

Insulin therapy in adult type 1 diabetes patients: Multiple Dose Insulin Injection (MDI) or Continuous Subcutaneous Insulin Infusion (CSII)

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Educational aims

- To give an overview of MDI therapy and introduce associated technologies
- To highlight the various types of insulin pumps available
- To summarise clinical evidence regarding treatment with MDI and CSII in type 1 diabetes patients

Key words

type 1 diabetes, multiple dose insulin injection, continuous subcutaneous insulin infusion, continuous glucose monitors, sensor-augmented insulin pumps, closed loop insulin delivery systems

Abstract

Insulin therapy in type 1 diabetes is recommended as multiple dose injections (MDI) or continuous subcutaneous insulin infusion (CSII) to deliver a basal background insulin dose together with bolus insulin doses prior to meals. Use of automated bolus calculators and / or continuous glucose monitors with MDI have been shown to improve glycaemic control in type 1 diabetes patients. Several models of insulin pumps with various features are available. CSII offers greater flexibility with a reduced number of injections but in view of its complexity, patients who will benefit from this therapy need to be carefully selected.

Introduction

In type 1 diabetes, autoimmune destruction of the beta cells of the pancreas results in insulin deficiency and insulin dependence. The ultimate aim of treatment is to provide type 1 diabetes patients with an insulin therapy which mimics the physiological basal and meal-related insulin secretion from the pancreas and maintain normoglycaemia thus preventing the development of complications. The latest clinical guidance on the diagnosis and management of type 1 diabetes in adults issued by the National Institute for Health and Care Excellence (NICE) in August 2015¹ and the Standards of Medical Care in Diabetes 2016 issued by the American Diabetes Association² both recommend insulin therapy in the form of multiple dose insulin (MDI) injection of a basal-bolus regimen or continuous subcutaneous insulin infusion (CSII) for adult type 1 diabetes patients.

Multiple Dose Insulin (MDI) Injection

MDI regime includes a long acting insulin injected once or twice daily (the basal insulin), together with a rapid acting insulin injected at meal times (the bolus insulin) translating to at least 3 to 4 insulin injections per day. To achieve optimal glycaemic control with this regimen, the rapid acting insulin dose should be calculated according to the carbohydrate content of meals, the glucose level before the meal and the expected level of physical activity.² This highlights the importance of educating the patient who is being considered for MDI on the various aspects of diabetes self-management including carbohydrate counting, frequent blood glucose monitoring, pre-meal and post-meal glucose targets, and insulin dose adjustments in relation to exercise and general health status. Education minimises the episodes of hypoglycaemia that are more likely to occur with intensive insulin regimes.³ Use of insulin analogues, rather than human sequence insulin, for the MDI regimen has been associated with decreased rates of hypoglycaemia. Type 1 diabetes patients, who reported at least 2 episodes of severe hypoglycaemia in the previous 12 months, had a reduced rate of severe hypoglycaemic episodes by 0.51 episodes (95% CI 0.19-0.84) per patient-year or 29% (95% CI 11-48; p=0.010) when treated with insulin analogues for one year as compared to treatment with human sequence insulin for one year.⁴



With the availability of automated bolus calculators, the dose of insulin that is required prior to meals is recommended to the patient and generated using patient-specific data combined with meal-specific data. The patient specific data is pre-set and includes carbohydrate to insulin ratios, insulin sensitivity factors and blood glucose targets. On the other hand, meal-specific data includes carbohydrate intake and pre-meal glucose levels. Automated bolus calculators facilitate the complex and laborious task of calculating bolus insulin doses prior to each meal.⁵ In the multicentre randomised controlled trial ABACUS, the use of a bolus advisor in patients with diabetes on MDI therapy was associated with a significantly greater percentage of patients who achieved >0.5% reduction in HbA1c (56.0 vs 34.4%; $P < 0.01$) without an increase in severe hypoglycaemia and significantly greater treatment satisfaction when compared to patients with diabetes on MDI therapy who manually calculated the bolus insulin dose.⁶ Type 1 diabetes patients on MDI therapy who used an automated bolus calculator had decreased fear of hypoglycaemia and increased confidence in bolus dose accuracy in a separate study.⁷

