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Metabolic control and complications in Italian people with diabetes treated with continuous subcutaneous insulin infusion

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Diabetes mellitus

Abstract *Background and aim:* The objective of this cross-sectional study was to evaluate the degree of glycaemic control and the frequency of diabetic complications in Italian people with diabetes who were treated with continuous subcutaneous insulin infusion (CSII).
Methods and results: Questionnaires investigating the organisation of diabetes care centres, individuals' clinical and metabolic features and pump technology and its management were sent to adult and paediatric diabetes centres that use CSII for treatment in Italy. Information on standard clinical variables, demographic data and acute and chronic diabetic complications was derived from local clinical management systems. The sample consisted of 6623 people with diabetes, which was obtained from 93 centres. Of them, 98.8% had type 1 diabetes mellitus, 57.2% were female, 64% used a conventional insulin pump and 36% used a sensor-augmented insulin pump. The median glycated haemoglobin (HbA_{1c}) level was 60 mmol/mol (7.6%). The HbA_{1c} target (i.e. <58 mmol/mol for age <18 years and <53 mmol/mol for age >18 years) was achieved in 43.4% of paediatric and 23% of adult participants. Factors such as advanced pump functions, higher rate of sensor use, pregnancy in the year before the study and longer duration of diabetes were associated with lower HbA_{1c} levels.

The most common chronic complications occurring in diabetes were retinopathy, microalbuminuria and hypertension. In the year before the study, 5% of participants reported ≥1 episode of severe hypoglycaemic (SH) episodes (SH) and 2.6% reported ≥1 episode of ketoacidosis.
Conclusions: Advanced personal skills and use of sensor-based pump are associated with better metabolic control outcomes in Italian people with diabetes who were treated with CSII. The reduction in SH episodes confirms the positive effect of CSII on hypoglycaemia.
Clinical trial registration number: NCT 02620917 (ClinicalTrials.gov).

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Introduction

In the past 25 years, continuous subcutaneous insulin infusion (CSII) has become a viable alternative to multiple daily insulin injections (MDIs) in people with type 1 diabetes mellitus (T1DM). Meta-analyses of both randomised controlled trials (RCTs) and observational studies have found lower glycated haemoglobin (HbA_{1c}) level, less severe hypoglycaemic (SH) episodes and a better quality of life in people on CSII than those on MDI [1–3]. The limitations of these reviews, however, are the inclusion of MDI-treated individuals who do not use basal insulin analogue and CSII-treated individuals who use regular insulin. Recent studies comparing treatments with CSII and MDI along with insulin analogue showed less evident benefits for CSII [4,5].

A sensor-augmented insulin pump (SAP) is an insulin pump that has the feature of continuous glucose monitoring (CGM). RCTs have shown that SAPs improve metabolic control without increasing SH episodes in individuals with T1DM with elevated HbA_{1c} levels, and SAPs reduce the frequency and duration of hypoglycaemic events in individuals with satisfactory glucose control [6–8]. Recent studies have also suggested the protective role of CSII against chronic diabetic complications and cardiovascular mortality [9–13].

In 2013, we performed a survey on CSII in Italy and addressed the organisation of diabetes centres and care recipients and device characteristics [14]. Factors such as quality of glycaemic control and acute and chronic metabolic complications were not considered in that survey. In this study, we report a new survey to investigate metabolic control and diabetic complications in CSII-treated individuals in Italy.

Methods

Study design

In this multicentre cross-sectional study, data were collected using questionnaires sent by e-mail to adult and paediatric diabetes care centres that use CSII for treatment. Centres were identified from previous surveys and through information from companies selling CSII devices. Incomplete data were obtained by phone or e-mail and integrated.

Participants

Subjects treated with CSII for at least 1 year were consecutively enrolled among people who attended diabetes outpatient clinics between September 2015 and October 2016. Exclusion criteria were previous diagnosis of dementia or psychosis and pregnancy in progress. Before enrolment, informed consent was obtained from each participant. The study was approved by the ethical committee of each centre and registered on ClinicalTrials.gov (NCT 02620917). Procedures complied with the ethical standards of the institutional and national committees on human experimentation and with the Helsinki Declaration of 1975.

