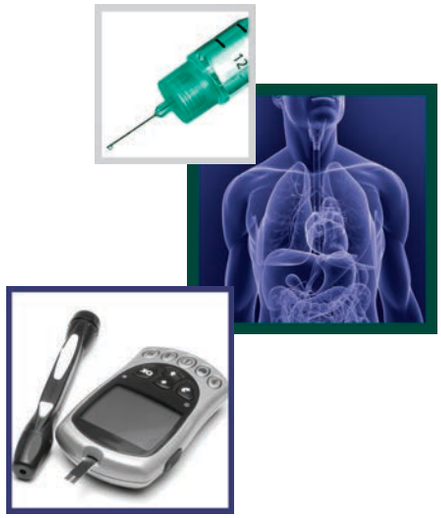
REVIEW



Establishing a good pump clinic: successes and challenges

Nataša Bratina*[1] & Tadej Battelino[1]

Practice Points

- The number of diabetic patients is increasing steadily worldwide with a shift to patients being of a younger age.
- Long-term complications (micro- and macro-vascular) of diabetes are associated with significant morbidity and mortality in adult patients with a longer duration of diabetes.
- Insulin treatment, healthy diet and regular physical activity are the main ways to ensure good metabolic control. Patients in different age groups, pregnant women with diabetes and patients with Type 2 diabetes have special requirements but the same goal – good metabolic control.
- Continuous subcutaneous insulin infusion therapy has documented superiority over multiple daily injections and is becoming the treatment of choice all over the world for all age groups.
- Early start of continuous subcutaneous insulin infusion therapy and its effect on long-term metabolic control is frequently discussed.
- Predictors of improvement in metabolic control are also studied.
- In long-term follow-up studies, safety concerns are of extreme importance. Data about severe hypoglycemia and ketoacidosis events are compared between continuous subcutaneous insulin infusion therapy and multiple daily injection therapy.
- Continuous glucose monitoring systems can be the next step in improving metabolic control and reducing the number of severe hypoglycemia events that impact on the patients' quality of life.
- There is a lack of data on pregnancy, Type 2 diabetes and insulin pump treatment.
- Insulin pump therapy use has its limitations in groups of patients such as patients refusing self-control, patients with emotional problems or those addicted to illicit substances.

[1]University Children's Hospital Ljubljana, Department of Endocrinology, Diabetes & Metabolic diseases, Bohoriceva 20, 1000 Ljubljana, Slovenia
*Author for correspondence: Tel.: +386 1522 9270; Fax: +386 1232 0190; natasa.bratina@kks-kamnik.si

Future Medicine part of fsg

SUMMARY Type 1 diabetes mellitus is a chronic autoimmune disease affecting mainly young people. In the last few decades the incidence of Type 1 diabetes has been increasing worldwide by 3–4% per year. Data in many countries have shown that patients are being diagnosed at a younger age. The management of Type 1 diabetes is a challenge for patients, their families and for other caregivers. Insulin pumps and continuous glucose management systems are helping patients to improve their metabolic control. In many cases, good metabolic control cannot be reached for many years; the reasons can be socioeconomic or psychological, due to a lack of education, as well as refusal to control their diabetes themselves.

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease mainly affecting young people, including babies, toddlers, children, adolescents and young adults. In the last few decades, the incidence of T1DM has been increasing worldwide by 3–4% per year [1], the latest published standardized incidence in Europe, as shown in the Eurodiab study, ranges between 10.3 per 100,000 in Lithuania and 52.6 per 100,000 in Finland [2]. Data in many countries have shown that patients are being diagnosed at a younger age, with peak incidence still in adolescence, but also with an extreme rises in incidence in the age group ranging from 0 to 4 years [3,4].

The management of T1DM is a challenge for every patient, his or her family, and in many cases also for the kindergarten and school personnel. Timing of blood sugar measurements, sports activities, meal times and insulin dosages are main topics of education in hospitals all over the world. The American Diabetes Association (ADA), International Diabetes Federation (IDF) and International Society for Pediatric and Adolescent Diabetes (ISPAD) published general guidelines for diabetes management in an attempt to set uniform standards for patients' care [5–7].

However, the daily routine for affected individuals is nonetheless complicated. Individuals with diabetes are frequently confused by blood sugar excursions while having an acute illness or unexpected hypoglycemia. They need extra knowledge on how to react in stressful situations, while traveling and on holidays. As teenagers are approaching emotional maturity, insulin requirements can be very high, and eating disorders and serious emotional problems can be frequently discovered. These years are also often accompanied by depression and risky behavior [8]. Women with T1DM require particularly strict metabolic control during pregnancy and parents with babies or toddlers with diabetes need additional support [9]. Active and top athletes with T1DM have special requirements for different types of training or competitive events.

The importance of strict metabolic control has been emphasized since the results of the DCCT and UKPDS were published. Optimal glycemic control resulting in lower HbA1c levels is reducing the frequency of chronic complications such as diabetic retinopathy, nephropathy, neuropathy and macrovascular complications [10,11].

Technological improvements entered modern diabetology in the 1970s with the development of hand-held blood glucose meters and were followed by the introduction of continuous subcutaneous insulin infusion therapy (CSII, insulin pumps) [12,13]. With development, these instruments became gradually more and more precise and safe for use in the most vulnerable populations – babies, toddlers and pregnant women [9].

The use of insulin pumps has been steadily increasing over the last 20 years in patients with T1DM of all age groups. It is estimated that more than 40% of T1DM patients in the USA are using insulin pumps. In Europe, the percentage of pump users differs from country to country. There are still countries with a low percentage of pump users – such as Spain, the UK or Portugal, where fewer than 5% of T1DM patients are using pumps. On the other hand, in Germany, Slovenia and Sweden, more than 15% of T1DM patients use the insulin pump. In Slovenia, 75% of children are using CSII and insulin pump treatment is encouraged from an early age. These big differences in insulin pump use in Europe are partly the result of the policy of national healthcare systems that in many countries only recently approved the cost coverage for insulin pump treatment. This can also be the reason why, in many countries, the number of trained physicians for pump therapy is still low; many European countries have no diabetes educators, and pump manufacturers are also not involved in the education process [14].

