Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 1110–1117

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Long-term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: A 10-year retrospective controlled study

Antonio Alderisio, Lutgarda Bozzetto, Luca Franco, Gabriele Riccardi, Angela A. Rivellese, Giovanni Annuzzi*

Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

Received 22 March 2019; received in revised form 3 June 2019; accepted 13 June 2019
Handling Editor: A. Giaccari
Available online 20 June 2019

KEYWORDS
Body weight;
Obesity;
Type 1 diabetes;
HbA1c;
Insulin pump

Abstract *Background and aims:* Overweight/obesity is a clinical concern also in patients with Type 1 diabetes (T1DM). These patients' body weight may vary depending on whether treatment consists in continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI), as these treatments lead to different blood glucose control, insulin doses, and eating behaviors. We compared long-term body weight trajectories in persons with diabetes on CSII or MDI regimens.
Methods and results: Annual changes in body weight, HbA1c, and daily insulin doses over 6–10 years were retrospectively analyzed in T1DM adult patients on CSII (n = 90) or MDI (n = 90), strictly matched for sex, age, BMI, and diabetes duration. Mean follow-up was 9.1 ± 1.4 years. Body weight increased linearly (~0.5 kg per year) throughout the observation period (p = 0.001, repeated measures ANOVA) with no significant difference between the CSII and MDI cohorts (p = 0.74), in either normal-weight or overweight/obese patients. HbA1c over follow-up was lower with CSII than with MDI (p = 0.037), maintaining the initial reduction after starting pump therapy. Insulin doses over follow-up were stably lower than baseline (~20%) with CSII, while linearly increasing (~20% from baseline to the end of observation) with MDI (p = 0.002). Mean annual weight changes correlated directly with total insulin dose changes (r = 0.191; p = 0.011) and baseline HbA1c level (r = 0.267; p = 0.001), and inversely with HbA1c changes (−0.173; p = 0.021) and baseline age (r = −0.254; p = 0.001).
Conclusion: T1DM patients on CSII or MDI showed comparable body weight gain over a 10-year follow-up, despite improved glycemic control and decreased insulin doses with CSII.
© 2019 The Italian Society of Diabetology, the Italian Society for the Study of Atherosclerosis, the Italian Society of Human Nutrition, and the Department of Clinical Medicine and Surgery, Federico II University. Published by Elsevier B.V. All rights reserved.

Introduction

Poor glycemic control in patients with Type 1 Diabetes Mellitus (T1DM) leads to higher risk of diabetes complications [1,2]. Although intensive insulin therapy efficiently brings about better glycemic control, consequently slowing down the onset and progression of chronic complications, main issues in achieving blood glucose control are the greater risk of hypoglycemia and weight gain [1–3]. Overweight and obesity are an emerging issue also for patients with T1DM [4–9]. Increased weight gain has been reported as a side effect of intensified insulin therapy in pediatric T1DM patients.

* Corresponding author. Department of Clinical Medicine and Surgery, Federico II University, Via Pansini 5, 80131, Naples, Italy. Fax: +39 0817462311.
E-mail address: annuzzi@unina.it (G. Annuzzi).

https://doi.org/10.1016/j.numecd.2019.06.008
0939-4753/© 2019 The Italian Society of Diabetology, the Italian Society for the Study of Atherosclerosis, the Italian Society of Human Nutrition, and the Department of Clinical Medicine and Surgery, Federico II University. Published by Elsevier B.V. All rights reserved.

However, studies in this young population are complicated by the age- and gender-dependency of body mass index (BMI) [10,11]. Clinical evidence shows that obesity in T1DM patients is related to higher odds of presenting other cardiovascular risk factors, notably hypertension and dyslipidemia [12], and an increased risk of coronary heart disease [13].

Continuous subcutaneous insulin infusion (CSII) therapy has been associated with better glycemic control and lower rates of severe hypoglycemia events [14,15]. For a number of reasons, CSII might potentially influence body weight differently from multiple daily insulin injections (MDI). On the one hand, switching to CSII therapy leads to a reduction in total insulin doses [16], which may positively influence weight gain [17]. Similarly, the lower rate of hypoglycemia during CSII [15] results in a lower intake of carbohydrate/calories to correct hypoglycemia. On the other hand, the higher flexibility and grade of freedom attained with pump therapy could lead to unhealthy nutritional behaviors because of the easier access to extra insulin boluses. Moreover, better glycemic control would translate into less calories lost with glycosuria.

