CHAPTER 4

A long-term comparison between continuous intraperitoneal insulin infusion and sub-cutaneous insulin therapy among patients with poorly controlled T1DM: a 7 year case-control study

PUBLISHED AS

Van Dijk PR, Logtenberg SJ, Groenier KH, Gans RO, Bilo HJ, Kleefstra N.
Report of a 7 year case-control study of continuous intra-peritoneal insulin infusion and subcutaneous insulin therapy among patients with poorly controlled type 1 diabetes mellitus: favourable effects on hypoglycaemic episodes. Diabetes Res Clin Pract 2014

Abstract

INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) is a last-resort treatment option for patients with type 1 diabetes mellitus (T1DM) who fail to reach adequate glycaemic control with subcutaneous (SC) insulin therapy. Aim of the present study was to compare the long-term effects of CIPII and SC insulin therapy among patients with T1DM in poor glycaemic control.

PATIENTS AND METHODS

Patients in which CIPII was initiated in 2006 were compared with a control group of T1DM patients who continued SC therapy. Linear mixed models were used to calculate differences between the baseline (2006) and final (2013) measurements within and between groups.

RESULTS

A total of 95 patients of which 21 were using CIPII and 74 using SC insulin were included. Within the CIPII group, the number of hypoglycaemic episodes decreased with -5 (95% confidence interval (CI) -8, -3) per 2 weeks while it remained stable among SC patients. Over time, only the number of hypoglycaemic episodes decreased more with CIPII as compared to SC insulin treatment (difference: -6 (95% CI -9, -4)). There were no differences between treatment groups regarding HbA1c, clinical parameters and quality of life scores over time. Pump or catheter dysfunction led to ketoacidosis in 6 patients: 2 using CIPII and 4 using SC insulin therapy.

CONCLUSIONS

After 7 years of follow-up, there is a persistent decline of hypoglycaemic events among CIPII treated T1DM patients. Besides less hypoglycaemic episodes with CIPII therapy, there are no differences between long-term CIPII and SC insulin therapy.

Introduction

The mainstay of type 1 diabetes mellitus (T1DM) treatment consists of subcutaneous (SC) insulin administration using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with an external pump. Although most patients achieve acceptable glycaemic control using MDI or CSII, a relatively small group of patients fails to reach adequate glycaemic control, have high blood glucose variability, frequent hypoglycaemic episodes (often with hypoglycaemia unawareness) or SC insulin resistance, despite intensive SC insulin therapy.

One alternative treatment option for this group of patients is continuous intraperitoneal insulin infusion (CIPII) using an implanted pump. With CIPII the SC compartment is bypassed and the physiological route of insulin is largely mimicked as intraperitoneally administered insulin diffuses predominantly through the portal vein flow bed, which results in higher hepatic insulin uptake, alleviation of peripheral plasma insulin concentrations and a more rapid and predictable insulin action [1–4].

The 3 randomized clinical studies that compared CIPII with SC insulin treatment in T1DM patients reported improved glycaemic control without an increase in hypoglycaemic episodes [5–7]. In addition, quality of life (QoL) and treatment satisfaction improved during CIPII treatment [8]. However, the duration of these studies was rather short (6 months) and available long-term observational studies lack a control group of patients treated with SC therapy [9,10].

In order to compare the long-term effects of CIPII and SC insulin administration, we performed a case-control study among patients with T1DM and poor glycaemic control.

Patients and methods

STUDY DESIGN

This is a retrospective case-control study in the period 2006 to 2013 performed in a single centre (Isala, Zwolle, the Netherlands). In the present study, cases and controls were derived from 2 different cohorts of T1DM patients. Cases, using CIPII therapy, were derived from a cohort which initiated CIPII therapy in 2006 and controls, using SC insulin therapy, were selected from another T1DM cohort in the Isala.

STUDY POPULATION

Cases were derived from a previous randomized, cross-over study in 2006 in which CIPII was initiated [5]. Primary aim of that 16-month study was to investigate the effects of CIPII compared to intensive SC insulin treatment. In brief, patients with T1DM in poor glycaemic control, defined as HbA1c ≥7.5% (58 mmol/mol) and/or ≥5 incidents of hypoglycaemia (<4.0 mmol/l) per week, who were aged 18-70 years and treated with SC insulin, were included.

Control patients were selected from a prospective T1DM cohort study, initiated in 1995 at the Isala. The full study design has been published in detail previously [11]. In brief, from 1995 onwards all patients were examined (both physical and biochemical) annually at the same diabetes outpatient clinic and completed questionnaires, all according to standardized protocol. Patients were selected as controls for the present study if (1) they would have been eligible to participate in the 2006 cross-over study according to abovementioned criteria but (2) did not participate and instead continued SC insulin (both MDI and CSII) treatment over time and (3) completed participation in the prospective cohort study from 2006 until 2013.

Exclusion criteria were identical for cases and controls and included: impaired renal function (plasma creatinine ≥150 µmol/l or estimated glomerular filtration rate ≤50ml/min/1,73m^2), cardiac problems (unstable angina or myocardial infarction within the previous 12 months or New York Heart Association class III or IV congestive heart failure), cognitive dysfunction, current or past psychiatric treatment for schizophrenia, cognitive or bipolar disorder, current use or oral corticosteroids or suffering from a condition which necessitated oral or systemic corticosteroids use more than once in the previous 12 months, substance abuse other than nicotine, current pregnancy or plans to become pregnant during the trial and plans to engage in activities that require going >25 feet below sea level [5,8].

After completion of the 2006 cross-over study all CIPII treated patients chose to continue with CIPII. Between 2006 and 2013, all patients received standard care at our outpatient clinic which consisted of insulin refills every 6-12 weeks and an rinse procedure with NaOH was performed every 9 months or in case of insulin underdelivery. Insulin (U-400 HOE 21PH, semi synthetic human insulin of porcine origin, trade name: Insuplant® Hoechst, Frankfurt, Germany, nowadays Sanofi-Aventis) was administered with the implantable pump. Since there were no batches left of the U400 semi synthetic human insulin, a new human recombinant insulin (400 IU/ml; human insulin of E. Coli origin, trade name: Insuman Implantable®, Sanofi-Aventis) was used from 2010 onwards. Details about the implantable pump and CIPII treatment (e.g. insulin dosage and refill procedures) have been described in detail previously [12,13].

MEASUREMENTS

For cases, measurements prior to pump implantation were used as baseline measurements and the last available measurements in 2013 were used as final measurements. For controls, the measurements during the annual check-up at the outpatient clinic in 2006 were used as baseline measurements and the last available measurements in 2013 were used as final measurements.

