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Treatment with insulin lispro changes the insulin profile but does not affect the plasma concentrations of IGF-I and IGFBP-1 in type 1 diabetes

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Summary

OBJECTIVE IGF-I levels in patients with type 1 diabetes without endogenous insulin production are low. Our aim was to examine whether the plasma insulin profile obtained by treatment with the insulin analogue lispro has a different effect on plasma concentrations of IGF-I and IGFBP-1 than that seen during treatment with conventional human insulin (regular insulin).

DESIGN AND PATIENTS Twelve patients with type 1 diabetes, age 47·8 ± 2·4 years (mean ± SEM), body mass index 26·5 ± 1·0 kg/m^2, diabetes duration 30·5 ± 3·2 years participated in this open label randomized cross-over study. IGF-I and IGFBP-1 levels were measured at the end of 6 weeks treatment with each insulin being administered by a continuous subcutaneous insulin infusion. IGF-I was measured fasting while IGFBP-1, free insulin and blood glucose were measured fasting and repeatedly after a morning meal preceded by an insulin bolus dose.

RESULTS Lispro gave a marked insulin peak of 135 ± 20 pmol/l 50 minutes after injection. After an initial rapid rise, human regular insulin reached a plateau of approximately 50 pmol/l. The plasma free insulin area under the curve (AUC) from 0710 h to 0910 h was more than twice as large on lispro as on regular insulin ($P = 0·01$). Plasma IGF-I concentration was 78·8 ± 10·9 μg/l on lispro and 82·3 ± 10·5 μg/l on human regular insulin (not significant). AUC for IGFBP-1 did not show a significant difference even when divided from 0710 h to 0910 h and from 0930 h to 1430 h. Blood glucose AUC after administration of the bolus was significantly lower during treatment with lispro ($P = 0·006$) but glycosylated haemoglobin (HbA1c) was 6·4 ± 0·2% on both therapies.

CONCLUSIONS Our results indicate that the effect of lispro on IGF-I and IGFBP-1 in patients with type 1 diabetes does not differ from that of human regular insulin.

Under physiological conditions in healthy individuals, insulin secreted from the β-cells reaches the liver by the portal vein in which the insulin concentration is several fold higher than in peripheral blood (Polonsky *et al*., 1988). The insufficient portal concentration of insulin in type 1 diabetes causes hepatic GH-resistance and increased production of IGFBP-1 (Berket *et al*., 1999). GH-resistance results in decreased hepatic IGF-I production (Berket *et al*., 1999) and impaired negative feedback of IGF-I on GH-secretion causes hypersecretion of GH (Hansen & Johansen, 1970). In patients with type 1 diabetes without endogenous insulin secretion, IGF-I in plasma is 30–40% lower compared to a population based reference material (Jehle *et al*., 1998; Ekman *et al*. 2000) and is not correlated to glycaemic control (Ekman *et al*. 2000). Intraperitoneal insulin delivery has been shown to raise IGF-I plasma levels (Hanaire-Broutin *et al*., 1996) suggesting that the low IGF-I concentrations in patients with type 1 diabetes on subcutaneous insulin therapy are due to portal hypoinsulinaemia.

Using insulin analogues such as lispro for subcutaneous therapy, it is possible to achieve higher peripheral insulin peaks of shorter duration than it is with human regular insulin (Howey *et al*., 1994). It is conceivable that this could alter portal vein levels of insulin and by this, or by other means, affect liver production of IGF-I and IGFBP-1. The aim of this study was to investigate whether the different insulin profiles obtained with human regular insulin and insulin lispro affect the plasma levels of IGF-I and IGFBP-1 in patients with type 1 diabetes treated with subcutaneous insulin infusion.