In addition to the insulin pumps, systems for continuous glucose monitoring (CGMS) in subcutaneous tissue were developed at the

end of the 20th Century. Studies analyzing the use of the CGMS in the last decade report an improved metabolic control and reduced danger of severe hypoglycemic events in patients using CGMS continuously. Many studies also highlight an improved quality of life (QoL) in different groups of patients participating in these studies. However, despite the fact that several randomized controlled trials and meta-analyses demonstrated safety and efficacy of CSII [9,15] and continuous glucose monitoring [9,16], and contrary to published professional recommendations, their use in routine practice is only gradually increasing. A major barrier to successful implementation of technology in routine diabetes management is its implementation within a successful pump clinic.

Successes and challenges of pump clinics are the result of the amount of intensive education the patient and his or her family recieve at pump start and in the following months. An emergency 24-h telephone support line and good technological support from pump providers are needed, as well as patients being followed up by frequent outpatient visits. Alongside outpatient visits, other technological connection possibilities (email and social networks) are offering further access to advice and support. Patients will be able to improve their metabolic control with support from their pump clinic if they inject bolus insulin frequently and check their blood glucose appropriately.

Search methodology

A literature search was performed to identify all publications related to the organization of a clinical service for CSII in Type 1 diabetes patients. The authors searched databases for papers published between May 2007 and May 2012 in PubMed, Ovid Medline, Cochrane and Embase. There were no language restrictions. Published articles were screened based on their titles, keywords and abstracts. Potentially relevant articles were then subjected to a full-text review. Additional references cited by the articles were obtained where appropriate. From articles stating similar facts, only the most recent were used.

Children, adolescents and adult studies were included; Type 1 and 2 diabetes studies were searched for.

Keywords for the search were: 'continuous subcutaneous insulin infusion therapy'; 'CSII'; 'insulin pumps'; 'continuous glucose monitoring systems'; 'sensor-augmented insulin pumps'; and 'real-time continuous glucose monitoring systems'. A total of 26 studies were finally chosen for this review. The papers selected are given in **(Table 1)**, together with their characteristics.

Efficacy of an early start for CSII

Berghaeuser *et al.* published a German–Austrian study in 2008 [17]. The results showed stable HbA1c and less severe hypoglycemic events ($p = 0.009$) in 104 preschool children who started pump treatment in the first weeks after diagnosis of T1DM compared with 145 children matched by age and using multiple daily injections (MDIs) for a longer period; HbA1c was stable in both groups – between 7 and 7.5% in the observed period of at least 12 months. No statistically significant changes in HbA1c were found between both groups ($p = 0.16$). Insulin dose was similar at first (0.75 ± 0.41 in the MDI group compared with 0.83 ± 0.98 international unit [IU]/kg in the CSII group) and increased to 0.83 IU/kg in the MDI group and decreased to 0.79 IU/kg in the CSII group after the fourth quarter of the observed year. The total daily dose was relatively high during these 12 months, since children showed no remission phase signs. The differences were not described as statistically significant. Diabetic ketoacidosis was rare – only 1.76 cases per 100 patient-years were described in both groups. The rate of severe hypoglycemia differed; it was statistically significant in the fourth quarter due to a remarkable increase in MDI-treated patients. In CSII-treated children, the rate was stable and low ($p = 0.009$) [17].

A French analysis published by Sulmont *et al.* showed that long-term metabolic control improved more in children who started with CSII soon after diagnosis [18]. They analyzed data for a period of 8 years in a group of 66 children; 34 were using MDI initially and 32 started with CSII from the time of diagnosis. A total of 31 out of 34 children switched to CSII after their initial treatment with MDI (duration of MDI treatment was 3.9 ± 2.7 years). In the last year of analysis, HbA1c in CSII users was 7.6%; it was 8.3% in children who started as MDI users. Even if children switched from MDI to CSII at a later time, their average HbA1c remained higher than in children who started with CSII soon after diagnosis. For the patients as a whole, those using CSII had a lower rate of hypoglycemic events. In patients using MDI the incidence of severe hypoglycemia reduced from

Table 1. Overview of some recent studies about continuous subcutaneous insulin infusion therapy and continuous glucose monitoring use in children, adolescents and adults with Type 1 diabetes, as well as in pregnant women with diabetes and patients with Type 2 diabetes.

Study (year)	Number of patients	Country	Study design	Age of participants (years)	Results	Ref.
Berghaeuser *et al.* (2008)	145/104 (MDI/CSII)	Germany, Austria	Prospective	<5	Stable HbA1c, less severe hypoglycemia, low DKA frequency	[17]
Farrar *et al.* (2007)	60	UK	Prospective	Adults	Slight increase in birthweight, but not macrosomia. No changes in perinatal mortality, fetal anomaly, or maternal hypo- or hyperglycemia	[36]
Danne *et al.* (2008)	1041	17 countries	Retrospective	0–18	Lower HbA1c in younger children, lower HbA1c with higher number of boluses	[20]
Mukhopadhyay *et al.* (2007)	200 (six clinical trials)	Several countries	Meta-analysis	Pregnant women	No difference between MDI and CSII	[34]
Pickup and Sutton (2008)	1414 (22 studies)	Several countries	Meta-analysis (parallel, crossover and before/after)	Children and adults	Severe hypoglycemia is reduced during CSII use compared with MDI, rate ratio: 4.19; HbA1c is reduced in CSII use, the overall effect is -0.62%	[28]
Shalitin *et al.* (2010)	421	Israel	Retrospective	2.6–39.8	Better HbA1c in younger children; shorter duration of T1DM; more frequent BS measurements	[21]
Olinder *et al.* (2011)	90	Sweden	Cross-sectional	12–18	Insulin omission and lower QoL, more boluses and SMBG – better HbA1c	[23]
Pankowska *et al.* (2009)	165 (six clinical trials)	Several countries	Meta-analysis (crossover trials)	1–21	HbA1c -0.24% on CSII compared with MDI, no differences in severe hypo-ketoacidosis	[25]
Aberle *et al.* (2009)	51	Germany	Retrospective	14–36	Lower HbA1c on CSII compared with MDI (7.1 vs 8.2%), patients' responsibility for CSII leading to better outcomes	[29]
Müller-Godeffroy *et al.* (2009)	107	Germany	Prospective	8–16	QoL better with CSII, reduced parental stress and worries about hypoglycemia	[30]
Jankovec *et al.* (2009)	13	Czech republic	Prospective	Mean: 58.8	No HbA1c improvement, better atherogenic profile, lower insulin resistance	[38]
Fatourechi *et al.* (2009)	908 (15 clinical trials)	Several countries	Meta-analysis (crossover or parallel)	Children and adults	The use of CSII is reducing HbA1c for -0.2% with no significant difference in severe or nocturnal hypoglycemia	[27]
Sulmont *et al.* (2010)	34/32 (MDI/CSII)	France	Prospective	3.8–3.2; standard deviation: ± 1.5	Lower HbA1c if pump use started early	[18]
Misso *et al.* (2010)	976 (23 clinical trials)	Several countries	Meta-analysis	Children and adults	Lower HbA1c in CSII -0.3%	[15]
González-Romero *et al.* (2010)	35	Spain	Prospective	Pregnant women	No differences between MDI and CSII; lower HbA1c at conception on CSII; safe in pregnancy	[35]
Monami *et al.* (2010)	(11 clinical trials)	Several countries	Meta-analysis (crossover or parallel)	Children and adults	CSII use is reducing HbA1c by -0.3%, no difference in the rate of severe hypoglycemia	[26]
Molff-McDonagh *et al.* (2010)	15	USA	Prospective	40–64	T2DM patients reduced average HbA1c by 0.7%, basal insulin needs, BMI and body weight increased	[39]

