CHAPTER 10

Different effects of intraperitoneal and subcutaneous insulin administration on the growth-hormone-insulin-like growth factor-1 axis in type 1 diabetes

Abstract

INTRODUCTION

In patients with type 1 diabetes mellitus (T1DM), low levels of insulin-like growth factor -1 (IGF1) and high levels of growth hormone (GH) and IGF binding protein-1 (IGFBP1) are present, probably due to low insulin levels in the portal vein. We hypothesized that the GH-IGF1 axis is affected by the route of insulin administration and that continuous intraperitoneal insulin infusion (CIPII) has a more pronounced effect than subcutaneous (SC) insulin therapy.

PATIENTS AND METHODS

This is a prospective, observational matched-control study. IGF1, IGFBP1 and GH were measured at baseline and after 26 weeks in T1DM patients treated with CIPII and SC insulin therapy.

RESULTS

A total of 183 patients, 39 using CIPII and 144 SC insulin therapy, with a mean age of 50 (standard deviation (SD) 12) years, diabetes duration of 26 (SD 13) years and HbA1c of 64 (SD 11) mmol/mol were analysed. IGF1 concentration were higher among CIPII treated patients as compared to patients treated with SC insulin therapy: 123.7 µg/l (95% CI 110.8, 138.1) versus 108.1 µg/l (95% CI 101.7, 114.9), p=0.035. IGFBP1 and GH concentrations were significantly lower among CIPII treated patients as compared to subjects treated with SC insulin therapy: 50.9 µg/l (95% CI 37.9, 68.2) versus 102.6 µg/l (95% CI 87.8, 119.8) (p<0.001) for IGFBP1 and 0.68 µg/l (95% CI 0.44, 1.06) versus 1.21 µg/l (95% CI 0.95, 1.54) (p=0.027) for GH, respectively. During the study period there were no changes in IGF1 and GH concentrations within both groups. Only IGFBP1 decreased more during CIPII as compared to SC insulin therapy.

CONCLUSION

CIPII treated T1DM patients have higher IGF1 concentrations as compared to patients treated with SC insulin therapy. Furthermore, IGFBP1 and GH concentrations are lower among CIPII treated patients. These findings suggest that CIPII has beneficial effects as compared to SC insulin on the altered GH-IGF1 axis in T1DM.

Introduction

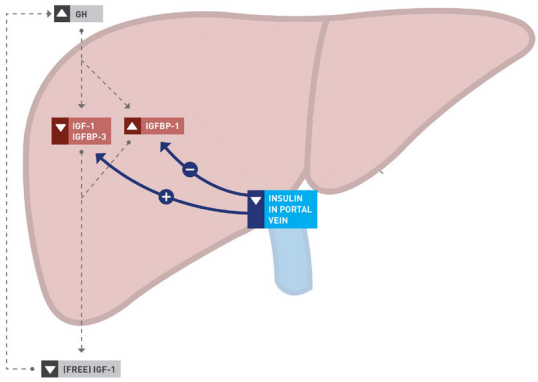
Insulin and insulin-like growth factor 1 (IGF1) are structurally and functionally closely related peptides. IGF1, mainly synthesized in the liver after stimulation of the growth hormone (GH) receptor, plays a central role in cell metabolism and growth regulation [1–3]. In plasma, IGF1 is bound to IGF-binding proteins (IGFBPs) of which IGFBP3 binds approximately 80% of the total amount of IGF1 present in the circulation. It is only the free fraction of IGF1, comprising less than 1% of the circulating IGF1, which is biologically active. IGFBP1 is produced in the liver and regulated acutely (in the opposite direction) by insulin thereby allowing insulin to regulate IGF1 bioactivity [4–7].

Evidence suggests that through an up-regulation of hepatic GH-receptor expression, insulin increases the hepatic sensitivity of GH stimulation and subsequent increases IGF1 production [8]. Furthermore, insulin down-regulates IGFBP1 synthesis in the liver which may increases IGF1 bioactivity [5]. In patients with type 1 diabetes mellitus (T1DM), it is hypothesized that insulinopenia in the portal system leads to insufficient insulinization of the liver and subsequent alterations of the GH-IGF1 axis. These alterations are characterized by low concentrations of total IGF1 and IGFBP3 and high concentrations of IGFBP1 and GH (Figure 1) [9–16].