Another tool that has been shown to be beneficial in self-management of type 1 diabetes is real time continuous glucose monitors (CGM). These display the current interstitial glucose level from a subcutaneous glucose sensor, provide glucose trends based on changes in previous glucose readings and alarm at pre-set glucose values and following rapid changes in glucose readings. These devices still require sensor calibration with self-monitoring of blood glucose (SMBG) at least 12 hourly. In a randomised controlled trial comparing CGM to SMBG in patients with type 1 diabetes with poor metabolic control treated with MDI or CSII, the CGM group showed improved glycaemic control with 50% of patients achieving a 1% minimum reduction in HbA1c and 25% of patients achieving a 2% minimum reduction

in HbA1c.⁸ The Juvenile Diabetes Research Foundation (JDRF) CGM randomised trial, also registered improvement in glycaemic control with CGM use, without an increase in severe hypoglycaemia, when compared to SMBG (mean difference in change in HbA1c -0.53% ; 95% CI, -0.71 to -0.35 , $P < 0.001$) in type 1 diabetes patients >25 years of age on MDI or CSII with a baseline HbA1c of 7-10%.⁹ The greatest reductions in HbA1c associated with CGM use were documented in patients who had the highest HbA1c and in frequent users of CGM.¹⁰

Continuous subcutaneous insulin infusion (CSII)

Delivery of CSII requires an external pump device which includes an insulin pump, an insulin storage reservoir and an insulin infusion set consisting of a tubing set and a cannula for subcutaneous insertion. The pump delivers a basal rate of insulin, which can be programmed to vary according to different basal insulin requirement throughout the day and night, with bolus doses at meal times triggered manually by the patient. The delivery of the bolus can be of various types and duration including normal (standard), extended (square wave) and dual wave, depending on the macronutrient composition of the meal. There are several models of insulin pumps available with various features, alerts and alarms. Bolus calculators can be integrated in insulin pumps with the insulin on board (IOB) calculation available in most insulin pump models. The IOB is the calculation of how much insulin is still active from previous bolus doses.

Sensor-augmented insulin pumps (SAP), which incorporate continuous subcutaneous glucose monitors, have been shown to improve glycaemic control with frequent CGM use, but whether the associated risk of hypoglycaemia is increased or not is unclear. In a randomised treat-to-target study of patients with type 1 diabetes, use of a SAP for 6 months was associated with a

significant reduction in HbA1c ($P = 0.0456$) in patients who utilised the CGM sensors for >60% of the time, and an increased number of severe hypoglycaemic events (11 events in the SAP group vs 4 events in the CSII and SMBG group) ($P = 0.04$), when compared to insulin pump therapy with SMBG. The probability of a 0.5% reduction in HbA1c was increased by 41% for each 10% increase in CGM sensor compliance.¹¹ Significant improvement in HbA1c in patients using SAP who utilised CGM for $\geq 70\%$ of the time ($P = 0.004$) (SAP group $-0.96 \pm 0.93\%$, $P < 0.001$; CSII and SBGM group $-0.55 \pm 0.93\%$, $P < 0.001$) was confirmed in the RealTrend Study which studied patients during their initial 6 months of insulin pump therapy with SAP compared to CSII and SBGM. No associated increase in hypoglycaemic events was reported in this study.¹²

SAPs with the added function of low-glucose suspension have been associated with improved rates of hypoglycaemia. These devices stop insulin delivery automatically, for up to 2 hours, once the glucose level falls below a certain threshold. The rate of moderate and severe hypoglycaemia was found to be reduced in type 1 diabetes patients on SAP with low glucose suspension compared to SAP only, with an adjusted incidence rate per 100 patient-month of 34.2 (95% CI, 22.0-53.3) for patients using SAP only and 9.5 (95% CI, 5.2-17.4) for patients using SAP with low-glucose suspension.¹³ In the ASPIRE In-Home study, the rate and severity of nocturnal hypoglycaemia was also documented to be decreased in type 1 diabetes patients using SAP with low-glucose suspension who had improving or low HbA1c at baseline, compared with SAP alone.¹⁴

Closed Loop (CL) insulin delivery systems or 'Artificial Pancreas' comprise a CSII, a CGM and complex algorithms to control glucose and ensure safety, incorporated in one device or separately, fully automated or combining user input with automated periods of insulin administration.¹⁵ During periods of automated insulin administration, the rate of insulin delivery is determined by real-time interstitial glucose levels which feed into a control algorithm.¹⁶ Use of CL insulin delivery system day-and-night for 12 weeks, in 33 adult type 1 diabetes patients resulted in a lower mean glucose level (difference, -0.6mmol/L ; 95% CI, -17 to -6 ; $P < 0.001$), lower mean HbA1c (difference, -0.3% ; 95% CI, -0.5 to -0.1 ; $P = 0.002$), less time spent with glucose $< 3.5\text{mmol/L}$ (39% lower; 95% CI, 24 to 51; $P < 0.001$) and more time spent

in target glucose range (95% confidence interval [CI], 8.1 to 13.8) ($P < 0.001$) when compared to SAP therapy.¹⁷

While CSII offers the advantages of greater flexibility with variable rates of basal insulin delivery and frequent boluses of various type and duration with fewer injections, it is also associated with a number of possible complications including cannula site reactions and infections, insulin infusion blockage and pump malfunction.

