Glycaemic variability (GV) is, apart from HbA1c, a measure for glycaemic control. As continuous intraperitoneal insulin infusion (CIPII) results in a more physiologic action of insulin than subcutaneous (SC) insulin administration, we hypothesized that CIPII would result in less GV than SC insulin therapy among T1DM patients.

**Patients and Methods**

Data from continuous glucose measurements (CGM) performed during a prospective, observational matched-control study were analysed. Measurements were performed at baseline and after 26 weeks. The coefficient of variation (CV) was the primary measure of GV. In addition, the standard deviation (SD) of the mean glucose, mean of daily differences (MODD) and mean amplitude of glycaemic excursions (MAGE) were calculated. Analysis was performed with ANCOVA, taking baseline differences into account.

**Results**

A total of 176 patients (36% male) with a mean age of 49 (standard deviation (SD) 13) years, a median diabetes duration of 24 [interquartile range 17, 35] years and HbA1c of 63 (SD 10), of which 37 used CIPII and 139 SC insulin therapy were analysed. CGM data were available for 169 patients at baseline (CIPII n=35 and SC n=134) and for 164 patients at 26-weeks (CIPII n=35 and SC n=129). After adjustment for baseline differences, the CV was 4.9% (95% CI 1.0, 8.8) higher among SC treated patients as compared to CIPII treated patients. Subgroup analysis demonstrated that this difference remained present when comparing SC treated patients using multiple daily injections or continuous subcutaneous insulin infusion with CIPII treated patients: 4.7% (95% CI 0.3, 9.2) and 5.0% (95% CI 0.8, 9.2) respectively. There were no differences in other indices of GV between groups.

**Conclusions**

Despite higher blood glucose concentrations, the GV is slightly lower with CIPII as compared to SC insulin therapy in T1DM patients. Future studies are needed to study whether this reduced GV results in prevention of hypoglycaemia and even possibly fewer microvascular complications.

Continuous intraperitoneal insulin infusion versus subcutaneous insulin therapy in the treatment of type 1 diabetes: positive effects on glycaemic variability
Abstract

INTRODUCTION
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CONCLUSIONS
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Introduction

Continuous intraperitoneal insulin infusion (CIPII) using an implantable pump is a last-resort treatment option for selected patients with type 1 diabetes mellitus (T1DM) who fail to achieve glycaemic control with intensive subcutaneous (SC) insulin therapy and subsequently experience high HbA1c concentrations or blood glucose variability. Intraperitoneal (IP) administered insulin is almost entirely absorbed in the portal system, resulting in higher insulin concentrations in the portal vein catchment area, higher hepatic uptake of insulin, lower peripheral plasma insulin concentrations and — thus — a mode of insulin administration mimicking the normal physiology contrary to SC insulin administration. Previous randomized studies have demonstrated favorable effects of CIPII versus SC insulin therapy on HbA1c concentrations among T1DM patients. However, the effects of CIPII on glycaemic variability (GV), another facet of glycaemic control and suggested to help predict hypoglycaemia and diabetes related complications, are relatively unknown.

The only 3 previous studies that assessed GV among CIPII treated T1DM subjects demonstrated less GV, expressed as the standard deviation (SD) of the mean capillary glucose from blood glucose self-measurement, during CIPII therapy as compared to SC therapy. However, the mean capillary glucose was also lower during CIPII, the number of participants in these studies was small (n=10 to 24) and most of these studies were performed before the era of rapid acting insulin analogues and continuous glucose measurement (CGM) systems.

In order to test the hypothesis that CIPII would result in less GV than SC insulin therapy in T1DM patients, we studied the effects of CIPII on GV as compared to SC insulin therapy in a large group of T1DM patients, all using rapid acting insulin analogues.

Patients and methods

STUDY DESIGN

This investigator initiated study had a prospective, observational matched-control design. Inclusion took place at the Isala (Zwolle, the Netherlands) and Diaconessenhuis hospital (Meppel, the Netherlands). Primary aim of the original study was to compare the effects of
CII to SC insulin therapy, with respect to glycaemic control. As a secondary outcome, and presented in this article, GV was assessed.

PATIENT SELECTION
Cases were subjects on CII 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. In brief, patients with T1DM, aged 18 to 70 years with a HbA1c ≥ 7.5% (58 mmol/mol) and/or ≥ 5 incidents of hypoglycemia glucose (< 4.0 mmol/l) per week, were eligible.