Measures

Information on standard clinical variables (i.e. serum HbA_{1c}, total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides and creatinine), demographic data (i.e. age, gender, type of diabetes, duration of diabetes, duration of treatment with CSII and body mass index) and presence of hypertension and chronic diabetic complications (i.e. retinopathy, nephropathy and vasculopathy [cerebral, cardiac and peripheral]) was derived from local clinical management systems. The mean HbA_{1c} level of participants from the year before the study was calculated. Information on pump characteristics, use of advanced pump functions (i.e. different bolus types, bolus calculator and temporary basal rates), days of sensor use and frequency of self-monitoring of blood glucose was obtained from insulin pumps or glucometers or recovered from CGM receivers and was reported in the questionnaire.

Participants were asked to record the number of SH episodes experienced during the year preceding enrolment in the study, and the frequency of episodes was expressed as the cumulative number of SH episodes per participant. For adult participants, an SH episode was defined as an event requiring assistance and the administration of carbohydrates (CHOs) or glucagon [15]. For paediatric participants, the SH episode referred to an event associated with coma, seizures or neurological symptoms requiring parenteral treatment. The number of diabetic ketoacidosis (DKA), defined as acidosis and hyperglycaemia, and the number of visits to the emergency room for acute metabolic complications of diabetes were collected from medical records. Information about the organisation of each centre included the number of people with T1DM, start of CSII treatment, team composition (physicians, nurses, dieticians and psychologists) and around-the-clock availability.

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR). Categorical data were compared between groups using the chi-square test, whereas

continuous data were compared between groups using the Mann–Whitney or Kruskal–Wallis test. All tests were two sided, and a p value less than 0.05 was considered to be significant. A linear mixed-effect regression model was used to identify the predictors of HbA_{1c} among clinically relevant variables (i.e. age, duration of diabetes, duration of CSII treatment, type of device, use of sensor-based treatment, CHO counting and use of advanced pump functions) that account for the centre's effects. The centre was included in the model as a random effect because participant outcomes were expected to differ from centre to centre, possibly owing to differences among centres instead of differences among participants who present at different centres. Statistical analysis was performed using R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) [16].

Results

Study participants and centres

Italy has 272 diabetes care centres that use CSII for treatment. Of them, 93 were included in the study – 21 offering paediatric care and 72 offering adult care – caring for 6623 patients.

In 41% of the adult care centres, the caring team composed of physician, dietician and nurse, whereas 71% of the paediatric centres had a team composed of physician, nurse, dietician and psychologist. Among the centres, 71% offering adult care and 86% offering paediatric care were available around the clock.

Demographic and clinical data are presented in Table 1. Most participants who received CSII treatment had T1DM (98.8%) and were older than 18 years. Compared to paediatric participants, adults had longer CSII use and were more frequently female, likely for pump use during pregnancy. Blood glucose levels were checked less often for adult participants than paediatric participants (median blood glucose tests per day: 5.0 [IQR = 4.0–5.0] vs 6.1 [IQR = 6.0–7.0]; $p < 0.05$).

Chronic complications of diabetes (i.e. retinopathy and microalbuminuria) and hypertension were more prevalent among adult participants (Supplementary Table 1). Total cholesterol, HDL-cholesterol, triglycerides and creatinine were in the normal range across the different age groups (Supplementary Table 2).

Use of devices

Irrespective of age, 4263 (64.3%) participants used a conventional insulin pump and 2360 (35.7%) of them used a pump with an associated or integrated CGM system (SAP).

Among participants who used a SAP, a glucose sensor was used, on average, 15 days per month (IQR = 7–24); 785 participants (33.2%) used the sensor less than 10 days per month, 739 (31.3%) of them used 10–19 days per month and 836 (35.5%) of them used 20 or more days per month. The rate of sensor use was higher in subjects less than 18 years of age (Table 1), with the highest rate among participants 0–5 years old (median: 30 days per month [IQR = 25.0–30.0]).

Table 1 Clinical characteristics of study participants.

