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## **Insulin pump in people with type 2 diabetes mellitus**

Article summarizes results of important clinical studies targeting on potential benefits of continuous subcutaneous insulin infusion (CSII) by means of an insulin pump in people with type 2 diabetes. The problems are comprised into four chapters: (1) Historical introduction; (2) Effectiveness of CSII in type 1 diabetes; (3) Influence of CSII on HbA1c and global metabolic indices in type 2 diabetes; (4) Influence of temporary CSII on beta-cell recovery in recent type 2 diabetes. Conclusion: CSII appears to be an effective part of type 2 diabetes treatment aiming to early recovery of beta cell function (if introduced without delay in a recent diabetes) and to long-lasting improvement of metabolic indices (if introduced any time of diabetes development). Adequate education of pump treated persons and their family members is necessary.

*Key words:* diabetes mellitus, ominous octet, insulin pumps, HbA1c, Total daily insulin dose, body mass, incretins, gliflozins, metformin, therapeutic education, meta analysis.

### *Abbreviations:*

- AUC — area under the curve;  
CIT — conventional insulin therapy;  
CGMS — continuous glucose monitoring;  
CSII — continuous subcutaneous insulin infusion;  
MDI — multiple daily injections;  
OHA — oral hypoglycaemic agents;  
PWD1 — person with type 1 diabetes;  
PWD2 — person with type 2 diabetes.

### *(1) Historical introduction*

In the year 1921 *Paulesco* in Bucharest discovered the hypoglycaemic effect of pancreatic extract (pancrein) injected to a diabetic dog [1, 2]. Independently, in January 1922, *Banting, Best and Collip* in Toronto first successfully used purified extract (isletin/insulin) to save life of a boy with diabetes [3, 4]. In the course of the following 50 years various insulin preparations were produced and injected by means of reusable glass syringes and needles.

In the year 1978 *Pickup* in London described a new method of insulin administration, namely, the continuous subcutaneous insulin infusion (CSII) using Mill Hill Infusor [5] as the first small external personal insulin pump. Next, technical evolution together with motivating approach of physicians, nurses, health care givers, researchers and educators made insulin pumps available for more or less limited number of people with diabetes [6].

As late as five years after the first experience with a portable insulin pump, the era of manual insulin injectors (pens) started. The pens were developed since 1983 at Palacky University Olomouc and Institute of Diabetes «G. Katsch», Karlsburg (MADI, MD2) [7–9] as well as by companies Novo (Novopen) [10] and Nordisk (Insuject) followed by many others [11]. Some of the pens could be alternatively used as manually directed pumps called «catheter pens» [12–14]. Additional details have already been published elsewhere [15].

### *(2) Effectiveness of CSII in type 1 diabetes*

Since the year 1978 several papers demonstrated the advantages of insulin pump in persons with type 1 diabetes mellitus.

*Yki-Yarvinen* [16] studied in 1984 the influence of CSII for 6 weeks on sensitivity to insulin (euglycemic clamp technique) and hepatic glucose production in 10 type 1 diabetic patients whose mean du-

ration of diabetes was 8 yr. The improved metabolic control resulting from pump therapy was associated with enhancement in sensitivity to insulin, and reduction in basal hepatic glucose production.

*Chantelau* [17] in Düsseldorf performed in 1989 a follow-up study of 116 Type 1 diabetic patients on long-term continuous subcutaneous insulin infusion and concluded that CSII has proved to be beneficial to a large proportion of experienced adult Type 1 diabetic patients, who voluntarily had opted for, and continued with, this particular mode of insulin treatment.

*Chlup* [18] in the year 2000 summarized experience with CSII at Olomouc Teaching Hospital Diabetes centre, including the start schedule for substitution of basal rates during the day (Fig. 1).

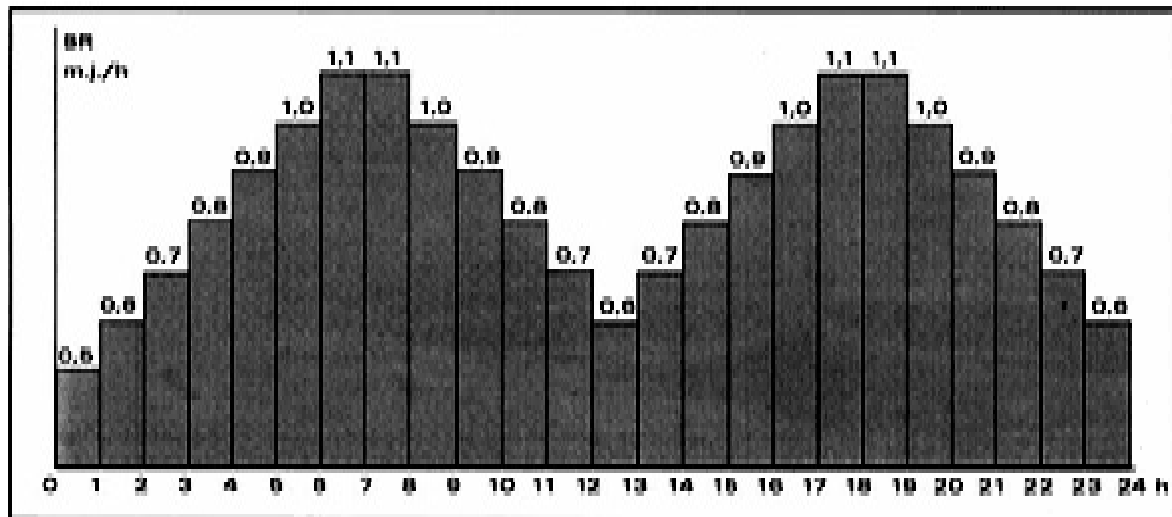


Figure 1. Basal rates in Continuous Subcutaneous Insulin Infusion (CSII) in persons with type 1 and type 2 diabetes mellitus — basal rates schedule at CSII start to be individually adopted according to plasma glucose evolution in the course of next weeks [18]

*Pickup* [19] performed in the year 2002 a meta-analysis of 12 randomised controlled trials to compare glycaemic control and insulin dosage in people with type 1 diabetes treated by CSII or optimised insulin injections. There were 301 people with type 1 diabetes allocated to insulin infusion and 299 allocated to insulin injections for between 2.5 and 24 months. Mean blood glucose concentration was lower in people receiving CSII compared with those receiving insulin injections (standardised mean difference 0.56, 95 % confidence interval 0.35 to 0.77), equivalent to a difference of 1.0 mmol/l. The percentage of glycated haemoglobin was also lower in people receiving insulin infusion (0.44, 0.20 to 0.69), equivalent to a difference of 0.51 %. Blood glucose concentrations were less variable during insulin infusion. This improved control during CSII was achieved with an average reduction of 14 % in insulin dose. So, glycaemic control was better during CSII compared with optimised injection therapy, and less insulin was needed to achieve this level of strict control. The difference in control between the two methods was small but should reduce the risk of microvascular complications.

*Doyle* [20] in the year 2004 studied the efficacy of the insulin analogs available for multiple daily injection (MDI) and CSII therapy in type 1 diabetes in pediatric patients. Lower HbA1c and premeal glucose concentrations were more achievable in this short-term study with CSII than with glargine-based MDI treatment. CSII appeared to be an efficacious treatment to improve metabolic control in youth with type 1 diabetes.

*Retnakaran* [21] performed in the year 2004 a pooled analysis of the randomized controlled trials that compared CSII and optimized MDI therapy using rapid-acting analogs in adults with type 1 diabetes. The three studies that met inclusion criteria provided data on 139 patients, representing 596 patient-months for CSII and 529 patient-months for MDI. Mean age was 38.5 years, with duration of diabetes of 18.0 years. When using rapid-acting insulin analogs in CSII and MDII regimens in adult patients with type 1 diabetes, insulin pump therapy was associated with better glycemic control, particularly in those individuals with higher baseline A1c. Thus, CSII emerges as an important modality for implementing intensive therapy and may be uniquely advantageous in patients with poor glycemic control.