In a patient survey, although more patients reported a perceived weight gain rather than a loss with CSII, most experienced no change in weight [18]. In short-term studies, similar body weight changes have been reported in persons with diabetes on CSII or MDI regimens, as also observed in a Cochrane meta-analysis in 2010 [14] and a meta-analysis by Yeh et al. reporting on four studies of short duration (1 year or less) [19]. In a retrospective analysis of a large cohort of adults with type 1 diabetes on CSII, an increased body weight after a median observation of 5 years was evidenced [20].

The effects of CSII on body weight have been scantily studied and, to our knowledge, no long-term controlled data are available in adult T1DM patients.

Therefore, the aim of this retrospective study was to compare the long-term (6–10 years) body weight trajectories in a cohort of adult T1DM patients on insulin pump therapy with that of a cohort of patients on MDI therapy, matched for sex and baseline age, BMI, and diabetes duration. In these cohorts, we also analyzed the long-term changes in blood glucose control (HbA1c) and daily insulin doses.

Methods

Study population

Eligible subjects for this study were patients with T1DM aged 18 years or older, who attended the Diabetes Unit of the Federico II University Hospital, Naples. Ninety patients on CSII were included in the study provided they had started insulin pump therapy in our center and whose clinical data were available for at least 6 years after starting CSII regimen. The patients had started insulin pump therapy after a structured training period with an experienced team consisting of diabetes nurses, dietitians, and physicians. Main reasons to start insulin pump therapy were high glycemic variability, high rate of hypoglycemia events, hypoglycemia unawareness, and/or quality of life. Ninety patients on MDI regimen with four or more insulin injections per day whose clinical data were available for at least 6 years were selected for the study to best match the CSII group for age, sex, and baseline levels of diabetes duration, HbA1c, body weight, and BMI. These potential confounders were chosen to account for the covariates that predict receiving the insulin treatment type or changing body weight. No participant switched from injections to pump treatment or vice-versa during the follow-up.

Data collection

Data (body weight, HbA1c) were collected from the electronic database wherein data from the annual screening of diabetes complications were recorded or, when not available, from the hardcopy of the outpatient medical records (insulin doses). Data refer to an observation time ranging from 6 to 10 years during the period between 2002 and 2017. For the CSII cohort, baseline data were the most recent values prior to starting insulin pump regimen; for the MDI cohort, baseline data were the first values available in our records. When more than one value per year was available, their mean value was registered. For females, data during pregnancy were excluded. Patients signed an informed consent for the treatment of their data.

Measurements

Body weight was measured using a scale provided with a weighing bar, with a precision of 0.1 kg, according to standardized methods. Height was measured with a fixed stadiometer with patients barefoot, with shoulders at the stadiometer. Body mass index was calculated by the ratio between weight (kg) and squared height (m^2). Glycated hemoglobin was measured by high performance liquid chromatography (HPLC).

Statistical analysis

Data are expressed as mean $\pm$ SD unless otherwise stated. Differences in patient characteristics between the two groups were evaluated by t test for independent samples. Changes vs. baseline over follow-up were evaluated by two-way repeated-measures ANOVA where yearly data for body weight, HbA1c, and insulin doses were included as levels of the within-subject factor time, and CSII and MDI therapy were included as levels of the between-subject factor insulin therapy.

Spearman correlations were performed between mean annual changes (absolute change from previous year of observation) in body weight, HbA1c, and insulin doses, and time-independent variables as baseline age, duration of diabetes, BMI, HbA1c, and total insulin dose. A p value <0.05 was considered statistically significant. The statistical analysis was performed according to standard

methods using the Statistical Package for Social Sciences software, version 21 (SPSS/PC; SPSS. Chicago, IL, USA).

Results

Main baseline characteristics of the participants were not significantly different between the CSII and MDI cohorts, as shown in Table 1. In both groups, males and females were similarly represented, age ranged from 18 to 69 years and duration of diabetes from 1 to 51 years. BMI ranged from 17.2 to 33.2 kg/m^2; 60.6% had normal weight and 39.3% were overweight or obese. Baseline HbA1c ranged from 5.4% to 13%; the median HbA1c was 7.9% in both groups. The mean duration of follow-up for the whole study population was 9.1 ± 1.4 years, being 8.9 ± 1.4 vs. 9.2 ± 1.4 years, p = 0.139, for the CSII and the MDI groups, respectively.

Body weight trajectories

The absolute annual changes in body weight from baseline over the 10-year follow-up are shown in Fig. 1. Both patients in the CSII and MDI cohorts had a linear body weight gain through the follow-up period, with ≈0.5 kg mean year-over-year increase. The time course of body weight gain was not different between the two groups (p = 0.740, group × time by repeated measures ANOVA).