BS: Blood sugar; CGMS: Continuous glucose monitoring system; CSII: Continuous subcutaneous insulin infusion therapy; DKA: Diabetic ketoacidosis; MDI: Multiple daily injection; QoL: Quality of life; SMBG: Self-monitoring blood glucose; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 1. Overview of some recent studies about continuous subcutaneous insulin infusion therapy and continuous glucose monitoring use in children, adolescents and adults with Type 1 diabetes, as well as in pregnant women with diabetes and patients with Type 2 diabetes (cont.).

Study (year)	Number of patients	Country	Study design	Age of participants (years)	Results	Ref.
Olinder *et al.* (2009)	12	Sweden	Cross-sectional	12–19	Demonstrated the importance of missed boluses for metabolic control	[22]
Shorer *et al.* (2011)	100 parents of children with T1DM	Israel	Cross-sectional	11–18	Demonstrated the importance of authoritative parenting style leading to better metabolic control	[24]
Wojciechowski *et al.* (2011)	1268 (14 clinical trials)	Several countries	Meta-analysis	9–52	HbA1c was -0.26% lower in CGMS compared with SMBG	[31]
Frias *et al.* (2011)	21	USA	Prospective	Mean: 57	HbA1c improvement in T2DM using CSII, HbA1c -1.1%	[37]
Pickup *et al.* (2011)	892 (six studies)	Several countries	Meta-analysis (parallel)	Children and adults	HbA1c decreased with CGMS use compared with BS monitoring group (-0.3%), continuous use of CGMS is of importance (every added day of CGMS use per week reduces HbA1c by 0.15%)	[33]
Shalitin *et al.* (2012)	488	Israel	Retrospective	2.6–39	No changes in HbA1c if CSII started early compared with a later CSII start	[19]
Szypowska *et al.* (2012)	948 (seven clinical trials)	Several countries	Meta-analysis (crossover or parallel)	Children and adults	The use of real-time CGMS and CSII compared with the use of CSII and BSM results in a -0.26% reduction in HbA1c and no increase in severe hypoglycemia	[32]
Langendam *et al.* (2012)	(22 clinical trials)	Several countries	Meta-analysis (crossover)	Children and adults	Patients with real-time CGMS and CSII had 0.7% lower HbA1c compared with MDI–SMBG, QoL improving, compliance important	[16]

BS: Blood sugar; CGMS: Continuous glucose monitoring system; CSII: Continuous subcutaneous insulin infusion therapy; DKA: Diabetic ketoacidosis; MDI: Multiple daily injection; QoL: Quality of life; SMBG: Self-monitoring blood glucose; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

22.3 episodes per 100 patient-years to 12 episodes per 100 patient-years after switching to CSII. Patients who started with CSII immediately had only 9.8 episodes per 100 patient-years ($p = 0.016$). A total of 9.1% of pump users discontinued pump use [18].

By contrast, Shalitin *et al.* recently published a paper where data from Israel were analyzed [19]. Again, the initiation of insulin pump treatment was of interest. No differences were found if the pump treatment was started at an early time point after diagnosis of T1DM or later. Data from a total of 488 patients were analyzed. Patients who started with pump treatment at an early stage were younger, were measuring blood sugar more frequently and had a shorter duration of diabetes (n = 93). Their mean HbA1c and the rate of acute complications such as diabetic ketoacidosis or severe hypoglycemia did not differ from the group who started with pump treatment later on [19].

Predictors of improved metabolic control

The European PedPump study involved the collaboration of a large number of diabetic centers. Danne, together with coworkers from 17 countries, analyzed data from 1041 patients who used an insulin pump for more than 90 days. Glycemic control (HbA1c) was better in preschool children (HbA1c: 7.5 ± 0.9%) and worst in adolescents (8.3 ± 1.4%). A strong predictor of metabolic control was the number of boluses. Less than 6.7 boluses per day was an important predictor of HbA1c >7.5% [20].

Shalitin *et al.* analyzed variables that could predict glycemic control after patients (children and adults) were switched to pump treatment [21]. Data for 421 patients were analyzed; their age range was between 2.6 and 39.8 years. Their average HbA1c at pump initialization was 8.13 ± 1.29%. Their data were followed for 8 years, with final HbA1c of 7.73 ± 1.46%. A total of 35.4% of patients achieved the goal of HbA1c as recommended by ADA (between 7 and 8.5% depending on the age of the patients) after 6 months of pump treatment, 29.7% remained in good control at the end of the follow-up period. Predictors of good metabolic control were younger age at pump start, shorter diabetes duration and more frequent blood sugar measurements (before pump start and during pump use). Patients in puberty more frequently failed to achieve good metabolic control, as well as those with very high HbA1c [21].