*Bruttomesso* [22] in the year 2009 concluded that when compared with traditional NPH-based multiple daily injections (MDI), CSII provides a small but clinically important reduction of HbA1c concentrations,

diminishes blood glucose variability, decreases severe hypoglycaemic episodes and offers a better way to cope with the dawn phenomenon. Insulin analogues have improved the treatment of diabetes, eroding part of the place previously occupied by CSII, but CSII still remains the first option for patients experiencing severe hypoglycaemic episodes, high HbA1c values or marked glucose variability while being treated with optimized MDI. Furthermore CSII is better than MDI considering the effects on quality of life and the possibility to adjust insulin administration according to physical activity or food intake. CSII may be limited by cost. The estimates suggest that CSII may be cost-effective just for patients experiencing a marked improvement in HbA1c or a decrease in severe hypoglycaemic episodes, but the effects on quality of life are difficult to measure. CSII does not merely imply wearing an external device; it requires a multidisciplinary team, intensive patient education and continuous follow up.

In the Czech Republic, *Jankovec* [23] in the year 2010 collected patient data from the Czech National Register of patients treated with CSII to evaluate treatment indication, efficacy and safety with specific regard to the type of diabetes. Evaluation was done on complete data sets of at least 3 years from either DM 1 ( $n = 730$ , 93.1 %) or DM2 ( $n = 54$ , 6.9 %) between 1995 and 2006. HbA1c decreased from 9.65 ( $\pm 0.07$ ) and 9.66 ( $\pm 0.05$ ) for DM1 and DM2 respectively to 8.24 ( $\pm 0.07$ ) for DM1 and 8.52 ( $\pm 0.27$ ) for DM2 after 1 year of treatment, 8.34 ( $\pm 0.07$ ) and 8.54 ( $\pm 0.26$ ) after 2 years and 8.44 ( $\pm 0.07$ ) and 8.71 ( $\pm 0.25$ ) after 3 years (adjusted mean values,  $\pm$ -SEM). This reduction is significant for both diabetes types. Results gathered from the safety analysis revealed almost comparable results for both patient groups (rates of adverse events of 42.5 and 34.8 for DM1 and DM2, per 100 patients and year). Both patient groups achieved substantial reduction of HbA1c. Safety evaluation showed that fewer patients with DM2 were affected by adverse events. Hence, CSII treatment DM2 is similarly effective with a slightly better safety profile.

### (3) Influence of CSII on HbA1c and global metabolic indices in type 2 diabetes

Clinical evidence on CSII effectiveness for DM2 were sought for in many studies. When compared to MDI, CSII has resulted in both equivalent and lower HbA1c values. However, the studies are heterogeneous in design and subject population. Some persons with diabetes have indicated a preference for the CSII. Two questions of paramount importance need to be answered: (i) whether CSII provides incremental clinical benefits after MDI has failed in treating DM2 and (ii) whether undelayed CSII start at the time of diagnosis of DM2 may support and prolong the potential recovery of beta cell. In this chapter, attempts are made to answer the first (i) question.

*Jennings* [24], 1991, compared the effects of CSII and conventional insulin therapy (CIT) in patients with poorly controlled sulfonylurea-treated diabetes mellitus. Outpatient treatment consisted of CIT (twice-daily injections of regular and NPH insulin) or CSII (basal infusion and prandial boluses of regular insulin). Glycemic control improved with both methods. Insulin treated patients achieved satisfactory control ( $HbA1 < 50$  mmol hydroxymethylfurfural/mol Hb), whereas only 3 of 10 CIT-treated patients achieved the values of CSII. Patients' satisfaction with treatment improved during insulin therapy.

*Pouwels* [25], 2003, investigated whether a period of euglycaemia using i.v. insulin, followed by CSII, would ameliorate the deleterious effects of hyperglycaemia on insulin sensitivity and result in sustained, improved metabolic control in DM2 who are poorly controlled despite high-dose s.c. insulin treatment. A period of 2 weeks of euglycaemia achieved by i.v. insulin reverses hyperglycaemia-induced insulin resistance and substantially improves metabolic control. Subsequent CSII treatment, using insulin analogues, appears to maintain improved metabolic control for at least 1 year.

*Raskin* [26], 2003, compared the efficacy, safety, and patient satisfaction of CSII with MDI therapy for patients with type 2 diabetes. A total of 132 CSII-naive MD2 were randomly assigned (1:1) to CSII (using insulin aspart) or MDI therapy (bolus insulin aspart and basal NPH insulin) in a multicenter, open-label, randomized, parallel-group, 24-week study. Efficacy was assessed with HbA1c and eight-point blood glucose (BG) profiles. Treatment satisfaction was determined with a self-administered questionnaire. Safety assessments included adverse events, hypoglycemic episodes, laboratory values, and physical examination findings. A total of 93 % of CSII-treated subjects preferred the pump to their previous injectable insulin regimen for reasons of convenience, flexibility, ease of use, and overall preference. Safety assessments were comparable for both treatment groups. Insulin aspart in CSII provided efficacy and safety comparable to MDI therapy. Patients with type 2 diabetes can be trained as outpatients to use CSII and prefer CSII to injections, indicating that pump therapy should be considered when initiating intensive insulin therapy for type 2 diabetes.

*Herman* [27], 2005, compared the efficacy and safety of CSII and MDI in older adults with insulin-treated type 2 diabetes and assessed treatment satisfaction and quality of life in 107 adults. Forty-eight CSII subjects (91 %) and 50 MDI subjects (93 %) completed the study. Mean A1C fell by  $1.7 \pm 1.0$  % in the CSII group to 6.6 % and by  $1.6 \pm 1.2$  % in the MDI group to 6.4 %. The difference in A1C between treatment groups was not statistically significant ( $P=0.20$ ). Eighty-one percent of CSII subjects and 90 % of MDI subjects experienced at least one episode of minor (self-treated) hypoglycemia ( $P=0.17$ ), and three CSII and six MDI subjects experienced severe hypoglycemia ( $P=0.49$ ). Rates of severe hypoglycemia were similarly low in the two groups (CSII 0.08 and MDI 0.23 events per person-year,  $P=0.61$ ). body mass gain did not differ between groups ( $P=0.70$ ). Treatment satisfaction improved significantly with both CSII and MDI ( $P=0.0001$ ), and the difference between groups was not statistically significant ( $P=0.58$ ). Hence, in older subjects with insulin-treated type 2 diabetes, both CSII and MDI achieved excellent glycemic control with good safety and patient satisfaction.

*Wainstein* [28], 2005, compared the efficacy of insulin pump treatment with multiple daily injections in the treatment of poorly controlled obese PWD2 already receiving two or more daily injections of insulin plus metformin. Forty obese PWD2 using insulin were randomized to CSII or MDI. At the end of the first 18-week treatment period, patients underwent a 12-week washout period during which they were treated with MDI plus metformin. Then they were crossed-over to the other treatment for an 18-week follow-up period. Patients performed 4-point daily self blood-glucose monitoring (SBGM) on a regular basis and 7-point monitoring prior to visits 2, 8, 10 and 16. A subset of patients underwent continuous glucose monitoring (CGMS, Minimed) at visits 2, 8, 10 and 16. A standard meal test was performed in which serum glucose was tested at fasting and once each hour for 6 h following a test meal. Glucose levels were plotted against time and the area under the curve (AUC) was calculated. HbA1c, body mass, daily insulin dose and hypoglycaemic episodes were recorded. Treatment with CSII significantly reduced HbA1c levels compared with treatment with MDI. An additional CSII benefit was demonstrated by reduced meal-test glucose AUC. Initial reduction of daily insulin requirement observed in CSII-treated subjects during the first treatment period was attributable to a period effect and did not persist over time. So, in the intent-to-treat analysis, CSII appeared to be superior to MDI in reducing HbA1c and glucose AUC values without significant change in body mass or insulin dose in obese, uncontrolled, insulin-treated Type 2 diabetic subjects.

