Insulin-like Growth Factors and Their Binding Proteins in Children with IDDM

SUTTIPONG WACHARASINDHU, M.R.C.P. (UK)*,
SUMARLEE SRIVUTHANA, M.D.*,
SUPHAB AROONPARKMONGKOL, B.SC.*

ABSTRACT

The structure of insulin-like growth factor (IGF), especially IGF-I, and its receptor is similar to that of insulin. Therefore, the changes of IGFs and IGF-binding proteins may be related to glucose homeostasis in children with insulin dependent diabetes mellitus (IDDM). Sixty-three fasting blood samples of 21 children with IDDM attending 3 consecutive diabetic clinics were studied. The HbA1c progressively decreased from the 1st to the 3rd visit. IGF-I levels, both total and free forms, were not significantly different from that of control. IGFBP-3 levels in 3 visits (3406±305, 3376±252, and 2406±247 ng/mL) were significantly lower than that of control (5020±415ng/mL) with the p value of 0.007, 0.002, and < 0.001 respectively. IGFBP-1 levels in the 1st and 2nd visits (102.1±12.9 and 114.1±14.5 ng/mL) were significantly higher than that of control (60.1±15.2 ng/mL) with the p value of 0.03 and 0.01 respectively, but not in the 3rd visit. IGF-I level had a positive correlation with IGFBP-3 (R=0.56, p=0.01) and free IGF-I (R=0.53, p=0.01). Free IGF-I had a negative correlation with IGFBP-1 (R=-0.64, p=0.01). IGF-II at the 1st visit had a negative correlation with HbA1c (R= -0.49, p=0.047). The authors found no correlations between IGF-I, IGFBP-3, free IGF-I, IGFBP-1 and HbA1c in the study. The patients' height SDS followed the genetic height potential. It was, therefore, postulated that a near normal free IGF-I level in diabetic children resulted from a balance of interaction between IGFBP-1 and IGFBP-3 to total IGF-I in order to keep the normal metabolic status as much as possible.

Key word : Insulin-Like Growth Factor-I (IGF-I), Insulin-Like Growth Factor-II (IGF-II), Free IGF-I, IGF-Binding Protein-1 (IGFBP-1), IGF-Binding Protein-3 (IGFBP-3), Insulin-Dependent Diabetes Mellitus (IDDM)

WACHARASINDHU S, SRIVUTHANA S, AROONPARKMONGKOL S
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* Endocrine Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

The structure and metabolic effects of insulin-like growth factors (IGFs), especially IGF-I, are very similar to that of insulin. In addition, the IGF-I receptor is also similar to that of insulin, comprising two extracellular alpha subunits and two beta subunits, with transmembrane and tyrosine kinase which are involved in intracellular signaling[1,2]. It is probable that IGF-I and insulin may share receptor interactions. The production of growth hormone binding protein (GHBP) representing the extracellular domain of GH receptors is influenced by the insulin and nutritional status[3,4]. Insulin had an effect on IGF-I production at the receptor or post-receptor levels. The difference between IGF-I and insulin is that the metabolic effects of IGF-I are under the control of IGF-binding proteins of which six classes, IGFBP-1,-2,-3,-4,-5,-6, have so far been identified[5]. IGF-I involves in the growth of children and in metabolic activity such as tonic hypoglycemic action. The IGFBP-3, the biggest one with the molecular weight of 42 kDa, binds with IGF-I and acid labile subunit to form the stable ternary complex leaving the free IGF-I, active metabolite, of less than 10 per cent[6]. The IGFBP-3 productions are under control of GH and IGF-I[7]. The IGFBP-1, MW 25 kDa, binds with IGF-I with less stability and its serum level had the diurnal variation. Its major metabolic action is involved in carbohydrate metabolism[8].

Changes of GH/IGF-I axis have already been reported in IDDM. However, the results were full of discrepancy. IGF-I and IGFBP-3 levels were found to be low or low/normal in many studies[9-11]. Free IGF-I, the biological active component, has rarely been reported in IDDM; and some of them were studied in acute metabolic derangement such as DKA. Free IGF-I was suggested to be a more sensitive indicator than IGF-I and it showed a faster pattern of normalization during treatment with insulin in children with DKA[12]. However, no study has been done on maintenance therapy with insulin in children with IDDM. The relationship between IGF-II and IDDM has been scantily reported although IGF-II may play a role in carbohydrate metabolism as seen in hypoglycemic patients with IGF-II producing tumor[13]. Therefore, the aims of this research were to study the pattern of IGFs/IGFBPs/free IGF in IDDM children who had already been treated with insulin replacement and to draw the relationship between IGFs and IGFBPs in glycemic control of children with IDDM.

MATERIAL AND METHOD

Patients

Sixty-three fasting blood samples of 21 children (11 girls, 10 boys) with IDDM, who had been treated and followed up regularly at the diabetic clinic, department of Pediatrics, Chulalongkorn Hospital every 3 months, were collected at 0800 a.m. on 3 consecutive visits. The serum and plasma were stored at -20°C until the time of analysis for the growth factors. In addition, the blood chemistries including HbA1c, fructosamine, fasting blood sugar and lipid profile were also routinely sent to the central laboratory.

Eighteen children (10 girls, 8 boys), who came to the growth clinic because of their height concerns and whose findings after investigations turned out to be normal, were recruited as the control group. The fasting blood samples were also measured for the growth factors.

Informed consent was obtained from the parents of each patient. This study was approved by our ethics committee for human investigation.