Olinder *et al.* published two papers trying to explain how missed boluses influenced the metabolic control [22,23]. A total of 90 Swedish adolescents participated in this study; they were 14.8 ± 2.1 years old and were using an insulin pump for more than 6 months. A total of 38% of the adolescents who had missed more than 15% of the boluses had higher HbA1c (7.8 ± 1.0%) compared with peers who missed less than 15% of boluses (HbA1c in this group was 7.0 ± 1.2%; $p < 0.001$). On average, they took 3.8 ± 1.7 boluses compared with 5.3 ± 1.7 in the better control group and measured blood sugar less frequently – just 2.4 ± 1.8 times daily. The group that did not miss boluses as frequently measured their blood sugar more often (3.6 ± 1.8 times daily; $p < 0.003$) [22]. Insulin omission is a common problem in school-age children and adolescents. It leads to bad metabolic control; patients are also less satisfied with their QoL and dislike their treatment. The next paper from the same authors published 2 years later tried to find the answer to this problem. A total of 12 adolescents were interviewed; interviews were tape recorded and transcribed immediately. The main reason for bolus omission (meal and correction boluses) was 'the loss of focus' that occurred if the adolescent wanted to bolus after a meal or at the start of the meal. Bolus omission was also the result of the teenagers neglecting the fact that they have diabetes (i.e., complete loss of focus – injecting almost no boluses for food or correction). Personal or technical reminders could help adolescents to improve the number of boluses they administered. Personal reminders were a better solution, since technical reminders were used only for a short period of time [23].

Shorer *et al.* analyzed the role of parenting on metabolic control in his paper published in 2011, pronouncing that authoritative parenting was led to better metabolic control in children and adolescents. Data from 100 patients aged 11–18 years were analyzed. Patients had diabetes for a mean of 4.02 years, had a mean age of 14.37 years and 32% were pump users. The role of authoritative parenting was especially important; worse metabolic control occurred if one of the parents felt helpless [24].

Safety (hypo-diabetic ketoacidosis)

The Cochrane review that was published in 2010 by Misso *et al.* analyzed data from 23 studies with 976 participants. Patients were compared according to insulin pump use or MDI therapy. One

of the goals was the analysis of HbA1c reduction. A total of 20 studies out of 23 analyzed HbA1c and showed statistically significant reduction of HbA1c in pump users, with less severe hypoglycemia. The mean reduction in HbA1c was 0.3%. The HbA1c reduction was not very high, but some of the trials included in this meta-analysis came from papers published more than 20 years ago [15].

Pańkowska *et al.* published another meta-analysis of six trials with 165 participants aged 1–21 years with a minimum duration of diabetes of 3 months. They investigated metabolic control, insulin dose, severe hypoglycemia and ketoacidosis, discontinuation rate and QoL. The HbA1c changed in favor of CSII at 3 months and at the end of the study (-0.29 and -0.24%, respectively), and patients using CSII needed less insulin; BMI standard deviation score analysis did not show uniform results. The differences in rates of severe hypoglycemia and ketoacidosis were not statistically significant; although the authors reported less severe hypoglycemia and ketoacidosis on CSII. Two studies analyzed the discontinuation rate after the trial ended. Both reported a low discontinuation rate (one out of 20 and seven out of 23 children switched to MDI after the study). QoL improved, but since different questionnaires were used, the results were difficult to interpret [25].

Monami *et al.* published a meta-analysis in 2010; 11 randomized clinical trials were included, showing that HbA1c significantly improved in patients who used CSII for at least 12 weeks compared with MDI-treated patients (difference: -0.3%; $p < 0.001$), regardless of whether they used lispro or aspart. Trials included patients with unsatisfactory metabolic control with an average HbA1c of 8.5%. No significant difference was found in the frequency of severe hypoglycemia between both groups; the HbA1c reduction was greater in trials where patients were older than 10 years compared with younger children [26].

Fatourechi *et al.* focused on hypoglycemia in intensive insulin therapy in a systematic review and meta-analysis comparing CSII and MDI. The review included trials published between 2002 and 2008. A total of 15 clinical trials were found eligible, including children and adult patients with Type 1 and 2 diabetes. Metabolic control, as idicated by HbA1c levels, improved on CSII (-0.2%; 95% CI: 0.1–0.3); only patients with Type 2 diabetes mellitus (T2DM) showed a nonsignificant trend toward worse metabolic control. Analysis of severe hypoglycemia showed no significant difference between both groups, but slightly favored CSII (OR: 0.48; 95% CI: 0.23–1.00); no correlation was found with the final HbA1c decrease. When analyzing night hypoglycemia, results were similar, but no significant difference was found between the groups of patients using CSII compared with MDI, with the point estimate favoring CSII (OR: 0.82, 95% CI: 0.33–2.03 in T1DM; OR: 0.61, 95% CI: 0.26–1.47 in T2DM). Data describing minor hypoglycemia (blood sugar above 3.3 mmol/l, no assistance from another person needed) showed, especially in children and adolescents with T1DM, fewer minor events in crossover trials, but not in parallel trials where minor hypoglycemia was more frequent (-0.08, 95% CI: -0.21–0.06; and +0.68, 95% CI: 0.16–1.2). In conclusion, this meta-analysis showed that CSII slightly reduces HbA1c in adult patients with T1DM as well as in T2DM patients. In both groups, the impact on hypoglycemia was unclear, especially when analyzing data from patients with severe hypoglycemia or hypoglycemia unawareness, where there is still a lack of data [27].

Pickup and Sutton published a review in 2008 in which 22 studies were analyzed (published between 1996 and 2006) with the primary goal of monitoring severe hypoglycemia. Only randomized controlled studies in subjects with more than 6 months of CSII use and a frequency of more than ten episodes of severe hypoglycemia per 100 patient-years were included. Severe hypoglycemia occurred more often in adult patients with a longer duration of diabetes on MDI treatment. During the CSII use, severe hypoglycemia was reduced compared with MDI therapy with an overall rate ratio of 4.19 (95% CI: 2.86–6.13). The reduction was higher in patients with the highest initial rate of severe hypoglycemia on MDI ($p < 0.001$) and older patients with a longer duration of diabetes. As well as severe hypoglycemia data, data about metabolic control were of interest. The HbA1c reduction was greatest in the poorly controlled patients ($p < 0.001$). The difference in HbA1c between MDI and CSII was 0.21% (range: 0.13–0.30%), but if studies were analyzed before and after, the difference was larger (0.72%; range: 0.55–0.90%); all studies together showed a mean difference in HbA1c of 0.63% [28].