Clinical and biochemical parameters were collected from standardized electronic patient charts and included: smoking (no or ever/current) and alcohol (yes/no) habits, married/cohabiting (yes/no), date of diagnosis of diabetes, presence of microvascular- (nephropathy, neuropathy or retinopathy) or macrovascular complications (angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, stroke, transient ischaemic attack, peripheral artery disease), body mass index (BMI), daily insulin dose, number of self-reported hypoglycaemic events <4.0 mmol/l and needing third party help during the last 14 days, systolic blood pressure, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL), triglycerides and HbA1c. HbA1c level was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 4.0-6.0% (20-42 mmol/mol)). For QoL assessment, the 36-item short-form health survey (SF-36) questionnaire was used. The SF-36 is a widely used, generic questionnaire with 36 items involving 8 subscales and a physical and mental component score. Scores range from 0 to 100, with higher scores indicating better QoL[14,15].

OUTCOMES

Primary outcome was the change in HbA1c from 2006 until 2013 between the patients treated with CIPII or SC insulin. Secondary outcomes included HbA1c change within groups and changes within and between groups in hypoglycaemic episodes, QoL, clinical and biochemical parameters. Additionally, the between group differences for HbA1c and QoL measures were corrected for the number of hypoglycaemic episodes (<4.0 mmol/l during the last 2 weeks) on baseline, accordingly, the change in hypoglycaemic episodes between groups was corrected for HbA1c. Furthermore, subanalysis were performed among patients with baseline HbA1c ≥7.5% (58 mmol/mol), ≥5 incidents of hypoglycaemia (<4.0 mmol/l) per week or both. Finally, complications related to the mode of insulin administration (i.e. CIPII, MDI and CSII) were analysed.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Results are expressed as mean (with standard deviation (SD)) or median (with interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. Q-Q plots were used to determine if the tested variable had a normal distribution or not. Where appropriate, paired parametric and non-parametric tests were used to compare baseline data between groups. Linear mixed models (with Bonferroni correction where applicable) were used to calculate and test estimated values and difference between the 2 moments in time and between patients treated with CIPII or SC (both MDI and CSII) insulin. Both observed and estimated values are reported. A (two-sided) p-value of less than 0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

Both studies were performed in accordance with the Declaration of Helsinki. For both studies informed consent was obtained from all patients. Both study protocols were approved by the local medical ethics committee.

Results

PATIENT SELECTION

Of all 23 patients who started CIPII in 2006 and completed the randomized cross-over trial, 22 were still treated with CIPII in 2013. One patient stopped CIPII treatment after 2 years due to neuropathic pains, for which the patient blamed the implanted pump. One female patient was excluded from the current analysis due to chronic corticosteroid use for myasthenia gravis. Therefore, 21 patients using CIPII were included as cases in the present analysis.

Concerning the control patients, of the 195 patients who were followed from 2006 onwards, 78 patients were not eligible for inclusion: 65 patients due to a mean HbA1c <7.5% (58 mmol/mol) in 2006, 9 patients were aged over 70 years, 2 patients switched from CSII to CIPII during follow-up, 1 patient had a C-peptide concentration of 0.4 nmol/l and 1 patient had a plasma creatinine ≥150 µmol/l. Of the remaining 117 patients, 13 switched from MDI towards CSII and 30 patients were lost to follow-up. Therefore, 74 control patients who used SC insulin therapy were included in the present analysis.

BASELINE PATIENT CHARACTERISTICS

The baseline characteristics of all patients (n=95), those initiating CIPII (n=21) and those continuing SC insulin therapy (n=74) are presented in Table 1 (more detailed information is available in Appendix 1). In the SC insulin group, 41 patients used MDI and 33 used CSII throughout follow-up. Patients who initiated CIPII therapy in 2006 had more frequent neuropathy and reported more hypoglycaemic episodes than those who continued SC insulin therapy. Furthermore, patients who initiated CIPII had significantly lower scores on the SF-36 subscales physical functioning, social functioning, role limitations due to physical problems, vitality, bodily pain, general health perception and on the mental component and physical component scores as compared to patients who continued SC insulin therapy. Patients who initiated CIPII had a higher systolic blood pressure and a lower LDL-cholesterol as compared to patients who continued SC therapy with CSII. Within the SC group, there were no baseline differences between patients on MDI or CSII (see Appendix 2).

CHANGES DURING FOLLOW-UP - HbA1c

The observed changes of HbA1c during the 7 (1) years follow-up are presented in Table 1 and in Figure 1. The estimated differences within and between the treatment groups are presented in Table 2. HbA1c decreased significantly from 8.7 to 8.1% (72 to 65 mmol/mol) with a difference of -0.6% (95% CI -1.1, -0.1) (-7 mmol/mol (95% CI -12, -1)) among CIPII treated patients. For patients on SC insulin therapy, HbA1c did not change. Over time, there was no significant difference between the CIPII and SC insulin therapy group regarding the HbA1c (difference: -0.5% (95% CI -1.0, 0.2)) (-5 mmol/mol (95% CI -11, 2)). After adjustment for hypoglycaemic episodes at baseline the difference between treatment groups was -0.2% (95% CI -0.8, 0.4) (-2 mmol/mol (95% CI -9, 4)). In subanalysis among patients with a baseline HbA1c concentration ≥7.5% (58 mmol/mol) (n=92), there were also no differences in HbA1c over time between the CIPII and SC insulin therapy present (see Appendix 3).

CHANGES DURING FOLLOW-UP - HYPOGLYCAEMIC EPISODES

The number of hypoglycaemic episodes decreased from 9 to 3 episodes per 2 weeks with a difference of -5 (95% CI -8, -3) among CIPII treated patients while it remained stable among patients treated with SC insulin therapy (see Table 2). The difference over time between the two treatment modalities was -6 (95% CI -9, -4) episodes per 2 weeks in favour of CIPII treated patients, remained the same after adjustment for HbA1c and was also present when comparing MDI and CSII treated patients with CIPII (see Appendix 4).

TABEL 1 Observed data at the start and end of follow-up for all-, CIPII- and SC insulin treated patients.