*Lane* [29], 2006, determined the safety and efficacy of U-500 regular insulin delivered by CSII as treatment for PWD2 ( $n = 9$ ) and severe insulin resistance (mean 24-hour insulin requirement, 1.46 U/kg daily) who had failure of previous insulin therapy with either MDI or CSII using U-100 insulin analogues. After 3 months, treatment with U-500 regular insulin by CSII resulted in mean decrease in HbA1c ( $P = 0.026$ ) of 1.14 %, a marginal mean increase in body mass of 4.1 lb ( $P = 0.078$ ), no significant change in total daily insulin dose ( $P = 0.622$ ), and no clinically significant hypoglycaemic episodes. Moreover, all study patients preferred the new treatment option over their previous regimens. So, U-500 regular insulin by CSII is a safe and effective therapeutic intervention for patients with type 2 diabetes who have had treatment failure with MDI insulin regimens or CSII with use of U-100 insulin or insulin analogues.

*Berthe* [30], 2007, compared the effectiveness of two intensified insulin regimens, i.e., pump delivery versus multiple daily injections in PWD2 ( $n = 17$ ) not optimally controlled with CIT by two daily injections of regular plus NPH; they were randomly assigned in a cross-over fashion to either three daily injections of lispro plus NPH or pump device delivering lispro. HbA1c, 6 points capillary blood glucose, 24-hour CGMS and global satisfaction score were evaluated at the end of each 12-week treatment period. Pump therapy provides a better metabolic control than injection regimens, and seems to be safe and convenient in PWD2 who fail to respond to CIT.

*Labrousse-Lhermine* [31], 2007, compared over 3 years the efficacy of two treatment regimens combining CSII and oral hypoglycaemic agents (OHA) in PWD2 with HbA1cs $>8$  % despite OHA $\pm$ insulin. Fifty-nine patients were randomized. During the 3 years follow-up, overall mean HbA1c values decreased similarly for both groups from baseline ( $9.45 \pm 0.83$  %) to 1, 2, 3 years ( $7.76 \pm 0.85$  %;  $8.06 \pm 1.10$  %;  $8.27 \pm 1.06$  %  $P < 0.0001$ ). The mean frequency of minor hypoglycaemia was  $1.3 \pm 2.3$  events per month per patient and 14 severe hypoglycaemic events occurred with no difference between the two groups. In both groups we observed a significant and similar body mass gain and improvement in quality of life. Hence, long-term combination therapy with OHA and CSII with only basic manipulation and optimization of insulin doses exerted on basal rate or on boluses is feasible, effective and well accepted in PWD2.

*Jeitler* [32], 2008, compared the effects of CSII with MDI on glycaemic control, risk of hypoglycaemic episodes, insulin requirements and adverse events in type 1 and type 2 diabetes mellitus. The electronic data-

bases MEDLINE, EMBASE and CENTRAL were systematically searched for randomised controlled trials up to March 2007. A systematic review and meta-analysis were performed. Overall, 22 studies were included (17 with PWD1, 2 with PWD2, 3 with children). In PWD1, our meta-analysis found a between-treatment difference of  $-0.4\%$  HbA1c (six studies) in favour of CSII therapy. Available median rates of mild or overall hypoglycaemic events were comparable between the different interventions (1.9 [0.9–3.1] [CSII] vs 1.7 [1.1–3.3] [MDI] events per patient per week). Total daily insulin requirements were lower with CSII than with MDI therapy. In PWD2, CSII and MDI treatment showed no significant difference for HbA1c. In adolescents with type 1 diabetes mellitus, glycated haemoglobin and insulin requirements were significantly lower in the CSII groups; no data were available on hypoglycaemic events. So, CSII in adults and adolescents with type 1 diabetes mellitus resulted in a greater reduction of HbA1c. No beneficial effect of CSII therapy could be detected for PWD2.

*Chlup* [33], 2009, demonstrated that CSII in PWD2 may in comparison to MDI improve the metabolic control with less insulin and was from all investigated PWD2 well accepted.

*Health Quality Ontario* [34], 2009. In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. The objective of this analysis is to review the efficacy of CSII pumps as compared to MDI for the type 1 and type 2 adult diabetics. The database search identified 519 relevant citations published between 1996 and March 24, 2009. Of the 519 abstracts reviewed, four RCTs and one abstract met the inclusion criteria outlined above. While efficacy outcomes were reported in each of the trials, a meta-analysis was not possible due to missing data around standard deviations of change values as well as missing data for the first period of the crossover arm of the trial. Meta-analysis was not possible on other outcomes (quality of life, insulin requirements, frequency of hypoglycemia) due to differences in reporting. HbA1c: In studies where no baseline data was reported, the final values were used. Two studies (Hanaire-Broutin et al. 2000, Hoogma et al. 2005) reported a slight reduction in HbA1c of 0.35% and 0.22% respectively for CSII pumps in comparison to MDI. A slightly larger reduction in HbA1c of 0.84% was reported by DeVries et al.; however, this study was the only study to include patients with poor glycaemic control marked by higher baseline HbA1c levels. One study (Bruttomesso et al. 2008) showed no difference between CSII pumps and MDI on HbA1c levels and was the only study using insulin glargine (consistent with results of parallel RCT in abstract by Bolli 2004). While there is statistically significant reduction in HbA1c in three of four trials, there is no evidence to suggest these results are clinically significant. Three of four studies reported a statistically significant reduction in the mean daily blood glucose for patients using CSII, though these results were not clinically significant. One study (DeVries et al. 2002) did not report study data on mean blood glucose but noted that the differences were not statistically significant. There is difficulty with interpreting study findings as blood glucose was measured differently across studies. Three of four studies used a glucose diary, while one study used a memory meter. In addition, frequency of self monitoring of blood glucose (SMBG) varied from four to nine times per day. Measurements used to determine differences in mean daily blood glucose between the CSII pump group and MDI group at clinic visits were collected at varying time points. Two studies use measurements from the last day prior to the final visit (Hoogma et al. 2005, DeVries et al. 2002), while one study used measurements taken during the last 30 days and another study used measurements taken during the 14 days prior to the final visit of each treatment period. All four studies showed a statistically significant reduction in glucose variability for patients using CSII pumps compared to those using MDI, though one, Bruttomesso et al. 2008, only showed a significant reduction at the morning time point.

*Parkner* [35], 2008, compared insulin and glucose profiles during basal CSII of a rapid-acting insulin analogue and once daily subcutaneous injection of a long-acting insulin analogue in PWD2. Twenty-one PWD2 diabetes treated with oral glucose-lowering agents were randomized in this two-period crossover study to an equivalent 24-h dose of CSII of insulin aspart and subsequently once-daily bedtime subcutaneous injection of insulin glargine, or vice versa, for eight consecutive days. Plasma profiles of insulin and glucose were recorded. Basal CSII of a rapid-acting insulin analogue improved plasma insulin (more flat insulin profile with a lower variability) and glucose (lower AUC) profiles compared with once-daily subcutaneous injection of a long-acting insulin analogue in PWD2.

*Edelman* [36], 2010, demonstrated that CSII using a simple dosing regimen significantly improved glycaemic control in PWD2. Patients experienced limited body mass gain, there was no severe hypoglycemia, and overall treatment preference improved significantly.

*Monami* [37], 2009, compared CSII and MDI for at least 12 weeks in PWD2 assessing between-group differences in HbA<sub>1c</sub> and insulin daily dose at endpoint, and incidence of hypoglycemia. However data do not justify the use of CSII for basal-bolus insulin therapy in type 2 diabetes.

