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Effect of intraperitoneal insulin delivery on growth hormone binding protein, insulin-like growth factor (IGF)-I, and IGF-binding protein-3 in IDDM

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Summary Low plasma insulin-like growth factor (IGF)-I despite high circulating growth hormone (GH) in insulin-dependent diabetes mellitus (IDDM) indicate a hepatic GH resistance. This state may be reflected by the reduction of the circulating GH binding protein (GHBP), corresponding to the extracellular domain of the GH receptor, and the reduction of insulin-like growth factor binding protein (IGFBP)-3, major IGF-I binding protein, upregulated by GH. We carried out two studies. In the first, plasma GHBP activity was compared in patients with IDDM on continuous subcutaneous insulin infusion (CSII) or on conventional therapy and in healthy subjects. In the second study, the 18 patients on CSII at baseline were then treated by continuous intraperitoneal insulin infusion with an implantable pump (CPII) and prospectively studied for GH-IGF-I axis. Although HbA_{1c} was lower in patients on CSII than in those on conventional therapy, GHBP was similarly reduced in both when compared to control subjects (10.2 ± 0.8 and 11.6 ± 0.9 % vs 21.0 ± 1.3, $p < 0.01$). CPII for 12 months resulted in: a slight and transient improvement in HbA_{1c} (Time (T)0: 7.6 ± 0.2 %, T3:7.1 ± 0.2 %, T12: 7.5 ± 0.2 %, $p < 0.02$), improvement in GHBP (T0: 10.2 ± 0.8 %, T12: 15.5 ± 1.5, $p < 0.0001$), near-normalization of IGF-I (T0: 89.4 ± 8.8 ng/ml, T12: 146.9 ± 15.6, $p < 0.002$) and normalization of IGFBP-3 (T0: 1974 ± 121 ng/ml, T12: 3534 ± 305, $p < 0.0001$). The hepatic GH resistance profile in IDDM does not seem to be related to glycaemic control, but partly to insufficient portal insulinization. Intraperitoneal insulin delivery, allowing primary portal venous absorption, may influence GH sensitivity, and improve hepatic IGF-I and IGFBP-3 generation. [Diabetologia (1996) 39: 1498–1504]

Keywords Insulin-dependent diabetes mellitus, implantable pumps, insulin-like growth factor I, growth hormone binding protein, IGF binding proteins.

The relationships between the growth hormone-insulin-like growth factor-1 (GH-IGF-I) axis and diabetes mellitus are complex. GH has been incriminated in the development of diabetic microvascular disease, particularly retinopathy [1]. Circulating GH is increased in poorly controlled IDDM [2–4], whereas plasma IGF-I levels are inappropriately low [5, 6]. Growth is impaired in children with poorly controlled insulin-dependent diabetes (IDDM) [7]. These abnormalities could reflect a resistance to GH action, at least at the hepatic level. A high affinity GH-binding protein (GHBP), corresponding to the extracellular domain of the GH receptor [8, 9], may provide an indirect estimate of hepatic GH receptor density [10, 11]. Decreased GHBP activity has been described in young and adult patients with IDDM [6,12–14].

The aim of this study was first, to elucidate the relationship between glycaemic control and GH

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Abbreviations: GH, Growth hormone; IGF-I, insulin-like growth factor I; GHBP, growth hormone binding protein; IGFBP-3, insulin-like growth factor binding protein 3; IP, intraperitoneal; CPII, continuous intraperitoneal insulin infusion; SC, subcutaneous; CSII, continuous subcutaneous insulin infusion.