	All patients (n=95)	CIPII (n=21) Start	End	SC (n=74) Start	End
Clinical and biochemical					
Age (years)	47 (10)	44 (11)		47 (9)	
Female sex (n)	40 (42)	10 (48)		30 (41)	
Diabetes duration (years)	22 (10)	21 (9)		22 (10)	
BMI (kg/m²)	28 (5)	27 (5)	26 (5)	28 (4)	29 (5)*
Systolic blood pressure (mmHg)	137 (16)	142 (21)	140 (16)	136 (14)*	129 (14) *
Microvascular complication (n) †	44 (46)	9 (43)	12 (57)	35 (47)	49 (66)
Retinopathy (n)	39 (41)	5 (24)	6 (29)	34 (46)	52 (70)*
Neuropathy (n)	14 (15)	9 (43)	10 (48)	5 (7) *	8 (11)*
Nephropathy (n)	8 (8)	2 (10)	2 (10)	6 (8)	6 (8)
Macrovascular complication (n)	9 (9)	1 (5)	3 (14)	8 (11)	13 (18)
Total cholesterol (mmol/l)	5.2 (1.0)	4.9 (0.8)	4.7 (0.9)	5.2 (1.0)	4.8 (0.9)
LDL cholesterol (mmol/l)	2.9 (0.8)	2.7 (0.7)	2.5 (0.8)	3.0 (0.9)	2.6 (0.7)
HbA1c (%)	8.4 (0.9)	8.7 (1.4)	8.1 (1.1)	8.4 (0.7)	8.2 (0.7)
HbA1c (mmol/mol)	68 (10)	72 (15)	65 (12)	68 (8)	66 (8)
Hypoglycaemic events‡	2 [1, 4]	9 [4, 10]	2 [0, 5]	1 [0, 2]*	2 [1,4]
Hypoglycaemic events needing help	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Total insulin dose (IU/day)	53 [42, 69]	50 [35, 70]	57 [46, 47]	56 [45, 69]	55 [43, 69]
SF-36 subscales					
Physical functioning	95 [80, 100]	80 [61, 90]	85 [65, 95]	95 [85, 100]*	95 [85, 100]
Social functioning	88 [62.5,100]	69 [50,75]	75 [63, 100]	88 [75, 100]*	88 [74, 100]
Role limitations-physical	100 [50, 100]	25 [0, 75]	25 [0, 100]	100 [75, 100]*	100 [63, 100]
Role limitations-emotional	100 [75, 100]	100 [8, 100]	100 [67, 100]	100 [100, 100]	100 [100, 100]
Mental health	80 [64, 88]	74 [53, 88]	84 [72, 92]	84 [68, 88]	80 [71, 80]
Vitality	60 [45, 80]	53 [30, 60]	55 [45, 75]	65 [50, 80]*	65 [55, 80]
Bodily pain	84 [62, 100]	62 [41, 83]	72 [51, 84]	100 [62, 100]*	84 [64, 100]
General health	62 [47, 73]	36 [25, 55]	42 [35, 57]	67 [50, 77]*	67 [52, 77]
SF-36 component scores					
Mental	74 [58, 87]	60 [48, 72]	71 [62, 84]	77 [66, 88]*	81 [68, 88]
Physical	77 [56, 88]	53 [43, 69]	56 [45, 82]	82 [68, 90]	84 [63, 89]

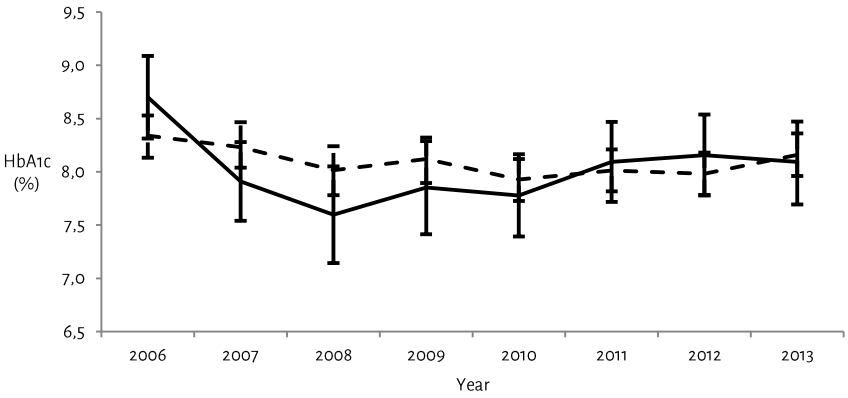
Data are presented as n (%), mean (SD) or median [IQR]. Abbreviations: BMI; body mass index, CIPII; continuous intraperitoneal infusion, MCS; mental component score, PCS; physical component score, SC; subcutaneous. † Categories may not add up due to multiple complications per patient. ‡ Defined as the number of blood glucose value <4.0 mmol/l during the last 2 weeks. *p<0.05 as compared to CIPII, p-values are based on appropriate parametric and non-parametric tests. Additional clinical and biochemical variables are presented in Appendix 1.

TABEL 2 Estimated data and changes during follow-up for CIPII and SC insulin treated patients.

	CIPII			SC			Δ Between CIPII and SC
	Start	End	Within group Δ	Start	End	Within group Δ	
Clinical and biochemical							
Systolic blood pressure (mmHg)	142 (134, 148)	140 (134, 146)	-2 (-11, 8)	135 (132, 139)	129 (127, 133)	-6 (-11, -1) *	4 (-6, 14)
BMI (kg/m²)	27 (25, 28)	26 (24, 28)	-1 (-4, 2)	28 (27, 29)	29 (28, 30)	1 (-1, 2)	-1 (-5, 2)
Total cholesterol (mmol/l)	4.9 (4.5, 5.4)	4.7 (4.3, 5.1)	-0.3 (-0.8, 0.3)	5.2 (4.9, 5.4)	4.8 (4.6, 5.0)	-0.4 (-0.7, -0.1)*	0.2 (-0.5, 0.8)
LDL cholesterol (mmol/l)	2.7 (2.4, 3.1)	2.6 (2.3, 3.0)	-0.1 (-0.6, 0.4)	3.1 (2.8, 3.4)	3.1 (2.6, 3.5)	0.0 (-1, 1)	-0.1 (-0.8, 0.6)
HbA1c (%)	8.7 (8.3, 9.1)	8.1 (7.7, 8.5)	-0.6 (-1.1, -0.1)	8.4 (8.1, 8.6)	8.2 (8.0, 8.4)	-0.2 (-0.5, 0.1)	-0.5 (-1.0, 0.2)
HbA1c (mmol/mol)	72 (67, 76)	65 (61, 69)	-7 (-12, -1)*	68 (65, 70)	66 (64, 68)	-2 (-5, 1)	-5 (-11, 2)
Hypoglycaemic events ‡	9 (7, 10)	3 (2, 5)	-5 (-8, -3)	2 (1, 3)	3 (2, 3)	1 (-0.3, 2)	-6 (-9, -4)*
Hypoglycaemic events needing help	0.4 (0.1, 0.6)	0.1 (-0.1, 0.2)	-0.3 (-0.7, -0.0)*	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.0 (-0.1, 0.2)	-0.3 (-0.7,-0.0)*
Total insulin dose (IU/day)	54 (44, 63)	65 (51, 78)	11 (-5, 27)	57 (51, 63)	59 (51, 67)	2 (-8, 12)	9 (-10, 28)
SF-36 subscales							
Physical functioning	75 (67, 83)	76 (68, 84)	2 (-9, 13)	89 (85, 93)	89 (84, 93)	-1 (-7, 5)	2 (-10, 15)
Social functioning	66 (58, 75)	74 (66, 83)	8 (-4, 20)	85 (81, 90)	85 (80, 89)	-1 (-7, 6)	9 (-5, 23)
Role limitations-physical	41 (26, 57)	51 (34, 68)	10 (-13, 33)	80 (73, 89)	80 (71, 89)	-1 (-13, 11)	11 (-14, 37)
Role limitations-emotional	70 (55, 86)	77 (62, 93)	7 (-15, 29)	85 (77, 93)	86 (78, 95)	1 (-10, 13)	6 (-19, 31)
Mental health	69 (60, 78)	79 (66, 92)	11 (-5, 26)	77 (72, 81)	81 (74, 88)	5 (-4, 13)	6 (-12, 24)
Vitality	48 (39, 57)	58 (49, 67)	10 (-3, 22)	65 (60, 70)	65 (60, 69)	0 (-7, 7)	10 (-4, 24)
Bodily pain	62 (53, 72)	67 (56, 76)	4 (-9, 18)	83 (78, 88)	83 (78, 87)	0 (-7, 7)	5 (-10, 20)
General health	41 (33, 49)	48 (38, 57)	7 (-5, 19)	64 (60, 69)	62 (58, 68)	-2 (-8, 5)	8 (-5, 22)
SF-36 component scores							
MCS	59 (51, 67)	67 (58, 75)	9 (-2, 19)	75 (71, 79)	76 (71, 80)	1 (-5, 7)	8 (-5, 20)
PCS	56 (49, 63)	63 (55, 70)	7 (-4, 17)	78 (74, 82)	77 (73, 81)	-1 (-6, 5)	8 (-4, 19)

