CHAPTER 9

After 6 years of intra-peritoneal insulin administration IGF1 concentrations in T1DM patients are at low-normal level

Abstract

BACKGROUND

Low concentrations of insulin-like growth factor-1 (IGF1) have been reported in type 1 diabetes mellitus (T1DM). This has been suggested to be due to low insulin concentrations in the portal vein. Aim was to describe the long-term course of IGF1 concentrations among T1DM subjects treated with continuous intraperitoneal (IP) insulin infusion (CIPII).

METHODS

Nineteen patients that participated in a randomized cross-over trial comparing CIPII and subcutaneous (SC) insulin therapy in 2006 were followed until 2012. IGF1 measurements were performed at the start of the 2006 study, after the 6 month SC- and CIPII treatment phase in 2006 and during CIPII therapy in 2012. Linear mixed models were used to calculate estimated values and to test differences between the moments in time.

RESULTS

In 2012, IGF1 concentrations (123.1 µg/l; 95% confidence interval (CI) 111.1, 135.0) were significantly higher than at the start of the 2006 study (62.0 µg/l; 95% CI 44.7, 79.3), the end of the SC (69.4 µg/l; 95% CI 55.8, 82.9) and CIPII (81.5 µg/l; 95% CI 68.7, 94.3) treatment phase with a mean difference of: -61.1 µg/l (95% CI -82.1, -40.0), -53.7 µg/l (95% CI -71.3, -36.0) and -41.5 µg/l (95% CI -58.6, -24.4), respectively. As compared to a non-DM reference population the Z-score for IGF1 in 2012 was -0.7 (95% CI -1.3, -0.2) and this score was significantly higher than the Z-scores measured in 2006.

CONCLUSIONS

After 6 years of treatment with CIPII, IGF1 concentrations among T1DM patients increased to a level that is higher than during prior SC insulin treatment and is in the lower normal range compared to a non-DM reference population. The results of this study suggest that long-term IP insulin administration influences the IGF system in T1DM.

Introduction

Insulin-like growth factor-1 (IGF1) is synthesized in the liver after stimulation of the growth hormone (GH)-receptor and plays a central role in cell metabolism and growth regulation [1]. Insulin seems to increase the sensitivity of the liver to GH stimulation, probably by up regulating GH receptor expression, and thereby augments IGF1 production [2]. Insulin may also increase IGF1 bioactivity indirectly by down regulating the hepatic production of the IGF binding protein (IGFBP)-1 [3,4].

In type 1 diabetes mellitus (T1DM), a decrease in IGF1 concentrations has been described together with low concentrations of IGFBP3 and high concentrations of IGFBP1 and GH [5–7]. It has been suggested that these abnormalities in the IGF-system are due to poor glycaemic control, however, there is increasing evidence for a role of insufficient insulinization of the liver secondary to low insulin concentrations in the portal vein [8–13].

With continuous intraperitoneal insulin infusion (CIPII), insulin is directly infused in the intraperitoneal (IP) space where it is absorbed via the peritoneum into the catchment area of the portal vein, resulting in higher insulin concentrations in the portal vein, higher hepatic uptake of insulin and lower peripheral plasma insulin concentrations as compared to SC insulin administration [14,15]. Although some previous studies among CIPII treated T1DM patients demonstrated increases in IGF1 concentrations, the long-term effects of CIPII therapy on IGF1 concentrations are unknown.

Patients and methods

STUDY DESIGN AND POPULATION

In order to describe long-term course of the IGF1 during CIPII therapy, also in comparison with previous SC insulin therapy, we compared data from IGF1 measurements in 2012/2013 with data derived from an open-label, randomized cross-over trial in 2006. Aims, design, population, procedures and outcomes of these studies, including analysis of IGF1 concentrations during the previous cross-over study, have been reported previously [16–19].