Although these abnormalities have been described in situation of poor glycaemic control, intensified exogenous subcutaneous (SC) insulin therapy only attenuates these disturbances but does not correct them [15–18]. With continuous intraperitoneal insulin infusion (CIPII), insulin is infused directly in the intraperitoneal (IP) space, resulting in higher concentrations in the portal vein catchment area, higher hepatic extraction of insulin and lower peripheral plasma insulin concentrations compared with SC insulin administration [19,20].

Some of the previous studies towards the effects of IP insulin administration on the IGF1-GH axis in T1DM patients showed an increase of IGF1, and a decrease of GH and IGFBP1 as compared to SC insulin therapy [21–23], while other studies found no changes in IGF1 [24]. Most of these studies had a short duration (ranging from days to 1 year) and the number of patients was limited (ranging from 10 to 36) [21–24].

FIGURE 1 **Alterations in GH-IGF1 axis in T1DM.**



The (+) and (-) indicate positive and negative associations, respectively. The (▲) and (▼) indicate increases and decreases of concentrations as found in previous studies 9–16. Abbreviations: GH, growth hormone; IGF1, insulin-like growth factor-1, IGFBP1/-3, insulin-like growth factor binding protein -1/-3.

We hypothesized that the GH-IGF1 axis is affected by the route of insulin administration and that IP administration of insulin has a different effect compared to SC insulin therapy. Therefore we investigated the effects of CIPII, as compared to SC insulin therapy, on the GH-IGF1 axis in T1DM patients.

Patients and methods

STUDY DESIGN

This investigator initiated study had a prospective, observational matched-control design. Inclusion took place at Isala (Zwolle, the Netherlands) and Diaconessenhuis hospital (Meppel, the Netherlands). Primary aim was to compare the effects of long-term CIPII to SC insulin therapy, with respect to glycaemic control. As secondary outcome, and presented in this chapter, measures of the GH-IGF1 axis were assessed.

PATIENT SELECTION

Cases were subjects on CIPII therapy using an implanted insulin pump (MIP 2007D, Medtronic/Minimed, Northridge, CA, USA) for the past 4 years without interruptions of >30 days, in order to avoid effects related to initiating therapy. Inclusion criteria for cases were identical to those of a prior study in our centre and have been described in detail previously [25].

In brief, patients with T1DM, aged 18 to 70 years who fulfilled abovementioned criteria for CIPII and had a HbA1c ≥ 58 mmol/mol and/or ≥ 5 incidents of hypoglycaemia glucose (< 4.0 mmol/l) per week, were eligible.
The SC control group of the present study was age and gender matched to the cases. The SC control group consisted of T1DM patients, with SC insulin as mode of insulin administration (both multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII)), for the past 4 years without interruptions of >30 days and a HbA1c at time of matching ≥ 53 mmol/mol. Exclusion criteria, similar to the previous cross-over study, were identical for both cases and controls included impaired renal function, cardiac problems and current use or oral corticosteroids [25]. The ratio of participants on the different therapies (CIPII:MDI:CSII) was 1:2:2.

STUDY PROTOCOL

There were four study visits. During the first visit, baseline characteristics were collected using a standardized case record form. During the second visit (5-7 days later) laboratory measurements were performed. During the third visit, 26 weeks after visit 1, clinical parameters were collected. During the fourth visit, 5-7 days after the third visit, laboratory measurements were performed. Patients were instructed to visit the laboratory in a fasting state.

Throughout the study period, insulin (human insulin of E. Coli origin, 400 IU/ml, trade name: Insuman Implantable®, Sanofi-Aventis) was administered with an implantable pump for CIPII users and patients using CSII or MDI continued their own insulin regime consisting of fast-acting insulin analogues and for MDI patients also long-acting insulin analogues or NPH-insulin. All patients received standard care. The implanted insulin pump and related procedures have been described in more detail previously [24,26].