Data are presented as estimated mean (95% confidence interval) and mean changes (95% confidence interval) with linear mixed models. Abbreviations: BMI; body mass index, CIPII; continuous intraperitoneal infusion, MCS; mental component score, PCS; physical component score SC; subcutaneous. * p<0.05.

FIGURE 1 Course of the HbA1c over time.



Course of the HbA1c (estimated mean with 95% CI) in the period 2006 (baseline) and 2013 (end) among T1DM patients treated with CIPII (consecutive line) or SC (dotted line) insulin therapy.

The number of hypoglycaemic episodes needing help decreased among CIPII treated patients (difference: -0.3 (95% CI -0.7, 0.0)). Because the number of hypoglycaemic episodes needing help among SC patients remained the same the difference in the change over time between treatment modes was the same as the decrease for CIPII patients (difference: -0.3 (95% CI -0.7, 0.0)) unadjusted as well as adjusted for baseline HbA1c. Subanalysis among patients with ≥5 incidents of hypoglycaemia per week at baseline (n=15) demonstrated that among patients who started CIPII treatment, the number of hypoglycaemic episodes decreased from 11 to 4 episodes per 2 weeks with a difference of -7 (95%CI -12, -3) (see Appendix 3).

CHANGES DURING FOLLOW-UP - CLINICAL AND BIOCHEMICAL PARAMETERS AND QoL

Among patients who started CIPII, clinical and biochemical parameters other than HbA1c and hypoglycaemic episodes remained stable (see Table 2). For patients who continued SC insulin therapy there was a decrease of the systolic blood pressure, from 135 to 129 mmHg with a difference of -6 mmHg (95% CI -11, -1). Furthermore, among these patients the total cholesterol decreased from 5.2 to 4.8 mmol/l in 2013 (difference: -0.4 (95% CI -0.7, -0.1)).

There were no changes in the SF-36 scores within and between the CIPII and SC group (see Table 2). However, after adjustment for the number of hypoglycaemic episodes there was significant change of the component scale 'general health' (difference: 12 (95% CI 4, 20) and physical component score (difference: 10 (95% CI 3, 18) in favour of CIPII treated patients.

TREATMENT RELATED COMPLICATIONS

Over time, 2 cases of dysfunction and 3 cases of expected battery end-of-life necessitated replacement of the implanted pump. In 2 patients a laparoscopic procedure was performed to replace the catheter and in 3 patients a fibrin plug from the tip of the catheter had to be removed. These complications resulted in 2 [0,4] days of hospital admission and 2 episodes of ketoacidosis among CIPII treated patients. Among patients treated with CSII there were 4 episodes of ketoacidosis: 2 due to dysfunction of the external pump and 2 due to an unknown cause (all among CSII treated patients). One patient treated with MDI was hospitalized due to (accidentally) overdosing insulin. Median duration of hospital admission due to complications in the SC group was 4 [2, 5] days. No mortality was reported.

Discussion

This is the first study to compare the long-term effects of CIPII and SC insulin administration among inadequately controlled T1DM patients. Over a period of 7 years, there was a persistent decline in the number of hypoglycaemic events among CIPII treated patients. As compared to patients using SC insulin, only the number of hypoglycaemic decreased significantly more with CIPII.

Previous randomized clinical studies that compared both insulin administration modes in T1DM patients reported an improvement of HbA1c of ~0.7 to 1.0% (8 to 11 mmol/mol) during CIPII as compared to SC therapy [5–7]. Two long-term follow-up studies among T1DM patients (one from our centre) confirmed the effectiveness of CIPII therapy by showing that HbA1c levels are equal or better than previous SC insulin therapy after 6 years of CIPII treatment [9,16]. The present study extends these results by finding a sustained HbA1c improvement of 0.6% (7 mmol/mol) after a period of 7 years among all CIPII treated patients, which was not significant as compared to the HbA1c course among patients treated with SC insulin. Several explanations can account for this latter finding. First, it is likely that the small sample size of this study led to relatively wide confidence intervals. Second, previous results were found under strict study conditions while our findings reflect real-life clinical practice, meaning that outside of study conditions, CIPII in daily practice has less beneficial effect on glycaemic control than during study circumstances.

Of notice, there was a significant decrease of the number of hypoglycaemic events among CIPII treated patients, also as compared to subjects treated with SC insulin. This finding could

be explained by the pharmacodynamic and pharmacokinetic properties of IP administered insulin [3,4,17,18]. In addition, IP insulin is reported to improve the impaired glucagon secretion and enhances hepatic glucose production in response to hypoglycemia [19–23].