Quality of life

Aberle *et al.* investigated the influence of psychological factors on metabolic control. A total of 51 patients participated in this study, and the results showed that HbA1c was lower in patients using CSII compared with MDI (HbA1c was 7.1% on CSII and 8.2% on MDI; $p < 0.001$). Patients with higher HbA1c were more likely to show signs of depression. QoL and treatment satisfaction were associated with high self-efficacy [29].

Müller-Godeffroy *et al.* published a paper in 2009 showing how significantly parental stress is reduced after switching to pump therapy. A total of 107 children aged 4 –6 years as well as their parents completed this study. They were switched to CSII treatment between 2005 and 2006 and were followed-up for 6 months. Parents of all children as well as children in the age group 8–16 years filled out questionnaires on QoL (general and diabetes associated), parenting stress, meals, fear of hypoglycemia and family conflicts before and after starting CSII treatment. The QoL of children increased significantly after switching to CSII in all age groups. Parents reported reduced overall parenting stress and fear of hypoglycemia, and parents of young children reported fewer problems with nutrition management [30].

Sensor-augmented pumps

Modern CGMS have been on the market for more than 10 years. Initially, CGMS were an educational tool for the diabetes-management team to learn more about blood sugar excursions, and the next step was to teach the patient about effectively reducing blood sugar excursions in different situations. Today, an insulin pump with CGMS can be used in everyday life in different patient groups. CGMS with real-time data can be used as a therapeutic help in critically ill patients. In addition, blinded CGMS can be used as a diagnostic tool in suspected diabetes in cystic fibrosis patients.

Wojciechowski *et al.* analyzed data from 14 clinical trials including 1268 patients with T1DM; 670 were using CGMS and the rest were self-monitoring blood glucose (SMBG). Patients were aged 9–52 years; seven trials included patients of all age groups, while seven focused on children and adolescents. Patients were using pumps and MDI therapeutic options. The CGMS group of patients showed a bigger decrease of HbA1c, compared with the SMBG group in all trials; the effect was seen in children as well as adults (HbA1c difference: -0.26 and -0.33%, respectively) when using real-time CGMS. Four studies included in the meta-analysis also reported a reduction of hypoglycemic events in the CGMS group; severe hypoglycemia was reported in five trials, with comparable cumulative risk between both groups [31].

A similar meta-analysis was published by Szypowska *et al.* Data from seven trials were compared; an HbA1c reduction of -0.25% ($p < 0.001$) was documented in patients using CGMS compared with the group using SMBG. The data suggest that it is important to use CGMS more than 60–70% of the time to benefit from improvement in metabolic control. Children, adolescents and adult patients with T1DM participated in those trials, using pumps and MDI. The patients were using different CGMS, and the metabolic control varied from extremely good (HbA1c: 6.5%) to uncontrolled (HbA1c: 11.5%). Severe hypoglycemic events were analyzed as well as incidences of minor hypoglycemia. There was no statistically significant difference between the groups. Ketoacidosis was an infrequent event in all trials. Compliance with the sensor use was high, but declined over time [32].

Langendam *et al.* published the largest report in 2012 (Dutch Cochrane Database revised). A total of 22 trials out of more than 1300 published between 2001 and 2011, which were identified in different databases, were included in this review. Ten of them included trials with children or adolescents; different CGMS were used, including retrospective and real-time CGMS. Patients ranged between good and poor metabolic control. No studies included pregnant women. Again, the results of the meta-analysis for the metabolic control highlighted the importance of CGMS use for patients of all age groups compared with patients using MDI with SMBG. The decline in HbA1c level was the highest among patients using real-time CGMS with insulin pumps. Compared with patients using MDI with SMBG they had significantly lower HbA1c (HbA1c difference: -0.7%) [16].

If the patients were only using CGMS, without the pump, the reduction in HbA1c levels 6 months after baseline was again statistically significantly larger for CGMS users compared with SMBG users. The difference was smaller if compared with patients who used CGMS together with the insulin pump (change in HbA1c level: -0.2%).

Compliance with sensor use was emphasized. Adults and young children who were using the sensor regularly (50% of children and 83% of adults, 6 days per week) were achieving a mean decrease of HbA1c of -0.6%. Only 30% of adolescents reached this goal. The frequency of sensor use was a predictor of HbA1c reduction.

QoL was reported in five out of the 22 studies. None of these studies found a significant difference between CGMS and SMBG. The risk of severe hypoglycemia or ketoacidosis was analyzed as well. It seems that in CGMS users the risk for ketoacidosis or severe hypoglycemia was not increased, but in most of the studies these acute complications were quite rare [16].

Pickup *et al.* published a meta-analysis in 2011 in which six trials were identified with 449 adult, nonpregnant patients with Type 1 diabetes and the same insulin delivery system randomized to CGMS and 443 in the SMBG group. Patients using CGMS showed an overall change in mean HbA1c of -0.30% (95% CI: -0.43–0.17). A best fit regression model of determinants for final HbA1c showed how important regular usage of CGMS is. Every extra day of increase of sensor use per week increased the effect of CGMS compared with self-monitoring of blood glucose by 0.15% HbA1c. If the CGMS was used in patients with poor metabolic control, every increase in the initial HbA1c value by 1% increased the effect of regular CGMS use by 0.125% HbA1c. Age had only a small effect – every 1 year increase in age increased the CGMS effect by 0.002% HbA1c. Therefore, a 40-year old using the CGMS continuously would be expected to reduce his/her HbA1c level by just an extra 0.05% compared with a teenager of 15 years of age.

The final calculation showed that a patient with HbA1c of 10% could expect a 0.9% reduction in HbA1c while wearing a CGMS continuously. Again, a correlation with the frequency of sensor use was shown.

Hypoglycemia was another important topic in this meta-analysis. Patients in the studies already had initially low levels of hypoglycemia, but the analysis showed a 23% reduction in the median exposure to hypoglycemia if patients used the CGMS continuously [33].