Weight changes were similar in the CSII and MDI groups in both patients who at baseline were normal-weight and in those who were overweight/obese (Fig. 1B, C). Weight gain was similar between the two groups independent of baseline blood glucose control, as observed in the patients who at baseline were below (<7.9%) or above (≥7.9%) the median HbA1c (p = 0.59 or p = 0.50 by repeated measures ANOVA, respectively). In both cohorts, body weight gain was independent of gender (p = 0.69 in the CSII group, p = 0.41 in the MDI group, by repeated measures ANOVA, data not shown).

HbA1c trajectories

The absolute changes in HbA1c from baseline over the 10-year follow-up are shown in Fig. 2. In the CSII cohort, HbA1c decreased significantly the first year after initiating pump therapy (7.6 ± 0.9% vs. 8.1 ± 1.2% at baseline, p < 0.001). The decreased HbA1c level was maintained rather constant over the following years of observation. In the MDI cohort, HbA1c level did not change significantly during the observation period. The mean change in HbA1c throughout the follow-up period was significantly different between the CSII and the MDI group (p = 0.037 group × time by repeated measures ANOVA).

HbA1c levels changed differently according to baseline blood glucose control. Among patients with worse baseline glucose control (HbA1c ≥ 7.9%), mean HbA1c levels over the whole follow-up period were significantly lower than at baseline in both groups, without statistically significant differences between CSII or MDI (p = 0.185 group x time by repeated measures ANOVA) (Fig. 2B). Among patients with better baseline glucose control (HbA1c <7.9%), mean HbA1c levels increased over follow-up significantly more in the MDI than in the CSII group (p = 0.048 by repeated measures ANOVA) (Fig. 2C).

Table 1 Main baseline characteristics of persons with Type 1 diabetes on insulin pump (CSII) or multiple daily injections (MDI) regimens participating in the retrospective study.

	CSII (n = 90)	MDI (n = 90)
Male/Female (n)	42/48	46/44
Age (years)	36.3 ± 10.7	37.3 ± 10.8
Body weight (kg)	67.4 ± 11.6	70.0 ± 12.0
Height (cm)	166 ± 9	169 ± 10
Body mass index (kg/m^2)	24.3 ± 3.0	24.7 ± 3.1
Diabetes duration (years)	16.6 ± 10.3	16.2 ± 9.9
HbA1c (%)	8.1 ± 1.2	8.0 ± 1.2
HbA1c (mmol/mol)	65 ± 13.1	64 ± 13.1
Daily insulin dose (IU)	45.0 ± 12.5	48.1 ± 17.1

Data are Mean ± Standard Deviation.

Insulin dose trajectories

Changes in total daily insulin doses from baseline throughout follow-up are shown in Fig. 3. Patients on CSII therapy experienced a significant reduction in total insulin doses the first year after initiating pump therapy (39.2 ± 11.2 IU vs. 44.9 ± 12.5 IU at baseline, p < 0.001), which was maintained all through the follow-up. On the contrary, patients in MDI therapy had a constant, significant increase in total insulin doses (∼20% increase from baseline to the end of observation). Mean changes in total daily insulin doses throughout the 10-year observation period were significantly lower with CSII than with MDI (p = 0.002 by repeated measures ANOVA).

The difference between the two groups concerned both basal and bolus insulin doses. Basal insulin doses were increased significantly in both CSII and MDI groups but insulin changes were significantly higher in the MDI group (p = 0.001, group × time by repeated measures ANOVA) (Fig. 3B). Bolus insulin doses significantly decreased during the first year of follow-up (17.2 ± 6.0 vs. 24.1 ± 9.4 IU, p < 0.001) and remained constantly lower than at baseline in the CSII group. On the contrary, there were no significant variations in bolus doses throughout the follow-up period for patients on MDI (p = 0.103) (Fig. 3C). Insulin bolus changes over follow-up were constantly lower in the CSII group than in the MDI group (p = 0.02).