MEASUREMENTS

Demographic and clinical parameters included: age, gender, weight, length, blood pressure, smoking and alcohol habits, co-morbidities, medication use, year of diagnosis of diabetes, presence of microvascular (nephropathy, neuropathy and/or retinopathy) and macrovascular complications (angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, stroke, transient ischaemic attack, peripheral artery disease) and previous days insulin therapy (kind of insulin, dosage and, | if applicable, the number of daily injections). Blood pressure was measured using a blood pressure monitor (M6 comfort; OMRON Healthcare) using the highest mean of

4 measurements (2 on each arm). Laboratory measurements included, creatinine, c-peptide, total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), y-glutamyl transpeptidase (gamma-GT), alkaline phosphatase and urine albumin/creatinine ratio and HbA1c. HbA1c was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 20-42 mmol/mol). Serum samples for specific measurements were stored at -80°C until analysis, performed at the Department of Clinical and Experimental Medicine, Linköping University. Serum IGF1 was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE® 2000 immunoassay system, Siemens Healthcare Diagnostics, Mölndal, Sweden). Interassay coefficients of variation (CV) were 5.7% and 6.6% at IGF1 levels of 105 and 330 µg/l, respectively. Total plasma IGFBP1 was measured by a one-step enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA). Interassay CV was for high (2051 µg/l) and low (4 µg/l) controls 8.9% and 20.0% respectively. GH was analysed with a solid-phase, two-site chemiluminescent immunometric assay, (IMMULITE® 2000 immunoassay system, Siemens Healthcare Diagnostics, Mölndal, Sweden).

OUTCOME MEASURES

The primary outcome measure was the difference in IGF1 concentrations over the study period between CIPII and SC treated subjects. Secondary outcomes included differences in GH and IGFBP1 concentrations between CIPII and SC treated subjects, differences within groups during the study period, and differences between the different SC treatment modalities (e.g. MDI and CSII) and CIPII.

STATISTICAL ANALYSIS

Results were expressed as mean (with standard deviation (SD)) or median (with interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. A significance level of 5% (two sided) was used. Normality was examined with Q-Q plots. IGF1, IGFBP1 and GH concentrations were log transformed for the analysis and results were back transformed to geometric means. In addition concentrations of IGF1 were compared with the age-specific normative range values using Z-scores [27]. Differences between CIPII and SC groups averaged over the study period and in time were estimated using the general linear model. Multivariate regression analysis was performed with the mean score over the study period of either IGF1, IGFBP1 or GH as dependent variables and age, gender, BMI, mode of insulin therapy, total insulin dose and HbA1c as covariates.
Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The study protocol was registered prior to the start of

the study (NCT01621308 and NL41037.075.12) and approved by the local medical ethics committee. All patients gave informed consent.

Results

PATIENTS

From December 2012 through August 2013, a total of 335 patients were screened and received information about the study; 190 agreed to participate. After baseline laboratory measurements, 6 patients were excluded because of C-peptide concentrations exceeding 0.2 nmol/l (n=4) and an eGFR<40 ml/min (n=2). Consequently, 184 patients were followed during the 26-week study period. After the first visit one patient withdrew informant consent due to lack of interest. Therefore, 183 patients were analysed.

TABLE 1 **Baseline characteristics.**

	All (n=184)	**CIPII** (n=39)	**SC** (n=145)	**MDI** (n=71)	**CSII** (n=74)
Clinical					
Male sex (%)	67 (36)	14 (36)	53 (37)	23 (33)	30 (41)
Age (years)	50 (12)	50 (12)	50 (12)	52 (13)	48 (12)†
Current smokers (%)	78 (43)	20 (51)	58 (40)	28 (39)	30 (41)
Current alcohol use (%)	58 (32)	10 (26)	48 (33)	24 (34)	24 (32)
BMI (kg/m^2)	26.4 (4.5)	25.9 (4.4)	26.5 (4.6)	26.4 (4.9)	26.6 (4.3)
Diabetes duration (years)	26 (13)	29 (10)	26 (13)	24 (14)*	27 (12)
Retinopathy present (%)	64 (35)	17 (44)	47 (32)	19 (27)	28 (38)
Neuropathy present (%)	53 (29)	20 (51)	33 (23)*	19 (27)	14 (19)
Nephropathy present (%)	5 (3)	2 (5)	3 (2)	1 (1)	2 (3)
Macrovascular complication present (%)	26 (14)	7 (18)	19 (13)	10 (14)	9 (12)
Total insulin dose (IU/day)	46 [36, 64]	55 [42, 73]	45 [35, 62]*	48 [38, 64]	42.0 [33, 60]*†
Biochemical					
HbA1c (mmol/mol)	64 (11)	67 (14)	63 (9)	62 (9)	63 (4)
Fasting glucose (mmol/l) [a]	8.6 (3.7)	8.4 (3.8)	8.6 (3.7)	8.6 (3.8)	8.8 (3.7)
Creatinin (micromol/l)	69 (13)	70 (12)	69 (13)	69 (14)	69 (12)
Alkaline phosphatase (U/l)	73 (20)	78.1 (18.6)	71.6 (20.3)	72 (20)	72 (22)
Gamma-GT (U/l)	19 [14, 27]	22 [14, 36]	19 [14, 27]	17 [13, 24]	21 [14, 27]
AST (U/l)	23 [19, 27]	24 [20, 25]	23 [19, 27]	23 [20, 27]	23 [18, 28]
ALT (U/l)	18 [14, 24]	20 [15, 24]	18 [14, 25]	18 [15, 24]	18 [13, 25]
Total cholesterol (mmol/l)	4.8 (0.9)	4.9 (1.0)	4.8 (0.8)	4.8 (0.8)	4.7 (0.8)