CSII in pregnancy

Randomized trials are rare in the pregnant population, so it is difficult to conclude how important insulin pump treatment is for women with a history of poor metabolic control when pregnancy is being planned. A meta-analysis was published in 2008 by Mukhopadhyay *et al.*, in which 68 papers were identified and six out of nine trials met all the inclusion criteria. The number of patients was less than 200 in both groups (in nine papers together: there were 94 pregnant women using CSII compared with 88 using MDI). The authors looked for differences in total daily insulin dose, gestational age and mode of delivery, acute complications such as hypoglycemia or ketoacidosis as well as late diabetic complications (e.g., an advanced degree of retinopathy). In children, data on birth weight, neonatal hypoglycemia and intrauterine fetal death were analyzed. Finally, data from six trials were interpreted showing that pregnancy outcomes and glycemic control were not significantly different between women using insulin pumps and MDI. The results showed a slightly higher rate of ketoacidosis on insulin pumps, but no statistical significance was found. Therefore, the authors concluded that there is no advantage or disadvantage of using CSII over MDI in pregnant diabetic women and emphasized that there is a need for larger multicenter controlled trials [34].

González-Romero *et al.* compared metabolic control and perinatal outcomes in pregnant T1DM women who were using insulin pumps or MDI. A total of 35 women were using insulin pumps during pregnancy compared with 64 women using MDI. Women using CSII had lower HbA1c at the start of pregnancy (6.6 vs 7.6%), but control during pregnancy was similar in both groups. No differences were found in the rate of ketoacidosis or hypoglycemia. Other complications were also analyzed (retinopathy progression, miscarriage, birth weight, eclampsia, stillbirth and neonatal hypoglycemia) and no differences were noticed [35].

Farrar *et al.* made a statistical analysis for the Cochrane database that was published in 2007. Only two studies were included. There was a significant increase in mean birth weight associated with CSII as opposed to MDI treatment (weighted mean difference was 220.56; 95% CI: -2.09–443.2). But there was no difference in the rate of macrosomia (birth weight above 4000 g), so this is not viewed as clinically significant by the authors. No significant differences were found in perinatal mortality, fetal anomaly, or maternal hypo- or hyper-glycemia. These results were partly attributed by the authors to the low number of trials and participants. Therefore, Farrar *et al.* conclude that the evidence to support one form of insulin administration

over another in pregnancy is weak, but since trials are rare, more adequately powered randomized trials are needed [36].

Insulin pumps for T2DM patients

In the year 2011, Frias *et al.* published a study about the efficacy and safety of insulin pump use in T2DM patients. A total of 21 patients (average age: 57 years; BMI: 34; HbA1c: 8.4%; total daily dose: 99 IU) used insulin pumps for 16 weeks. Initially, they were treated with MDI therapy with or without oral antidiabetic agents. They started with insulin treatment after discontinuation from all other drugs apart from metformin. All participants used the same insulin, one basal rate was programmed, and patients were instructed to inject boluses for their regular meals. During the first 4 weeks CGMS was also used. HbA1c declined after 4 weeks of pump treatment; the overall reduction was 1.1%. At the end of the study, 38% of the patients reached the final goal of HbA1c <7%. In the first 8 weeks patients gained 2.5 kg; in the second 8 weeks their weight remained stable. The total daily insulin dose was 122 IU, 57% of the total daily insulin dose was delivered as basal insulin. At the end of the study 80% of patients used only one basal level rate. Patients reported improvements in QoL (treatment satisfaction, preference and clinical efficacy) [37].

On the other hand, Jankovec *et al.* included 13 obese T2DM patients in their trial. On average, the particiants' BMI was above 30, they were 58.8 years old (similar to the patients taking part in the study of Frias *et al.*) and using MDI with a total daily dose of more than 0.8 IU/kg per day. They checked their glycemic control after 6 months. Compared with the study by Frias *et al.*, the results of this study showed no reduction in HbA1c (9.6 vs 9.8% at the end of the study); BMI and total daily insulin dose showed no difference. However, they reported a statistically significant improvement in insulin resistance – M-value (insulin-mediated glucose uptake in euglycemic clamp) increased from 2.55 to 3.32 mg/kg per min. Improvements were also shown in atherosclerosis risk factors – blood coagulation and endothelial dysfunction (fibrinogen, factor VII, factor VIII, vWF:RiCo, PAI-1 and thrombomodulin Ag) [38].

Molff-McDonagh *et al.* carried out a study in poorly controlled patients with T2DM. The study group was small – 15 patients in the 40–64 years age group, with an average HbA1c of 9.4% (range: 8–11.2%). They were followed for 1 year; data on HbA1c, BMI, and basal and bolus insulin use were collected. The results showed a significant reduction of HbA1c after 12 months, which started already after 3 months of CSII use. The final HbA1c was lower for 8.2%. The final HbA1c was 8.7%. Unfortunately this resulted in a significant BMI increase from 38.6 to 40; the average weight gain was 4.3 kg. The number of boluses increased, which could be the result of changed eating behavior; patients were eating more carbohydrates with each meal. In the whole study period, the basal levels of insulin decreased and this resulted in a cost saving of several thousand US dollars if the initial basal insulin needs were high (more than 150 U of basal insulin) [39].

More randomized long-term crossover clinical trials are needed in T2DM patients. Bode published a review about the use of insulin pumps in T2DM, and discussed the use of simple patch pumps with one basal rate that could be used in this group of patients. Owing to insulin resistance problems, U-500 insulin could be important, but the cost–benefit should be investigated as well [40].

In patients with T2DM, another important topic has also been discussed. Studies published in the last 5 years showed that some insulin analogs could be associated with an increased risk of cancer. Hernandez-Diaz and Adami published a paper in 2010 where data on four reports about the association between hypoglycemic agents and the risk of cancer were summarized. Among them, one study showed that the risk of cancer increased with the dose for any type of insulin and, among high doses, insulin glargine-only users had a higher risk for cancer than subjects on human insulin. Two studies showed that insulin glargine alone increased the risk of breast cancer, but another study found no association. Therefore, the latest epidemiological evidence is insufficient to confirm a carcinogenic effect of specific types of insulin on specific cancers. However, the potential dose effect of insulin could be of importance if patients with T2DM using CSII compared with MDI needed less insulin for a long period of time [41].