*Chlup* [38], 2010, in an open prospective uncontrolled study compared development of HbA<sub>1c</sub> concentration, daily insulin dose, BMI and well-being in PWD2 using IP. Data are presented as medians with minimum and maximum values. A total of 44 poorly controlled PWD2 previously on intensive plasma glucose selfmonitoring (up to 10 measurements/d) and supplementary insulin therapy, aged 58.5 (27–75) y, diabetes duration 13 (0–36) y, C-peptide 534.5 (101–4038) nmol/l, 33 men, were put on IP (various models; short-acting insulins or insulin aspart were used) and checked in 1- to 3-month intervals as before. Well-being incl. satisfaction with the IP therapy was assessed according to the routine questionnaire and interviews. Wilcoxon Signed Ranks Test was applied to compare the results (Table 1).

Table 1

**Comparison of investigated parameters before IP (at start) and at the last check-up of the period on IP (n = 44)**

| Parameter                                  | Before IP<br>median<br>(min – max) | Last check-up on IP<br>median<br>(min – max) | Difference                 | P<br>(Wilcoxon) |
|--|------------------------------------|--|----------------------------|-----------------|
| HbA <sub>1c</sub> (IFCC <sup>a</sup> ) [%] | 7.3<br>(3.9–14.1)                  | 6.8<br>(2.9–12.0)                            | 0.4<br>(–3.9–9.6)          | 0.560           |
| Insulin aspart [IU/d]                      | 48.0<br>(16–138)                   | 37.9<br>(1.2–87)                             | 11.0<br>(–45–101)          | 0.0003          |
| BMI [kg/m <sup>2</sup> ]                   | 30.9<br>(21.2–42.5)                | 30.7<br>(24.5–41.8)                          | 0.3<br>(–5.3–6.7)          | 0.763           |
| Well-being<br>(satisfaction with therapy)  | unsatisfactory                     | satisfactory                                 | improved<br>(in 43/44PWD2) | N/A             |

<sup>a</sup> Conversion of HbA<sub>1c</sub> values: NGSP = (0.915 \* IFCC) + 2.15 [%].

The treatment period on IP lasted 3.0 (0.1–8) y. One PWD2 gave up using the pump 2 y after the start due to discomfort. Eight PWD2 died (coronary heart disease 3, stroke 2, Alzheimer disease 2, renal failure 1) at the age of 68 (66–78) y and diabetes duration of 23.5 (15–34) y having used the pump for 4 (2–6) y. In this trial, IP therapy contributed to a significant reduction of insulin dose/d, and, in approximately 50 % of PWD2 to a better metabolic control in comparison to conventional therapy. There was no change in BMI. IP was well accepted in the majority of educated PWD2.

*Rubin* [39], 2010, found out that insulin pump therapy improved quality of life and treatment preference in PWD2.

*Bode* [40], 2010, performed a metaanalysis of CSII treatments for PWD2 and found out that large randomized controlled trials have concluded that CSII was equivalent to MDI, whereas smaller trials have concluded that CSII was superior. The presently available evidence demonstrates that CSII improves glucose control, even with a simple insulin regimen. CSII also improves measures of quality of life and treatment satisfaction. As such, CSII may be a suitable option for PWD2 who have not reached their glycemic goals.

*Reznik* [41], 2010, evaluated the long-term efficacy of CSII for treating PWD2 uncontrolled by MDI and concluded that the use of CSII in PWD2 is safe and effective for improving glycemic control, particularly in those patients with baseline HbA<sub>1c</sub> above 8 %. Such beneficial effect of CSII may persist until 6-year follow-up, suggesting the durability of CSII efficacy in our study population.

*Peyrot* [42], 2011, assessed the relationship between changes in glucose control and changes in patient-reported outcomes (PRO)—health-related quality of life (HR-QoL) and treatment satisfaction (TxSat)—in PWD2 initiating insulin pump therapy. Findings suggest that A1C, representing an «average» of both high and low blood glucose values throughout the day, may not capture aspects of glucose control with the greatest impact on HR-QoL. Although TxSat was more strongly associated with A1C and mean glucose readings than with glycemic variability, HR-QoL was more strongly associated with glycemic variability.

*King* [43], 2012. It has been reported that most pump-treated PWD2 require only two or fewer basal rates. Using daily continuous glucose monitoring (CGM)-directed titration, this premise was re-evaluated at near-normal glycemic control. This study confirms that one basal rate is adequate for the majority of subjects with type 2 diabetes. The mathematical proportionality between dosing factors closely agrees with those obtained in CGM-titrated pump-treated type 1 diabetes but differs from those derived from clinical studies in

which insulin titration was based on infrequent self-monitored plasma glucose testing and while on an unstructured diet.

Aronson [44, 45], 2014, reported on the ongoing project: OpT2mise study is a multicenter, randomized, trial comparing CSII with MDI in a large cohort of subjects with evidence of persistent hyperglycemia despite previous MDI therapy.

Reznik [44, 45], 2014, reported on first outcomes of study OpT2mise: 495 of 590 screened patients entered the run-in phase and 331 were randomised (168 to pump treatment, 163 to MDI). Mean glycated haemoglobin at baseline was 9 % (75 mmol/mol) in both groups. At 6 months, mean glycated haemoglobin had decreased by 1,1 % (SD 1,2; 12 mmol/mol, SD 13) in the pump treatment group and 0,4 % (SD 1,1; 4 mmol/mol, SD 12) in the MDI group, resulting in a between-group treatment difference of -0,7 % (95 % CI -0,9 to -0,4; -8 mmol/mol, 95 % CI -10 to -4,  $p < 0,0001$ ). At the end of the study, the mean total daily insulin dose was 97 units (SD 56) with pump treatment versus 122 units (SD 68) for MDI ( $p < 0,0001$ ), with no significant difference in body mass change between the two groups (1,5 kg [SD 3,5] vs 1,1 kg [3,6],  $p = 0,322$ ). Two diabetes-related serious adverse events (hyperglycaemia or ketosis without acidosis) resulting in hospital admission occurred in the pump treatment group compared with one in the MDI group. No ketoacidosis occurred in either group and one episode of severe hypoglycaemia occurred in the MDI group. Hence, in patients with poorly controlled type 2 diabetes despite using MDI of insulin, pump treatment can be considered as a safe and valuable treatment option.

Reznik [46], 2014. Insulin pump therapy may be offered to PWD2 not controlled by MDI. PWD2 may suffer from unrecognized cognitive disabilities, which may compromise the use of a pump device. A total of 39 PWD2 from our database ( $n = 143$ ) after CSII initiation using (1) an autonomy questionnaire evaluating the patient's cognitive and operative capacities for CSII utilization, (2) the Montreal Cognitive Assessment (MOCA) for the detection of mild cognitive disabilities, (3) the Hospital Anxiety and Depression Scale (HADS) for the detection of anxiety and depression, and (4) the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were evaluated. Patients were selected to constitute 3 groups matched for age, with different degrees of autonomy at discharge after the initial training program: complete ( $n = 13$ ), partial ( $n = 13$ ), or no autonomy ( $n = 13$ ). The satisfaction level with the pump device was high. At the last follow-up visit, only 23 % of patients did not reach complete autonomy. The autonomy score correlated fairly with the MOCA score ( $R = 0.771$ ,  $P < .001$ ). A receiver operating characteristic (ROC) analysis showed that at a cut-off score of 24, the MOCA identified autonomous versus dependent patients at long-term follow-up (area under the ROC curve [AUC], 0.893; sensitivity, 81 %; specificity, 81 %). The HADS correlated negatively with the autonomy score, and the sociocultural level also influenced autonomy with pump utilization. Hence, PWD2 with partial autonomy at discharge may progress to complete autonomy. The MOCA and HADS may help predict a patient's ability to manage with a pump device.