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 as compared to CIPII. † p<0.05 for MDI versus CSII. P-values are based on appropriate parametric and non-parametric tests. Retinopathy, neuropathy and nephropathy categories do not add up. Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CSII; continuous intraperitoneal insulin infusion, CIPII; continuous intraperitoneal infusion, Gamma-GT; Gamma-glutamyl transpeptidase, MDI; multiple daily injections, SC; subcutaneous. [a] based on n=32 (CIPII), n=125 (SC), n=56 (MDI), and n=69 (CSII).

Baseline characteristics are presented in Table 1. All patients treated with SC insulin used a regimen consisting on short-acting analogues with, for MDI treated patients, additionally a long-acting insulin analogue (85.7%) or NPH-insulin (14.3%). Compared to patients using SC insulin therapy, CIPII patients used more units of insulin per day and had neuropathy more often.

PRIMARY OUTCOME - IGF1

Estimated geometric mean IGF1 concentration over the whole study period was higher among CIPII treated patients as compared to patients treated with SC insulin therapy: 123.7 µg/l (95% CI 110.8, 138.1) versus 108.1 µg/l (95% CI 101.7, 114.9), p=0.035. In addition, the Z-scores for IGF1 over the whole study period were significantly higher among CIPII treated patients as compared to patients treated with SC insulin therapy: -1.3 (95% CI -1.5, -1.1) versus -0.7 (95% CI -1.1, -0.4), p=0.02. During the study period, there were no differences in IGF1 concentrations within both groups (Table 2). There was no difference in the change of IGF1 concentrations over time between both groups (p=0.70)

TABLE 2 **Estimated outcomes at baseline and end for all, CIPII and SC treated T1DM patients.**

	All patients		**CIPII**		**SC**	
	Baseline	End	Baseline	End	Baseline	End
IGF1	116.9 (109.4, 124.8)	114.4 (107.0, 122.2)	124.5 (110.9, 139.6)	122.9 (109.4, 138.1)	109.7 (102.9, 116.9)	106.5 (99.9, 113.6) *
GH	0.96 (0.72, 1.29)	0.85 (0.65, 1.13)	0.74 (0.45, 1.23)	0.63 (0.38, 1.02)	1.25 (0.95, 1.65)	1.17 (0.89, 1.52) *
IGFBP1	83.3 (69.0, 100.5)	62.7 (51.9, 75.7) #	64.5 (46.2, 90.0)	40.2 (28.7, 56.0) #	107.4 (90.1, 128.0)*	98.0 (82.2, 116.9) *

Data are presented as estimated concentrations (95% CI). Concentrations are in µg/l. # p<0.05 compared to baseline. *p<0.05 SC compared with CIPII.

SECONDARY OUTCOME - IGFBP1 AND GH

Concentrations of IGFBP1 and GH were significantly lower among CIPII treated patients as compared to subjects treated with SC insulin therapy: 50.9 µg/l (95% CI 37.9, 68.2) versus 102.6 µg/l (95% CI 87.8, 119.8) (p<0.001) for IGFBP1 and 0.68 µg/l (95% CI 0.44, 1.06) versus 1.21 µg/l (95% CI 0.95, 1.54) (p=0.027) for GH, respectively. Over time, there were no significant differences in GH within the groups, while for IGFBP1 there was a significant difference between baseline and end of the study in the CIPII group (p=0.003) (Table 2).