Table 1. Characteristics of the three populations studied

	Group I IDDM patients on CSII	Group II IDDM patients on conventional insulin therapy	Group III non-diabetic control subjects
n (male/female)	18 (11/7)	18 (11/7)	18 (11/7)
Age (years)	43.0 ± 3.1 (25–65)	39.9 ± 2.8 (20–65)	42.0 ± 3.0 (25–65)
Body mass index (kg/m^2)	22.9 ± 0.5 (20–26)	24.0 ± 0.8 (20.8–28)	22.3 ± 0.5 (19.5–26.1)
Duration of diabetes (years)	20.0 ± 2.3 (3–34)	14.1 ± 2.2 (2–39)[a]	
Daily insulin doses (IU/day)	39.1 ± 2.5 (20–53)	39.6 ± 2.1 (24–60)	

Data are mean ± SEM (range)
[a] $p < 0.01$

resistance in IDDM. Second, to evaluate the impact of intraperitoneal (IP) insulin therapy, which results in preferential insulin absorption by the portal system [15], on the hepatic GH-resistant state of IDDM. To answer the first question, we compared IDDM patients on conventional insulin therapy with IDDM patients on intensified insulin therapy. To answer the second, we studied two types of intensified insulin therapy, using two modes of insulin injection: subcutaneous (SC) and IP insulin infusion.

Patients and methods

Patients. The GH-IGF-I axis was studied in two groups of patients with IDDM and in control subjects. All the diabetic patients involved in the study were recruited and followed in the same centre, followed the same educational programme, received the same dietary recommendations, i.e. normocaloric diet containing 50 % carbohydrates, and were advised to practice daily home blood glucose monitoring. Group I was composed of the 18 adult IDDM patients of our centre who were involved in the French multicentre study of the feasibility of IP insulin therapy with programmable implantable pumps in IDDM from December 1991 to April 1992 [16]. Selection criteria included unreactive plasma C-peptide to 1 mg glucagon, good compliance with intensive diabetes management (at least four home blood glucose tests daily [Glucometer M Memory Meter, Miles, Elkart, Ind., USA]), and adherence to treatment goals (i.e. near-normal glycaemia, avoidance of severe hypoglycaemia, and monthly clinic visits). Before implantation, they were all treated for at least 3 months by continuous SC insulin infusion (CSII) via an external pump (mean duration of treatment by CSII: 2.6 ± 0.6 years, range: 3 months – 7.2 years), their glycated haemoglobin remaining stable during the last 3 months. These patients were then treated by continuous IP insulin infusion (CPII) via an implantable pump (MIP 2001; Minimed, Sylmar, Calif., USA). Exclusion criteria included pregnancy, chronic renal failure and liver failure. Group II was composed of 18 adult IDDM patients with unreactive plasma C-peptide to 1 mg glucagon, on conventional diabetes management, with two or three daily insulin injections, at least two home blood glucose tests daily, and a clinic visit every 3 months. Group III was composed of 18 non-diabetic control subjects. The patients' characteristics are summarized in Table 1. Subjects of groups I, II, and III, were matched for age, sex and BMI. Subjects of groups I and II were also matched for insulin doses. The study was approved by the ethical committee of Toulouse, France, and informed consent was obtained from each of the subjects.

Study design

Comparison of GH-IGF-I axis in the different groups. In the first part of the study, GH and GHBP activity were compared in patients treated by CSII (group I), or SC multiple injections (group II) and in non-diabetic control subjects (group III). All measurements, including HbA_{1c} determination, were performed on the same fasting blood sample drawn at 09.00 hours for each subject.

Comparison of the effects of SC and IP insulin infusion on GH-IGF-I axis. During this second, prospective, longitudinal part of the study, the 18 patients with IDDM comprising group I, and treated at baseline by CSII, were implanted with a Minimed pump with IP catheter, and prospectively followed over 12 months. GH, GHBP activity, IGF-I, IGFBP-3, and HbA_{1c} were measured after 3 and 12 months of IP insulin therapy and compared to baseline.

GH-IGF-I axis

hGH RIA. Human (h) GH was measured using a double monoclonal antibody method (ELISA HGH; CIS-Bio International, Gif-sur Yvette, France). The first was coated on the solid phase; the second, radiolabelled with ^{125}I, was used as tracer. The detection limit of the assay was 0.04 μg/l, and the intra and interassay coefficients of variation (CV) were less than 2.8 and 4.4 %, respectively. This RIA recognizes both free and BP-bound GH equally.

hIGF-I RIA. IGF-I was separated from its serum carrier proteins by acid chromatography. Serum was introduced onto a Sephadex G-50 column and eluted with 0.25 mol/l formic acid [17]. IGF-I was measured by RIA using the IGF-I antiserum of Van Wyk and Underwood, as previously described [18].