Relationship between changes in body weight, HbA1c, and insulin doses

Correlation analyses were performed between the changes in weight and the changes in insulin dose and HbA1c, and baseline age and HbA1c. In the whole study population, mean annual weight changes correlated directly with total insulin dose changes (r = 0.191; p = 0.011) and baseline HbA1c level (r = 0.267; p = 0.001), and inversely with HbA1c changes (−0.173; p = 0.021) and baseline age

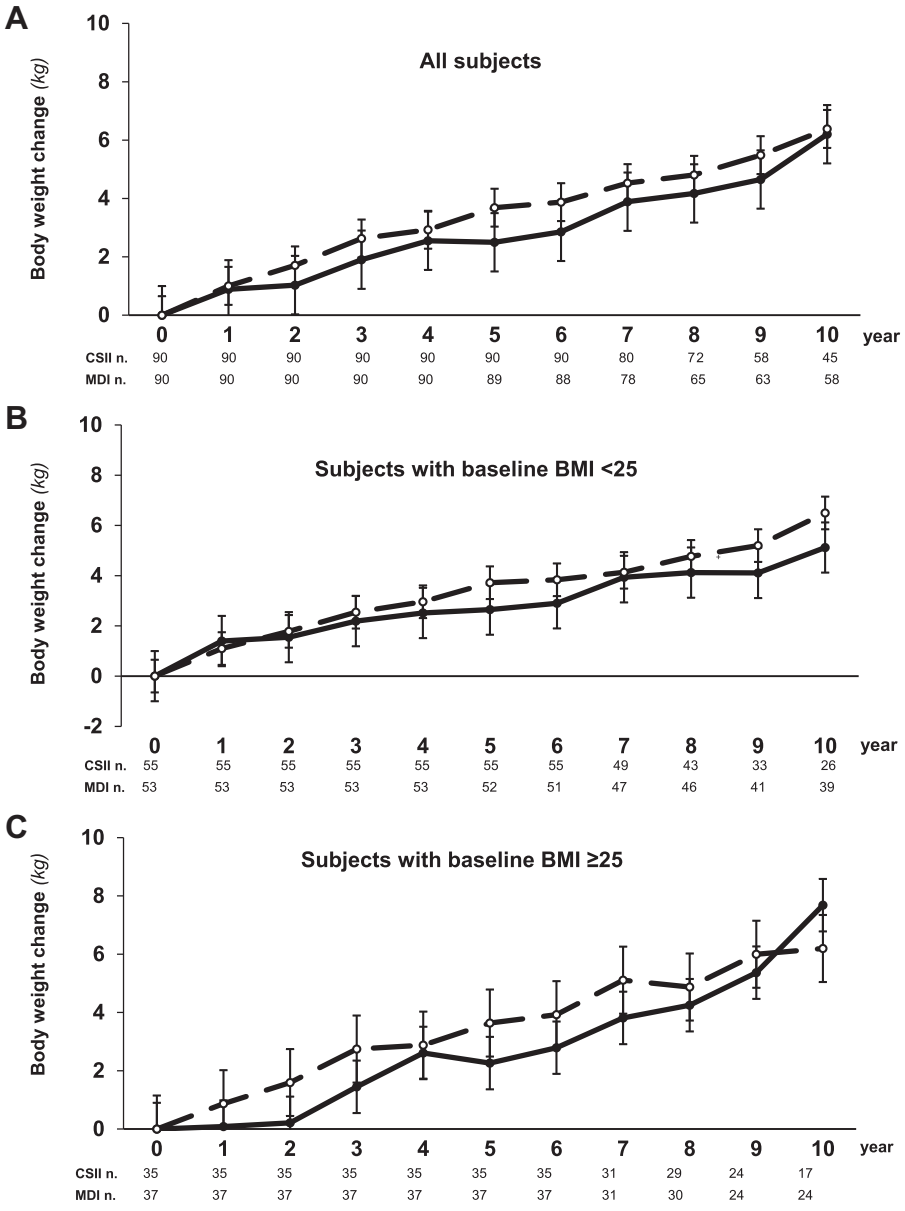

Figure 1 Absolute changes from baseline in body weight throughout the 10-year observation in Type 1 diabetes patients on insulin pump (**CSII: black circles, continuous line**) or multiple daily injections (**MDI: white circles, dashed line**), shown as whole cohorts **(A)** or divided by baseline BMI <25 kg/m^2 **(B)** or ≥ 25 kg/m^2 **(C)**. Data are Mean and SEM. **(A)** p = 0.740, **(B)** p = 0.59, **(C)** p = 0.50, group x time by repeated measures ANOVA.

(r = −0.254; p = 0.001). In the CSII cohort, weight changes were significantly associated directly with changes in insulin dose (r = 0.221, p = 0.037) and baseline HbA1c (r = 0.289, p = 0.006) and inversely with HbA1c changes (r = 0.271, p = 0.010). In the MDI cohort, weight changes were significantly associated directly with baseline HbA1c (r = 0.257, p = 0.014) and inversely with baseline age (r = −0.378, p < 0.001).