The control group of the present study was age and gender matched to the cases and 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 ≥ 7.0% (53 mmol/mol). The ratio of participants on the different therapies (CII:MDI:CSII) was 1:2:2. Exclusion criteria for both cases and controls included impaired renal function, cardiac problems and current use of oral corticosteroids (described in detail in Chapter 5).

STUDY PROTOCOL
There were four study visits. During the first visit, baseline characteristics were collected using a standardized case record form and a blinded continuous glucose measurement (CGM) device was inserted for a period of six days. During the second visit (five to seven days later) the CGM device was removed and laboratory measurements were performed. During the third visit, 26 weeks after visit 1, clinical parameters were collected and again a CGM device was inserted for a period of six days. During the fourth visit, five to seven days after the third visit, laboratory measurements were performed and the CGM device was removed. During the study period all patients received usual care.

OUTCOME MEASUREMENTS
The 24-hours interstitial glucose profiles were recorded using a blinded CGM device (iPro2, Medtronic, Northridge, CA, USA). The CGM device was inserted in the periumbilical area, and in pump users contralateral to the (implanted) insulin pump. Patients injecting insulin were asked not to inject insulin on the same side of the sensor insertion side. Patients were instructed to perform a minimum of 4 blood glucose self-measurements daily during the CGM period, using a blood glucose meter (Contour XT; Bayer) to calibrate the sensor.
All procedures related to the CGM were performed by one, trained physician (PRVD).

To account for the higher mean glucose level expected in CIPII treated patients, as CIPII therapy is used as a last-resort treatment and CIPII treated patients are more complex than SC treated patients, the coefficient of variation (CV), which measures intra-day variation of glucose patterns and is defined as the SD divided by the mean of blood glucose values, was chosen as the primary outcome measure of CV. As secondary outcomes, additional measures of GV were used. First, as measure of intra-day GV the mean amplitude of glucose excursions (MAGE), defined as the mean of absolute differences between glycaemic oscillation (peak and nadirs exceeding 1 SD), was used. As a measure of inter-day variation, the mean of the daily differences (MODD), defined as the mean of absolute values of differences between glucose values taken in two consecutive days was chosen. In order to make comparisons with previous literature, the mean glucose with standard deviation (SD) was used. In addition, comparisons between CIPII and patients using MDI and CSII were made and data from self-measurements of blood glucose (SMBG) were analysed.

STATISTICAL ANALYSIS
Results were expressed as mean (with 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. A regression model based on covariate analysis (ANCOVA) was applied in order to take possible baseline imbalance into account. In the model the fixed factors CIPII and SC insulin therapy were used as determinants. The difference in scores was determined based on the b-coefficient of the particular (CIPII or SC) group. Significance of the b-coefficient was investigated with the Wald test based on a p<0.05. The quantity of the b-coefficient, with a 95% confidence interval (CI), gives the difference between both treatment modalities over the study period adjusted for baseline differences. 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 at the appropriate local and international registers (NCT01621308 and NL41037.075.12). The study protocol was approved by the local medical ethics committee and 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) or an eGFR<40 ml/min (n=2). Consequently, 184 patients were followed during the 26-week study period. Seven patients refused to wear the CGM device and 1 patient withdrew informed consent due to lack of interest after the first visit. Therefore, 176 patients were analysed of which 37 used CIPII and 139 SC insulin infusion (65 MDI and 74 CSII).

Main baseline characteristics of these patients are presented in Table 1. Patients treated with CIPII were more often known with a microvascular complication, used more units of insulin per day, had a higher HbA1c and a higher number of self-reported hypoglycaemic events. CGM data were available for 169 (CIPII n=35 and SC n=134) and 164 (CIPII n=35 and SC n=129) patients at baseline and final measurement, respectively. The mean time patients wore the CGM device was 5 (1) days.

Primary outcome: coefficient of variation
Over time, there was no significant change of the CV within groups (see Table 2). After adjustment for baseline differences, the CV of CGM was 4.9% (95% CI 1.0, 8.8) higher among patients treated with SC insulin therapy as compared to patients treated with CIPII. After additional adjustment for differences in baseline HbA1c, number of hypoglycaemic episodes and total daily insulin dose, the CV was 4.7% (95% CI 0.5, 8.8) higher among patients treated with SC insulin therapy as compared to patients treated with CIPII.