GHBP measurement by high pressure liquid chromatography (HPLC). GHBP activity was measured according to the methods described by Tauber et al. [19], adapted from Tar et al. [20]. Briefly, 100 μl plasma was incubated for 22 h at 4 °C with ^{125}I-hGH (100 μl = 2×10^5 cpm, SB-hGH ^{125}I 55.5 kBq, CIS-Bio International). After filtration through a 0.45 μm Millipore minifilter (Bedford, Mass., USA), 100 μl of the incubation mixture was injected into an HPLC Protein-Pak 300 SW column (Waters, Milford, Mass, USA; 0.75 × 30 cm). Radioactivity was recorded on a Berthold HPLC monitor LB 506 C-1 connected to a PC computer (Soft Berthold 1.51 version). Each sample was analysed, once in the presence, and once in the absence of an excess of unlabelled hGH (5 μg), in order to calculate specific binding. Interassay CV was 2.65 %. In serum containing

GH levels above 7 ng/ml, a correction was made, according to the result of the measurement of specific GH binding in serum supplemented with increasing amounts of GH. An increase of 7 % was necessary in five cases.

IGFBP-3 RIA. IGFBP-3 RIA was performed according to the method described by Gargosky et al. [21], adapted from Baxter and Martin [22]. The intra and inter-assay CVs for a reference serum measured in triplicate in 12 assays were 4.4 and 12.0 %, respectively.

Metabolic control. Glycaemic control was assessed by HbA_{1c}, using HPLC [23], in all the diabetic patients (normal range 4–6 %). Inter and intra-assay CV were 2.83 and 1.30 %, respectively. The patients were advised to immediately notify the medical staff of any adverse event, such as severe hypoglycaemia or ketoacidosis, as defined by the Diabetes Control and Complications Trial [24].

Data analysis. Results are expressed as mean ± SEM. The comparisons between the three groups were done using an analysis of variance, followed by Dunnett's post hoc test. This test was used for all the parameters except GH. Because of the absence of equality of the variances, the comparisons for GH were made after logarithmic transformation, and using a non-parametric test (Kruskal and Wallis). A stepwise regression analysis was used to assess the relationships between GHBP, GH, IGF-I, IGFBP-3, and different patient characteristics such as age, duration of diabetes, BMI, insulin doses, HbA_{1c}. An analysis of variance for repeated measures and a multivariate analysis of variance were performed to study the changes in GHBP, GH, IGF-I, IGFBP-3, HbA_{1c} and insulin doses during CPII, and to determine the partial contributions of the various parameters (BMDP statistical software, 4V, univariate and multivariate analysis of variance and covariance including repeated measures).

Results

Comparison of control subjects, patients with IDDM on conventional SC therapy and patients with IDDM on CSII. Plasma GHBP activity was significantly lower in diabetic patients on CSII (group I) than in control subjects (group III) (10.2 ± 0.8 % (range: 3.5–16.5) vs 21.0 ± 1.3 % (range 10.4–31.6), $p < 0.01$). There was no significant difference in GHBP activity between patients on CSII and patients on conventional insulin therapy (group II) (10.2 ± 0.8 vs 11.6 ± 0.9 (range 4.9–20.1)) (Fig. 1). Basal plasma GH levels were significantly higher in group I than in group III (2.23 ± 0.52 vs 0.84 ± 0.19 ng/ml, $p < 0.05$), and did not significantly differ between group I and group II (2.23 ± 0.52 vs 1.62 ± 0.41 ng/ml).

HbA_{1c} was significantly lower in patients on CSII than in patients on conventional therapy (7.6 ± 0.2 vs 9.2 ± 0.4 %, $p < 0.01$).

Stepwise regression analysis showed no effect of age, BMI, duration of diabetes, insulin requirements, GH and HbA_{1c} on GHBP activity. Gender was the only parameter that exerted an effect on GHBP activity (women 12.6 ± 1.1 %, men 9.8 ± 0.6 %, $r = 0.39$, F level = 599).