Chlup [47], 2015, reported on a prospective single-center study which recruited insulin-resistant CSII-naive PWD2, uncontrolled, using insulin analogues-based MDI therapy (+ metformin). Insulin dosing was optimized over an 8-week run-in period and subjects with persistent  $HbA1c \geq 8\%$  were randomly assigned to the CSII arm or to MDI continuation arm to explore global metabolic improvement: glucose control, body mass loss, reduction of insulin and insulin resistance. After 6 months, the MDI arm crossed over to CSII therapy as well. A total of 23 PWD2 (16 men) were randomized (mean  $\pm$  SD, age  $57.6 \pm 7.94$  y, BMI  $35.4 \pm 6.54$  kg/m<sup>2</sup>, diabetes duration  $14.3 \pm 5.93$  y,  $HbA1c$   $10.0 \pm 1.05\%$ ). At 6 months, subjects, assigned to the CSII arm, achieved a significant mean  $HbA1c$  reduction of -0.9 % (95 % CI = -1.6, -0.1) while reducing their total daily insulin dose (TDD) by  $-29.8 \pm 28.41$  U/d (33 % of baseline  $92.1 \pm 20.35$  U/d) and achieving body mass reduction of  $-0.8 \pm 5.61$  kg (0.98 % of baseline  $104.8 \pm 16.15$  kg). PWD2 on MDI demonstrated a non-significant  $HbA1c$  reduction of -0.3 % (95 % CI = -0.8, 0.1) with TDD reduction of 5 % from baseline  $99.0 \pm 25.25$  U/d to  $94.3 \pm 21.25$  U/d, and body mass reduction of  $-1.0 \pm 2.03$  kg (0.99 % of baseline  $108.9 \pm 20.55$  kg). At 12 months, patients continuing on CSII demonstrated an additional mean 0.7 %  $HbA1c$  reduction with 54.6 % achieving  $HbA1c < 8\%$ . TDD and body mass increased during the perusing 6 months, the final reduction achieved in TDD was -9.7 U/d in comparison to baseline; body mass increased by 1.1 kg from baseline. MDI patients crossed to CSII showed a  $HbA1c$  reduction of  $-0.5 \pm 1.04\%$ ,  $HbA1c$  response rate 27.3 %, TDD reduction of  $-17.4 \pm 21.06$  U/d and body mass reduction of  $-0.3 \pm 3.39$  kg. No ketoacidosis or severe hypoglycemia occurred in either group. Hence, in insulin resistant PWD2, CSII significantly and safely improved meta- bolic control with less insulin and with no sustainable reduction of body mass.

Thrasher [48], 2015, provided clinical information regarding the use of insulin lispro versus insulin aspart in CSII in adult PWD2. Insulin lispro and insulin aspart performed similarly after 16 weeks of treat-

ment, with noninferiority for HbA1c and no significant difference in parameters measured. These findings indicate that insulin lispro and insulin aspart can both be used safely and effectively in PWD2 using CSII.

*Conget* [44, 45, 49, 50], 2016, reported on the Opt2mise randomized trial designed to compare the effects of CSII and MDI on glucose profiles in PWD2. Changes in glucose profiles were evaluated using continuous glucose monitoring data collected over 6-day periods before and 6 months after randomization. After 6 months, reductions in HbA1c were significantly greater with CSII ( $-1.1 - 1.2\%$  [ $-12.0 - 13.1$  mmol/mol]) than with MDI ( $-0.4 - 1.1\%$  [ $-4.4 - 12.0$  mmol/mol]) ( $P < 0.001$ ). Similarly, compared with patients receiving MDI, those receiving CSII showed significantly greater reductions in 24-h mean sensor glucose (SG) (treatment difference,  $-17.1$  mg/dL;  $P = 0.0023$ ), less exposure to SG  $> 180$ mg/dL ( $-12.4\%$ ;  $P = 0.0004$ ) and SG  $> 250$ mg/dL ( $-5.5\%$ ;  $P = 0.0153$ ), and more time in the SG range of 70–180 mg/dL ( $12.3\%$ ;  $P = 0.0002$ ), with no differences in exposure to SG  $< 70$  mg/dL or in glucose variability. Changes in post-prandial (4-h) glucose area under the curve 180 mg/dL were significantly greater with CSII than with MDI after breakfast ( $-775.9 - 1,441.2$  mg/dL/min vs.  $-160.7 - 1,074.1$  mg/dL/min;  $P = 0.0015$ ) and after dinner ( $-731.4 - 1,580.7$  mg/dL/min vs.  $-71.1 - 1,083.5$  mg/dL/min;  $P = 0.0014$ ). Hence, compared with MDI, CSII treatment in suboptimally controlled PWD2 provides a significant improvement in glucose profile, with increased time spent within target ranges and less exposure to hyperglycemia, without increasing time spent in hypoglycemia.

*Aronson* [44, 45, 49, 50], 2016 (*Randomized multicentric study Opt2mise 2011–2014*). This overview deals with the first outcomes of the 4-year study (Opt2mise) to compare insulin pump therapy and (MDI) (Table 2) in PWD2 diabetes receiving basal and prandial insulin analogues. After a 2-month dose-optimization period, 331 patients with glycated haemoglobin (HbA1c) levels  $\geq 8.0\%$  and  $\leq 12\%$  were randomized to pump therapy or continued MDI for 6 months [randomization phase (RP)]. The MDI group was subsequently switched to pump therapy during a 6-month continuation phase (CP). The primary endpoint was the between-group difference in change in mean HbA1c from baseline to the end of the RP. The mean HbA1c at baseline was 9% in both groups. At the end of the RP, the reduction in HbA1c was significantly greater with pump therapy than with MDI ( $-1.1 \pm 1.2\%$  vs  $-0.4 \pm 1.1\%$ ;  $p < 0.001$ ). The pump therapy group maintained this improvement to 12 months while the MDI group, which was switched to pump therapy, showed a 0.8% reduction: the final HbA1c level was identical in both arms. In the RP, total daily insulin dose (TDD) was 20.4% lower with pump therapy than with MDI and remained stable in the CP. The MDI-pump group showed a 19% decline in TDD, such that by 12 months TDD was equivalent in both groups. There were no differences in body mass gain or ketoacidosis between groups. In the CP, one patient in each group experienced severe hypoglycaemia. Hence, pump therapy has a sustained durable effect on glycaemic control in uncontrolled type 2 diabetes (see Fig. 2 and Fig. 3).

In addition, several studies demonstrated further improvement of metabolite indices in PWD 1 and in PWD 2 treated by means of an insulin pump when continuous glucose monitoring have been used (so called sensor augmented CSII). We have participated in the following studies.

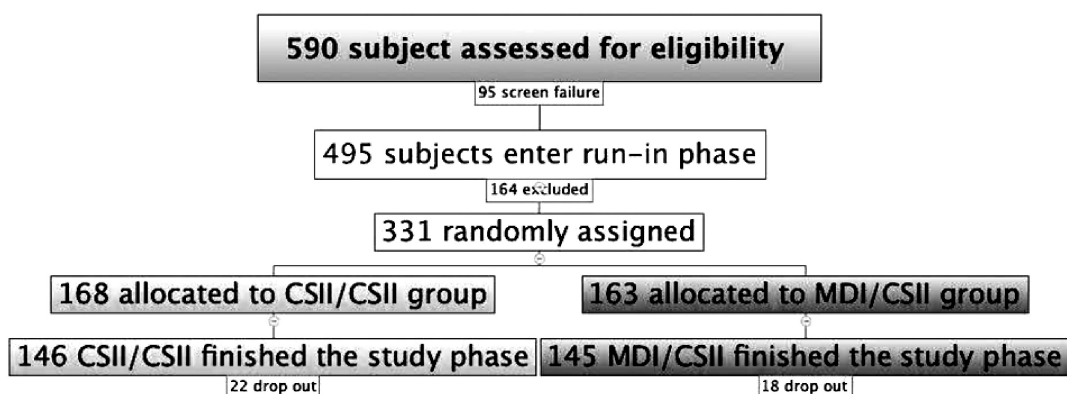


Figure 2. Study OpT2mise: Randomization of PWD2 at the end of run-in period [44, 45, 49, 50]