SECONDARY OUTCOME - MDI AND CSII VERSUS CIPII

No statistically significant differences were present between and within MDI and CSII treated patients in IGF1, IGFBP1 and GH concentrations (Table 3). Mean IGF1 concentrations among MDI and CSII treated patients were non-significantly lower in CIPII treated subjects. IGFBP1 concentrations among MDI (p<0.001) and CSII (p=0.004) treated patients were higher as compared to CIPII treated patients. GH concentrations were significantly higher for CSII (p=0.039) treated subjects but not for MDI treated patients (p=0.39) as compared to CIPII treated patients.

TABLE 3 Estimated outcomes for MDI and CSII treated T1DM patients.

	MDI			CSII		
	Baseline	End	Mean	Baseline	End	Mean
IGF1	109.5 (99.9, 120.1)	106.4 (96.4, 119.7)	107.9 (98.8, 117.9)	109.8 (100.7, 119.7)	106.7 (97.3, 116.9)	108.2 (99.6, 117.7)
GH	1.12 (0.75, 1.66)	0.98 (0.67, 1.48)	1.05 (0.74, 1.48)	1.40 (0.95, 2.08)	1.39 (0.95, 2.02)	1.39 (0.99, 1.96)*
IGFBP1	120.2 (94.0, 153.7)	116.4 (91.7, 147.7)	118.3 (93.8, 149.2)*	98.2 (78.8, 122.4)	85.4 (69.1, 105.6)	91.2 (38.0, 68.2)*

Data are presented as estimated concentrations (95% CI) at baseline, end and over the whole study period. Concentrations are in µg/l. *p<0.05 compared with CIPII.

SECONDARY OUTCOME - MULTIVARIATE REGRESSION ANALYSIS

In multivariate regression analysis with mean IGF1 score over the whole study period as dependent variable, age, BMI and total daily insulin dose were significant while gender, mode of insulin therapy and HbA1c were not (Table 4). In the same model with mean IGFBP1 score as dependent variable, age, gender,and mode of insulin therapy were significant. When using the mean GH score as dependent variable, gender and mode of insulin therapy were significant.

For hypothesis generation ultivariate regression analysis with IGF1, IGFBP1 or GH as dependent variable and HbA1c and total insulin dose as covariates was repeated within both the CIPII and SC group separately. Among SC treated patients, the total daily insulin dose was significant associated with IGF1, IGFBP1 and GH (B= 0.47 (standard error (SE) 0.17, 95% CI 0.13, 0.81 and adjusted r2= 0.05) for IGF1; B=-1.06 (SE -0.25, 95% CI -1.84, -0.28 and adjusted r2=0.06) for IGFBP1; B=-0.03 (SE 0.01, 95% CI -0.05, -0.001 and r2=0.16) for GH) but not among CIPII treated subjects. HbA1c was not significant in any of the models.

TABLE 4 **Outcomes of multivariate regression analysis for IGF1, IGFBP1 and GH.**

	IGF1	IGFBP1	GH
Age	-1.54 (0.23) (-2.00,-1.08)*	1.18 (0.59) (0.02, 2.33)*	-0.02 (0.02) (-0.05, 0.02)
Gender	10.24 (6.3) (-2.23, 22.71)	46.51 (16.17) (14.54, 78.47)*	2.60 (0.53)(1.55, 3.65)*
BMI	-1.61 (0.76) (-3.11, -0.12)*	-3.13 (1.9) (-6.89, 0.63)	-0.09 (0.06) (-0.21, 0.04)
Total daily insulin dose	0.49 (0.15) (0.19, 0.80)*	-0.39 (0.39) (-1.17, 0.38)	0.01 (0.01) (0.02, 0.03)
HbA1c	-0.33 (0.30) (-0.93, 0.26)	-1.02 (0.77) (-2.54, 0.51)	0.02 (0.02) (-0.03, 0.07)
Mode of insulin therapy	10.17 (7.15) (-3.94, 24.29)	-42.54 (18.42) (-78.95, -6.13)*	-1.32 (0.6) (-2.50, -0.14)*

Data are presented as B (SE) (95% CI). R2=0.30 for the model with IGF1, R2=0.16 for the model with IGFBP1 and R2=0.15 for the model with GH as dependent variable.*p<0.05.