Discussion

This study shows that persons with T1DM on CSII or MDI regimens had a comparable progressive increase in body weight − averaging 0.5 kg per year over a 10-year observation time. This clinically significant increase was observed in patients who were either normal-weight or overweight/obese at baseline. The body weight gain observed in our study is in line with previous results in individuals with type 1 diabetes ranging from around 0.4 kg/year in an 18-year follow-up in USA [6], to 0.64 kg/year in a 5-year follow-up in patients on CSII in France [20]. Whether these trends in adult individuals with type 1 diabetes differ from those in the general population is difficult to ascertain from the few available data. International comparisons are challenging and differences in sampling and design make adequate comparisons difficult. In US cohorts of white men (n = 845) and white women (n = 907), the linear increase in body weight between 1985 and 2000 was attenuated between 2000 and 2010,

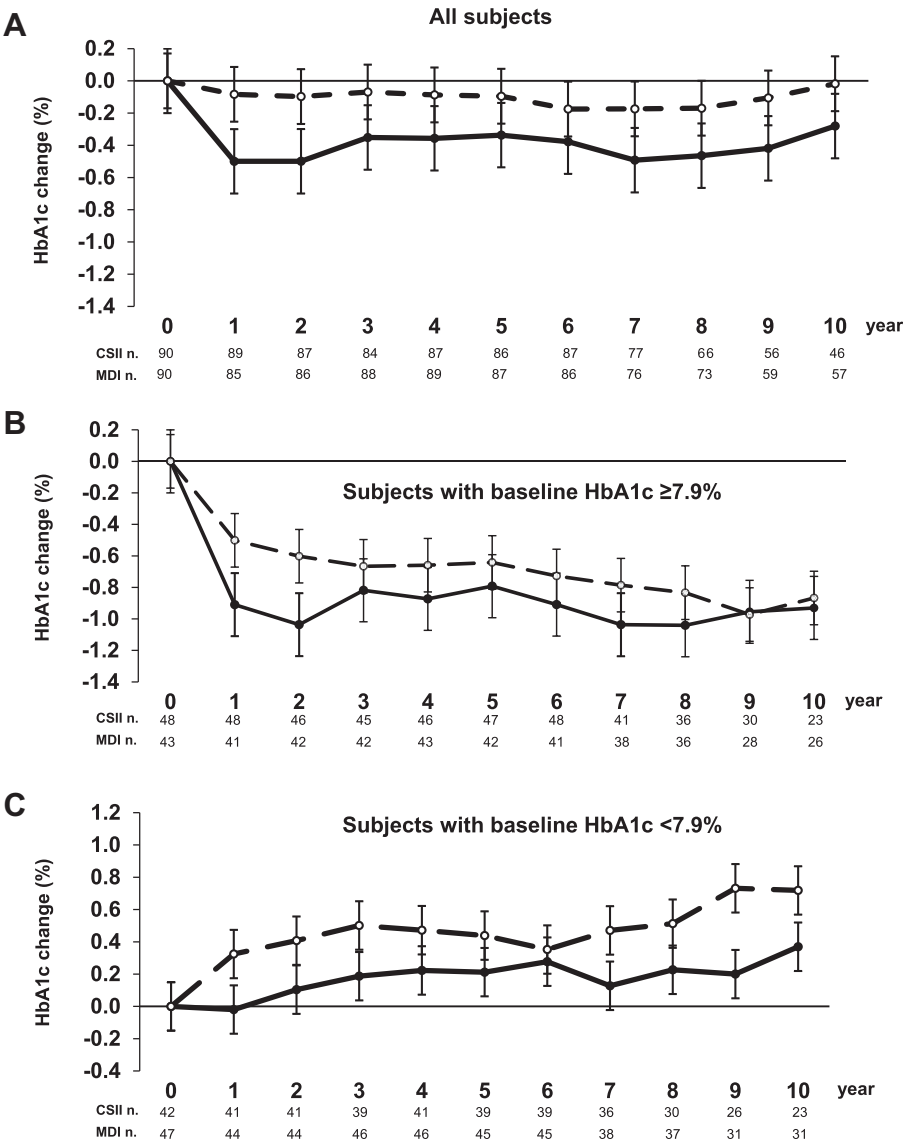

Figure 2 Absolute changes from baseline in HbA1c (%) during the 10-year observation in Type 1 diabetes patients on insulin pump (**CSII: black circles, continuous line**) or multiple daily injections (**MDI: white circles, dashed line**), shown as whole cohorts **(A)** or divided by baseline median HbA1c <7.9% **(B)** or ≥7.9% **(C)**. Data are Mean and SEM. (**A**) p = 0.037, (**B**) p = 0.185, (**C**) p = 0.048 group x time by repeated measures ANOVA.

the average increase being 0.56 kg/year in men and 0.55 kg/year in women [21]. In Italy, a survey of the CUORE Project [22] on different populations showed a body weight increase from 1998 to 2002 to 2008–2012 of 3.8 kg in men and 4.6 kg in women, corresponding to 0.38 and 0.46 kg/year, respectively.

