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van Dijk, Peter R.

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CHAPTER 8

Effect of intraperitoneal insulin administration on IGF1 and IGFBP1 in type 1 diabetes

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Abstract

INTRODUCTION

In type 1 diabetes mellitus (T1DM), low IGF1 concentrations and high levels of IGF binding protein-1 (IGFBP1) have been reported. It has been suggested that these abnormalities in the GH-IGF1 axis are due to low insulin levels in the portal vein. We hypothesized that the intraperitoneal (IP) route of insulin administration increases IGF1 concentrations as compared to subcutaneous (SC) insulin.

PATIENTS AND METHODS

Determination of IGF1 and IGFBP1 concentrations in samples derived from an open-label, randomized cross-over trial comparing the effects of SC and IP insulin delivery on glycaemia. T1DM patients were randomized to receive either 6 months continuous intraperitoneal insulin infusion (CIPII) through an implantable pump (MIP 2007C, Medtronic) followed by 6 months SC insulin or vice versa with a washout phase in between.

RESULTS

Data from 16 patients, 6 males and 10 females with a median age of 42.4 [30.4, 49.4] years and a diabetes duration of 21.7 [10.4, 30.5] years, who completed measurements during both treatment phases was analysed. The change in IGF1 during CIPII was 10.4 µg/l (95% confidence interval (CI) -0.94, 21.7 µg/l; $p=0.06$) and -2.2 µg/l (95% CI -13.5, 9.2 µg/l; $p=0.69$) during SC insulin. Taking the effect of treatment order in account, the estimated change of IGF1 was 12.6 µg/l (95% CI -3.1, 28.5 µg/l; $p=0.11$) with CIPII compared to SC insulin. IGFBP1 concentrations decreased with -100.7 µg/l (95% CI -143.0, -58.3 µg/l; $p<0.01$) with CIPII.

CONCLUSIONS

During CIPII treatment parts of the growth hormone-IGF1 axis changed compared to SC treatment. This supports the hypothesis that the IP route of insulin administration is of importance in the IGF1 system.

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 regulation¹⁻³. 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 an inverse direction) by insulin thereby allowing insulin to regulate IGF1 bioactivity⁴⁻⁷.

Through an up-regulation of hepatic GH-receptor expression, insulin increases the hepatic sensitivity of GH stimulation and subsequent increases IGF1 production⁸. Furthermore, insulin may increase IGF1 bioactivity by a down-regulation of IGFBP1 in the liver⁵. In type 1 diabetes mellitus (T1DM), with insufficient insulinization of the liver due to lack of endogenous insulin in the portal vein, there appears to be a dysfunction of the growth hormone-IGF1 axis. This is characterized by low concentrations of total IGF1 and IGFBP3 and high concentrations of IGFBP1 and GH⁹⁻¹⁴. Although these abnormalities have been described in situation of poor glycaemic control, exogenous subcutaneous (SC) insulin only attenuate these disturbances but do not completely reverse them¹⁵⁻¹⁸.

With continuous intraperitoneal insulin infusion (CIPII) insulin is infused directly in the intraperitoneal (IP) space and is almost entirely absorbed in the portal system, resulting in higher portal insulin concentrations, higher hepatic uptake and lower peripheral plasma insulin concentrations compared with SC insulin administration^{19,20}. This results in a more physiologic mode of insulin administration compared to SC insulin administration and could thus have a beneficial effect on the impaired GH-IGF1 axis²¹. We tested the hypothesis that IP administered insulin as compared to SC insulin results in an increase of IGF1 concentrations in samples derived from a randomized cross-over trial.