Secondary outcome: other indices of glycaemic variability
After adjustment for baseline differences, the mean glucose during CGM was -0.9 mmol/l (95% CI -1.6, -0.1) lower among patients using SC insulin therapy as compared to CIPII treated patients (see Table 2). Although the MODD increased over time with 0.5 mmol/l (95% CI 0.01, 1.0) among CIPII treated patients, there were no significant differences in the SD, MAGE and MODD between the SC and CIPII treatment groups.

Secondary outcome: subgroup analysis and data from SMBG
Subgroup analysis demonstrate that patients using MDI and CSII had a lower mean glucose, -0.9 mmol/l (95% CI -1.7, -0.1) and -0.9 mmol/l (95% CI -1.6, -0.1) respectively, and a higher
p<0.05.

**Continuous glucose measurement.** Mean glucose, SD, MAGE and MODD are all expressed in mmol/l. The CV is expressed in %.

MDI, multiple daily injections; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences, CGM, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; Data are presented as estimated mean (SD), median [IQR] or mean change (95% CI) within and between groups. Abbreviations: BMI; body mass index, CIPII; continuous intraperitoneal infusion, SC; subcutaneous.

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 as compared to CIPII, P-values are based on appropriate parametric and non-parametric tests. † Defined as the number of self-reported hypoglycaemic events < 4mmol/l (grade 1) during the last 14 days. ‡ Defined as the number of self-reported hypoglycaemic events< 3.5mmol/l (grade 2) during the last 14 days. Abbreviations: BMI, body mass index, CIPII, continuous intraperitoneal infusion, SC, subcutaneous.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>All (n=176)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64 (36)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 (13)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>75 (43)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>Microvascular complication present (%)</td>
<td>87 (47)</td>
</tr>
<tr>
<td>Macrovascular complication present (%)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Total daily insulin dose (IU/24h)</td>
<td>46 [36, 64]</td>
</tr>
<tr>
<td>HbAtc (mmol/mol)</td>
<td>63 (10)</td>
</tr>
<tr>
<td>Hypoglycaemia grade 1†</td>
<td>1 [0, 4]</td>
</tr>
<tr>
<td>Hypoglycaemia grade 2‡</td>
<td>2 [0, 4]</td>
</tr>
</tbody>
</table>

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 as compared to CIPII, P-values are based on appropriate parametric and non-parametric tests. † Defined as the number of self-reported hypoglycaemic events < 4mmol/l (grade 1) during the last 14 days. ‡ Defined as the number of self-reported hypoglycaemic events< 3.5mmol/l (grade 2) during the last 14 days. Abbreviations: BMI, body mass index, CIPII, continuous intraperitoneal infusion, SC, subcutaneous.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Outcomes of glycaemic variability during baseline and last visit and changes between the CIPII and SC insulin therapy groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIPII</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>SMBGC</td>
<td></td>
</tr>
<tr>
<td>Mean glucose</td>
<td>10.1 (3.1)</td>
</tr>
<tr>
<td>SD</td>
<td>4.5 (1.7)</td>
</tr>
<tr>
<td>CV</td>
<td>43.2 (10.1)</td>
</tr>
<tr>
<td>CGM</td>
<td></td>
</tr>
<tr>
<td>Mean glucose</td>
<td>10.6 (2.4)</td>
</tr>
<tr>
<td>SD</td>
<td>3.9 (1.1)</td>
</tr>
<tr>
<td>CV</td>
<td>37.2 (8.4)</td>
</tr>
<tr>
<td>MAGE</td>
<td>7.7 (2.6)</td>
</tr>
<tr>
<td>MODD</td>
<td>3.9 (1.1)</td>
</tr>
</tbody>
</table>

Data are presented as estimated mean (SD), median [IQR] or mean change (95% CI) within and between groups. Abbreviations: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; MDI, multiple daily injections; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences, CGM, continuous glucose measurement. Mean glucose, SD, MAGE and MODD are all expressed in mmol/l. The CV is expressed in %. * p<0.05.
CV, 4.7% (95% CI 0.3, 9.2) and 5.0% (95% CI 0.8, 9.2) respectively, during CGM as compared to CIPII treated patients (see Appendix 1).