In brief, 23 T1DM patients (fasting C-peptide concentrations <0.20 nmol/l) in intermediate or poor glycaemic control, defined as HbA1c ≥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, initiated CIPII therapy in 2006. After the cross-over study all patients chose to continue CIPII. Follow-up measurements for the present analysis were performed in December 2012 until March 2013 (referred to as '2012 measurements'). Between 2006 and 2012, all patients received standard care at the outpatient clinic of the Isala (Zwolle, The Netherlands) [20].

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 (MIP 2007D, Medtronic/Minimed, Northridge, CA, USA). Insulin pump, implantation, insulin dosage and -refill procedures have been described [17,21]. 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®, Frankfurt, Germany, Sanofi-Aventis) was used from 2010 onwards.

MEASUREMENTS

HbA1c was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 20-42 mmol/mol). IGF1 in the 2006 samples was measured by a one-step ELISA after acid-ethanol extraction from its binding protein using a commercial kit (Human IGF-I Quantikine ELISA Kit R&D Systems, Minneapolis, MN, USA) [22]. Interassay coefficients of variation (CV) were 10.9%, 5.9%, and 18.2% for high (278 µg/l), medium (116 µg/l), and low (45 µg/l) controls respectively. In the 2012/2013 samples IGF1 was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE® 2000 immunoassay system, Siemens Healthcare Diagnostics, Mölndal, Sweden). Interassay CV were 5.7% and 6.6% at IGF1 levels of 105 and 330 µg/l, respectively.

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. Linear mixed models with Bonferroni correction were used to calculate and to test differences in time. Correlations were investigated using the nonparametric Spearman's rho. In order to compare the IGF1 concentrations with age-specific normative range values of a non-DM reference population, Z-scores were calculated [22,23]. Statistical analysis were performed with SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Studies were performed in accordance with the Declaration of Helsinki and approved by the medical ethics committee of Isala (Zwolle, the Netherlands).

Results

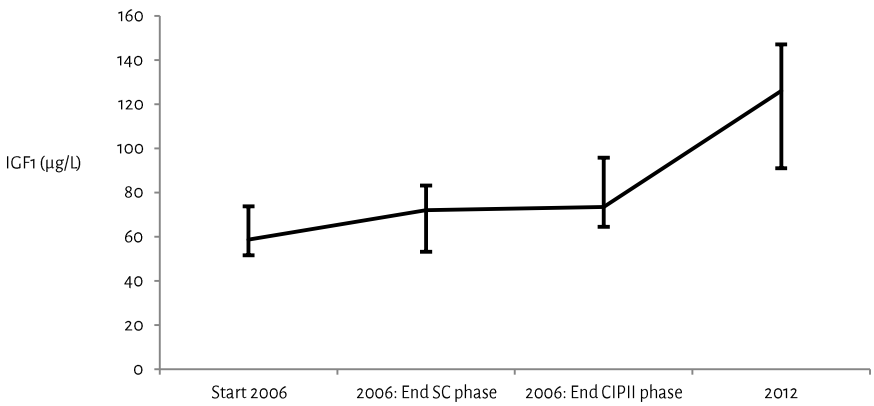
PATIENTS

Of 23 patients who participated in the previous cross-over study, 22 were still treated with CIPII in 2012. Two patients were excluded from the current analysis: 1 due to chronic glucocorticosteroid use for myasthenia gravis and 1 due to participation in an in vitro fertilization program. One patient refused participation. Therefore, 19 patients (53% male) are included in the present analysis, with a mean age of 45 (10) years and a diabetes duration of 23 [16, 33] years at the start of the 2006 study. Baseline HbA1c was 69 (12) mmol/mol and the total insulin dose was 50 [35, 70] IU/day, of which 28 [22, 31] U/day were given in a basal and 16 [10, 25] IU/day in a bolus manner: these parameters did not change over time.

IGF1

The observed outcomes for IGF1 are presented in Figure 1. IGF1 concentrations measured in 2012 were 123.1 µg/l (95% CI 111.1, 135.0), with a subsequent Z-score of -0.7 (95% CI -1.3, -0.2) in comparison to a non-DM reference population. As presented in Table 1, both the IGF1 concentrations and the Z-scores measured in 2012 were higher than during measurements at the start, end of the SC- and the end of the CIPII treatment phase of the 2006 cross-over study.