Patients and methods

STUDY DESIGN AND POPULATION

The full study design has been published previously²². In brief, the study from which the samples were derived had an open-label randomized, crossover design and was conducted

at a single center (Isala, Zwolle, the Netherlands). The study consisted of 4 phases: the qualification phase, the first treatment phase, the crossover phase, and the second treatment phase. During a 3-month qualification phase, the patients' prestudy insulin therapy was used to attempt optimization of their glycemic control. Patients with T1DM (aged 18–70 with fasting C-peptide concentrations <0.20 nmol/l, HbA1c ≥ 58 mmol/mol and/or ≥ 5 incidents of hypoglycaemia (<4.0 mmol/l) per week and treated with multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII) were randomly allocated to continue their current SC mode of therapy or start with IP insulin administration using an implantable pump. These 2 groups (start IP or continue SC) differed only in the sequence of the mode of insulin administration. Randomisation was carried out using sealed non-transparent envelopes, with adequate blinding of the content of the envelope. Patients were assigned to the treatment order as defined by the code in the envelope (start IP or continue SC). The randomization system used blocks of 4. In the original study, of the 50 patients that were screened for eligibility 25 entered the qualification phase. One patient reached acceptable glycaemic control during the qualification phase, thus 24 patients were randomly assigned and started the first treatment phase; 12 patients were assigned to continue SC insulin and 12 patients to start with CIPII during the first phase of the trial. One patient, with CIPII at start, withdrew consent during the trial. In the present analysis we only included patients with complete IGF1 results in both treatment phases, therefore 7 patients were excluded.

Insulin (U400 semi synthetic human insulin of porcine origin; Hoechst, Frankfurt, Germany, nowadays Sanofi-Aventis) was administered with an implantable pump (MIP 2007C; Medtronic/Minimed, Northridge, CA). The CIPII pump was implanted under general anaesthesia at the start of the CIPII phase in all subjects. For subjects who received SC insulin during the second treatment phase, the CIPII pump was filled with an inert fluid at the end of the first treatment phase. SC insulin was delivered with either MDI or CSII, according to what was used prior to the study.

Patients treated with MDIs continued to use their own insulin regime, i.e. rapid acting insulin analogues before meals and a daily dose of long acting insulin. Between both treatment phases of 6 months, a crossover phase of 4 weeks was instituted to minimize the carryover effects of CIPII. During the crossover phase insulin was administered SC.

If the subject was using more than 40 IU of SC insulin per day prior to starting the CIPII phase of the study, his or her starting dose was set at 90% of the prior SC dose. Subjects

using less than 40 IU of SC insulin received a starting dose of 80% of the prior SC dose. Initially the dose was equally divided between a basal rate (50%) and a bolus before meals. During all study visits, the 7-point glucose readings were used to adjust the dose regimen if necessary to achieve pre-prandial glucose levels between 4.0-7.0 mmol/l and post-prandial levels between 4.0-9.0 mmol/l. Patients were instructed not to start a specific diet or weight reduction program during the trial.

MEASUREMENTS

Measurements of clinical and biochemical parameters were performed at baseline, the end of the qualification phase, at the start, at the halfway point, and at the end of both treatment phases. HbA_{1c} levels were measured using a Primus Ultra2 using high-performance liquid chromatography (reference value 20-42 mmol/mol). IGF1 and IGFBP1 levels, reported as µg/l, were measured in 1.5 cc serum samples collected at random and nonfasting at the start and end of each treatment phase and stored at -80°C until analysis in 2011, performed at the department of clinical and experimental medicine of the Linköping University, Linköping, Sweden. Total IGF1 was measured by a one-step ELISA after acid-ethanol extraction from its binding protein using a commercial kit (Human IGF-1 Quantikine ELISA Kit R&D Systems, Minneapolis, MN, USA)²³. Interassay coefficients of variation were 10.9, 5.9, and 18.2% for high (278 µg/l), medium (116 µg/l), and low (45 µg/l) controls respectively. IGFBP1 was measured with ELISA (human IGFBP1 DuoSet, DY871, R&D Systems, Minneapolis, MN, USA). The assay was performed according to the protocol provided by the manufacturer. Microtiterplates, MaxiSorp (Nunc Roskilde Denmark), normal goat serum (Fisher Scientific) and (tetramethylbenzidinedehydrochloride (Sigma Life Science) were used. The microtiterplates were coated overnight with capture antibody. Interassay coefficients of variation (CV) was for high (1688 µg/l) and low (4 µg/l) controls 7.8% and 20.0% respectively.