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Patients and methods

Subjects

Twelve patients with type 1 diabetes, who were patients attending our diabetes unit, were recruited for the study, four men and eight women, aged 47·8 ± 2·4 years (range: 35–62 years), body mass index 26·5 ± 1·0 kg/m^2 (range: 21·9–32·2 kg/m^2), duration of diabetes 30·5 ± 3·2 years. Except for one patient who had barely detectable levels, all patients were C–peptide negative. They had been treated with continuous subcutaneous insulin infusion (CSII) for 12 ± 0·8 years (range: 7–15 years). MiniMed 506 (Minimed Inc., Sylmar, Northridge, California, USA) and Disetronic H-Tron-100 (Disetronic Medical System AG, Burgdorf, Switzerland) pumps were used as infusion devices. Glycosylated haemoglobin (HbA_{1c}) at baseline was 6·7 ± 0·9% (reference range: 3·2–5·4%). Three of the patients had received laser photocoagulation for proliferative retinopathy, five patients had background retinopathy and four patients had no retinal changes. Only one patient had microalbuminuria (albuminuria 20–200 μg/minute) and none had manifest nephropathy. The study was performed according to the recommendations of the Declaration of Helsinki and the protocol was approved by the local ethical committee. All patients gave their informed consent.

Study design

The study was designed as an open label randomized cross-over study. After a run-in period, patients were randomized to insulin lispro (Humalog®, U-100, Lilly, Indianapolis, IN, USA) or their ordinary human regular insulin which was Isuhuman Infusat® (U-100, Hoechst Marion Roussel, Germany) or Velosulin® (U-100, Novo Nordisk, Denmark). One-half of the patients started with lispro and the other half of the patients with human regular insulin. Treatment was given for a period of 6 weeks and all patients were then switched to the alternative insulin for another 6 weeks. During the 6-week treatment with the assigned insulin, the patients were instructed to monitor blood glucose frequently, at least four times a day (tests before main meals and at bedtime were required) for adjusting the therapy. During the last 4 weeks, blood glucose was measured before and 2 h after each meal, at bedtime and occasionally at 0200 h on two consecutive days, one work day and one day during the weekend. Adjustment of insulin doses were made in cooperation with the staff of the diabetes unit. Patients were instructed to inject the bolus doses immediately before the meal with insulin lispro and 20 minutes before with regular insulin.

At the end of the 6-week period, a profile day with frequent blood sampling was performed. The insulin doses were not changed during the last week before the profile day. All patients arrived fasting at 0700 h to the clinic. After an initial blood sampling at 0700 h, the patients injected their usual bolus insulin dose at 0710 h and had breakfast immediately in the lispro group while the group using regular insulin had breakfast 20 minutes later at 0730 h. The energy content of the breakfast was 1256 ± 349 kJ and the nutrient content was 15·1 ± 5·4 g protein (20·2 ± 5·4 E%, percentage of the total energy intake of the breakfast), 10·2 ± 4·0 g fat (29·7 ± 7·9 E%) and 36·7 ± 10·9 g carbohydrate (50 ± 6·9 E%). The energy content of the snack, which was administered only during treatment with human regular insulin, was 834 kJ and the nutrient content was 9·4 g protein, 6·5 g fat and 25·6 g carbohydrate. Total IGF-I was measured in the fasting state. Blood samples for IGFBP-1 were taken fasting at 0700 h and at 0730 h, thereafter every hour until 1430 h when the sampling was finished. Plasma free insulin levels as well as blood glucose levels were measured every 10 minutes from 0700 h to 0800 h, every 20 minutes from 0800 h to 0930 h, every 30 minutes from 0930 h to 1130 h and thereafter every hour until 1430 h.

Biochemical analysis

Total serum IGF-I was measured by radioimmunoassay after acid-ethanol-extraction from its binding protein with a commercial kit from Nichols institute (San Juan Capistrano, CA, USA). The assay was performed according to the manufacturer's protocol. Interassay coefficient of variation for serum IGF-I was 13%.

Serum IGFBP-1 was determined with an immunoenzymometric assay containing two monoclonal antibodies against IGFBP-1, using a kit from Medix Biokemica (Kauniainen, Finland). Intra- and interassay coefficients of variation were 2·4% and 9·7%, respectively.

Plasma free insulin was measured by Mercodia Iso-Insulin ELISA (Mercodia AB, Uppsala, Sweden), a two-site enzyme immunoassay containing two monoclonal antibodies against insulin. Human insulin was used for the standard curve. When equimolar concentrations of human insulin and insulin aspart were tested, identical results were obtained indicating 100% cross-reactivity between lispro and human insulin in this assay. Intra- and interassay coefficients of variation were both 2·8%.