FIGURE 1 **Observed outcomes of IGF1 at different points in time.**



The line represents IGF1 concentrations at different points in time with 95% CI (vertical). Abbreviations: CIPII, continuous intraperitoneal insulin infusion; IGF1, insulin-like growth factor-1; SC, subcutaneous.

TABLE 1 **Estimated outcomes and differences between the different points in time.**

	Start 2006 study	End SC phase	End CIPII phase	2012 study
Estimated outcomes				
IGF1 (µg/l)	62.0 (44.7, 79.3)	69.4 (56.4, 82.4)	81.5 (69.3, 93.8)	123.1 (111.1, 135.0)
Z-score	-2.5 (-3.3, -1.8)	-2.0 (-2.6, -1.5)	-1.6 (-2.1, -1.0)	-0.7 (-1.3, -0.2)
Difference with 2012 measurements				
IGF1 (µg/l)	-61.1 (-82.1, -40.0)*	-53.7 (-71.3, -36.0)*	-41.5 (-58.6, -24.4)*	-
Z-score	-1.8 (-2.7, -0.9)*	-1.3 (-2.1, -0.5)*	-0.8 (-1.6, -0.1)*	-

Data are presented as mean (95% CI) IGF1 in µg/l. Abbreviations: CIPII, continuous intraperitoneal insulin infusion; IGF1, insulin-like growth factor-1; SC, subcutaneous. * p<0.05.

There were no significant correlations between the mean difference of measurements at the end of the IP phase of the 2006 study and 2012 follow-up measurements for IGF1 and HbA1c (r=-0.18, p=0.47) and daily insulin dose (r= 0.25, p=0.33).

Discussion

With long-term use of IP insulin administration, IGF1 levels approach concentrations as measured in a non-DM reference population. In addition, IGF1 concentrations seem to be significantly higher on long-term CIPII treatment as compared to previous intensive SC insulin therapy. Taken together, the results of this study support the hypothesis that IP insulin administration influences the IGF system in T1DM.

Few studies have investigated the effects of IP insulin on IGF1 concentrations in T1DM. Although a previous post-hoc analysis of IGF1 concentrations derived from samples from the cross-over period did not demonstrated differences in IGF1 between the CIPII and SC treatment phase in the short-term, most studies did find increases of IGF1 during IP insulin administration [17]. Shishko *et al*. demonstrated that IP insulin infusion, but not SC insulin therapy, among newly diagnosed T1DM patients normalized IGF1 concentrations [11]. It should be noted that remaining endogenous insulin production, which has reported to be of more importance than glycaemic control in normalizing the IGF system, may have been present among these subjects [5]. Hanaire-Broutin *et al*. demonstrated that after one year of CIPII therapy IGF1 concentrations were higher among 18 C-peptide negative T1DM patients, also when compared to prior intensive SC therapy [10]. Further evidence was provided recently by Hedman *et al*. by finding, in addition to higher IGF1 concentrations, increased IGF1 bioactivity during CIPII as compared to CSII in T1DM patients [12].

For the interpretation of this study, some limitations should be taken into account including the small sample size, lack of a SC reference population and a change in insulin formulation during the study period. Importantly, the results should be interpreted with caution since IGF1 levels obtained by different assays may differ [24]. In normal reference populations lower IGF1 values were obtained by the IGF1 method from R&D used in our previous report than with the Immulite method used in the present follow-up [22,23,25]. Finally, although IGF1 has been suggested to be involved in improvement of insulin resistance and development of long-term complications, the clinical relevance of our findings are unclear at present [26,27].

Conclusion

After 6 years of treatment with CIPII among T1DM patients, IGF1 concentrations increased to a level that seems to be higher than during prior SC insulin treatment and is in the lower normal range compared to subjects without DM.

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