Variable	Total	<18 years	≥18 years
Number of participants	6623	1025	5598
Type of diabetes:			
type 1	6543 (98.8)	1025 (100)	5518 (98.6)
type 2	80 (1.2)	0 (0)	80 (1.4)
Age, years[a]	37 (22–49)	14 (11–16)	41 (29–51)
Sex:			
Male	2796 (42.2)	497 (48.5)	2299 (41.1)*
Female	3827 (57.8)	528 (51.5)	3299 (58.9)
Duration of diabetes, years[a]	16 (9–26)	5 (3–8)	19 (12–28)*
Duration of diabetes at CSII start, years[a]	10 (4–19)	2 (1–4)	12 (6–21)*
Duration of CSII, years[a]	5 (2–8)	2 (1–4)	5 (3–8)*
Blood glucose tests, n/day[a]	5.2 (4.0–6.0)	6.1 (6.0–7.0)	5.0 (4.0–6.0)**
Type of device:[b]			
CSII	4206 (64.1)	606 (59.1)	3600 (65.0)***
SAP	2360 (35.9)	419 (40.9)	1941 (35.0)
SAP: sensor use, days/month[a,c]	15 (7–24)	21 (10–30)	15 (7–21)*

Data are presented as n (%) or [a]median (IQR), where appropriate.
Data not available for. [b]57 patients and. [c]84 patients.
*$p < 0.0001$ for <18 years.
**$p < 0.05$ for <18 years.
***$p < 0.0005$ for <18 years.

Most participants, whether paediatric or adult, utilized the advantages of advanced pump features: 81.2% of participants used temporary basal, 82.2% used bolus options, 56.5% used the bolus calculator and 75.9% used CHO counting. The prevalence was greater among participants who used SAPs than among those who used a conventional pump (temporary basal: 84.2% vs 79.1%, $p < 0.0001$; bolus options: 89.2% vs 77.8%, $p < 0.0001$; bolus calculator: 72.5% vs 64.3%, $p < 0.0001$; and CHO counting: 81.8% vs 72.2%, $p < 0.0001$).

Metabolic control

Median HbA_{1c} during the year before enrolment in the study was 60.0 mmol/mol (7.6%) and tended to be lower in participants aged 6–12 years (Supplementary Table 2). Male participants had lower HbA_{1c} than female participants (58.5 [IQR = 53.0–67.0] mmol/mol or 7.5% [IQR 7.1%–8.3%] vs 60.0 [IQR = 54.0–68.0] mmol/mol or 7.6% [IQR = 7.1%–8.4%]; $p < 0.05$).

The median HbA_{1c} level was less than 53.0 mmol/mol (7.0%) in 23.0% of participants and less than 58.0 mmol/mol (7.5%) in 42.0% of participants (Fig. 1). Considering that the target HbA_{1c} level varies between children and adults, a target of <58.0 mmol/mol (7.5%) was achieved in 43.4% of participants below 18 years of age, whereas only 23.0% of adults met the target of <53.0 mmol/mol (7%).

Annual levels of HbA_{1c} were lower in 217 women who became pregnant in the year before data collection than the levels of the remaining 3610 female participants (51.0 [IQR = 45.0–51.0] mmol/mol or 6.8% [IQR = 6.3%–6.8%]