C-peptide was measured with an enzyme-linked immmunosorbent assay (ELISA) from DAKO diagnostics Ltd (Cambridge, UK) based on two monoclonal antibodies against C-peptide. Intra- and interassay coefficients were $< 6\%$. HbA1c was analysed with our routine hospital method (reference range: 3·2–5·4%). Blood glucose was analysed by the Hemocue method (Hemocue Inc., Mission Viejo, CA, USA).

Statistical analysis

Statistical analysis was made using Statview® 4·5 software

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(Abacus Concepts, Inc. Berkeley, CA, USA). Results are given as means ± SEM. Differences between groups were tested with ANOVA and Student's *t*-test. $P < 0{\cdot}05$ was considered statistically significant.

Results

All 12 patients completed the study and there was no case of severe hypoglycaemia or ketoacidosis. Body weight was similar at the end of the treatment periods, 73·7 ± 2·5 kg on insulin lispro and 72·8 ± 2·6 kg on regular human insulin (not significant). HbA1c was 6·4 ± 0·2% on both treatments (not significant).

The mean total insulin dose was 36·2 ± 3·0 U on lispro and 37·3 ± 2·7 U on human regular insulin (not significant), 45% of which was basal dose on both regimens. The breakfast bolus was 6·0 ± 0·7 U on both lispro and human regular insulin.

Insulin lispro gave a marked peak of free insulin with maximum concentration at 0800 h (i.e. 50 minutes after injection) of 135 ± 20 pmol/l while human regular insulin after an initial rapid rise gave a wide plateau at approximately 50 pmol/l which lasted for 2·5 h and with no obvious peak (Fig. 1). The area under the curve (AUC) for free insulin from 0710 h to 0910 h was 11807 ± 1671 during insulin lispro and 4860 ± 591 on regular insulin ($P < 0{\cdot}001$). No significant difference was found during the later part of the profile. During insulin lispro, the postprandial rise of blood glucose was smaller (Fig. 2) and the total AUC lower compared to during regular insulin treatment, 3505 ± 446 and 5087 ± 465, respectively ($P = 0{\cdot}006$). There was no significant difference

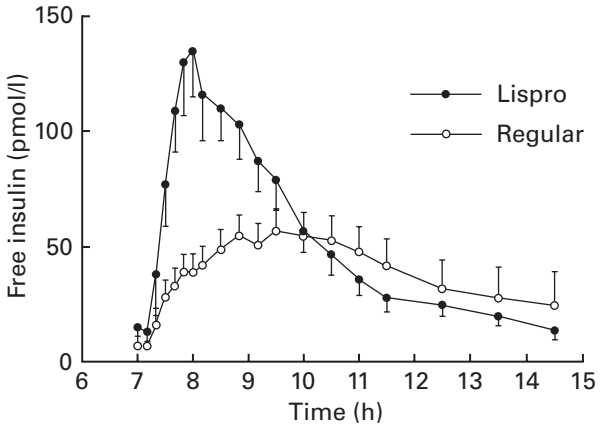

Fig. 1 Plasma concentrations of free insulin in 12 patients with type 1 diabetes treated with insulin lispro (●) and with human regular insulin (○) with CSII. A bolus insulin dose was given at 0710 h immediately before breakfast when treated with insulin lispro while breakfast was served at 0730 h when treated with human regular insulin. The values are means ± SEM.