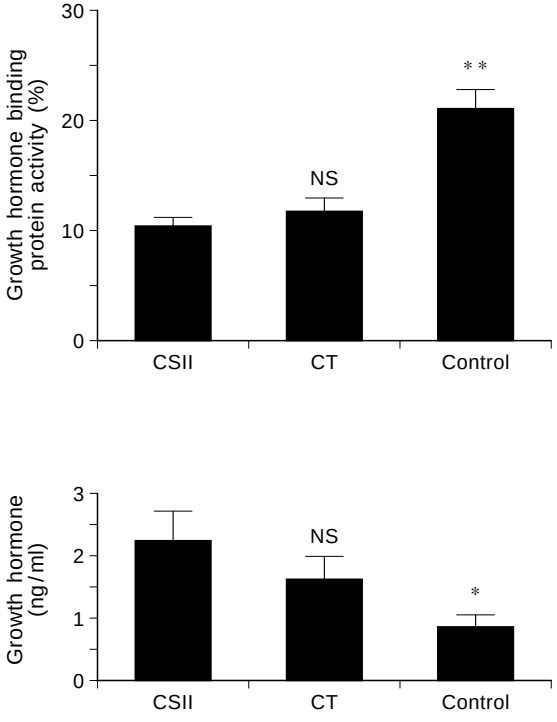

Fig. 1. Comparison of GHBP activity and of plasma basal GH concentrations in IDDM patients treated by continuous subcutaneous insulin infusion (CSII), in IDDM patients treated by conventional insulin therapy (CT), and in healthy control subjects. (mean ± SEM; analysis of variance)
NS: not significant; *$p < 0.05$; **$p < 0.01$

Comparison of the effects of CSII and CPII on GH-IGF I axis (Table 2). The analysis of variance, parameter by parameter, showed the following results: In 18 patients with IDDM treated at baseline by CSII, and then during 12 months by CPII, GHBP activity increased significantly during IP insulin therapy (T0: 10.2 ± 0.8 %, T3 months: 14.5 ± 1.1 % (range 5.2–22.8), T12 months: 15.5 ± 1.5 % (range 7–29.9), $p < 0.0001$), but this increase was moderate after the third month, and the values still remained below those of non-diabetic control subjects after 1 year of IP treatment ($p < 0.05$). Basal GH levels did not vary significantly throughout the study (T0: 2.23 ± 0.52; T3: 3.46 ± 1.13 ng/ml; T12: 1.47 ± 0.49 ng/ml).

Plasma IGF I, low at baseline, rose steadily to reach low normal values after 1 year of CPII (T0: 89.4 ± 4.7 ng/ml (range 51–129.6), T3: 114.0 ± 8.8 ng/ml (range 55.7–166.6), T12: 146.9 ± 15.6 ng/ml (range 65.0–278.0), $p < 0.002$), the normal values ranging from 150 to 250 ng/ml in adults with this method [25]. Plasma IGF-I was normalized in 7 of the 18 patients, and never exceeded the upper limit of normal. IGFBP-3 levels were low at baseline, and increased significantly during CPII, slightly after 3 months, and markedly afterwards, reaching the normal range (T0: 1974 ± 121 ng/ml (range 866–2884), T3: 2275 ± 150

Table 2. GHBP activity, plasma IGF-I and IGFBP-3 in IDDM patients on CSII at (0), and after 3 and 12 months of CPII

