, respectively \((P = 0.61)\). The incidence of mild hypoglycemia was similar in both groups \((1.08 \text{ vs. 1.22 per patient-week}, \ P = 0.33, \text{CSII vs. MDI})\) \((9)\). The percentage of patients who reported at least one minor hypoglycemic episode during these two studies was also similar for both treatments \((\text{Table 1})\). In the two crossover studies \((10,11)\), the same percentage of patients reported at least one hypoglycemic episode \((\text{Table 2})\), and 24-h CGMS recordings in the former study showed no difference of hypoglycemic duration between both treatment groups \((10)\). Other adverse events reported with the use of CSII included hyperglycemia \((8)\), injection site reaction \((8,9)\), and technical problems \((8)\).

Is pump a useful adjunct for type 2 diabetic women during pregnancy?

Pregnancy outcomes in women with pregestational type 2 diabetes seem to be either similar \((25)\) or worse \((26–28)\) in comparison with type 1 diabetic patients. Lack of comprehensive and intensive metabolic control of pregestational type 2 diabetic patients before and during gestation has been hypothesized to underlie such serious adverse fetal outcome \((29)\). Several organizations such as the National Institute for Health and Clinical Excellence and International Diabetes Federation’s Global Diabetes in Pregnancy Guideline recommend insulin as optimal therapy ideally initiated prior to pregnancy, which is often not done \((29–31)\). As the glycemic target in type 2 diabetic pregnancies is similar to that in type 1, the majority of women will therefore require complex multiple daily dose regimens. Additionally, insulin requirements vary according to the phase of the pregnancy, adding to the complexity of treatment in patients who usually are unaccustomed to intensive insulin therapy. Intensification in the management of pregnancy in type 2 diabetes women would greatly improve pregnancy outcome, as shown in the Atlantic Diabetes in Pregnancy (Atlantic DIP) intervention \((32)\). In such circumstances, CSII use has the potential to be one of the components in assisting patients with type 2 diabetes with the complexity of insulin therapy regimens during gestation. The potential advantages of CSII use in type 2 during pregnancy includes 1) a better glucose control than with MDI; 2) allowance of temporary basal rates and flexible boluses, which are important throughout pregnancy and are not available with MDI; 3) a decrease in hypoglycemia rate; 4) assistance for weight maintenance; and 5) an improvement in quality of life. Data downloads from insulin pumps, glucometers, and continuous glucose monitoring systems facilitate insight into patients’ control, behavior, and educational needs. Average insulin requirements for women with type 2 diabetics using CSII range from 0.6 units/kg during the first trimester to 0.8 units/kg in second trimester and 1.03 units/kg in the last trimester, but the variability is high \((\text{O. Cohen, unpublished observation})\). Approximately 50% of the total daily insulin is administered as long-acting insulin analog. Hitherto, no randomized control study on pump use in type 2 diabetes during pregnancy has been published. Retrospective data have shown that in selected “difficult to manage” patients with type 2 diabetes from ethnic backgrounds with high prevalence of obesity and type 2 diabetes, failing to reach target glycemia or with fetal growth...
acceleration on high doses of insulin with at least four injections per day, insulin pump therapy was safe and effective (33). It is our prediction that with the growing concern over pregnancy outcomes in type 2 diabetes (34), more retrospective data and prospective randomized trials will be available using current pumps, modern consumables (catheters, tubing, etc.), and updated data-management systems.

Insulin pump therapy may be offered to pregnant women with gestational diabetes mellitus or type 2 diabetes who fail to obtain adequate glycemic control with a basal/bolus regimen, need very high insulin requirements, or experience persistent accelerated fetal growth despite optimal conventional MDI regimen.

**Is the use of oral or other injectable antihyperglycemic agents recommended with CSII?**

The use of oral antihyperglycemic agents may be beneficial in type 2 diabetic patients treated with intensive insulin therapy in order to promote better glycemic control, reduce insulin requirement, and limit weight gain (35). Few studies have tested such a hypothesis in CSII-treated type 2 diabetic patients. An approach was proposed consisting of the maintenance of sulfonylurea together with CSII, with a titration of the oral antihyperglycemic agent aiming to control either fasting glucose or postprandial glucose level. Both strategies were safe and effective for lowering HbA1c (20). Metformin may be a helpful adjunct to CSII for long-term maintenance of HbA1c lowering together with weight gain limitation (35,36). In one study, CSII was provided overnight to type 2 diabetes patients not at goal on oral medications and effectively reduced fasting plasma glucose without occurrence of major hypoglycemia (37). Novel injectable antihyperglycemic agents such as glucagon-like peptide-1 analogs and mimetics have been recently combined with insulin therapy for the treatment of type 2 diabetes with positive results on weight reduction and glycemic control (38). It is foreseeable that combination therapy with CSII in type 2 diabetes will bring similar advantages. No study on type 2 diabetes management has yet demonstrated the efficacy of oral antihyperglycemic agents or glucagon-like peptide-1 analogs in adjunct with CSII in a randomized controlled fashion.