in plasma IGF-I concentrations, 78·8 ± 10·9 on lispro *vs.* 82·3 ± 10·5 μg/l on human regular insulin. On both insulins, the plasma level of IGFBP-1 tended to increase during the first 30 minutes of the study ($P = 0{\cdot}09$ for regular human insulin and $P = 0{\cdot}17$ for lispro). After approximately 2 h, there was a rapid decline which levelled off 3–4 h after the insulin bolus and the plasma level of IGFBP-1 subsequently remained at a plateau (Fig. 3). The total IGFBP-1 AUC was 3678 ± 485 during insulin lispro and 3860 ± 495 during regular insulin (not significant) and there was no difference between the profiles when dividing from 0710 h to 0930 h and from 0930 h to 1430 h. Fasting IGFBP-1 in the patients with type 1 diabetes was 10·9 ± 1·5 μg/l on lispro and 12·8 ± 1·9 μg/l on human regular insulin (not significant). A negative significant correlation was found between IGFBP-1 levels and fasting insulin levels during treatment with human regular insulin ($r = 0{\cdot}67$; $P = 0{\cdot}02$) but not during treatment with insulin lispro. There was no significant correlation at 1430 h between these variables. Total AUC for IGFBP-1 was not correlated to total AUC for insulin while there was a positive significant correlation between total AUC for IGFBP-1 and total blood glucose AUC on regular insulin ($r = 0{\cdot}63$; $P < 0{\cdot}04$) and a non significant tendency ($P < 0{\cdot}08$) on insulin lispro.

Discussion

We found that, after a small initial increase, the IGFBP-1 concentration in plasma declined during the morning hours and there were no significant differences between lispro and human regular insulin in spite of marked differences in insulin profiles. Also for IGF-I, no difference was found between the two types of treatment. These results suggest that insulin lispro, although having other chemical characteristics than human regular insulin, does not in these aspects have different biological effects. To our knowledge, this is the first report comparing the effects of insulin lispro with human insulin on circulating IGF-I and IGFBP-1 levels in patients with diabetes.

The fasting plasma insulin levels were the same during both regimens. After infusion of a bolus dose, the rise in plasma insulin was faster, the peak higher and the decline faster with insulin lispro than with human regular insulin in agreement with previous studies (Howey *et al*., 1994). Circulating IGFBP-1 is considered to be produced mainly in the liver and to be regulated by insulin (Brismar *et al*., 1994). Our hypothesis was that insulin lispro could affect the IGF-I and IGFBP-1 production in the liver by giving a higher peak insulin concentration in the portal vein. A negative correlation between IGFBP-1 and fasting insulin levels has been shown in several studies in both healthy subjects and patients with diabetes (Hilding *et al*., 1995) and this was confirmed in the

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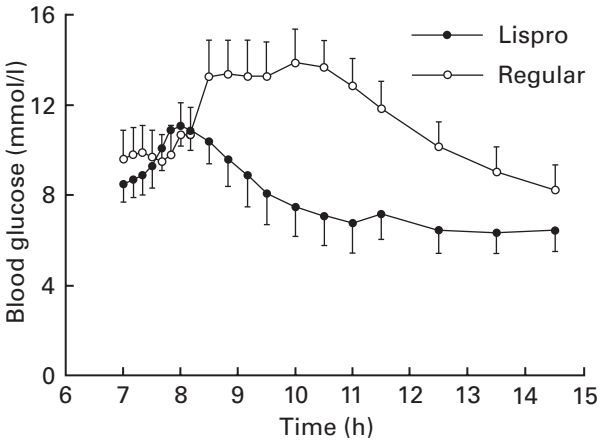

Fig. 2 Blood glucose concentrations in 12 patients with type 1 diabetes treated with insulin lispro (●) and with human regular insulin (○) with CSII. A bolus insulin dose was given at 0710 h immediately before breakfast when treated with insulin lispro while breakfast was served at 0730 h when treated with human regular insulin. During treatment with human regular insulin, a snack was given at 0910 h. The values are means ± SEM.

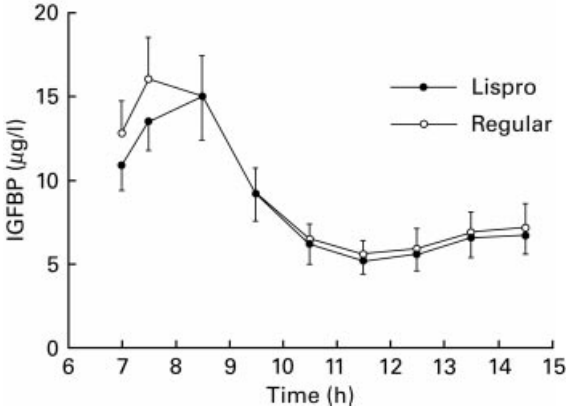

Fig. 3 Plasma concentrations of IGFBP-1 in 12 patients with type 1 diabetes treated with insulin lispro (●) and with human regular insulin (○) with CSII. A bolus insulin dose was given at 0710 h immediately before breakfast when treated with insulin lispro while breakfast was served at 0730 h when treated with human regular insulin. The values are means ± SEM.