Conclusion

Modern studies suggest that insulin pumps are a safe and important therapeutic tool for different age groups and different patient groups. Not only adults but also children and toddlers can profit from this intensive insulin treatment

possibility, as well as pregnant women, women in the preconception period and patients with T2DM. Real-time CGMS together with insulin pumps is increasing our understanding of how to react in different everyday situations and helps patients and their families to stabilize their glycemia [40, 42].

The future development of insulin pumps is reported from several research centers in the world. The development of the automated closed-loop insulin delivery – also referred to as the artificial pancreas – is becoming a reasonable goal that is already being tested in different clinical trials in adults and children, in clinical settings and in outpatient facilities. Research groups from several important diabetic centers such as Tel Aviv (Israel), Cambridge (UK) and Virginia (VA,USA) are testing different algorithms for a tight control of glycemia, mainly in overnight trials. New studies are needed for different groups of patients to bring the artificial pancreas from hospitals to the home environment [43–46].

Costs of diabetes treatment are high, especially if we discuss real-time CGMS with CSII. Calculation costs of CSII are between €2200 and €2500 per year, the costs of the pump (calculated based on a 4-year life) is another €500–850 per year. The cost for one sensor is approximately €5–10 per day, meaning that costs per patient per year can reach almost €3000 for continuous use of the sensors, with an additional cost for the transmitter of €600 per year (costs may differ in different countries). Therefore, the sum of the costs without insulin, strips and lancets is between €6300 and 6950 per year. Savings through better metabolic control must be calculated (reduced hospitalization and fewer late complication) and patients who can profit from pump treatment must be identified [47–48].

Future perspective

CSII and CGMS have developed significantly in the last decade. How the development will proceed in the next decade is one of the most important topics. Pumps could be developed to a form similar to smart phones, incorporating new technologies such as global positioning systems, pedometers or even more sophisticated physical activity recognition systems. New forms of patch pumps may be developed. Sensors could last longer, their size will reduce, and perhaps two or three sensors in one patch near the insulin set will inform the patients about their interstitial sugar values. Other technologies (e.g., bioimplants and fluorescent glucose biosensors) are being developed, which need less calibration. Improvements will bring closed-loop systems nearer to the patients, first for night time and perhaps physical activity, and later to control postprandial blood sugar excursions.

Financial & competing interests disclosure

The authors are employees of University Children's Hospital Ljubljana (Slovenia), which receives research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense and Diamyd. T Battelino received honoraria for participating on the speaker's bureau of Eli Lilly, Novo Nordisk, Bayer and Medtronic, and consulting fees as a member of scientific advisory boards from Bayer, LifeScan, Eli Lilly, Sanofi-Aventis and Medtronic. The authors are supported, in part, by the Slovenian National Research Agency grants P3-0343, J3-2412 and J3-4116. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Patterson CC, Gyürüs E, Rosenbauer J *et al.* Trends in childhood Type 1 diabetes incidence in Europe during 1989–2008: evidence of non-uniformity over time in rates of increase. *Diabetologia* 55(8), 2142–2147 (2012).

2 Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 373, 2027–2033 (2009).

3 Pundziute-Lycká A, Dahlquist G, Nyström L *et al.* The incidence of Type 1 diabetes has not increased but shifted to a younger age at diagnoses in the 0–34 years group in Sweden 1983–1998. *Diabetologia* 47, 377–384 (2002).

4 Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith GJ, Dabelea D. Childhood growth and age at diagnosis with Type 1 diabetes in Colorado young people. *Diabet. Med.* 26(10), 961–967 (2009).

5 American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 35(Suppl. 1), S11–S63 (2012).

6 *Guidelines for Diabetes in Childhood and Adolescence.* International Diabetes Federation, Brussels, Belgium, 1–128 (2011).

7 International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2009. *Pediatr. Diabetes* 10(Suppl. 12), S1–S210 (2009).

8 Radobuljac MD, Bratina NU, Battelino T, Tomori M. Lifetime prevalence of suicidal and self-injurious behaviors in a representative cohort of Slovenian adolescents with Type 1 diabetes. *Pediatr. Diabetes* 10(7), 424–431 (2009).

9 Pickup JC. Insulin-pump therapy for Type 1 diabetes mellitus. *N. Engl. J. Med.* 366(17), 1616–1624 (2012).

■ **Latest review on continuous subcutaneous insulin infusion therapy (CSII) treatment compared with multiple daily injection treatment.**

10 Nathan DM, Zinman B, Cleary PA *et al.*; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of Type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005). *Arch. Intern. Med.* 169(14), 1307–1316 (2009).

11 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352, 837–853 (1988).

12 Stubbs SM, Brudenell JM, Pyke DA, Watkins PJ, Stubbs WA, Alberti KG. Management of the pregnant diabetic: home or hospital, with or without glucose meters? *Lancet* 1(8178), 1122–1124 (1980).

13 Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *BMJ* 1(6107), 204–207 (1978).

14 Renard A. Insulin pump use in Europe. *Diabetes Technol. Ther.* 12(Suppl. 1), S29–S32 (2010).

15 Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for Type 1 diabetes mellitus. *Cochrane Database Syst. Rev.* 1, CD005103 (2010).

■■ **Large meta-analysis comparing 23 studies, focusing on HbA1c improvement and hypoglycemia in patients using CSII compared with multiple daily injection.**

16 Langendam M, Luijf YM, Hooft L, DeVries JH. Continuous glucose monitoring systems for Type 1 diabetes mellitus. *Cochrane Database Syst. Rev.* 1, CD008101 (2012).

■■ **Continuous glucose monitoring meta-analysis included 22 trials published between 2001 and 2011. Metabolic control improved in patients of all age groups using continuous glucose monitoring compared with patients using multiple daily injection with self-monitoring blood glucose.**

17 Berghaeuser MA, Kapellen T, Heidtmann B, Haberland H, Klinkert C, Holl RW; German Working Group for Insulin Pump Treatment in Paediatric Patients. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of Type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatr. Diabetes* 9(6), 590–595 (2008).

18 Sulmont V, Souchon PF, Gouillard-Darnaud C *et al.* Metabolic control in children with diabetes mellitus who are younger than 6 years at diagnosis: continuous subcutaneous insulin infusion as a first line treatment? *J. Pediatr.* 157(1), 103–107 (2010).