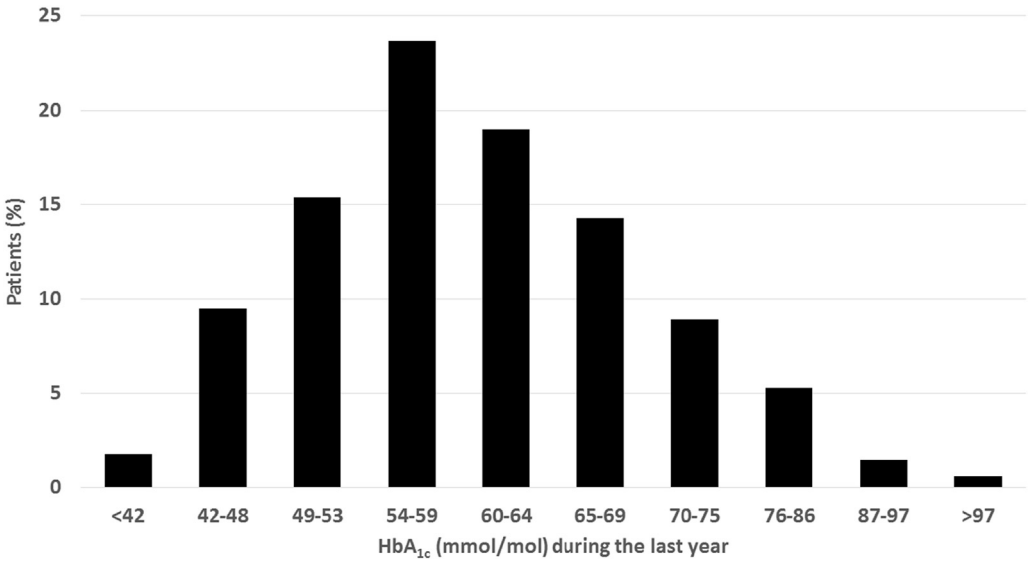

Figure 1 Distribution of mean glycated haemoglobin levels during the year before the study among 6623 Italian individuals treated with continuous subcutaneous insulin infusion.

vs 60.0 [IQR 54.0–68.0] mmol/mol or 7.6% [IQR = 7.1%–8.4%]; $p < 0.0001$).

CHO counting and use of advanced pump functions were associated with lower HbA_{1c} levels (Fig. 2). Participants who used SAP had a lower HbA_{1c} level than those who used the conventional pump (58.0 [IQR = 52.0–66.0] mmol/mol or 7.5% [IQR = 6.9%–8.2%] vs 60.0 [IQR = 54.0–67.0] mmol/mol or 7.6% [IQR = 7.1%–8.3%]; $p < 0.0001$). In addition, participants who used a sensor more than 20 days per month had a lower HbA_{1c} level than those who used it less than 20 days per month (58.0 [IQR = 51.0–65.0] mmol/mol or 7.5% [IQR = 6.8%–8.1%] vs 59.0 [IQR = 53.0–66.0] mmol/mol or 7.6% [IQR = 7.0%–8.2%]; $p = 0.0008$).

The HbA_{1c} level was lower in adult and paediatric participants who were monitored by a team composed of physician, nurse, dietician and psychologist than in those monitored without a psychologist (58.5 [IQR = 53.0–66.0] mmol/mol or 7.5% [IQR = 7%–8.2%] vs 60.0 [IQR = 54.0–68.5] mmol/mol or 7.6% (IQR = 7.1%–8.4%], $p < 0.0001$). The results of the multivariable analysis revealed that longer duration of diabetes ($\beta = -0.04$; 95% C.I. = −0.09 to −0.01), SAP use ($\beta = -1.47$; 95% C.I. = −2.43 to −0.51), sensor use ($\beta = -0.09$; 95% C.I. = −0.13 to −0.04), bolus option ($\beta = -1.76$; 95% C.I. = −2.90 to −0.63) and CHO counting ($\beta = -2.66$; 95% C.I. = −3.83 to −1.49) were associated with lower HbA_{1c} levels (Table 2). The effect of using a bolus calculator on HbA_{1c} levels was nearly statistically significant ($\beta = -1.02$; 95% C.I. = −2.09 to 0.06).

Acute complications

Concerning metabolic emergencies in the previous year, 5.0% of participants at least one SH episode, 2.6% reported an episode of ketoacidosis and 3.5% reported a visit to the emergency room for either reason.

SH episodes occurred in 52 of 533 participants with cardiovascular disease and in 243 of 5471 participants without cardiovascular disease (9.8% vs 4.4%, $p < 0.0001$).

They also occurred more frequently in adults than in participants aged less than 18 years (5.6% vs 2.1%, $p < 0.0001$), especially among those more than 50 years old (6.1%). Most participants who reported SH episodes (200 of 337; 59.3%) experienced one episode per year, although 63 participants (18.7% among participants with SH episodes and 0.9% overall) experienced three or more episodes per year.