present study during treatment with human regular insulin. The plasma profile of IGFBP-1 was similar to that previously described (Batch *et al*., 1991; Crosby *et al*., 1992; Hilding *et al*., 1995) with a high fasting concentration in the morning and lowering during the morning hours. It has been postulated from several studies that insulin has to exceed a critical plasma level for suppression of IGFBP-1 in healthy individuals (Suikkari *et al*., 1989; Conover *et al*., 1990, 1992) and that there are little changes in IGFBP-1 levels with insulin concentrations over this level (Conover *et al*., 1992). The concept of a threshold for the suppression of IGFBP-1 production by insulin might explain why we did not observe a difference between the two types of insulins in spite of marked differences in insulin profiles. The production of IGFBP-1 is regulated at the transcription level by insulin (Cichy *et al*., 1998) but other factors such as cortisol (Katz *et al*., 1998) and amino acids (Jousse *et al*., 1998) are also of importance. It has been shown that during a hypoinsulinaemic euglycaemic clamp, a cortisol infusion gave a more than three-fold increase of IGFBP-1 levels (Conover *et al*., 1993). A rapid rise of IGFBP-1 might, in some conditions, be due to a relatively greater effect of cortisol on IGFBP-1 levels in the hypoinsulinemic state as previously suggested (Lewitt *et al*., 1992; Katz *et al*., 1998). In the study by Katz *et al*., where children fasted for 13–32 h, a stronger positive correlation was seen between IGFBP-1 and cortisol levels than negative correlation for insulin levels. It is possible that during our test period, factors such as cortisol levels are of importance in modulating circulating IGFBP-1, which might also be the case in previous studies that have been performed during the early morning hours when cortisol levels are usually high (Attia *et al*., 1999).

Some but not all IGFBP-1 transgenic mice, overexpressing IGFBP-1, have been shown to have altered glucose homeostasis (D'Ercole *et al*., 1994; Rajkumar *et al*., 1996; Gay *et al*., 1997), suggesting that plasma levels of IGFBP-1, by modulating IGF-I bioactivity, could affect blood glucose levels. The observed positive correlation (which only reached statistical significance on human regular insulin) between IGFBP-1 AUC and blood glucose AUC is in favour for this concept.

The patients in our study had low plasma levels of IGF-I and high levels of IGFBP-1 compared to nondiabetic individuals in a recently published population based reference material (Nyström *et al*., 1997). In age- and sex-matched controls from that material, IGF-I was 221 ± 18 μg/l compared to 78·8 ± 10·9 μg/l on lispro in this study ($P < 0{\cdot}001$). In addition, fasting IGFBP-1 was higher on lispro compared to the control subjects in the previous study, 10·9 ± 1·5 μg/l *vs.* 6·1 ± 0·7 μg/l ($P < 0{\cdot}05$). Low plasma levels of IGF-I and high levels of IGFBP-1 have been reported previously in patients with type 1 diabetes (Ekman *et al*. 2000; Hilding *et al*., 1995; Hanaire-Broutin *et al*., 1996; Jehle *et al*., 1998; Nyström *et al*., 1997). The glycaemic control of our patients, assessed by HbA1c, was approximately the same as that in the intensively treated group of the DCCT study, when adjusted for differences in methodology (The Diabetes Control & Complications Trial Research Group, 1993; Kullberg *et al*., 1996). This suggests that the low IGF-I levels were not due to poor glycaemic control and, in a previous study, we found no correlation between HbA1c and IGF-I in patients with type 1

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diabetes with a diabetes duration of ≥ 6 years (Ekman *et al*. 2000). The patients in our study were, except for one, C-peptide negative, lacking endogenous insulin secretion. Portal hypoinsulinaemia is a probable cause of low IGF-I levels and high levels of IGFBP-1 in patients with type 1 diabetes (Hanaire-Broutin *et al*., 1996; Berket *et al*., 1999).