OUTCOMES

The primary outcome of this post-hoc analysis is the difference in IGF1 concentrations between the two treatment phases. Secondary outcomes include changes in IGFBP1 during both treatment phases, changes in IGF1 and IGFBP1 for patients with and without detectable C-peptide and correlations of changes in HbA_{1c}, total insulin dose, C-peptide and with IGF1 and IGFBP1.

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. To calculate the mean difference with a 95% confidence interval (CI) the Hills-Armitage approach was used, which accounts for any period effect. Linear mixed models (PROC MIXED, SAS 9.2) were used to test differences, taking treatment order into account. The assumption of normal distribution of the residuals was examined using Q-Q plots. In addition Q-Q plots were used to determine if the tested variable had a normal distribution or not. Correlations were investigated using the Pearson product-moment correlation coefficient or, when appropriate, the nonparametric Spearman's rho. Comparisons between outcomes during both treatment modalities were performed using t-test for paired comparisons for IGF1 and Wilcoxon match-pair signed-rank tests for IGFBP1. Patients with and without detectable C-peptide were compared with unpaired t-test. The IGFBP1 concentrations had a skewed distribution (right tail) and are presented as median and the IQR. The differences of IGFBP1 were normal distributed. Besides the linear mixed models, all analyses were performed using SPSS version 18.0, Inc, Chicago, IL, USA. A (two-sided) p-value of less than 0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients for the initial study. The protocol was approved by the medical ethics committee of the Isala in Zwolle. For the present study additional informed consent was obtained.

Results

PATIENTS

The study sample consisted of 16 patients, 6 males and 10 females, with a median age of 42.4 [30.4, 49.4] years and a diabetes duration of 21.7 [10.4, 30.5] years. Three patients used MDI and 13 CSII before the study, the qualification- and SC phase. The mean IGF1 concentrations at the start of the SC and IP insulin phase did not differ: 83.7 (31.9) and 76.3 (24.5) µg/l, respectively.

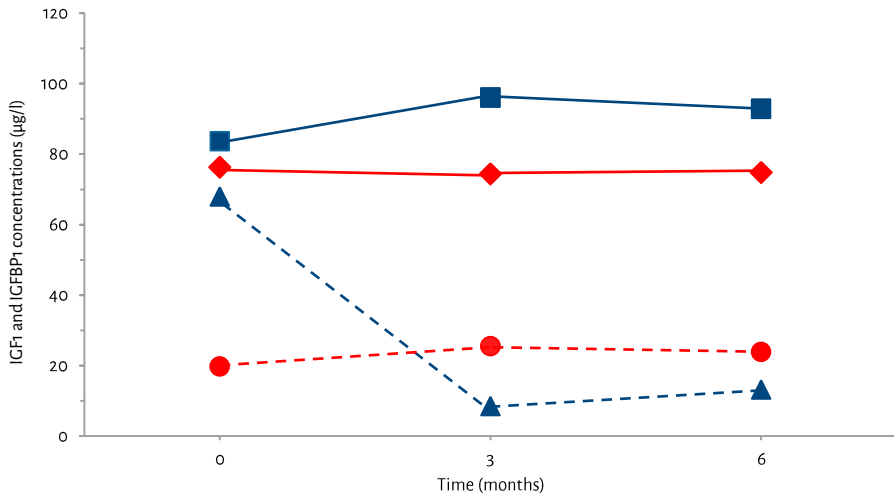
IGF1 AND IGFBP1

The observed results of the IGF1 and IGFBP1 measurements during the different treatment modalities are depicted in Table 1 and Figure 1. The observed IGF1 and IGFBP1 concentrations were significant different between both treatment modalities at 3 and 6 months.

TABLE 1 Observed IGF1, IGFBP1 and HbA1c concentrations and estimated changes during SC- and IP insulin treatment.