Results of the SMBG demonstrate that, after adjustment for baseline differences, the CV of the self-measured glucose was 5.6% (95% CI 1.2, 9.9) higher among patients using SC insulin as compared to those using CIPII. Mean glucose was lower for patients using MDI, but not for those using CSII (-0.8 mmol/l, 95% CI -1.6, -0.1), as compared to CIPII treated patients. Adjusted for baseline differences, the CV of self-measured glucose concentrations was 6.5% (95% CI 1.9, 11.2) higher among CSII treated patients as compared to subjects using CIPII.

Discussion

CIPII treated patients had a lower CV as compared to patients treated with SC insulin therapy. Furthermore, despite a higher mean glucose concentration among CIPII treated patients there were no differences in other indices of intra- and inter-day GV. Taken together, the results of this study confirm our hypothesis that T1DM patients treated with CIPII have less GV as compared to patients treated with SC insulin therapy. The magnitude of this effect was approximately 5% as compared to both MDI and CSII treated patients, it was found during both CGM- and SMBG and remained present after adjustment for baseline differences in HbA1c, hypoglycaemic episodes and total daily insulin dose.

These findings suggest a positive influence of CIPII therapy on GV and may well be explained by the pharmacokinetic and pharmacodynamic properties of IP administered insulin. After IP administration, insulin takes approximately 15 minutes to reach its peak effect and allows blood glucose values to return to baseline values more rapidly with reproducible and more predictable insulin profiles as compared to SC insulin injections. In addition, IP insulin improves the impaired glucagon secretion, also during exercise, and enhances hepatic glucose production in response to hypoglycaemia. Although the exact mechanisms behind these latter two phenomena are unknown it has been hypothesized that lower peripheral plasma insulin concentrations with CIPII may (partly) restore glucagon release or that CIPII increases hepatic sensitivity to glucagon or hepatic glucose utilization during hypoglycaemia.

The present study confirms the results of 3 previous studies reporting less CV among CIPII treated patients. The most recent study by Catargi et al. demonstrated among 14 T1DM...
patients, who were treated sequentially with CSII (using short acting insulin lispro) and CIPPII, a significant decrease of the SD of all SMBG during a 45-day period: 3.8 versus 4.4 mmol/l. The results of the present study add by describing different measures of CV, based on both (blinded) CGM and SMBG data, on two different occasions, in a large T1DM population during usual care circumstances. As all subjects were on their current mode of insulin administration for ≥ 4 years, this may suggest that the pharmacokinetic and pharmacodynamic properties of IP administered insulin perpetuate over time. Although hypothetically, this may also indicate that the course of the HbA1c among CIPPII treated patients, which has been reported to decrease shortly after initiation of CIPPII but increases during long-term use, is due to other factors (e.g. compliance) than physiologic adaption to the effects of IP insulin.

At present, CIPPII is a last-resort treatment option for selected patients and indications include, amongst others, frequent episodes of severe hypoglycaemia (especially combined with hypoglycaemia unawareness). Although long-term CIPPII treatment does not seem to offer further improvements of HbA1c and general quality of life as compared to short-term results, treatment satisfaction remains high and patients report less hypoglycaemic events as compared to previous SC insulin therapy. The reduced GV found in this study may well account for this discrepancy.

It should be mentioned that debate exists in literature concerning the ‘optimal’ measure of GV. There is no consensus at the moment. Therefore, based on available literature we chose a limited set of indices and a primary outcome which adjusts for different levels of mean glucose concentrations. In addition, post-hoc analysis demonstrated significant correlations between CV, MAGE and the MODD during both measurements (see Appendix 2).

For the interpretation of the results of this study several limitations should be acknowledged. First and foremost, since CIPPII is a last-resort treatment option for T1DM, the group of CIPPII treated patients is considered selected and more complex as compared to SC treated patients and bias may well have occurred. Second, as there is no data available of GV during SC therapy prior to CIPPII therapy in the current study, it can only be assumed that the presence of less GV among the CIPPII group is due to CIPPII. Furthermore, it should be acknowledged that the magnitude of the reduction (approximately 5%) is relatively small. Since the clinical importance of GV with respect to diabetes related complications (including quality of life) is unsure, the relevance of our findings with respect to clinical outcomes
are unknown. In addition, we found no change in the number of self-reported hypoglycaemic episodes between the both treatment groups in the present cohort (see Chapter 5). Nevertheless, as current closed-loop systems using SC insulin therapy struggle to reach postprandial normoglycaemia the favorable effects of IP insulin on GV may be of importance for the question which route of insulin administration is the development for a closed-loop system.