Patient code	Age (years)	GHBP (%)			IGF-I (ng/ml)			IGFBP-3 (ng/ml)		
		0	3 months	12 months	0	3 months	12 months	0	3 months	12 months
3	25	9.2	14.2	29.9	80.2	135.3	210	2232	1967	5329
12	26	12.6	16.1	12.5	109.4	106.8	218	2355	2428	4522
7	29	9.8	11.3	25.8	129.6	163	278	2635	1179	2412
6	30	8.9	16.6	15.3	119	114.5	138	2884	2948	4265
15	30	5.4	9.4	10.3	108.1	99	198	2164	2141	3383
17	33	10.8	11.5	12.7	73	118	108	1752	1869	3323
8	36	13.4	14	12.2	94.3	89.3	89.9	2480	2716	5381
5	37	10.5	13.2	14.2	90.3	68.7	182.5	2146	2068	2625
18	42	11.8	15.6	16.9	109	155	256	2276	2902	6347
2	44	13.5	21.6	17.5	72.5	80.9	120.5	1871	1834	3574
14	44	7.5	7.3	11.7	85.3	166.6	106	1398	1318	2329
1	45	13.5	21	27	75.2	135.7	81	1962	2989	4255
10	53	13	16	13.7	71.1	194	127	1782	2986	2811
11	55	6.4	16.6	13.4	90.5	86.9	113	1516	2313	2248
9	58	16.5	22.8	21.3	83.8	110.4	100.5	2255	2591	3713
13	59	8.6	15.6	8.8	51	55.7	106	866	1157	1450
16	63	8.6	12.3	9.6	72.4	88	147	1779	3177	3402
4	65	3.5	5.2	7	93.7	83.2	65	1195	2384	2242

ng/ml (range 1157–3177), T12: 3534 ± 305 ng/ml (range 1450–6347), $p < 0.0001$) (normal values in adults 3556 ± 508 ng/ml [21]).

During treatment by CPII, HbA_{1c} improved slightly after 3 months, but rose again afterwards (T0: 7.6 ± 0.2; T3:7.1 ± 0.2 %; T12:7.5 ± 0.2 %, $p < 0.02$). Insulin doses remained unchanged throughout the study (T0: 39.1 ± 2.5; T3: 40.1 ± 3.2; T12: 39.4 ± 3.1 IU/day), as well as BMI (T0: 22.9 ± 0.5, T12: 22.9 ± 0.5 kg/m^2).

Besides these effects of time (0, 3 and 12 months), the analysis of variance showed an effect of gender on GHBP, and an absence of effect of BMI, age and duration of diabetes on all the parameters described above.

The multivariate analysis of variance, performed to determine the partial contribution of different parameters on the changes in GH, GHBP activity, IGF-I, IGFBP-3, HbA_{1c} and insulin doses, showed a significant effect related to gender ($p < 0.006$, Hotelling's T2 = 5.86), and a significant effect of time (0, 3, 12 months) ($p < 0.02$, Hotelling's T2 = 8.68), but no effect of BMI, age and duration of diabetes.

Changes in GHBP activity, plasma IGF-I and IGFBP-3 are shown in Figure 2.

After 1 year of CPII, GHBP did not correlate with age, BMI, duration of diabetes or HbA_{1c}, but slightly with insulin doses ($r = 0.51$, $F = 9.22$). There was a significant correlation between IGF-I and IGFBP-3 at baseline ($r = 0{,}71$, $p < 0.001$), but not after 3 and 12 months of IP therapy.

IGF-I/IGFBP-3 ratio slightly increased after 3 months, and returned to baseline values after 12 months (T0: 0.047 ± 0.003, T3: 0.055 ± 0.007, T12: 0.045 ± 0.05, NS).

None of the patients presented with severe hypoglycaemia, ketoacidosis, or a device-related complication, nor did they require subcutaneous insulin injections.

Discussion

This study confirms inappropriately low plasma IGF-I levels in IDDM, as previously described [26], suggesting a state of resistance to GH, especially in the liver, the main source of circulating IGF-I [27, 28].We did not evaluate 24 h GH secretion, but performed a single sampling, insufficient to make conclusions about GH secretion. However, basal GH levels were higher in the diabetic patients than in the control subjects. The low GHBP activity found in all diabetic patients on SC insulin therapy might reflect a decrease in GH receptors (GHBP corresponding to the extracellular domain of GH receptor [29–31]), and explain a decrease in IGF-I production [32], although the role of post-receptor mechanisms is not excluded [33–35]. GHBP may be designed to maintain steady plasma GH levels, despite its pulsatile secretion. Low GHBP in IDDM might increase the exposure of peripheral tissues to GH action during GH pulses.