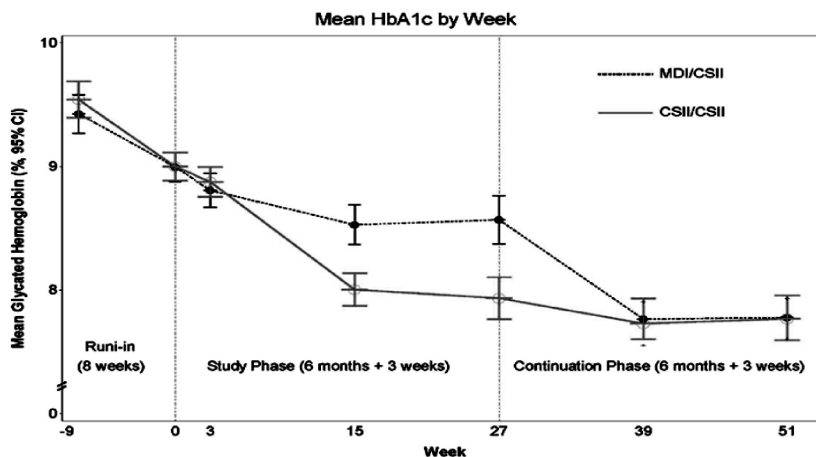


Figure 3. Development of HbA1c in the course of run-in period and throughout the study and continuation phase in MDI/CSII arm and CSII/CSII arm [50]

Table 2

Selected studies comparing CSII and MDI in PWD2

| Author                                 | Year                         | Ref.                 | Type                             | n   | Observ. time | Assessed parameters |         |    |       |       |         |                               |
|--|------------------------------|----------------------|----------------------------------|-----|--------------|---------------------|---------|----|-------|-------|---------|-------------------------------|
|  |                              |                      |                                  |     |              | A1c                 | Ins./D. | BM | Hypo. | Keto. | Satisf. | Satisfaction Results          |
| Raskin                                 | 2003                         | 26                   | Parallel randomized              | 132 | 6 m          | +                   | +       | +  | +     | -     | +       | Posit. for CSII               |
| Herman                                 | 2005                         | 27                   | Parallel                         | 107 | 1 y          | +                   | -       | -  | +     | -     | +       | Posit. for CSII               |
| Wainstein                              | 2005                         | 28                   | Crossover randomized             | 40  | 18 w         | +                   | +       | +  | +     | -     | +       | Posit. for CSII               |
| Labrousse..                            | 2007                         | 31                   | Parallel                         | 51  | 3 y          | +                   | -       | +  | +     | -     | +       | Posit. in both groups         |
| Chlup                                  | 2010                         | 38                   | Prospective observational        | 44  | 0,1-8 y      | +                   | +       | +  | -     | -     | +       | 43 % use CGSM after the study |
| Reznik                                 | 2010                         | 41                   | Retrospective observational      | 102 | 0-13 y       | +                   | +       | +  | -     | -     | -       | -                             |
| Aronson<br>Reznik<br>Conget<br>Aronson | 2014<br>2014<br>2015<br>2016 | 44<br>45<br>49<br>50 | Multicenter crossover randomized | 331 | 1 y          | +                   | +       | +  | +     | +     | -       | -                             |
| Chlup                                  | 2015                         | 48                   | Prospective single center        | 23  | 1 y          | +                   | +       | +  | +     | +     | -       | -                             |

Note. Ref. — reference number of citation in resources; n — number of patients in the study; Observ. Time — observation time; w — week; m — month; y — year; A1c — HbA1c; Ins/D. — dosage of insulin per day; BM — body-mass; Hypo. — hypoglycemia; Keto. — ketoacidosis; Satisf. — satisfaction with the treatment; Labrousse.. — Labrousse-Lhermine.

Mlčák [51], 2004. This pilot study deals with the possibilities of a CGMS (Minimed-Medtronic) to optimize insulin substitution. Ten persons with type 1 diabetes mellitus treated by means of an insulin pump entered the study and eight of them completed the protocol. CGMS was introduced for a period of 5 days. The standard dinner (60 g of carbohydrates) and overnight fasting were designed to ensure standard night conditions in all persons in the study while maintaining their usual daily eating routine, physical exercise and assessment of prandial insulin boluses. The only adaptation of basal rates of insulin pump was performed on day 3. Comparison of the mean plasma glucose concentration (0:00-24:00 hrs) between day 2 (before adaptation) and day 4 (following adaptation) was made. An independent comparison of the mean plasma glucose concentration between the night from day 2 till day 3 (22:00-6:00 hrs) and the night from day 4 till day 5

(22:00–6:00 hrs) was performed. The mean plasma glucose investigated by means of CGMS improved in the 24-hour period in 5 out of 8 persons and in the night fasting period (22:00 to 6 hrs) in 6 out of 8 persons. The CGMS is a useful means for assessment of the effectiveness of basal rate and prandial insulin doses in persons with type 1 diabetes treated by means of an insulin pump.

*Chlup [52], 2008.* The aim of this prospective study was to assess the demands for long-lasting use of sensors in persons with diabetes (PWD) on insulin pumps. Forty PWD aged 19 to 83 years, duration of diabetes 1 to 44 years, using insulin pump Paradigm X22 were given a concise 30-min lecture on CGM and offered transcutaneous sensors for a 3-month period free of charge. The education of PWD was performed individually or in small groups by an experienced educator. Several months later the same offer was repeated. The diabetes control at start and end of the study was compared. Twenty two of 40 PWD (55 %) accepted the suggestion and entered the 3-month sensor study. The reasons for a primary sensor refusal ( $n = 18$ , 45 %) were insufficient educational capacity of the center ( $n = 9$ ), lack of time due to occupation ( $n = 5$ ) or family ( $n = 2$ ) and blindness ( $n = 1$ ), nevertheless, 13 of them (33 % of 40) would be interested in a short use of sensor (up to one week) without being involved in the study. In the course of 3 study-weeks, 5 persons (12 %) interrupted CGM due to technical problems with the transmitter ( $n = 1$ ) or due to personal reasons ( $n = 4$ ); To date, 17 PWD (43 %) are using the sensor continuously, all of them are showing interest in long-lasting use in the future. Hence, the sensors (free of charge) are demanded for long-lasting use by about 43 % of PWDs on insulin pumps Paradigm X22. The main reason for the CGM denial was the insufficient educational capacity of the diabetes center.

*Peterson [53], 2009.* The Paradigm 722 insulin pump, Medtronic MiniMed, USA, enables daily reading of 288 interstitial fluid glucose concentrations determined by a sensor inserted into subcutaneous tissue; the sensor signals are transmitted into the insulin pump, enabling the patient to see real-time glucose concentration on the display and adapt further treatment. The purpose of this study was to assess the evolution of HbA1c over the course of a 3-month period in two cohorts of PWD1 ( $n = 39$ ) or PWD2 ( $n = 3$ ) diabetes (PWD): 1) PWD on Paradigm 722 using sensors for continuous glucose monitoring (CGM group), 2) PWD on other types of insulin pumps performing intensive self-monitoring as before (3 to 6 times/d) on glucometer Linus, Wellion, Agamatrix (control group). Compliant PWDs using insulin pump with insulin aspart for several previous months were included in the study. Seventeen were put on Paradigm 722 with CGM and 25 were included in the control group. Paired t-test and the statistical program SPSS v.15.0 were used to analyze the data. There was no significant difference in age between the two groups ( $P = 0.996$ ), in diabetes duration ( $P = 0.482$ ) or in daily insulin dose ( $P = 0.469$ ). In the CGM group (but not in the control group) HbA1c/IFCC dropped from  $6.98 \pm 0.43$  % to  $5.98 \pm 0.36$  % ( $P = 0.006$ ) within 1 month and remained reduced. Hence the use of the Paradigm 722 insulin pump with CGM resulted in significant improvement in HbA1c which appeared within one month and remained throughout the whole 3-month study period. No significant improvement in HbA1c was seen in the control group.