Adult participants with HbA_{1c} levels <48.0 mmol/mol (6.5%) had significantly more SH episodes per year than those with levels ≥48.0 mmol/mol (6.5%) (0.17 vs 0.10, respectively; $p < 0.05$). No such differences emerged among paediatric participants. SH episodes were more frequent in participants who used CGM than those who did not use (7.3% vs 3.9%, $p < 0.0001$).

Occurrence of ketoacidosis differed across age groups: 12.1% among participants 0–5 years old, 2.0% among those 6–12 years old, 4.1% among those 13–17 years old, 2.6% among those 18–50 years old and 1.8% among those older than 50 years ($p = 0.0003$). HbA_{1c} level was 64.0 (IQR = 57.0–75.0) mmol/mol or 8.0% (IQR = 7.4%–9.0%) among participants who experienced episodes of ketoacidosis and 60.0 (IQR = 53.0–67.0) mmol/mol or 7.6% (IQR = 7.0%–8.4%) among those who did not ($p < 0.0001$).

Discussion

We analysed metabolic control and acute and chronic diabetic complications in a cohort of Italian paediatric and adult individuals with diabetes mellitus who were treated with CSII. Participants belonged to 16 of the 19 regions of Italy.

We found that 43% of paediatric and 23% of adult individuals achieved age-specific HbA_{1c} targets. Concerning

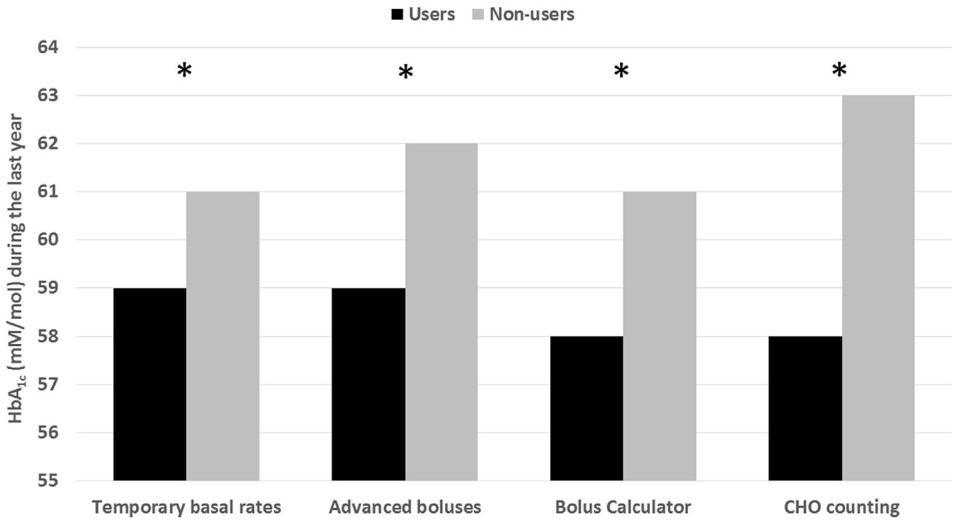

Figure 2 Median glycated haemoglobin levels during the year before the study according to the use of advanced pump functions and CHO counting (*$p < 0.0001$). Non-users of the bolus calculator include only participants who count carbohydrates.

adults, our data agree with the US T1D Exchange clinic registry, but considering the paediatric population, the fraction on target in Italy is almost twofold than that in the United States [17]. The difference in treatment between adults and younger people could have different reasons. Adults could be started on CSII with higher HbA_{1c} level compared to paediatric individuals, who began CSII mostly to improve their quality of life. Alternatively, paediatric individuals could be benefitted from a more complete caring time or a better use of new technologies.