At baseline, QoL measures were significantly worse for patients who started CIPII as compared to patients who continued SC insulin therapy. This may indicate that CIPII is used as a last-resort treatment and that for these patients the complexity of their diabetes, e.g. frequent hypo- and hyperglycaemic episodes and hospital admissions, impose a great burden on their (poor) QoL. And although all QoL scores improved over time among CIPII treated patients these changes were not significant, also as compared to SC treated patients. Although a reduction in the number of hypoglycaemic events could explain this finding, since there was a significant difference in some QoL measures after adjustment for the baseline number of hypoglycaemic events, other explanations should be considered as well.
Possibly, aforementioned study limitations are of concern. In a previous study, the presence of psychiatric disorders was speculated to be a determinant of poor QoL among CIPII treated patients [24]. Since the presence of psychiatric disorders was an exclusion criteria for CIPII therapy in the present study, we hypothesize the presence of other pre-existent but not measured determinants of poor QoL such as poor coping skills, social functioning and support.

Since it is unlikely that a mode of insulin administration could alleviate the full burden of poor QoL and glycaemic control, it should be acknowledged that our results are limited by the use of a generic QoL questionnaire which is poorly sensitive to change and lack of data regarding glycaemic variability. This study is also limited by the fact that the number of eligible patients was low, which necessitated a non-random inclusion of all available patients. Furthermore, as many SC controls were included due to a high HbA1c, and not due to a high frequency of hypoglycaemic episodes, this may well have resulted in differences in baseline characteristics between treatment groups and insufficient power to detect differences, in particular in the subgroup analysis. Taken together, these limitations limit the generalizability of the present study. Nevertheless, despite these limitations the present study gives an impression of the course of CIPII, as compared to SC, treatment among selected T1DM patients.

Conclusions

Over a period of 7 years, there was a persistent decline in the number of hypoglycaemic events among CIPII treated patients. As compared to patients using SC insulin, the number of hypoglycaemic decreased significantly more with CIPII while HbA1c, clinical parameters and QoL remained stable. The results of this study support the effectiveness and current indications of CIPII therapy as a last-resort treatment option for selected T1DM patients who experience frequent hypoglycaemic episodes.

REFERENCES

1 Giacca A, Caumo A, Galimberti G, et al. Peritoneal and subcutaneous absorption of insulin in type I diabetic subjects. J Clin Endocrinol Metab 1993; 77: 738–42.

2 Bratusch-Marrain PR, Waldhäusl WK, Gasić S, Hofer A. Hepatic disposal of biosynthetic human insulin and porcine C-peptide in humans. Metabolism 1984; 33: 151–7.

3 Nathan DM, Dunn FL, Bruch J, et al. Postprandial insulin profiles with implantable pump therapy may explain decreased frequency of severe hypoglycemia, compared with intensive subcutaneous regimens, in insulin-dependent diabetes mellitus patients. Am J Med 1996; 100: 412–7.

4 Schaepelynck Bélicar P, Vague P, Lassmann-Vague V. Reproducibility of plasma insulin kinetics during intraperitoneal insulin treatment by programmable pumps. Diabetes Metab 2003; 29: 344–8.

5 Logtenberg SJ, Kleefstra N, Houweling ST, et al. Improved glycemic control with intraperitoneal versus subcutaneous insulin in type 1 diabetes: a randomized controlled trial. Diabetes Care 2009; 32: 1372–7.

6 Selam JL, Raccah D, Jean-Didier N, Lozano JL, Waxman K, Charles MA. Randomized comparison of metabolic control achieved by intraperitoneal insulin infusion with implantable pumps versus intensive subcutaneous insulin therapy in type I diabetic patients. Diabetes Care 1992; 15: 53–8.

7 Haardt MJ, Selam JL, Slama G, et al. A cost-benefit comparison of intensive diabetes management with implantable pumps versus multiple subcutaneous injections in patients with type I diabetes. Diabetes Care 1994; 17: 847–51.

8 Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, Bilo HJ. Health-related quality of life, treatment satisfaction, and costs associated with intraperitoneal versus subcutaneous insulin administration in type 1 diabetes: a randomized controlled trial. Diabetes Care 2010; 33: 1169–72.

9 Schaepelynck P, Renard E, Jeandidier N, et al. A recent survey confirms the efficacy and the safety of implanted insulin pumps during long-term use in poorly controlled type 1 diabetes patients. Diabetes Technol Ther 2011; 13: 657–60.

10 Logtenberg SJJ, van Ballegooie E, Israêl-Bultman H, van Linde A, Bilo HJG. Glycaemic control, health status and treatment satisfaction with continuous intraperitoneal insulin infusion. Neth J Med 2007; 65: 65–70.

11 Hart HE, Bilo HJG, Redekop WK, Stolk RP, Assink JH, Meyboom-de Jong B. Quality of life of patients with type I diabetes mellitus. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2003; 12: 1089–97.

12 Haveman JW, Logtenberg SJJ, Kleefstra N, Groenier KH, Bilo HJG, Blomme AM. Surgical aspects and complications of continuous intraperitoneal insulin infusion with an implantable pump. Langenbecks Arch Surg Dtsch Ges Für Chir 2010; 395: 65–71.

13 Van Dijk PR, Logtenberg SJJ, Groenier KH, Kleefstra N, Bilo HJG, Arnqvist HJ. Effect of i.p. insulin administration on IGF1 and IGFBP1 in type 1 diabetes. Endocr Connect 2014; 3: 17–23.

14 Ware J, Snow K, Gandek KM: SF-36 Health Survey: Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center 1993.

15 Ware JE, Kosinski M, Keller S: SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston: The Health Institute, New England Medical Center 1994.

16 Van Dijk PR, Logtenberg SJ, Groenier KH, Gans RO, Kleefstra N, Bilo HJ. Continuous intraperitoneal insulin infusion in type 1 diabetes: a 6-year post-trial follow-up. BMC Endocr Disord 2014; 14: 30.

17 Schade DS, Eaton RP, Spencer W, Goldman R, Corbett WT. The peritoneal absorption of insulin in diabetic man: a potential site for a mechanical insulin delivery system. Metabolism 1979; 28: 195–7.

18 Micossi P, Cristallo M, Librenti MC, et al. Free-insulin profiles after intraperitoneal, intramuscular, and subcutaneous insulin administration. Diabetes Care 1986; 9: 575–8.

19 Oskarsson PR, Lins PE, Backman L, Adamson UC. Continuous intraperitoneal insulin infusion partly restores the glucagon response to hypoglycaemia in type 1 diabetic patients. Diabetes Metab 2000; 26: 118–24.

20 Wan CK, Giacca A, Matsuhisa M, et al. Increased responses of glucagon and glucose production to hypoglycemia with intraperitoneal versus subcutaneous insulin treatment. Metabolism 2000; 49: 984–9.