Against the background of the increasing prevalence of overweight/obesity also in patients with T1DM, this study was performed envisaging that using CSII could help reduce this risk. Some characteristics of CSII therapy – including the reduced rate of hypoglycemia events [15], possibly leading to a lower intake of carbohydrate/calories for their correction, and the need for lower doses of insulin compared to MDI – were expected to favorably influence body changes. Indeed, in this study, while we have no information on the occurrence of hypoglycemia, we observed that total insulin doses were significantly lowered once pump therapy was started, and this decrease persisted over the whole follow-up period, at odds with the constant linear increase in the MDI cohort. Changes in total daily insulin dose during the observation period were positively associated with changes in body weight. This indicates that insulin dose is one of the factors contributing to weight gain and, therefore – at least for this factor – insulin pump therapy would be of advantage.

Independent of insulin dose, a better blood glucose control is associated with weight gain [1–3]. In our study, CSII therapy maintained over time the advantages of improving glycemic control compared with MDI. The significantly lower HbA1c in the CSII cohort over the 10-year follow-up period (on average 0.3%) was the result of a greater HbA1c reduction among the patients with worse glycemic control at baseline, but also of a smaller HbA1c increase among the patients with better glycemic control

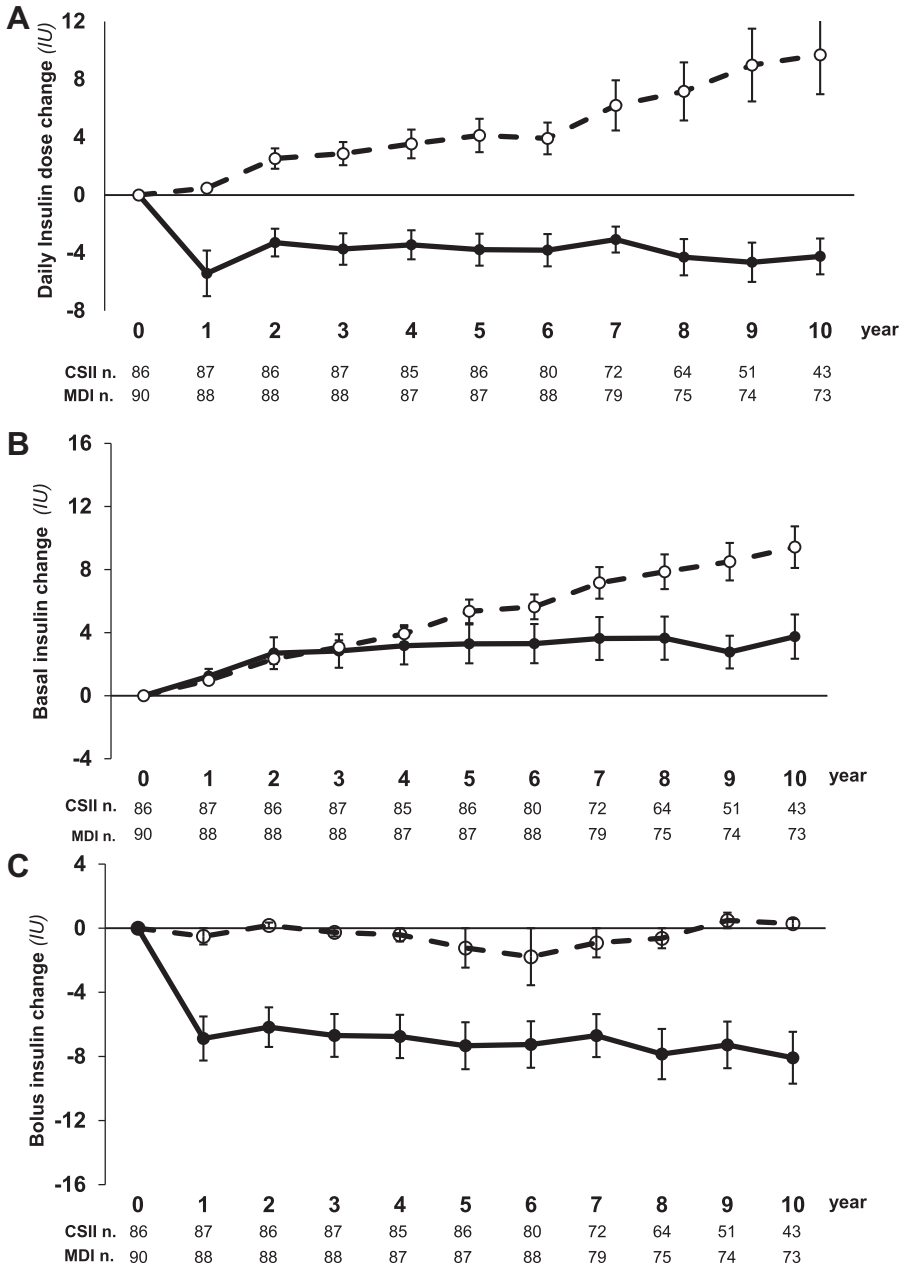

Figure 3 Absolute changes from baseline in daily insulin doses during the 10-year observation in Type 1 diabetes patients on insulin pump (**CSII: black circles, continuous line**) or multiple daily injections (**MDI: white circles, dashed line**), shown as daily total **(A)**, basal **(B)**, or bolus **(C)** insulin dose. Data are Mean and SEM. **(A)** $p = 0.002$, **(B)** $p = 0.001$, **(C)** $p = 0.103$ group x time by repeated measures ANOVA.

at baseline (Fig. 2). Only in the CSII cohort was mean change in body weight during follow-up inversely correlated with mean change in HbA1c and directly with baseline HbA1c. This may indicate that by improving overall blood glucose control insulin pump therapy favored weight gain.

Body weight gain was inversely associated with patients' ages at the beginning of the observation. This relation, observed in the whole study population although more significant in the MDI cohort, suggests that T1DM patients may became more stable as they get older and that therefore younger patients may be a more suitable target for the prevention of weight gain.

The results of this study show that, although the long-term body weight trajectories were similar between CSII and MDI cohorts, the factors influencing weight changes likely differed between the two cohorts.