CGM use in Italy covers only 16 days per month, and our questionnaire did not specifically investigate the reasons for suboptimal CGM. We speculate that the limited coverage may stem from the fact that the national healthcare system does not completely cover sensor costs. Moreover, because CGM technology is relatively novel, training in its use could be insufficient. Interestingly, in contrast to other studies addressing CGM, the rate of sensor use in our population was greater in the paediatric section, especially below the age of 12 years, a finding likely due to parents' motivation and active role in diabetes management. Conversely, the rate of sensor use among participants aged 12–17 years was very low (15 days per month). In any case, our data indicate that CGM use is associated with a significantly lower HbA_{1c} level and confirm existing evidence that the benefit of CGM relates to the frequency of its use [18]. In this study, SH episodes (0.1 episodes per participant per year) were few compared to both real-world data and data from RCTs (Refs. [17] and [19–21], respectively). In our sample, the frequency of SH episodes was greater among participants using a glucose sensor. A possible explanation is that CGM is recommended for persons with disabling hypoglycaemia despite optimal CSII use. Pumps with a low-glucose suspend (LGS) or predictive low-glucose suspend (PLGS) system can be expected to reduce further the risk of SH episodes. However, although 35.9% of participants used SAP therapy, we do not know which type of instrument they used (i.e. with or without an LGS or PLGS function), and thus, we cannot speculate further about this point.

Table 2 Multivariable analysis of HbA_{1c}.

	Regression coefficient (with 95% C.I.)	p value
Age, years	−0.01 (−0.05 to 0.02)	0.33
Duration of diabetes, years	−0.05 (−0.09 to −0.01)	0.03
Duration of CSII, years	0.06 (−0.03 to 0.16)	0.19
Type of device: SAP vs CSII	−1.47 (−2.43 to −0.51)	0.003
Sensor use, days/month	−0.09 (−0.13 to −0.04)	0.0001
Temporary basal: yes vs no	−0.74 (−1.78 to 0.31)	0.17
Bolus options: yes vs no	−1.76 (−2.90 to −0.63)	0.002
CHO counting: yes vs no	−2.66 (−3.83 to −1.49)	<0.0001
Bolus calculator: yes vs no	−1.02 (−2.09 to 0.06)	0.06

The regression coefficients represent (i) the change in HbA_{1c} according to a change in 1 unit of the continuous predictor or (ii) the change in HbA_{1c} that is associated with the first category with regard to the second category of the binary predictor.

Adults with HbA_{1c} levels less than 48.0 mmol/mol (6.5%) exhibited significantly more SH episodes than those with HbA_{1c} levels greater than 48.0 mmol/mol, which confirms that tight glycaemic control increases the risk of hypoglycaemia. Among paediatric participants, no correlation emerged between SH episodes and HbA_{1c} levels, which confirms the results of a recent Italian multicentre study [22].

Participants who experienced SH episodes had diabetes for longer duration than those who had not experienced (20 years [IQR = 13–28] vs 15 years [IQR = 9–25]; $p < 0.0001$). An increase in the frequency of SH episodes with increased age and duration of diabetes was also observed in the US T1D Exchange clinic registry [17]. Increased hypoglycaemia unawareness or greater glucose variability could explain this finding.

Participants with cardiovascular disease had significantly more episodes of hypoglycaemia than those without cardiovascular disease. A possible explanation is that participants with cardiovascular complications were

older (57 [IQR = 48–65] years vs 35 [IQR = 22–46] years; $p < 0.0001$) and had diabetes for longer duration (31 [IQR = 20–40] years vs 15 [IQR = 9–24] years; $p < 0.0001$), which confirms the idea that individuals with diabetes and cardiovascular disease represent a particularly fragile subgroup with a greater propensity to exhibit metabolic derangement.

We found that DKA is a problem for some participants. Because the risk for DKA was higher in participants with HbA_{1c} levels greater than 64.0 mmol/mol (8.0%), poor compliance with diabetes treatment could have contributed to their increased risk for DKA.

The HbA_{1c} level was lower in participants who were monitored by a team comprising physician, nurse, dietician and psychologist than those who were monitored by a team without psychologist. However, the difference, albeit statistically significant, might not be clinically relevant. Complete diabetes care teams are associated with a superior use of technology, fewer dropouts, increased CGM and advanced bolus use [14], but many centres, especially the smallest ones, have a lack of personnel. In most adult care centres, teams have no psychologist, although psychological support is an important part of regular follow-up.

Our study had several limitations. First, only approximately 30.0% of the Italian diabetes care centres that use CSII participated. Our results, however, appear to be representative of the situation across the country because centre and patient characteristics were similar to those of a previous survey that reported data of 79.8% of Italian people with diabetes who were treated with CSII [14].