Discussion

Main finding of the present study is that CIPII treated T1DM patients have higher concentrations of IGF1 as compared to patients treated with SC insulin therapy. Furthermore, IGFBP1 and GH concentrations are significantly lower among patients treated with CIPII. Over the study period, IGF1 and GH concentrations were stable within groups: only IGFBP1 decreased more with CIPII as compared to SC insulin therapy. Taken together, these findings show a role of IP insulin in the GH-IGF1 axis.

Decreased hepatic insulinization due to insulinopenia in the portal vein has been suggested to cause alterations in the GH-IGF1 axis among T1DM patients. Although the low IGF1 levels are ascribed to insulinopenia, insulin has no direct effect on IGF1 synthesis but there is strong evidence that insulin is, indirectly, essential for GH-stimulation of hepatic IGF1 production. In experimental diabetes GH-binding to the liver is reduced and can be increased by insulin treatment indicating that GH-receptor number is regulated by insulin [28].
Data from human hepatocytes are lacking but in a human hepatoma cell line insulin has been reported to augment GH-receptor expression and affect surface translocation [8]. The higher IGF1 concentrations in combination with lower GH concentrations among CIPII treated patients as compared to SC treated patients found in this study, support the hypothesis that increased hepatic insulinization due to IP insulin administration results in increased hepatic GH sensitivity and, subsequently, higher IGF1 levels. Accordingly, as GH secretion is under negative feedback by concentrations of IGF1, the lower GH concentrations among CIPII treated patients is probably the result of a near-normalization of IGF1 concentrations.

Insulin also affects IGF1 concentrations by altering the concentrations of its binding proteins. The lower IGFBP1 concentrations among CIPII treated patients, as compared to patients treated with SC insulin, found in the present study are in line with previous reports [21,23]. Except in pregnancy, IGFBP1 is exclusively produced in the liver. In contrast to IGF1, IGFBP1 is directly regulated by insulin at the transcriptional level. As IGFBP1 is regulated in an inverse manner by insulin levels in the portal vein, IP insulin may causes higher IGF1-bioactivity/free IGF1 in addition to the change in total IGF1 enhancing the effect of IGF1 and the feedback on GH-secretion [21,23,24].

In addition to portal insulinopenia, metabolic control has also been suggested to impact the GH-IGF1 system. In the present study however, HbA1c had no significant association with IGF1 concentrations in multivariate analysis. On the other hand, the total daily insulin dose (positive) and BMI (negative) did have an significant association with IGF1 concentrations. Although no data on plasma insulin concentrations is available in the present study, this may suggest that the effects of insulin on IGF1 are dependent on the rate of absorption and degradation of insulin to create a subsequent more physiologic systemic to portal insulin gradient, and not via ordinary glycaemic control [15,16]. Accordingly, although all patients in the present study used insulin analogues, diversity in within and between the effects of MDI and CSII on the GH-IGF1 axis could be a result of differences in the rate of absorption and degradation of insulin precipitations.

To our knowledge, the present study is the largest investigating the effects of CIPII relative to SC insulin therapy among T1DM on the GH-IGF1 axis. Nevertheless, the lack of differences in IGF1 in subgroup analysis of MDI and CSII versus CIPII could be due to small numbers. Furthermore, the results of this unique study need confirmation. Other strengths of the present study include the use of patients who have been using their current mode of therapy for several year, thus creating a stable situation, patients used insulin analogues and measurements made on two points in time. At present, the clinical consequences of our findings remain to be determined. Nevertheless, based on the insulin antagonizing actions of GH and the insulin sensitizing actions of IGF1, increased insulin sensitivity among CIPII patients could be hypothesized and may also contribute to prevention of late-term complications [29–32].

Conclusion

Among T1DM patients treated with CIPII, concentrations of IGF1 are higher and closer to normal as compared to patients treated with SC insulin therapy. Additionally, IGFBP1 and GH concentrations were lower among CIPII treated patients as compared to SC treated patients. These findings suggest that CIPII is more beneficial than SC insulin in correcting the altered GH-IGF1 axis in T1DM.

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