With the complexity of intensive insulin therapy by CSII and with the possibility of associated complications which might result in severe adverse events like diabetes ketoacidosis, CSII therapy requires the selection of highly motivated patients who will benefit from this mode of insulin delivery safely and effectively. CSII therapy should be initiated in the setting of a highly specialised multidisciplinary diabetes management team whose members are specifically trained in insulin pump therapy to provide selected patients with the required support, education and training on the safe use of insulin pumps.

Multiple Dose Injection (MDI) vs Continuous subcutaneous insulin infusion (CSII)

Several systematic reviews and meta-analyses have been carried out to compare insulin treatment with MDI or CSII in patients with type 1 diabetes. A Cochrane systematic review which included 23 studies found a significant difference in HbA1c (weighted mean difference -0.3% (95% confidence interval -0.1 to -0.4), reduced severe hypoglycaemia and better quality of life in

Key points

- Insulin therapy in type 1 diabetes is recommended as multiple dose insulin (MDI) injections or as continuous subcutaneous insulin infusion (CSII)
- MDI consists of a once or twice daily basal long acting insulin dose and a bolus rapid acting insulin dose prior to meals, calculated according to the carbohydrate content of meals, the glucose level before the meal and the expected level of physical activity
- Automated bolus calculators and / or continuous glucose monitors have been shown to improve glycaemic control in type 1 diabetes patients on MDI
- Treatment with CSII has been associated with improved glycaemic control and reduced rates of severe hypoglycaemia when compared to MDI in observational studies
- CSII should only be initiated in the setting of a highly specialised multidisciplinary diabetes management team whose members are specifically trained in insulin pump therapy
- CSII therapy requires the selection of highly motivated patients who will benefit from this mode of insulin delivery safely and effectively

patients using CSII compared to MDI.¹⁸ In a previous systematic review and meta-analysis, Fatourechci showed that adult patients with type 1 diabetes on CSII had slightly reduced HbA1c (random-effects weighted mean difference, -0.2%; 95% confidence interval (CI), -0.3, -0.1) with no difference in the risk of hypoglycaemia when compared to patients on MDI.¹⁹ In a meta-analysis by Pickup et al, the rate of severe hypoglycaemia was less in patients on CSII with the greatest reduction noted in patients with the highest initial rates of severe hypoglycaemia on MDI and in patients with long diabetes duration. The greatest reduction in HbA1c was observed in patients who had highest HbA1c levels on MDI.²⁰ Adult type 1 diabetes patients on CSII were found to have a greater reduction in HbA1c without increased hypoglycaemia rates and

with a reduced total daily insulin dose when compared to patients on MDI, in a systematic review and meta-analysis by Jeitler *et al.*²¹ These meta-analyses are limited since older studies using old insulin pump technology, studies of short duration, small studies and studies comparing MDI therapy with human sequence insulin to insulin analogues in CSII were often included in the analysis.

Evidence from observational studies points towards reduced HbA1c levels and statistically significant reduced rates of severe hypoglycaemia with CSII when compared to MDI.²²

The ongoing Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial, a randomised controlled trial of 280 adult type 1 diabetes patients, recruited from 7 UK centres, assigned to either analogue MDI or analogue CSII following standard structured training in insulin adjustment and followed up for 2 years,²³ is expected to address several limitations of previous randomised controlled trials of MDI vs CSII, highlighting risks and benefits of both therapies.

Current guidelines for CSII therapy in adult type 1 diabetes patients recommend treatment with CSII in patients who have persistently high HbA1c despite intensive therapy with MDI and in patients with disabling hypoglycaemia.^{24,25} The American ACE/ACE recommendations for CSII therapy are broader but also specify characteristics of patients who would not benefit from pump therapy.²⁵

Conclusion

Type 1 diabetes is a chronic disease that requires a lot of input from the patient



together with regular review and support by the specialised diabetes teams who provide intensive education and training and recommend the most suitable insulin type, insulin delivery and accurate, reliable and safe technologies that best serve each individual patient based on clinical evidence and tailored to the patient's lifestyle, commitment, motivation, skills and expectations while striving to reduce disease burden and preserve quality of life.

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