We did not have a reference group of individuals treated with MDI; nevertheless, a partial comparison is possible with AMD-Annals [23], which have reported routine clinical data of a network of diabetes clinics. In the last report concerning 28,000 individuals with T1DM (84.5% treated with MDI), the mean HbA_{1c} level was 65.0 ± 16.0 mmol/mol (8.1 ± 1.5%). Only 22.3% of MDI-treated individuals reached the HbA_{1c} target of less than 53.0 mmol/mol (7.0%), whereas 44.5% showed HbA_{1c} levels greater than 64.0 mmol/mol (8.0%) compared to 29.8% in our study.

Another major limitation of the study is that the number of SH episodes experienced during the year before enrolment was based on recall, which obviously implies inaccuracies, although most people with T1DM have a good recall of SH episodes over a 1-year period [24].

Finally, because the study was cross-sectional, no conclusions can be drawn about the effect of CSII on chronic diabetic complications [25].

Conclusions

We provide an overview of the metabolic control and frequency of acute complications of diabetes in Italian individuals treated with CSII. Mean HbA_{1c} levels were satisfactory, but only 43% of children and 23% of adults achieved their age-specific HbA_{1c} target levels. Better metabolic control was associated with CHO counting, use of advanced pump functions, compliance with sensor use, pregnancy in the year before the study and longer duration of diabetes. The low frequency of SH episodes confirms the positive effect on hypoglycaemia.

Contributor statement

All authors contributed substantially to the study design; data collection, analysis and interpretation; and manuscript writing and revision. All authors approved the publication of the final version of the manuscript. No author received any specific grant from funding agencies in the public, commercial or non-profit sectors for the research.

Conflict of interest

GL acted as advisory board member for Eli Lilly, Boheringer Ingelheim and Merck Sharp & Dohme and received speaker honorary from Novo Nordisk, Sanofi Aventis and Astrazeneca.

RB acted as advisory board member for Lifescan, Novo Nordisk, Roche and Eli Lilly and received speaker honoraria from Eli Lilly, Abbott, Sanofi Aventis, Theras, Medtronic and Ypsomed.

LB none.

VDB none.

AG none.

GG acted as advisory board member for Johnson & Johnson and Novo Nordisk and received speaker honoraria from Novo Nordisk, Medtronic and PharmExtracta.

DI none.

LL has received speaker fees from Astra Zeneca, Eli Lilly, Medtronic, Menarini, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi Aventis and Takeda and has provided advisory services to Astra Zeneca, Eli Lilly, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi Aventis and Takeda.

IR acted as advisory board member for Roche Diagnostics and received speaker honoraria from Eli Lilly, Roche Diagnostics and Menarini.

RS acted as advisory board member for Abbott and Eli Lilly and received speaker honoraria from Roche Diagnostics, Sanofi Aventis and Medtronic.

DB acted as advisory board member for Abbott and Novo Nordisk and received speaker honoraria from Eli Lilly, Lifescan, Roche Diagnostics and Sanofi Aventis.

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Appendix. Members of the Italian Study Group on Diffusion of CSII

All the following primary investigators and clinical centres, listed by region or city (affiliation), participated in this study:

Calabria.

Locri, F. Mammì and M. Bruzzese.

Campania.

Caserta, M.Schettino and M.G. Nuzzo; Cava dè Tirreni, V. Di Blasi, R. Fresa and C. Lambiase; Napoli, D. Iafusco, A. Zanfardino and S. Confetto; Napoli, L. Bozzetto, G. Annuzzi A. Alderisio and G.Riccardi; Napoli, S.Gentile, G.Marino and G.Guarino.

Emilia Romagna

Bologna, S. Zucchini and G. Maltoni; Cesena - Ravenna, T. Suprani and V. Graziani; Forlì, M. Nizzoli and S. Acquati; Modena: R.Cavani and S.Romano; Montecchio Emilia, M. Michelini and E. Manicardi; Parma, R. Bonadonna and A. Dei Cas; Parma, E. Dall'aglio and M. Papi; Piacenza, S. Riboni; Reggio Emilia, V. Manicardi and E. Manicardi; Reggio Emilia, E. Manicardi and V. Pugni; Reggio Emilia: A. Lasagni and M.E. Street; Scandiano, U. Pagliani and C. Rossi.