*Cohen [54], 2009.* This study was conducted by highly experienced investigators with abundant time and resources, phase III studies of continuous glucose sensing (CGS) may lack generalizability to everyday clinical practice. Method: Community or academic practices in six Central and Eastern European or Mediterranean countries prospectively established an anonymized registry of consecutive PWD1-dependent diabetes mellitus starting CGS-augmented insulin pump therapy with the Paradigm® X22 (Medtronic MiniMed, Northridge, CA) under everyday conditions, without prior CGS with another device. We compared glycosylated hemoglobin (GHb) values before and after 3 months of CGS and assessed relationships between insulin therapy variables and glycemia-related variables at weeks 1, 4, and 12 of CGS. Of 102 enrolled patients, 85 (83 %) with complete weeks 1, 4, and 12 sensor data and baseline/3-month GHb data were evaluable. Evaluable patients were ~54 % male and ~75 % adult (mean age,  $33.2 \pm 16.9$  years) with longstanding diabetes and high personal/family education levels. Mean GHb declined significantly after 3 months of CGS ( $7.55 \pm 1.33$  % at baseline to  $6.81 \pm 1.08$  % after 12 weeks, 0.74 %).

*Valensi [55], 1996,* studied the effect of a CSII associated with a low-calorie diet and metformin 1,700 mg/day on glycaemic control and basal and stimulated insulin secretion in a series of 82 overweight NIDD before (T1), during CSII (T2), and after CSII withdrawal (T3). Patients were treated for 8 to 23 days with a mean amount of  $0.50 \pm 0.02$  IU/kg/day. Glycaemic control was very good after 3–5 days of CSII and remained good at T3. At T2, fasting and postprandial plasma C peptide levels decreased significantly. At T3, fasting C peptide was very similar to T1, and postprandial C peptide was significantly higher than at T1.

## (4) Influence of temporary CSII on beta-cell recovery in recent type 2 diabetes

The molar fasting and postprandial plasma C peptide/glycaemia ratios increased significantly at T3. After glucagon injection, the molar delta C peptide/glycaemia ratio was significantly increased at T2 and even higher at T3. At T2, as at T1 and T3, there were significant correlations between fasting and postprandial C peptide levels and between the glucagon-induced C peptide peak and fasting and postprandial C peptide levels. Between T1 and T3 body mass changes correlated significantly with the molar fasting C peptide/glycaemia ratio at T1. Twenty-nine of the 30 patients for whom this ratio was  $> 6.6 \times 10^{-8}$  lost body mass. The length of CSII treatment did not correlate with body mass changes or other biological parameters. Hence, CSII with moderate amounts of insulin associated with a low-calorie diet and metformin provided rapid glycaemic control, led to body mass loss, maintained regulation of insulin secretion and seemed to improve insulin secretion and sensitivity. These results were obtained in only 8 to 10 days.

Ilkova [56], 1997, (Table 3) studied whether the induction of euglycemia, using intensive insulin therapy at the time of clinical diagnosis, could lead to a significant improvement in insulin secretion and action and thus alter the clinical course of the disease. Thirteen newly diagnosed diet-unresponsive PWD2 were treated with CSII for 2 weeks and followed longitudinally while being treated with diet alone. Four patients were considered therapeutic failures since CSII failed to induce euglycemia ( $n = 1$ ) or glucose control deteriorated within 6 months after CSII ( $n = 3$ ). The remaining nine patients were maintained on diet alone with adequate control from 9 to  $> 50$  months (median  $\pm$  SE,  $26 \pm 4.8$  months). In five patients, glycemic control deteriorated after 9–36 months, but a repeat 2-week CSII treatment reestablished control in four patients. One of these patients underwent a third CSII treatment 13 months later. At the time this article was written, six patients of the initial group were still controlled without medication 16–59 months (median  $\pm$  SE,  $45.5 \pm 6.6$  months) after the initiation of treatment. Body mass remained unchanged in all patients. Hence, in a significant proportion of PWD2 who fail to respond to dietary measures, short-term intensive insulin treatment can effectively establish responsiveness, allowing long-term glycaemic control without medication. Further studies are required to establish whether simpler treatment regimens could be equally effective. If the hypothesis offered here finds support, present approaches to the management of newly diagnosed type 2 diabetes may need to be revised.

Table 3

Months of CGS ( $7.5 \pm 1.33$  % at baseline to  $6.81 \pm 1.08$  % after 12 weeks,  $0.74$  %)

| Author  | Year | Ref. | n   | Treating | CSII | MDI | Other     | Insulin/day                                     | OHA/d                | Duration of remission   |
|---------|------|------|-----|----------|------|-----|-----------|---|----------------------|---|
| Valensi | 1997 | 55   | 82  | 8–23 d   | –    | –   | CSII+met. | $0.50 \pm 0.02$ IU/kg                           | met: 1,7 g           | FCP, PCP — After treatment the remission was reached, but the length was not observed.                  |
| Ilkova  | 1997 | 56   | 13  | 9–50 m   | +    | –   | –         | –   | –                    | 9–59 months, in some still continued  |
| Li      | 2004 | 57   | 126 | 2 w      | +    | –   | –         | max. 0.7 units/kg                               | –                    | Remission rates third, sixth, twelfth, and twenty-fourth months were 72.6 %, 67.0 %, 47.1 %, and 42.3 % |
| Weng    | 2008 | 58   | 261 | 2 w      | +    | +   | SU, met.  | 0,4–0,5 IU/kg                                   | SU: 160 mg, met.: 2g | Remission after 1 year: CSII 51,1 %, MDI 44,9 %, PAD 26,7 %   |
| Wan     | 2016 | 60   | 60  | 2 w      | +    | –   | CSII+Sig. | $4.14 \pm 8.59$ CSII, $2.12 \pm 7.50$ CSII+Sig. | Sig: 100 mg          | CPI, SUI — after treatment the remission was reached, but the length was not observed.                  |

Note. Ref. — Ref. — reference number of citation in resources; n — number of patients in the study; Treatment — duration of treatment; PAD/D./day — dosage of PAD per day; d- day; w — week; m — month; met. — metformin; Sig — sitagliptin; FCP — Fasting C-peptide; PCP — Postprandial C-peptide; CPI — C-peptide reactivity index; SUI — Secretory unit of islet in transplantation index.

Li [57], 2004, (Table 3) investigated whether long-term optimal glycaemic control can be achieved without medication by transient CSII and the possible mechanisms responsible for this remission. Newly diagnosed PWD2 ( $n = 138$ , fasting glucose  $> 11.1$  mmol/l) were hospitalized and treated with CSII for 2 weeks. Intravenous glucose tolerance tests (IVGTTs) were performed, and blood glucose, HbA1c, lipid profiles, proinsulin, insulin, and C-peptide were measured before and after CSII. Patients were followed longitudinally on diet alone after withdrawal of insulin. Optimal glycaemic control was achieved within  $6.3 \pm 3.9$  days by CSII in 126 patients. The remission rates (percentages maintaining near euglycemia) at the third, sixth, twelfth, and twenty-fourth month were 72.6, 67.0, 47.1, and 42.3 %, respectively. Patients who maintained glycaemic control  $>12$  months (remission group) had greater recovery of beta-cell function than those who did not (non-remission group) when assessed immediately after CSII. Homeostasis model assessment of beta-cell function (HOMA-B) and the area under the curve (AUC) of insulin during IVGTT were higher in the remission group ( $145.4 \pm 89.6$  vs.  $78.5 \pm 68.5$ ,  $P = 0.002$ , and  $1,423.4 \pm 523.2$  vs.  $1,159.5 \pm 476.8$  pmol. $\times$  $\times 1^{-1} \times \text{min}^{-1}$ ,  $P = 0.044$ ). Change in acute insulin response was also greater in the remission group than that in the nonremission group ( $621.8 \pm 430.4$  vs.  $387.3 \pm 428.8$  pmol. $\cdot$  $1^{-1} \cdot \text{min}^{-1}$ ,  $P = 0.033$ ). Hence, short-term intensive insulin therapy can induce long-term glycaemic control in newly diagnosed PWD2 patients with severe hyperglycemia. The improvement of beta-cell function, especially the restoration of first-phase insulin secretion, could be responsible for the remission.