21 Mason TM, Gupta N, Goh T, et al. Chronic intraperitoneal insulin delivery, as compared with subcutaneous delivery, improves hepatic glucose metabolism in streptozotocin diabetic rats. Metabolism 2000; 49: 1411–6.

22 Oskarsson PR, Lins PE, Wallberg Henriksson H, Adamson UC. Metabolic and hormonal responses to exercise in type 1 diabetic patients during continuous subcutaneous, as compared to continuous intraperitoneal, insulin infusion. Diabetes Metab 1999; 25: 491–7.

23 Selam JL, Medlej R, M'bemba J, et al. Symptoms, hormones, and glucose fluxes during a gradual hypoglycaemia induced by intraperitoneal vs venous insulin infusion in Type I diabetes. Diabet Med J Br Diabet Assoc 1995; 12: 1102–9.

24 DeVries JH, Eskes SA, Snoek FJ, et al. Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay. Diabet Med J Br Diabet Assoc 2002; 19: 496–501.

APPENDIX 1 **Additional clinical and biochemical variables.**

	All patients (n=95)	CIPII (n=21) Start	End	SC (n=74) Start	End
Clinical and biochemical					
Alcohol use (n)	30 (32)	8 (38)		22 (30)	
Ever/Current smoker (n)	29 (31)	9 (43)		20 (27)	
Married/cohabiting (n)	81 (85)	17 (81)		64 (87)	
Macrovascular complication (n) †	9 (9)	1 (5)	3 (14)	8 (11)	13 (18)
Angina pectoris	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)
Myocardial infarction	2 (2)	0 (0)	0 (0)	2 (3)	4 (5)
Coronary artery bypass grafting	1 (1)	1 (5)	1 (5)	0 (0)	1 (1)
Percutaneous transluminal coronary angioplasty	2 (2)	0 (0)	0 (0)	2 (3)	2 (3)
Stroke	1 (1)	0 (0)	0 (0)	1(1)	3 (4)
Transient ischaemic attack	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)
Peripheral artery disease	2 (2)	0 (0)	1 (5)	2 (3)	3 (4)
HDL cholesterol (mmol/l)	1.7 (0.4)	1.7 (0.5)	1.6 (0.5)	1.6 (0.4)	1.5 (0.4)
LDL cholesterol (mmol/l)	2.9 (0.8)	2.7 (0.7)	2.5 (0.8)	3.0 (0.9)	2.6 (0.7)

Data are presented as n (%), mean (SD) or median [IQR]. † Categories may not add up due to multiple complications per patient. Abbreviations:, CIPII; continuous intraperitoneal infusion, SC; subcutaneous.

APPENDIX 2 Observed data at start and end of follow-up for MDI and CSII treated patients.

	MDI (n=41)		CSII (n=33)	
	Start	End	Start	End
Clinical and biochemical				
Age (years)	49 (10)		46 (9)	
Female sex (n)	14 (34)		16 (49)	
Diabetes duration (years)	22 (12)		21 (9)	
BMI (kg/m²)	28 (4)	28 (4)	27 (5)	29 (5)
Systolic blood pressure (mmHg)	143 (14)	133 (16)	131 (10)*	126 (9)*
Microvascular complication (n) †	23 (56)	28 (68)	12 (36)	21 (64)
Retinopathy (n)	22 (53)	28 (68)	12 (36)	21 (63)
Neuropathy (n)	4 (10)	11 (27)	1 (3)	5 (15)
Nephropathy (n)	4 (10)	3 (7)	2 (6)	2 (6)
Macrovascular complication (n)	7 (17)	10 (24)	1 (3)	3 (9)
Total cholesterol (mmol/l)	5.1 (1.1)	4.7 (1.0)	5.2 (0.9)	4.9 (0.8)
LDL cholesterol (mmol/l)	2.8 (0.9)	3.2 (0.7)	3.2 (0.6)*	3.0 (0.6)
HbA1c (%)	8.4 (0.7)	8.2 (0.8)	8.3 (0.6)	8.1 (0.7)
HbA1c (mmol/mol)	68 (8)	66 (9)	67 (6)	65 (8)
Hypoglycaemic events ‡	1 [0, 2]*	1 [1, 2]	2 [1, 3]*	2 [1, 5]
Hypoglycaemic events needing help	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Total insulin dose (IU/day)	60 [50, 79]	59 [43, 70]	50 [36, 60]	55 [40,65]
SF-36 subscales				
Physical functioning	95 [85, 100]*	95 [85, 100]*	95 [90, 100]*	90 [80, 100]
Social functioning	88 [75, 100]*	100 [88, 100]*	100 [63, 100]*	75 [63, 100]
Role limitations-physical	100 [75, 100]*	100 [100, 100]*	100 [75, 100]*	100 [25, 100]
Role limitations-emotional	100 [100, 100]	100 [100, 100]	100 [75, 100]	100 [100, 100]
Mental health	84 [64, 92]	84 [72, 92]	84 [70, 88]	80 [68, 88]
Vitality	65 [53, 85]*	70 [60, 80]*	65 [48, 75]*	60 [50, 75]
Bodily pain	100 [64, 100]*	100 [74, 100]*	100 [62, 100]*	84 [62, 100]
General health	65 [47, 77]*	70 [59, 82]*	67 [57, 76]*	62 [40, 72]
SF-36 component scores				
Mental	79 [61, 89]*	85 [78,90]	78 [67, 86]	80 [54, 88]
Physical	83 [61, 90]*	83 [75, 88]*	80 [70, 89]*	79 [58, 88]

Data are presented as n (%), mean (SD) or median [IQR]. † Categories may not add up due to multiple complications per patient. ‡ Defined as the number of blood glucose value <4.0 mmol/l during the last 2 weeks. *p<0.05 as compared to CIPII, p-values are based on appropriate parametric and non-parametric tests. Abbreviations: BMI; body mass index, CIPII; continuous intraperitoneal infusion, CSII; continuous subcutaneous insulin infusion, MCS; mental component score, MDI; multiple daily injections, PCS; physical component score.

APPENDIX 3A Subanalysis among patients with baseline HbA1c concentration ≥7.5% (58 mmol/mol).