This study has several strengths, the first being the long follow-up period. Secondly, the data refer to a single diabetes care center, which implies that a similar quality of care, provided by the same team, was offered to all participants. Although the retrospective design of the study is a limitation, the strict matching for relevant variables reduces the potential role of clinical confounders.

A limitation of this study is the lack of information on the number and severity of hypoglycemic events, as these

data were not recorded in a usable, standardized way. This prevented the evaluation of the possible role of hypoglycemia and consequent carbohydrate/calorie intake on weight changes. An additional limitation is the lack of information on nutritional habits and physical activity. Moreover, insulin doses refer to those prescribed to patients and recorded in their medical files and, therefore, the number of boluses may have been underestimated, in particular in patients on CSII.

Only few of the participants in the CSII cohort were on an integrated system or Sensor augmented pump (SAP) treatment, especially in the first observation period. Therefore, the results may differ with patients using a more advanced system, because of a potentially much smaller number of hypoglycemic episodes and better glycemic control achievable with these more recent treatment modalities [23,24].

In conclusion, to the best of our knowledge, this is the first observational study with a long follow-up analyzing body weight trajectories in adult patients with type 1 diabetes on CSII or MDI therapy, well matched for baseline variables potentially influencing weight changes. The results show a clinically relevant weight gain over time in these patients. At odds with some expectations, the sole use of CSII therapy seems insufficient to counteract the general trend towards a progressive increase in body weight in T1DM patients, despite the lower insulin doses and better glycemic control. More information is needed to identify and correct the factors determining the weight increase in this population. In the meantime, education on nutrition and physical activity remains an essential feature in these patients, also when on insulin pump therapy, in order to counter the development of overweight/obesity and prevent their unfavorable health effects.

Author disclosure statement

No competing financial interests exist.

Author contributions

A.A. designed the experiment, researched the data and wrote the manuscript. L.B. and L.F. researched the data and reviewed the manuscript. G.R. contributed to the discussion, and reviewed and edited the manuscript. A.A.R. contributed to the discussion, and reviewed and edited the manuscript. G.A. designed the experiment and wrote the manuscript. G.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

[1] Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–86.

[2] Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, 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 2009;169(14):1307–16.