Weng [58], 2008, (Table 3) hypothesized that early intensive insulin therapy in newly diagnosed PWD2 might improve beta-cell function and result in extended glycaemic remissions. Multicentre, randomised trial to compare the effects of transient intensive insulin therapy (CSII or MDI) with oral hypoglycaemic agents on beta-cell function and diabetes remission rate was performed. A total of 382 patients, aged 25–70 years, were enrolled from nine centres in China between September, 2004, and October, 2006. The patients, with fasting plasma glucose of 7.0–16.7 mmol/L, were randomly assigned to therapy with insulin (CSII or MDI) or oral hypoglycaemic agents for initial rapid correction of hyperglycaemia. Treatment was stopped after normoglycaemia was maintained for 2 weeks. Patients were then followed-up on diet and exercise alone. Intravenous glucose tolerance tests were done and blood glucose, insulin, and proinsulin were measured before and after therapy withdrawal and at 1-year follow-up. Primary endpoint was time of glycaemic remission and remission rate at 1 year after short-term intensive therapy. Analysis was per protocol. More patients achieved target glycaemic control in the insulin groups (97.1 % [133 of 137] in CSII and 95.2 % [118 of 124] in MDI) in less time (4.0 days [SD 2.5] in CSII and 5.6 days [SD 3.8] in MDI) than those treated with oral hypoglycaemic agents (83.5 % [101 of 121] and 9.3 days [SD 5.3]). Remission rates after 1 year were significantly higher in the insulin groups (51.1 % in CSII and 44.9 % in MDI) than in the oral hypoglycaemic agents group (26.7 %;  $p = 0.0012$ ). beta-cell function represented by HOMA B and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the insulin groups but significantly declined in the oral hypoglycaemic agents group at 1 year in all patients in the remission group. INTERPRETATION: Early intensive insulin therapy in PWD2 has favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission compared with treatment with oral hypoglycaemic agents.

Kohnert [59], 2015. Type 2 diabetes mellitus is a complex metabolic disorder characterized by a relative deficiency of insulin in the presence of hepatic, adipose tissue, and skeletal muscle insulin resistance. The pathological process underlying the  $\beta$ -cell dysfunction occurs already prior to the disease onset. While at the initial stage,  $\beta$ -cell mass and insulin secretory function are sufficiently well maintained in the majority of individuals with type 2 diabetes, the later stages are characterized by aggravating insulin deficiency. The clinical course of the disease requires escalating therapy with oral drugs over time and eventually consistent application of insulin at the late stage for control of glycemia. Oral therapies are quite effective in improving the short-term insulin secretory capacity, but are incapable of preventing the inexorable decline in  $\beta$ -cell function during diabetes progression. On the other hand, long-term use of antidiabetic agents is not without various side effects. Since a series of clinical trials have recently shown that implementation of short-term intensive insulin therapy in individuals with newly diagnosed type 2 diabetes can drastically improve and preserve  $\beta$ -cell function and induce glycaemic remission, this treatment strategy has gained considerable interest. However, whether early intensive treatment with insulin can really provide longer-term protection of the pancreatic  $\beta$ -cells and may be preferable to other therapy modalities is a question that is not yet clearly established and requires appropriate clinical studies.

Wan [60], 2016, (Table 3) tried to identify a new regimen to optimize treatment for patients with newly diagnosed type 2 diabetes (PWD2) by short-term CSII alone. Sixty newly diagnosed PWD2 were random-

ized into two groups ( $n = 30$  each) and treated for 2 weeks with CSII alone (CSII group) or with CSII plus sitagliptin (CSII + Sig group). The glycemic variability of the patients was measured using a CGMS for the last 72 hours. A standard meal test was performed before and after the interventions, and the levels of glycosylated albumin, fasting glucose, fasting C-peptide, postprandial 2 h blood glucose, and postprandial 2 h C-peptide were examined. Compared with the CSII group, the indicators of glycemic variability, such as the mean amplitude of glycemic excursion (MAGE) and the standard deviation of blood glucose (SDBG), were decreased significantly in the CSII + Sig group. The changes before and after treatment in the C-peptide reactivity index ( $\Delta$ CPI) and the secretory unit of islet in transplantation index ( $\Delta$ SUIT) indicated a significant improvement in the CSII + Sig group. So, add-on therapy with sitagliptin may be an optimized treatment for patients with newly diagnosed T2DM compared with short-term CSII alone.

*Cohen [61], 2016.* The goal is to assess the usability and satisfaction of implementing the Getting2Goal(SM) protocol by physicians transitioning PWD2 from MDI to CSII. PWD2 from three diabetes clinics were switched from MDI to CSII. Physicians used the Getting2Goal type 2 pumping protocol to prescribe and manage insulin pump therapy for T2DM. Surveys were conducted in which the physicians rated their feedback related to acceptability of the Getting2Goal on a 5-point Likert scale. The data indicate Getting2Goal materials as a standard approach that is simple and efficient to initiate pump therapy for T2DM. At the same time, it is safe and a useful tool for physicians that are starting to prescribe pump therapy for T2DM.

### Conclusion

Insulin pump (CSII) appears to be an effective part of both type 1 and type 2 diabetes complex treatment aiming to early recovery of beta cell function and/or to longlasting improvement of metabolic indices.

CSII may be considered either as a tool for potential recovery of beta-cells and also as a part of combined therapeutic approach for general recovery of metabolite state in longlasting (neglected) diabetes.

### Acknowledgement

This paper is dedicated to the memory of prof. MUDr. Ivo Krč, Dr. Sc. (1932–2016), suo tempore Head, II<sup>nd</sup> Department of Medicine, for his sustainable support of diabetes research at the Faculty of Medicine, Palacky University Olomouc, Czech Republic.

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Р. Хлуп

## **2-Типті қант диабетіне шалдыққан науқастарды емдеу барысында инсулинді сорғышты пайдалану**

Мақалада автор жүргізген 1- және 2-типті диабетпен ауыратын науқастарға инсулинді сорғышты тұрақты инсулин инфузиясын қолдануда аса маңызды және ұзақ уақыт бойы жүргізілген клиникалық зерттеулер нәтижесі берілген және ол 4 бөлімнен тұрады: 1) тарихи экскурс; 2) инсулинді (инсулинді насос) үздіксіз енгізуді қолдану тиімділігі; 3) инсулинді үздіксіз енгізуді қолдану қандағы гликолизденген гемоглобин деңгейі және 2-типті диабеттің глобалды метаболитті индексі тиімділігі; 4) инсулинді үздіксіз енгізуді қолдану 2-типті диабеттің В-жасушалары функциясын қалпына келтіру. Мақалада инсулинді насостарды ұзақ уақыт бойы қолдану емдеу тиімділігін жоғарылату ғана емес, сонымен қатар ұйқы безінің В-жасушаларын қалпына келтіруде аса маңыздылығы көрсетілді.

Р. Хлуп

## **Использование инсулиновых насосов при лечении диабета 2 типа**

В работе обобщен значительный объем результатов серьезных и длительных клинических исследований, проведенных автором и посвященных изучению применения инсулиновых насосов для постоянной инфузии инсулина в процессе лечения больных диабетом 1 и 2 типа. Исследование состоит из 4 разделов: 1) исторический экскурс; 2) эффективность применения непрерывного введения инсулина (инсулиновые насосы) при лечении диабета 1 типа; 3) эффективность применения непрерывного введения инсулина на уровень гликозилированного гемоглобина в крови и глобальные метаболические индексы при диабете 2 типа; 4) влияние непрерывного введения инсулина на восстановление функции В-клеток при диабете 2 типа. Показано, что длительное применение инсулиновых насосов не только весьма эффективно в плане повышения эффективности лечения, но и, что особенно важно, способствует восстановлению функции В-клеток поджелудочной железы.