Thus, we found low IGF-I levels and high IGFBP-1 levels in patients with type 1 diabetes treated with CSII and in good glycaemic control. There was no difference in plasma levels of IGFBP-1 and IGF-1 between treatment with insulin lispro and human regular insulin. This indicates that subcutaneous treatment with either lispro or human insulin cannot normalize the abnormalities in the IGF system in patients with type 1 diabetes.

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References

Attia, N., Capria, S., Jones, T.W., Heptulla, R., Holcombe, J., Silver, D., Sherwin, R.S. & Tamborlane, W.V. (1999) Changes in free insulin-like growth factor-1 and leptin concentrations during acute metabolic decompensation in insulin withdrawn patients with type 1 diabetes. *Journal of Clinical Endocrinology and Metabolism*, **84,** 2324–2328.

Batch, J.A., Baxter, R.C. & Werther, G. (1991) Abnormal regulation of insulin-like growth factor binding proteins in adolescents with insulin-dependent diabetes. *Journal of Clinical Endocrinology and Metabolism*, **73,** 964–968.

Berket, A., Lang, C.H. & Wilson, T.A. (1999) Alterations in the growth-hormone-insulin-like growth factor axis in insulin dependent diabetes mellitus. *Hormone and Metabolic Research*, **31,** 172–181.

Brismar, K., Fernqvist-Forbes, E., Wahren, J. & Hall, K. (1994) Effect of insulin on the hepatic production of insulin-like growth factor-binding protein-1 (IGFBP-1), IGFBP-3 and IGF-I in insulin-dependent diabetes. *Journal of Clinical Endocrinology and Metabolism*, **79,** 872–878.

Cichy, S.B., Uddin, S., Danilkovic, A., Guo, S., Klippel, A. & Unterman, T.G. (1998) Protein kinase B/Akt mediates effects of insulin on hepatic insulin-like growth factor-binding protein-1 gene expression through a conserved insulin response sequence. *Journal of Biological Chemistry*, **273,** 6482–6487.

Conover, C.A., Butler, P.C., Wang, M., Rizza, R.A. & Lee, P.D.K. (1990) Lack of growth hormone effect on insulin-associated suppression of insulinlike growth factor binding protein 1 in humans. *Diabetes*, **39,** 1251–1256.

Conover, C.A., Lee, P.D.K., Kanaley, J.A., Clarksson, J.T. & Jensen, M.D. (1992) Insulin regulation of insulin-like growth factor binding protein-1 in obese and non obese humans. *Journal of Clinical Endocrinology and Metabolism*, **74,** 1355–1360.

Conover, C.A., Divertie, G.D. & Lee, P.D.K. (1993) Cortisol increases plasma insulin-like growth factor binding protein-1 in humans. *Acta Endocrinologica*, **128,** 140–143.

Crosby, S.R., Tsigos, C., Anderton, C.D., Gordon, C., Young, R.J. & White, A. (1992) Elevated plasma insulinlike growth factor binding protein-1 levels in type 1 (insulin-dependent) diabetic patients with peripheral neuropathy. *Diabetologia*, **35,** 868–872.

D'Ercole, A.J., Dai, Z., Xing, Y., Boney, C., Wilkie, M.B., Lauder, J.M., Han, V.K. & Clemmons, D.R. (1994) Brain growth retardation due to the expression of human insulin like growth factor binding protein-1 in transgenic mice: an in vivo model for the analysis of igf function in the brain. *Brian Research and Developmental Brain Research*, **14,** 213–222.

Ekman, B., Nyström, F. & Arnqvist, H.J. (2000) Circulating IGF-I levels are low and not correlated to glycemic control in adults with type 1 diabetes mellitus. *European Journal of Endocrinology*, **143,** 505–510.