Friuli Venezia Giulia

Monfalcone, R. Assaloni, B. Brunato and C. Tortul; Pordenone, G. Zanette and P. Li Volsi; Udine, M. Zanatta; Udine, L. Tonutti, S. Agus and M.A. Pellegrini.

Lazio

Ceccano, P. Pozzilli and G. Beretta Anguissola; Latina, R. Buzzetti, C. Moretti C and G. Leto; Roma, P. Pozzilli, S. Manfrini and A.R. Maurizi; Roma, S. Leotta, M. Altomare, S. Abbruzzese, S. Carletti and C. Suraci; Roma, S. Filetti; Roma, M.L. Manca Bitti and S. Arcano; Roma, M.G. Cavallo and M. De Bernardinis; Roma, D. Pitocco, S.Caputo, A. Rizzi and A. Manto; Roma, R. Schiaffini, M. Cappa and D. Benevento; Roma, S. Frontoni and I. Malandrucco; Roma, S. Morano and T. Filardi; Roma, D. Lauro. M.A. Marini, E. Castaldo and D. Sabato; Terracina, F. Tuccinardi and E. Forte; Viterbo, C. Arnaldi.

Liguria

Genova, N. Minuto and G. d'Annunzio.

Lombardia

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Marche

San Benedetto del Tronto, M. Galetta and I. Meloncelli

Molise.

Campobasso, A. Aiello A and S. Di Vincenzo.

Piemonte

Alba e Bra, A. Nuzzi and E. Fraticelli; Alessandria, E.Ansaldi, M. Battezzati, M. Lombardi and M. Balbo; Alessandria, R. Lera and A. Secco; Cuneo, V.De Donno; Novara, F. Cadario and S. Savastio; Novara, C. Ponzani and G. Aimaretti; Torino, I. Rabbone, G. Ignaccolo, D. Tinti and F. Cerutti.

Puglia

Bari, F. Giorgino, F. Ortolani, E. Piccinno and O. Zecchino, Foggia, M.Cignarelli, O. Lamacchia and G. Picca; San Giovanni Rotondo, S. De Cosmo and A. Rauseo.

Sicilia.

Catania, L. Tomaselli, A. Tumminia and C. Egiziano; Marsala, A.M. Scarpitta and F. Maggio; Palermo, F. Cardella and R. Roppolo; Partinico, V. Provenzano, M. Fleres and A. Scorsone.

Toscana

Arezzo, A. Scatena; Carrara, G. Gregori; Livorno, S. Lucchesi and F. Gadducci; Livorno, S. Di Cianni Lucchesi and S. Pancani; Pisa, S. Del Prato, M. Aragona, I. Crisci and A. Calianno.

Trentino Alto Adige

Bolzano, B. Fattor and D. Crazzolara; Bolzano, P. Reinstadler and S. Longhi; Merano, G. Incelli and S. Rauch; Trento, T. Romanelli, M. Orrasch, V. Cauvin and R. Franceschi.

Umbria

Spoleto, C. Lalli.

Veneto.

Bassano del Grappa, A. Pianta and A. Marangoni; Belluno, C.N. Aricò; Castelfranco, N. Marin; Chioggia, N. Nogara; Cittadella, N. Simioni and A. Filippi; Conegliano, G.L. Gidoni Guarneri; Dolo-Mirano: M.L. Contin M.L. and A.P. Decata; Legnago, L. Bondesan; Montebelluna: L. Confortin and A. Coracina; Montecchio Maggiore, S. Lombardi and S. Costa; Padova, E.Cipponeri, R.Scotton, S.Galasso and F. Boscari; Portogruaro, M.S. Zanon and C .Vinci; Rovigo, G. Lisato; Venezia, L. Gottardo; Verona, E. Bonora, M. Trombetta, C. Negri and C. Brangani; Verona, C. Maffeis, A. Sabbion and M. Marigliano.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2017.12.001.

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