[3] Swedish Council on Health Technology Assessment. Intensive glucose-lowering therapy in diabetes: a systematic review. Stockholm: Swedish Council on Health Technology Assessment (SBU); 2009 Dec.

[4] Bae JP, Lage MJ, Mo D, Nelson DR, Hoogwerf BJ. Obesity and glycemic control in patients with diabetes mellitus: analysis of physician electronic health records in the US from 2009–2011. J Diabet Complicat 2016;30(2):212–20.

[5] Baskaran C, Volkening LK, Diaz M, Laffel LM. A decade of temporal trends in overweight/obesity in youth with type 1 diabetes after the Diabetes Control and Complications Trial. Pediatr Diabetes 2015;16(4):263–70.

[6] Conway B, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW, et al. Temporal patterns in overweight and obesity in type 1 diabetes. Diabet Med 2010;27(4):398–404.

[7] Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, et al. SEARCH for diabetes in youth study group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for diabetes in youth study. Pediatr Diabetes 2010;11(1):4–11.

[8] DuBose SN, Hermann JM, Tamborlane WV, Beck RW, Dost A, DiMeglio LA, et al. Type 1 diabetes exchange clinic network and diabetes prospective follow-up registry. Obesity in youth with type 1 diabetes in Germany, Austria, and the United States. J Pediatr 2015;167(3):627–32.

[9] Minges KE, Whittemore R, Weinzimer SA, Irwin ML, Redeker NS, Grey M. Correlates of overweight and obesity in 5529 adolescents with type 1 diabetes: the T1D Exchange Clinic Registry. Diabetes Res Clin Pract 2017;126:68–78.

[10] Fröhlich-Reiterer EE, Rosenbauer J, Bechtold-Dalla Pozza S, Hofer SE, Schober E, Holl RW. DPV-Wiss Study Group and German BMBF Competence Networks Diabetes mellitus and Obesity. Predictors of increasing BMI during the course of diabetes in children and adolescents with type 1 diabetes: data from the German/Austrian DPV multicentre survey. Arch Dis Child 2014;99(8):738–43.

[11] De Keukelaere M, Fieuws S, Reynaert N, Vandoorne E, Kerckhove KV, Asscherickx W, et al. Evolution of body mass index in children with type 1 diabetes mellitus. Eur J Pediatr 2018;177(11):1661–6.

[12] Redondo MJ, Foster NC, Libman IM, Mehta SN, Hathway JM, Bethin KE, et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. Acta Diabetol 2016;53(2):271–7.

[13] Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, et al. EURODIAB prospective complications study group. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB prospective complications study. Diabetes Care 2004;27(2):530–7.

[14] 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 2010 Jan 20;(1):CD005103.

[15] 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 2008;25(7):765–74.

[16] Chico A, Tundidor D, Jordana L, Saigi I, Maria MA, Corcoy R, et al. Changes in insulin requirements from the onset of continuous subcutaneous insulin infusion (CSII) until optimization of glycemic control. J Diabetes Sci Technol 2014;8(2):371–7.

[17] Mehta SN, Andersen HU, Abrahamson MJ, Wolpert HA, Hommel EE, McMullen W, et al. Changes in HbA1c and weight following transition to continuous subcutaneous insulin infusion therapy in adults with type 1 diabetes. J Diabetes Sci Technol 2017;11(1):83–6.

[18] Pickup JC, Yemane N, Brackenridge A, Pender S. Nonmetabolic complications of continuous subcutaneous insulin infusion: a patient survey. Diabetes Technol Ther 2014;16(3):145–9.

[19] Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012 Sep 4;157(5):336–47.

[20] Joubert M, Morera J, Vicente A, Rod A, Parienti JJ, Reznik Y. Cross-sectional survey and retrospective analysis of a large cohort of adults with type 1 diabetes with long-term continuous subcutaneous insulin infusion treatment. J Diabetes Sci Technol 2014 Sep;8(5):1005–10.

[21] Dutton GR, Kim Y, Jacobs JrJr, Li X, Loria CM, Reis JP, et al. 25-year weight gain in a racially balanced sample of U.S. adults: the CARDIA study. Obesity (Silver Spring) 2016 Sep;24(9):1962–8.

[22] Health Examination Survey. CUORE Project, National Institute of Health. http://www.cuore.iss.it/fattori/CuoreData.asp. Downloaded on 3 June 2019.

[23] Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, et al. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. Diabetes Care 2018;41(2):303–10.

[24] Forlenza GP, Li Z, Buckingham BA, Pinsker JE, Cengiz E, Wadwa RP, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care 2018 Oct;41(10):2155–61.