Gay, E., Seurin, D., Babajko, S., Doublier, S., Cazillis, M. & Binoux, M. (1997) Liver-specific expression of human insulin-like growth factor binding protein-1 in transgenic mice: repercussions on reproduction, ante- and perinatal mortality and postnatal growth. *Endocrinology*, **128,** 2937–2947.

Hanaire-Broutin, H., Sallerin-Caute, B., Poncet, M.F., Tauber, M., Bastide, R., Chalé, J.J., Rosenfeld, R. & Tauber, J.P. (1996) Effect of intraperitoneal insulin delivery on growth hormone binding protein, insulin-like growth factor (IGF)-I, and IGF-binding protein-3 in IDDM. *Diabetologia*, **39,** 1498–1504.

Hansen, A.P. & Johansen, K. (1970) Diurnal patterns of blood glucose, serum free fatty acids, insulin, glucagon and growth hormone in normals and juvenile diabetics. *Diabetologia*, **6,** 27–33.

Hilding, A.B., Degerblad, M., Thoren, M. & Hall, K. (1995) Altered relation between circulating levels of insulinlike growth factor-binding protein-1 and insulin in growth hormone-deficient patients and insulin-dependent diabetic patients compared to that in healthy subjects. *Journal of Clinical Endocrinology and Metabolism*, **80,** 2646–2652.

Howey, D.C., Bowsher, R.R., Brunelle, R.L. & Woodworth, J.R. (1994) [Lys (B28), Pro (B29)]-Human insulin: a rapidly absorbed analogue of human insulin. *Diabetes*, **43,** 396–402.

Jehle, P.M., Jehle, D.R., Mohan, S. & Böhm, B.O. (1998) Serum levels of insulin-like growth factor system components and relationship to bone metabolism in type 1 and type 2 diabetes mellitus patients. *Journal of Endocrinology*, **159,** 297–306.

Jousse, C., Bruhat, A., Ferrara, M. & Fafournoux, P. (1998) Physiological concentration of amino acids regulates insulinlike-growth-factor-binding protein 1 expression. *Biochemistry Journal*, **334,** 147–153.

Katz, L.E.L., Satin-Smith, M., Collett-Solberg, P., Baker, L., Stanley, C.A. & Cohen, P. (1998) Dual regulation of insulin-like growth factor binding protein-1 levels by insulin and cortisol during fasting. *Journal of Clinical Endocrinology and Metabolism*, **83,** 4426–4430.

Kullberg, C.E., Bergström, A., Dinesen, B., Larsson, L., Little, R.R., Goldstein, D.E. & Arnqvist, H.J. (1996) Comparisons of studies on diabetic complications hampered by differences in GHb measurements. *Diabetes Care*, **19,** 726–729.

Lewitt, M.S., Saunders, H. & Baxter, R.C. (1992) Regulation of rat insulin-like growth factor-binding protein-1: the effect of insulin-induced hypoglycemia. *Endocrinology*, **131,** 2357–2364.

Nyström, F.H., Öhman, P.K., Ekman, B.Å., Österlund, M.K., Karlberg,

13652265, 2001, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1046/j.1365-2265.2001.01327.x by Skolkovo Institute Of Science And Technology, Wiley Online Library on [18/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

B.E. & Arnqvist, H.J. (1997) Population based reference values for IGF-I and IGF-binding protein 1: relations with metabolic and anthropometric variables. *European Journal of Endocrinology*, **136,** 165–172.

Polonsky, K.S., Given, B.D. & Van Cauter, E. (1988) Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *Journal of Clinical Investigation*, **81,** 442–448.

Rajkumar, K., Krsek, M., Dheen, S.T. & Murphy, L.J. (1996) Impaired glucose homeostasis in insulin-like growth factor binding protein-1 transgenic mice. *Journal of Clinical Investigation*, **98,** 1818–1825.

Suikkari, A.-M., Koivisto, V.A., Koistinen, R., Seppälä, M. & Yki-järvinen, H. (1989) Dose–response caracteristics for suppression of low molecular weight plasma insulin-like growth factor-binding protein by insulin. *Journal of Clinical Endocrinology and Metabolism*, **68,** 135–140.

The Diabetes Control and Complications Trial Research Group. (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*, **329,** 977–986.

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