**Use of CSII in clinical practice: what are possible indications?**

Guidelines from the European Association for the Study of Diabetes and the American Diabetes Association advise a progressive intensification of insulin therapy in type 2 diabetic subjects who fail to respond to therapy with noninsulin antihyperglycemic agents. The basal/bolus regimen combining a rapid-acting and a long-acting insulin analog is recommended as the most precise and flexible regimen for the intensification of insulin therapy (39), while pump therapy is not even mentioned as an alternative. In the author’s opinion, pump therapy may be offered in situations of severe chronic hyperglycemia despite high insulin requirements. Such patients are generally obese, exhibit high abdominal fat content, and do not respond to nutritional counseling for restricting carbohydrate or fat intake. One may hypothesize that reduction of postmeal excursions with CSII (8,10,11) may limit the deleterious consequences of hyperglycemic peaks on diabetes complications such as cardiovascular lesions (40). Pump therapy may be offered to patients on at least two injections per day (41) and may be an alternative to the thrice daily premixed NPH/rapid analog combination or the four to five daily injections regimen combining a long-acting insulin analog plus a rapid-acting analog (10,11,13,16,17). Decision to switch from MDI to CSII may also be based on cost-effectiveness considerations (42,43).

Other indications of CSII in type 2 diabetes may include extreme insulin resistance syndromes such as lipodystrophy syndromes, pregnancy, and insulin allergy (44). Insulin allergy may occur in type 2 diabetic patients on insulin MDI, and local or generalized allergy manifestations were resolved by a switch to rapid analog insulin administered by CSII (44,45). The mechanism of antigenicity/immunogenicity modulation by CSII remains elusive (45).

Quality of life is also an end point to take into consideration for the indication of pump therapy and may be improved after switching from MDI to pump (22).

The ability to manage with the pump device may also be evaluated in order to select candidates for CSII. With proper training and when necessary a simplified approach, many patients can be candidates who may have otherwise not been considered, including aged patients who are not current users of electronic devices or patients with partial autonomy with their pump device who nevertheless may obtain an improved glucose control (13). The absence of cognitive or operative disability that would compromise pump use may be evaluated by a team experienced in pump therapy. Mild cognitive dysfunction or anxious or depressive mood may be detected with specialized questionnaires validated in this setting in order to reinforce educational strategies in these patients (46). Few contraindications should be ruled out such as proliferative retinopathy, psychiatric disorders, lack of motivation for using pump, or mental or physical disability. In partially autonomous or dependent patients, assistance may be provided by a nurse for managing the pump device, as allowed by health care authorities in some countries as in France (41).

**What are the caveats for the use of CSII in type 2 diabetes?**

Patients with insulin-resistant type 2 diabetes use large amounts of insulin per day (>0.8 units/kg). With the pharmacodynamics and pharmacokinetics of current short-acting insulin analogs, the level of circulating and active insulin is high throughout the day. Consequently, the need for fine-tuning of bolus dosage according to carbohydrate loads and for multiple basal rate, which proves efficiency in type 1 diabetic patients on CSII, may not be necessary in most patients with type 2 diabetes (47). In the French cohorts, better glycemic control was achieved using one or two basal rates and using fixed bolus dosages (13–15). Conversely, an unnecessarily complex educational approach for pump use in type 2 diabetic management might deter potential patients from using CSII.

Device handling might be complicated with current pump devices. High insulin daily dosages require frequent reservoir changes. Prefilling cartridges might simplify device handling. Finally, insulin omission is common in type 2 diabetic patients (mainly due to forgetfulness) and is a contributor to lack of glycemic control in MDI and CSII patients as well (48). The possibility of downloading a patient’s pump data may play a contributing role to addressing this issue, as it allows the health care professional to follow patient’s adherence and to intervene with personalized educational programs.

**Is pump use relevant from a medico-economic perspective in a strategy of type 2 diabetes insulin intensification?**

A retrospective study performed in the U.S. by Medtronic Inc. over a 4-year
period analyzed changes in antihyperglycemic agent use after CSII initiation in 943 type 2 diabetic patients. The mean number of antihyperglycemic drugs decreased by 46%, and more than one-third of type 2 patients previously taking oral antihyperglycemic agents discontinued oral therapy after CSII initiation. Moreover, the rate of emergency department visits and inpatient admissions significantly decreased after CSII initiation (42). A recent insurer cost-of-care study commissioned by Medtronic Inc. and performed among type 2 diabetic patients on 2009–2010 data from the Market-Scan Commercial Research Database from Thomson Reuters analyzed the diabetes treatment costs from 154,000 type 2 diabetic patients on MDI (78%) or pump therapy (22%). In the break-even analysis, savings were achieved with pump therapy from lower insulin doses and oral antihyperglycemic agents use, and the initial pump investment was offset by this savings after 2 years and 3 months of an average daily insulin consumption of 169 units (43).

These latter data do not take into account the potential cost-effectiveness of lowering HbA1c with an intensified CSII insulin regimen if the demonstration is made in future studies of its superiority compared with MDI intensified regimen. Pump therapy thus appears in some instances relevant for saving costs related to diabetes therapy.

Conclusions

Pump therapy is a promising approach for insulin therapy intensification in type 2 diabetes. Despite limited data from randomized control studies, longitudinal data in actual use settings suggest that CSII may be preferred to MDI in type 2 diabetic patients with severe insulin resistance and poor glycemic control despite sufficient insulin titration and adherence to recommendations on diet and exercise (13–15). The selection of candidates for pump therapy should integrate the patient’s ability to cope with the pump device, the absence of major cognitive or operative disability, acceptable adherence to self-monitoring glucose control, and personal willingness to use an insulin pump. A personalized approach of pump management may allow a substantial number of type 2 diabetic patients to be candidates for pump therapy. Pump treatment in patients with appropriate indications should be associated with limited incidence of adverse events and weight gain, although the individual patient response is not predictable.

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