	SC		Within group Δ	CIPII		Within group Δ	Δ Between CIPII and CSII
	Start	End		Start	End		
Clinical and biochemical							
Systolic blood pressure (mmHg)	136 (133, 139)	130 (137, 133)	-6 (-10, -1)*	142 (131, 152)	139 (131, 147)	3 (-10, 16)	3 (-8, 13)
BMI (kg/m²)	28 (27, 29)	29 (28, 30)	1 (-1, 2)	26 (24, 29)	25 (23, 28)	-1 (-4, 3)	-2 (-5, 2)
Total cholesterol (mmol/l)	5.2 (5.0, 5.4)	4.8 (4.6, 5.0)	-0.4 (-0.7, -0.1)*	5.0 (4.6, 5.4)	4.7 (4.3, 5.1)	-0.3 (-0.8, 0.3)	0.2 (-0.5, 0.8)
LDL cholesterol (mmol/l)	3.1 (2.8, 3.4)	3.1 (2.6, 3.5)	0.1 (-0.6, 0.5)	2.8 (2.5, 3.1)	2.7 (2.2, 3.1)	-0.1 (-0.6, 0.4)	-0.1 (-0.8, 0.7)
HbA1c (%)	8.4 (8.1, 7.7)	8.2 (8.0, 8.4)	-0.2 (-0.5, 0.1)	8.8 (8.2, 9.5)	8.2 (7.6, 8.7)	-0.6 (-1.5, 1.9)	-0.5 (-1.0, 0.2)
HbA1c (mmol/mol)	68 (65, 61)	66 (64, 68)	-2 (-5, 1)	73 (66, 80)	66 (60, 72)	-7 (-16, 21)	-5 (-11, 2)
Hypoglycaemic events	2 (1, 2)	3 (2, 3)	0.8 (-0.1, 1.8)	9 (5, 12)	3 (1, 5)	-6 (-9, -2)*	-7 (-9, -4)*
Hypoglycaemic events needing help	0.1 (0.0, 0.2)	0.2 (0.0, 0.2)	-0.0 (-0.1, 0.1)	0.2 (-0.1, 0.6)	0.0 (0.0, 0.0)	-0.2 (-0.6, 0.2)	-0.3 (-0.6, 0.1)
Total insulin dose (IU/day)	57 (52, 62)	59 (52, 66)	-2 (-10, 7)	50 (40, 61)	59 (45, 73)	9 (-8, 25)	7 (-12, 24)
SF-36 subscales							
Physical functioning	90 (85, 93)	89 (86, 93)	0 (-5, 5)	73 (62, 84)	76 (63, 88)	2 (-14, 18)	2 (-10, 15)
Social functioning	85 (81, 90)	84 (80, 89)	-1 (-7, 5)	68 (57, 79)	76 (65, 86)	8 (-7, 22)	9 (-6, 23)
Role limitations-physical	82 (74, 89)	80 (72, 89)	-2 (-12, 10)	46 (26, 65)	52 (29, 74)	6 (-23, 34)	7 (19, 34)
Role limitations-emotional	85 (77, 93)	86 (78, 94)	1 (-10, 12)	72 (51, 94)	80 (60, 100)	8 (-20, 37)	7 (-19, 32)
Mental health	77 (72, 81)	81 (73, 89)	5 (-4, 14)	70 (58, 82)	80 (71, 89)	10 (-4, 25)	6 (-13, 24)
Vitality	65 (60, 70)	65 (60, 69)	0 (-7, 7)	49 (38, 60)	57 (48, 66)	9 (-5, 22)	9 (-6, 24)
Bodily pain	84 (79, 88)	83 (78, 88)	0 (-7, 7)	65 (53, 77)	69 (59, 81)	5 (-11, 20)	5 (-10, 20)
General health	65 (60, 69)	63 (58, 68)	-2 (-9, 5)	42 (33, 51)	47 (38, 57)	5 (-7, 18)	7 (-7, 13)
SF-36 component scores							
MCS	75 (71, 79)	76 (72, 80)	1 (-5, 7)	60 (50, 70)	68 (60, 76)	8 (-4, 20)	7 (-6, 20)
PCS	78 (75, 82)	77 (73, 81)	1 (-5, 6)	57 (48, 66)	63 (53, 72)	6 (-7, 18)	6 (-6, 19)

Among patients who started CIPII therapy in 2006, 8 (38.1%) patients had a baseline HbA1c concentration ≥7.5% (58 mmol/mol), 2 (9.5%) patients had ≥5 incidents of hypoglycaemia per week and in 11 (52.4%) patients both inclusion criteria were present. Among SC treated patients, these numbers were 72 (97.3%), 1 (1.4%) and 1 (1.4%) respectively. Data are presented as estimated mean (95% confidence interval) and mean changes (95% confidence interval) with linear mixed models. *p<0.05. Abbreviations: BMI; Body Mass Index, CIPII; continuous intraperitoneal infusion, MCS; mental component score, PCS; physical component score SC; subcutaneous.

APPENDIX 3B Subanalysis among patients with ≥5 incidents of hypoglycaemia per week at baseline †.

	CIPII		Within group Δ
	Start	End	
Clinical and biochemical			
Systolic blood pressure (mmHg)	144 (133, 155)	144 (135, 153)	0 (-13, 13)
BMI (kg/m²)	26 (23, 28)	26 (23, 29)	0 (-4, 4)
Total cholesterol (mmol/l)	4.8 (4.2, 5.3)	4.5 (4.1, 4.9)	-0.3 (-1.0, 0.3)
LDL cholesterol (mmol/l)	2.6 (2.1, 3.1)	2.4 (2.1, 2.7)	-0.2 (-0.8, 0.4)
HbA1c (%)	7.9 (7.5, 8.3)	7.7 (7.4, 8.2)	-0.2 (-0.6, 0.4)
HbA1c (mmol/mol)	63 (59, 67)	61 (57, 66)	-2 (-7, 4)
Hypoglycaemic events	11 (8, 15)	4 (1, 7)	-7 (-12, -3)*
Hypoglycaemic events needing help	0.3 (-0.2, 0.9)	0.1 (-0.1, 0.3)	-0.3 (-0.8, 0.3)
Total insulin dose (IU/day)	49 (30, 66)	60 (35, 85)	12 (-17, 41)
SF-36 subscales			
Physical functioning	79 (68, 90)	78 (65, 92)	-1 (-17, 16)
Social functioning	64 (54, 75)	71 (56, 85)	6 (-11, 24)
Role limitations-physical	36 (10, 62)	42 (13, 71)	5 (-32, 42)
Role limitations-emotional	77 (53, 100)	75 (46, 100)	-2 (-37, 33)
Mental health	69 (56, 81)	78 (64, 91)	9 (-8, 26)
Vitality	47 (34, 60)	55 (44, 67)	8 (-8, 25)
Bodily pain	64 (49, 79)	66 (56,76)	2 (-16, 19)
General health	36 (26, 46)	48 (38, 58)	12 (-2, 25)
SF-36 component scores			
MCS	59 (49, 69)	65 (53, 78)	7 (-8, 22)
PCS	55 (45, 65)	60 (49, 71)	5 (-9, 19)

Among patients who started CIPII therapy in 2006, 8 (38.1%) patients had a baseline HbA1c concentration ≥7.5% (58 mmol/mol), 2 (9.5%) patients had ≥5 incidents of hypoglycaemia per week and in 11 (52.4%) patients both inclusion criteria were present. Among SC treated patients, these numbers were 72 (97.3%), 1 (1.4%) and 1 (1.4%) respectively. † As there were only 2 patients using SC insulin therapy in the control group with ≥5 incidents of hypoglycaemia per week at baseline these outcomes could not be calculated. Data are presented as estimated mean (95% confidence interval) and mean changes (95% confidence interval) with linear mixed models. *p<0.05. Abbreviations: BMI; Body Mass Index, CIPII; continuous intraperitoneal infusion, MCS; mental component score, PCS; physical component score, SC; subcutaneous.