Conclusions

CIPII treated patients had a lower CV as compared to patients treated with SC insulin therapy. Furthermore, despite a higher mean glucose concentration among CIPII treated patients there were no differences in other indices of intra- and inter-day GV. These findings suggest a positive influence of CIPII on GV as compared to SC insulin therapy. Future studies are needed to study whether this reduced variability results in prevention of hypoglycaemia and possibly fewer microvascular complications.
REFERENCES


## Appendix 1

Indices of glycaemic variability for patients treated with MDI and CSII.

<table>
<thead>
<tr>
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<th>Indices of glycaemic variability for patients treated with MDI and CSII.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MDI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SMBC</strong></td>
<td></td>
</tr>
<tr>
<td>Mean glucose</td>
<td>9.7 (1.0)</td>
</tr>
<tr>
<td>SD</td>
<td>4.2 (1.3)</td>
</tr>
<tr>
<td>CV</td>
<td>46.0 (10.4)</td>
</tr>
<tr>
<td><strong>CGM</strong></td>
<td></td>
</tr>
<tr>
<td>Mean glucose</td>
<td>8.9 (1.7)</td>
</tr>
<tr>
<td>SD</td>
<td>4.0 (1.0)</td>
</tr>
<tr>
<td>CV</td>
<td>44.8 (5.4)</td>
</tr>
<tr>
<td>MAGE</td>
<td>7.9 (2.7)</td>
</tr>
<tr>
<td>MOUU</td>
<td>4.2 (1.7)</td>
</tr>
</tbody>
</table>

Data are presented as estimated mean (SD), median [IQR] or mean change (95% CI) within and between groups. Abbreviations: CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; MDI, multiple daily injections; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences; CGM, continuous glucose measurement. Mean glucose, SD, MAGE and MODD are all expressed in mmol/l. The CV is expressed in %. * p<0.05.
Appendix 1

Indices of glycaemic variability for patients treated with MDI and CSII.

Data are presented as estimated mean (SD), median [IQR] or mean change (95% CI) within and between groups. Abbreviations: CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; MDI, multiple daily injections; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences; CGM, continuous glucose measurement. Mean glucose, SD, MAGE and MODD are all expressed in mmol/l. The CV is expressed in %. * p<0.05.

Appendix 2

Post-hoc analysis of the correlation coefficient (Pearson) between different measures of GV.

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>SD</th>
<th>CV</th>
<th>MAGE</th>
<th>MODD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>X</td>
<td>0.62</td>
<td>0.69</td>
<td>0.72</td>
</tr>
<tr>
<td>CV</td>
<td>0.62</td>
<td>X</td>
<td>0.57</td>
<td>0.47</td>
</tr>
<tr>
<td>MAGE</td>
<td>0.69</td>
<td>0.57</td>
<td>X</td>
<td>0.46</td>
</tr>
<tr>
<td>MODD</td>
<td>0.77</td>
<td>0.47</td>
<td>0.46</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 2</th>
<th>SD</th>
<th>CV</th>
<th>MAGE</th>
<th>MODD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>X</td>
<td>0.51</td>
<td>0.73</td>
<td>0.80</td>
</tr>
<tr>
<td>CV</td>
<td>0.51</td>
<td>X</td>
<td>0.51</td>
<td>0.33</td>
</tr>
<tr>
<td>MAGE</td>
<td>0.73</td>
<td>0.51</td>
<td>X</td>
<td>0.57</td>
</tr>
<tr>
<td>MODD</td>
<td>0.80</td>
<td>0.33</td>
<td>0.57</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; MAGE, mean amplitude of glucose excursions; MODD, mean of the daily differences; SD, standard deviation. SD, MAGE and MODD are all expressed in mmol/l. The CV is expressed in %. All correlations are significant at p<0.001.
Effect of intraperitoneal insulin administration on IGF1 and IGFBP1 in type 1 diabetes

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

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

Effects of intraperitoneal insulin therapy - beyond glycaemia

CHAPTER 8
Effect of intraperitoneal insulin administration on IGF1 and IGFBP1 in type 1 diabetes

CHAPTER 9
After 6 years of intraperitoneal insulin administration IGF1 concentrations in T1DM patients are at low-normal level

CHAPTER 10
Different effects of intraperitoneal and subcutaneous insulin administration on the growth-hormone - insulin-like growth factor-1 axis in type 1 diabetes