	IGF1 ($\mu\text{g/l}$)		IGFBP1 ($\mu\text{g/l}$)		HbA1c (mmol/mol)	
	CIPII	SC	CIPII	SC	CIPII	SC
0 months^a	83.7 (31.9)	76.3 (24.5)	68.0 [35.3, 213.6]	19.7 [11.9, 52.0] [*]	68 (16.5)	68 (15.4)
3 months	96.1 (44.9)	74.4 (28.0) [*]	8.5 [5.8, 14.4]	25.5 [9.5, 45.5] [*]	60 (6.6)	70 (14.3) [*]
6 months	92.9 (39.3)	74.8 (16.0) [*]	13.2 [6.6, 22.1]	23.9 [14.6, 56.2] [*]	61 (9.9)	69 (18.7) [*]
Change^b	10.4 (-0.94, 21.7; $p=0.06$)	-2.2 (-13.5, 9.2; $p=0.69$)	-100.7 (-143.0, -58.3; $p<0.01$)	9.4 (-33.0, 51.78; $p=0.64$)	-8.9 (-14.4, -3.3; $p<0.05$)	0.8 (-5.6, 6.7; $p=0.78$)

IGF1 and HbA1c are presented as mean (SD) and the IGFBP1 concentrations are presented as median [IQR]. N=16 for IGF1, IGFBP1 and HbA1c on all timepoints. ^{*} $p<0.05$ for CIPII versus SC at that moment in time. ^a 0 months: at end of 3-month qualification phase. ^b Estimated mean changes of IGF1, IGFBP1 (both in $\mu\text{g/l}$) and HbA1c (mmol/mol) per treatment modality (95% CI).

FIGURE 1 Course of mean IGF1 (consecutive line) and median IGFBP1 (dashed line) concentrations during 6 months on SC (red line) or IP insulin (blue line).

No significant carry-over effects between both treatment phases were present for IGF1 ($p=0.33$) and IGFBP1 ($p=0.83$). The estimated mean change in IGF1 concentrations during CIPII was $10.4 \mu\text{g/l}$ (95% CI $-0.94, 21.7$) and $-2.2 \mu\text{g/l}$ (95% CI $-13.5, 9.2$) during SC insulin therapy. When taking the effect of treatment order in account, the estimated difference between the IP phase and SC phase was $12.6 \mu\text{g/l}$ (95% CI $-3.1, 28.5$). The IGFBP1 concentrations decreased significantly during the IP phase, $-100.7 \mu\text{g/l}$ (95% CI $-143.0, -58.3$), but not during the SC phase, $9.4 \mu\text{g/l}$ (95% CI $-33.0, 51.8$). The estimated difference between both phases was $-110.4 \mu\text{g/l}$ (95% CI $-170.0, -50.1$).

GLYCEMIC CONTROL

HbA1c decreased with CIPII from 68 (16.5) mmol/mol to 60 (6.6) mmol/mol after 3 months and remained stable at 6 months (61 (9.9) mmol/mol), see Table 1. During SC treatment there was no change in HbA1c. No significant carry-over effects between both treatment phases were present ($p=0.05$). HbA1c improved with -10.0 mmol/mol (95% CI $-18.4, -1.6$) with CIPII compared to SC insulin treatment. During IP treatment, changes in HbA1c correlated with changes in IGF1 ($r=-0.5, p=0.04$), but not with IGFBP1 ($r=-0.3, p=0.33$).

TOTAL INSULIN DOSE, C-PEPTIDE AND ASSOCIATIONS WITH IGF1 AND IGFBP1

Mean daily insulin dose decreased with -2.0 IU/day (95% CI $-13.7, 9.6$) during IP treatment as compared to SC insulin treatment. The Spearman's correlation coefficient showed a non-significant association between the mean difference in insulin dose and IGF1 during IP treatment ($r=-0.02, p=0.95$). The change in IGFBP1 did not correlate with changes in total insulin dose ($r=0.19, p=0.48$) during the IP treatment phase. Changes in IGF1 and IGFBP1 during CIPII did not show any significant correlation ($r=-0.23, p=0.40$).

There was no significant difference in the change in IGF1 during the IP phase between patients with a undetectable (≤ 0.01 nmol/l, $n=6$) and detectable (>0.01 nmol/l, $n=10$) C-peptide: 12.6 (22.2) ng/ml vs. 3.7 (22.1) ng/ml ($p=0.45$). For IGFBP1 these concentrations were -49.5 [$-222.9, -17.4$] and -57.7 [$-182.7, -12.3$] $\mu\text{g/l}$, respectively. The association between the level of C-peptide and the change in IGF1 during the IP or SC phase was also not significant: $r=-0.02$ ($p=0.94$) and $r=-0.16$ ($p=0.56$).