APPENDIX 4 Estimated data and changes during follow-up for CIPII , MDI and CSII treated patients.

	MDI		Within group Δ	Δ Between CIPII and MDI	CSII		Within group Δ	Δ Between CIPII and CSII
	Start	End			Start	End		
Clinical and biochemical								
Systolic blood pressure (mmHg)	139 (135, 144)	133 (128, 138)	-6 (-13, 0)	5 (-8, 17)	131 (125, 136)	126 (121, 131)	-5 (-12, 2)	3 (-7, 14)
BMI (kg/m²)	28 (27, 29)	28 (27, 30)	0 (-2, 2)	-1 (-4, 3)	27 (26, 29)	29 (27, 30)	2 (-1, 4)	-2 (-6, 2)
Total cholesterol (mmol/l)	5.1 (4.8, 5.4)	4.7 (4.4, 5.0)	-0.4 (-0.8, 0.1)	0.1 (-0.7, 0.8)	5.3 (5.0, 5.7)	4.8 (4.5, 5.1)	-0.5 (-1.0, -0.1)*	0.3 (-0.3, 0.9)
HDL cholesterol (mmol/l)	1.6 (1.4, 1.8)	1.5 (1.3, 1.6)	-0.2 (-0.4, 0.0)	0.1 (-0.3, 0.4)	1.7 (1.5, 1.8)	1.5 (1.4, 1.7)	-0.1 (-0.4, 0.1)	0.0 (-0.3, 0.4)
LDL cholesterol (mmol/l)	2.8 (2.4, 3.3)	3.2 (2.3, 4.0)	0.4 (-0.6, 1.3)	-0.4 (-1.5, 0.6)	3.4 (3.0, 3.7)	3.0 (2.5, 3.6)	-0.1 (-0.6, 0.4)	0.1 (-0.6, 1.0)
Triglycerids	1.2 (1.0, 1.5)	1.5 (1.2, 1.8)	0.3 (-0.1, 0.7)	-0.3 (-1.0, 0.4)	1.2 (0.9, 1.4)	1.2 (0.9, 1.5)	0.0 (-0.4, 0.4)	-0.1 (-0.6, 0.5)
HbA1c (%)	8.4 (8.1, 8.6)	8.2 (7.9, 8.5)	-0.2 (-0.6, 0.2)	-0.5 (-1.2, 0.3)	8.3 (8.0, 8,6)	8.1 (7.8, 8.5)	-0.2 (-0.6, 0.2)	-0.5 (-1.2, 0.4)
HbA1c (mmol/mol)	68 (65, 71)	66 (63, 69)	-2 (-6, 2)	-5 (-13, 3)	67 (64, 71)	65 (62, 69)	-2 (-7, 2)	-5 (-13, 4)
Hypoglycaemic events	2 (1, 3)	2 (1, 3)	1 (-1, 2)	-5 (-9, -3)*	2 (1, 3)	3 (2, 4)	1 (-1, 3)	-7 (-10, -4)*
Hypoglycaemic events needing help	0.1 (0.0, 0.3)	0.1 (0.0, 0.2)	-0.1 (-0.3, 0.2)	-0.3 (-0.7, 0.1)	0.1 (-0.1, 0.3)	0.2 (0.0, 0.3)	0.1 (-0.1, 0.3)	-0.1 (-0.9, 0.0)
Total insulin dose (IU/day)	64 (57, 71)	62 (52, 72)	-2 (-14, 10)	13 (-9, 35)	46 (38, 55)	54 (41, 67)	8 (-8, 24)	3 (-19, 25)
SF-36 subscales								
Physical functioning	89 (83, 94)	92 (86, 98)	3 (-5, 11)	-2 (-15, 12)	90 (84, 96)	85 (79, 92)	-5 (-13, 4)	6 (-9, 22)
Social functioning	86 (79, 92)	90 (84, 96)	5 (-4, 13)	3 (-11, 18)	85 (78, 92)	78 (72, 85)	-7 (-16, 2)	15 (-1, 31)
Role limitations-physical	81 (69, 92)	87 (75, 100)	7 (-10, 23)	3 (-24, 31)	81 (69, 93)	72 (58, 85)	-10 (-27, 8)	19 (-12, 51)
Role limitations-emotional	85 (73, 96)	88 (76, 99)	3 (-13, 19)	4 (-25, 33)	85 (73, 98)	85 (73, 97)	-1 (-18, 17)	8 (-21, 37)
Mental health	76 (69, 82)	80 (71, 90)	4 (-7, 16)	6 (-9, 21)	78 (71, 84)	80 (71, 90)	5 (-7, 17)	6 (-17, 29)
Vitality	66 (59, 73)	70 (65, 77)	5 (-4, 14)	5 (-10, 20)	63 (56, 70)	57 (51, 64)	-6 (-15, 4)	16 (-0.4, 32)
Bodily pain	82 (75, 89)	87 (80, 93)	4 (-5, 14)	0 (-16, 16)	84 (76, 91)	78 (71, 85)	-6 (-16, 4)	10 (-7, 27)
General health	63 (57, 69)	68 (62, 74)	5 (-4, 14)	2 (-13, 16)	67 (61, 73)	58 (51, 65)	-9 (-18, 0.1)	16 (1, 31)*
SF-36 component scores								
MCS	77 (72, 83)	82 (77, 88)	5 (-3, 12)	4 (-10, 17)	78 (73, 84)	72 (66, 77)	-7 (-15, 1)	12 (-2, 26)
PCS	75 (69, 80)	79 (74, 85)	5 (-3, 13)	2 (-10, 14)	76 (69, 82)	72 (66, 78)	-3 (-12, 5)	14 (-0.3, 28)

Data are presented as estimated mean (95% confidence interval) and mean changes (95% confidence interval) with linear mixed models. *p<0.05. Abbreviations: BMI; Body Mass Index, CIPII; continuous intraperitoneal infusion, MCS; mental component score, PCS; physical component score, SC; subcutaneous.