19 Shalitin S, Lahav-Ritte T, Lebenthal Y, Devries L, Phillip M. Does the timing of insulin pump therapy initiation after Type 1 diabetes onset have an impact on glycemic control? *Diabetes Technol. Ther.* 14(5), 389–397 (2012).

20 Danne T, Battelino T, Jarosz-Chobot P *et al.*; PedPump Study Group. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with Type 1 diabetes: experience of the PedPump Study in 17 countries. *Diabetologia* 51(9), 1594–1601 (2008).

21 Shalitin S, Gil M, Nimri R, de Vries L, Gavan MY, Phillip M. Predictors of glycaemic control in patients with Type 1 diabetes commencing continuous subcutaneous insulin infusion therapy. *Diabet. Med.* 27(3), 339–347 (2010).

22 Olinder AL, Kernell A, Smide B. Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with Type 1 diabetes. *Pediatr. Diabetes* 10(2), 142–148 (2009).

23 Olinder AL, Nyhlin KT, Smide B. Reasons for missed meal-time insulin boluses from the perspective of adolescents using insulin pumps: 'lost focus'. *Pediatr. Diabetes* 12, 402–409 (2011).

24 Shorer M, David R, Schoenberg-Taz M, Levavi-Lavi I, Phillip M, Meyerovitch J. Role of parenting style in achieving metabolic control in adolescents with Type 1 diabetes. *Diabetes Care* 34(8), 1735–1737 (2011).

25 Pańkowska E, Błazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with Type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr. Diabetes* 10(1), 52–58 (2009).

■ **Meta-analysis on CSII use in children and adolescents.**

26 Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in Type 1 diabetes: a meta analysis. *Acta Diabetol.* 47(Suppl. 1), S77–S81 (2010).

27 Fatourechi MM, Yogish CK, Hassan Murad M, Elamin MB, Tabini CC. Clinical review: hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J. Clin. Endocrinol. Metab.* 94(3), 729–740 (2009).

28 Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet. Med.* 25(7), 765–774 (2008).

29 Aberle I, Scholz U, Bach-Kliegel B, Kliegel M. Psychological aspects in continuous subcutaneous insulin infusion: a retrospective study. *J. Psychol.* 143(2), 147–160 (2009).

30 Müller-Godeffroy E, Treichel S, Wagner VM; German Working Group for Paediatric Pump Therapy. Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus-a large-scale multicentre pilot study. *Diabet. Med.* 26(5), 493–501 (2009).

31 Wojciechowski P, Ryś P, Lipowska A, Gawęska M. Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in Type 1 diabetes: systematic review and meta-analysis. *Pol. Arch. Med. Wewn.* 121(10), 333–343 (2011).

32 Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in Type 1 diabetic patients: systematic review and meta-analysis of randomized trials. *Eur. J. Endocrinol.* 166(4), 567–574 (2012).

33 Pickup JS, Freeman SC, Sutton AJ. Glycaemic control in Type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 343, d3805 (2011).

- **Continuous glucose monitoring is compared with blood sugar measurements, with calculations of HbA1c reduction over time.**

34 Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and meta-analysis of randomized, controlled trials. *Am. J. Obstet. Gynecol.* 197(5), 447–456 (2007).

35 González-Romero S, González-Molero I, Fernández-Abellán M *et al.* Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with Type 1 diabetes. *Diabetes Technol. Ther.* 12(4), 263–269 (2010).

36 Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst. Rev.* 18(3), CD005542 (2007).

37 Frias JP, Bode BW, Bailey TS, Kipnes MS, Brunelle R, Edelman SV. A 16-week open-label, multicenter pilot study assessing insulin pump therapy in patients with Type 2 diabetes suboptimally controlled with multiple daily injections. *J. Diabetes Sci. Technol.* 5(4), 887–893 (2011).

- **Shows the importance of CSII use in Type 2 diabetes mellitus patients, reducing HbA1c and the total daily dose of insulin.**

38 Jankovec Z, Cechurova D, Krcma M, Lacigova S, Zourek M, Rusavy Z. The influence of insulin pump treatment on metabolic syndrome parameters in Type 2 diabetes mellitus. *Wien. Klin. Wochenschr.* 121(13–14), 459–463 (2009).

39 Molff-McDonagh P, Kaufman J, Foreman S, Wisotsky S, Wisotsky JA, Wexler C. Using insulin pump therapy in poorly controlled Type 2 diabetes. *Diab. Educator.* 36(4), 657–665 (2010).

40 Bode BW. Insulin pump use in Type 2 diabetes. *Diab. Technol. Ther.* 12(Suppl. 1), S17–S21 (2010).

- **Future development of insulin pumps for Type 2 diabetes mellitus patients is discussed.**

41 Hernandez-Diaz S, Adami HO. Diabetes therapy and cancer risk: causal effects and other plausible explanations. *Diabetologia* 53(5), 802–808 (2010).

42 Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F; European Society for Paediatric Endocrinology; Lawson Wilkins Pediatric Endocrine Society; International Society for Pediatric and Adolescent Diabetes; American Diabetes Association; European Association for the Study of Diabetes. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 30(6), 1653–1661 (2007).

43 Nimri R, Atlas E, Ajzensztejn M, Miller S, Oron T, Phillip M. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with Type 1 diabetes: the DREAM Project. *Diabetes Technol. Ther.* 14(8), 728–735 (2012).

44 Breton M, Farret A, Bruttomesso D *et al.*; The International Artificial Pancreas Study Group. Fully integrated artificial pancreas in Type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes* 61(9), 2230–2237 (2012).

45 Thabit H, Hovorka R. Closed-loop insulin delivery in Type 1 diabetes. *Endocrinol. Metab. Clin. North. Am.* 41(1), 105–117 (2012).

46 Kumareswaran K, Elleri D, Allen JM *et al.* Meta-analysis of overnight closed-loop randomized studies in children and adults with Type 1 diabetes: the Cambridge cohort. *J. Diabetes Sci. Technol.* 5(6), 1352–1362 (2011).

47 Cummins E, Royle P, Snaith A *et al.* Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health. Technol. Assess.* 14(11), iii–iv, xi–xvi, 1–181 (2010).

48 Heinemann L, Franc S, Phillip M *et al.* Reimbursement for continuous glucose monitoring: a European view. *J. Diabetes Sci. Technol.* 6(6), 1498–1502 (2012).