Discussion

Concentrations of IGFBP1 decreased significantly during CIPII compared to SC treatment. IGF1 did not change significantly during IP treatment and compared to intensive SC insulin treatment this was also not significant.

Since there is (almost) no insulin production in patients with T1DM it has been hypothesized that low insulin levels in the portal vein causes decreased IGF1 concentrations through both GH- receptor and IGFBP1 mediated mechanisms^{5,8}. In all three studies of the IGF system in which subjects with T1DM were treated with IP insulin infusion a rise in IGF1 was observed. Shishko *et al.* reported normalization of plasma IGF1 with intraportal infusion of insulin in newly diagnosed patients with T1DM²⁴. Unfortunately that study lacks data regarding the presence or absence of endogenous production of insulin. A longitudinal study by Hanaire-Broutin *et al.* showed a steady rise in plasma IGF1 concentrations to a low-normal level, one year after initiating CIPII despite a lack of improvement in HbA1c¹⁸. In the current study, IGF1 was significantly higher after 3 and 6 months with CIPII compared to SC and a non-significant change of 10.4 µg/l was seen within the IP treatment period of 6 months. Compared to SC insulin this change was not significant. These findings may be due to sample size (n=16) and/or the duration of the present study. In the study of Hanaire-Broutin, the IGF1 still tends to increase after 6 months. In severely uncontrolled diabetes IGF1 levels are low but ordinary glycemic control probably has little effect on IGF1 levels as this study suggests and Hedman *et al.* showed earlier^{17,25}.

At the start of the CIPII treatment several patients had very high IGFBP1 values. Due to these outliers, the IGFBP1 levels at the start of the IP phase were high. Of interest, all 5 patients with IGFBP1 concentrations >150 µg/l (range: 181.2 to 330.0) were in the 'IP first' crossover group. It was remarkable that additional analysis showed a significantly longer median duration between pump implantation and measurement of IGFBP1 for these 5 patients compared to the other patients (0.5 vs. 0.0 years, p<0.001). Therefore we hypothesize that the high IGFBP1 concentrations in these 5 individuals represent an acute effect in the start-up phase of IP insulin. It has been reported that insulin withdrawal for 8 hours in T1DM patients treated with CSII increased IGFBP1 levels 6-fold and it is conceivable that the high IGFBP1 values could be due to a lag in insulin delivery⁴. Nevertheless, post-hoc analysis of patients with IGFBP1 concentrations <150 µg/l still showed that the change in IGFBP1 during IP treatment remained significant (-46.3 µg/l, 95% CI -80.2, -12.4) and, since a right skew could influence the estimated difference between the treatment modalities, that the

estimated difference between the treatment groups remained present $-49.9 \mu\text{g/l}$ (95% CI $-97.9, -1.92$). When paired comparisons of IGFBP1 levels were made during treatment at 3 and 6 months, IGFBP1 was lower with CIPII than with CSII. The lowering of IGFBP1 suggest an increase in free IGF1 i.e. IGF1 bioactivity by CIPII ¹. Since there was no increase in insulin dose this is compatible with an enhanced insulin effect on the liver by CIPII ³. The observed decrease of IGFBP1 concentrations in the current study are in line with previous reports and, since IGFBP1 correlates to GH secretion and hepatic glucose production, may indicate importance of the IP route of insulin administration ^{24,26,27}.

For the interpretation of the results of this study, it must be acknowledged that the original study was powered to detect differences in hypoglycemic events between IP and SC insulin, and not in IGF1 or IGFBP1 concentrations. In contrast to the studies by Shishko and Hanaire-Broutin, samples were taken at random and information about the antecedent insulin dose is lacking ^{18,24}. Finally, lack of a large reference population impairs comparison of the IGF1 concentrations found in the present study with those of healthy subjects.

Conclusions

Although the clinical significance of low IGF1 concentrations in patients with T1DM remains unclear at the present, CIPII could have an additional benefit on top of glycemic control by altering the dysregulated GH-IGF-system through increasing portal insulin concentration. This is a hypothesis worth testing in future research.

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