The hepatic GH-resistance state in IDDM does not seem to be related to hyperglycaemia. GHBP activity was similar in patients on conventional SC insulin therapy and patients on CSII, although glycaemic control was significantly better in the latter. We found no correlation between IGF-I levels and HbA_{1c}, or between GHBP and HbA_{1c}, age or duration of diabetes in agreement with previous studies [13, 14]. In contrast with these studies, we found a gender-related effect, GHBP being higher in women, and no correlation between GHBP and BMI. These discrepancies might be explained by the small size of our population,

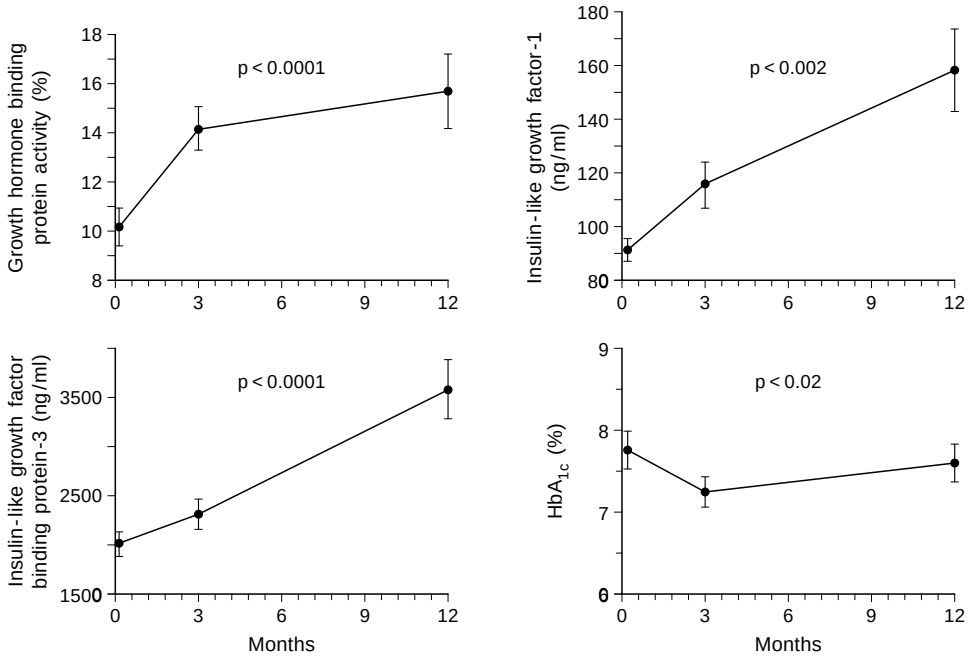

Fig. 2. Changes in GHBP activity, plasma IGF-I, plasma IGFBP-3 and HbA_{1c} in IDDM patients treated at baseline by continuous subcutaneous insulin infusion (CSII) and then during 12 months by continuous intraperitoneal insulin infusion (CPII). (mean ± SEM; analysis of variance for repeated measures)

and its homogeneity (only one of the patients was obese).

Insulin is needed for hepatic generation of IGF-I [36, 37]. Portal insulinopenia might be responsible for GH resistance in IDDM [13, 38]. Several studies give indirect or direct evidence of the importance of portal insulinaemia in GH sensitivity. Mercado et al. reported normal GHBP in NIDDM, in spite of high HbA_{1c} levels [13]. In patients with IDDM, IGF-I plasma levels induced by injections of recombinant GH correlate with residual C-peptide, which reflects direct hepatic insulinization, but not with HbA_{1c} [39]. GHBP is low in newly diagnosed IDDM children, and its recovery after the onset of insulin therapy is determined by residual beta-cell function at diagnosis [40].

SC insulin therapy results in high systemic insulinaemia and insufficient portal insulinaemia. Therefore, SC insulin therapy, while unable to restore normal hepatic sensitivity to GH, exposes peripheral tissues to both high levels of insulin and GH, which may lead to a local increase in IGF-I production, and provide one of the mechanisms of diabetic microvascular disease [38]. IP insulin delivery by implantable pumps, resulting in preferential insulin absorption by the portal system [15] and in lower peripheral levels of insulinaemia [41], might restore a more physiological portal-to-peripheral insulinaemia ratio. In our study, this treatment slightly improved glycaemic control at first, but not in a sustained manner. Nevertheless, it induced a rapid rise in GHBP activity and IGF-I plasma levels. This suggests an impact of portal insulin absorption on hepatic GH receptors, reflected by the rise of GHBP, resulting in an improvement in hepatic IGF-I generation. The correlation between GHBP and insulin doses during CPII suggests that the more portal insulin is increased, the more GHBP activity is restored. The great inter-individual variability was not explained by age, BMI, or diabetes duration, and might be partly due to genetic factors for GHBP, and other nutritional, hormonal or metabolic factors for IGF-I. GHBP activity and IGF-I levels were not totally normalized by CPII. Basal GH levels remained higher than those of the healthy control subjects. This suggests that other mechanisms may be involved in these anomalies, or that portal insulinization is only partly restored by the means of implantable pumps. We have shown that IP insulin therapy reduces the incidence rate of severe hypoglycaemic events and glycaemic fluctuations [16, 42]. A relationship between glycaemic stability and/or hypoglycaemia frequency, and GH sensitivity, cannot be excluded.

Of the circulating IGF-I, 80 % is bound to IGFBP-3 and forms a 150 kDa ternary complex after association to the acid-labile subunit [43], that does not cross the capillary barrier, preventing IGF-I diffusion to tissues. Circulating IGFBP-3 serves as a storage pool for IGF-I [44]. Its production is up-regulated by GH, a direct role of IGF-I is not excluded [44, 45]. IGFBP-3 levels are decreased in poorly controlled IDDM patients [46]. This might be related to a decrease in IGFBP-3 production, and/or an increase in

its degradation. Newly diagnosed patients with IDDM show decreased intact IGFBP-3 and increased serum IGFBP-3 protease activity [47], as previously described in situations of severe illness [48]. After the onset of insulin therapy, when the hypercatabolic state is over, IGFBP-3 increases and IGFBP-3 protease activity decreases, the respective role of insulin and glycaemic control not being explicit [47]. In our study, no abnormal IGFBP-3 protease activity was found in the sera of the patients, either on CSII, or on CPII (data not shown), those patients being on a normocaloric diet, and having a stable weight. Their plasma IGFBP-3 levels, low on CSII, were totally normalized by 12 months of CPII. This might reflect the effect of a better portal insulinization on GH sensitivity. A partial role of the slight, initial improvement in glycaemic control cannot be excluded. Other authors found that alterations in the IGF-IGFBP system could be partly accounted for by differences in metabolic control [49]. Nevertheless, one must point out that their diabetic population was very heterogeneous (untreated and treated subjects, prepubertal and pubertal), and be very careful when making conclusions about these results. The positive correlation between IGF-I and IGFBP-3 in our patients on CSII disappeared on CPII, indicating that the regulation of these two parameters is different. CPII did not significantly increase the IGF-I/IGFBP-3 ratio. In consequence, free IGF-I levels are probably not increased, although other IGFBPs contribute to IGF-I bioavailability. An improved portal insulinization might increase the insulin-mediated down-regulation of IGFBP-1, as previously suggested by Brismar et al. [50]. In the same study, the authors failed to demonstrate an effect of an acute intravenous insulin infusion on IGFBP-3. We cannot make comparisons between these results and ours, since insulin infusion was not IP in this case, and only acute and not chronic effects were studied.

In summary, our results suggest that IP insulin delivery, allowing primary portal venous absorption, may influence GH sensitivity, and improve hepatic IGF-I and IGFBP-3 generation. Glycaemic levels do not seem to play a key role in hepatic GH sensitivity. The influence of the insulin infusion route in patients with IDDM on IGF-I bioavailability and extra-hepatic tissue production need to be clarified by further studies.

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