Serum IGF-I

Serum IGF-I levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostic System Laboratories, Inc., Webster, TX). Briefly, the assay was an enzymatically amplified " one-step" sandwich-type immunoassay. After extraction to remove IGF binding proteins, the standards, controls and the unknown extracted were incubated with anti IGF-I antibody that was labeled with the enzyme horseradish peroxidase (HRP) in microtitration wells which were coated with another anti-IGF-I antibody. After the incubation and washing, the wells were incubated with the substrate tetramethylbenzidine (TMB). An acid stopping solution was then added, and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The intra-assay coefficient of variation (CVs) were: 7.1 per cent (at 26.47 ng/mL), 4.5 per cent (at 48.36 ng/mL), and 6.5 per cent (at 169.67ng/mL). The inter-assay CVs were: 8.8 per cent (at 42.94 ng/mL), 4.8 per cent (at 132.61ng/mL), and 6.4 per cent (at 379.12 ng/mL).

Serum IGF-II

Serum IGF-II levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostic System Laboratories, Inc., Webster, TX).

Briefly, the assay was an enzymatically amplified "two-step" sandwich-type immunoassay. In the assay, standards, control and unknown samples were incubated in microtitration wells that have been coated with anti IGF-II antibody. After incubation and washing, the wells were treated with another anti IGF-II detection antibody labeled with the enzyme horseradish peroxidase (HRP). After the second step of incubation and washing, the wells were incubated with the substrate tetramethylbenzidine (TMB). An acid stopping solution was then added and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The intra-assay coefficients of variation (CVs) were: 4.2 per cent (at 416 ng/mL), 3.5 per cent (at 672.3 ng/mL), and 1.7 per cent (at 1707.8 ng/mL). The inter-assay CVs were: 7.7 per cent (at 299.2 ng/mL), 5.2 per cent (at 939.1 ng/mL), and 6.2 per cent (at 1116.5 ng/mL).

Serum IGFBP-3

Serum IGFBP-3 levels were measured, using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostic System Laboratories, Inc., Webster, TX). Briefly, the assay was an enzymatically amplified "two-step" sandwich-type immunoassay. The standards, controls, and unknown were incubated in microtitration wells that were coated with anti-IGFBP-3 polyclonal antibody. After incubation and washing, the wells were treated with another anti-IGFBP-3 polyclonal antibody which was labeled with the enzyme HRP. After the second step of incubation and washing, the wells were then incubated with the substrate TMB. An acid stopping solution was then added, and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm.The intra-assay CVs were: 9.6 per cent (at 4.62 ng/mL), 9.5 per cent (at 27.43 ng/mL), and 7.3 per cent (at 74.40 ng/mL). The inter-assay CVs were: 11.4 per cent (at 5.64 ng/mL), 10.4 per cent (at 25.13 ng/mL), and 8.2 per cent (at 65.55 ng/mL).

Serum IGFBP-1

Serum IGFBP-1 levels were measured, using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostic System Laboratories, Inc., Webster, TX). Briefly, the assay was an enzymatically amplified "two-step" sandwich-type immunoassay. The standards, controls, and unknown were incubated in microtitration wells that were coated with anti-IGFBP-1 antibody. After incubation and washing, the wells were treated with another anti IGFBP-1 polyclonal antibody which was labeled with the enzyme HRP. After the second step of incubation and washing, the wells were then incubated with the substrate TMB. An acid stopping solution was then added, and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The intra-assay CVs were: 4.6 per cent (at 7.86 ng/mL), 2.5 per cent (at 31.16 ng/mL), and 1.7 per cent (at 106.57 ng/mL). The inter-assay CVs were: 7.6 per cent (at 7.5 ng/mL), 6.8 per cent (at 30.48 ng/mL), and 6.2 per cent (at 100.92 ng/mL).

Free IGF-I

Plasma free IGF-I levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Diagnostic System Laboratories, Inc., Webster, TX). Briefly, the assay was an enzymatically amplified "two-step" sandwich-type immunoassay. The standards, controls, and unknown were incubated with a Free IGF-I antibody in microtitration wells. After the incubation and washing, the wells were treated with another anti-Free IGF-I detection antibody which was labeled with the enzyme HRP. After the second step incubation and washing, the wells were incubated with the substrate TMB. An acid stopping solution was then added and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The intra-assay CVs were: 4.80 per cent (at 0.20 ng/mL), 3.61 per cent (at 0.83 ng/mL), and 3.74 per cent (at 1.87 ng/mL). The inter-assay CVs were: 11.1 per cent (at 0.18 ng/mL), 10.1 per cent (at 0.80 ng/mL), and 6.2 per cent (at 2.09 ng/mL).

Statistical analyses

The results are shown as means ± SEM otherwise indicated. Nonparametric statistical analysis was performed using the Statistical Package for Social Sciences (SPSS). The relationships between the different variables were calculated by linear regression analysis. $P < 0.05$ was considered significant.

RESULTS

The mean chronological age (CA) of all patients was 10.8 ± 1.1 years which was not different from the mean CA of the control of 10.7 ± 1.0 years.

The mean Ht SDS was 0.34±0.35 that was not significantly different from the mean mid-parental height SDS of 0.64±0.22.

Serum HbA1c

Serum HbA1c levels decreased from 11.6± 0.6 per cent at the 1st visit to 10.6±0.8 per cent and 8.8±1.1 per cent at the 2nd and 3rd visit respectively. The Kruskal-Wallis test showed the significance of 0.03.

Serum IGF-I

The serum IGF-I at the 1st visit (247.9± 42.1 ng/mL), 2nd visit (281.6±41.1 ng/mL), 3rd visit (247.2±59.0 ng/mL) and the control (434.2±83.9 ng/mL) were not significantly different. (Fig. 1)

Serum IGF-II

The serum IGF-II was measured in the first visit and the results showed the positive correlation with IGF-I (R=0.55, p=0.01) and IGFBP-3. (R=0.47, p=0.033) but the negative correlation with HbA1c (R=- 0.49. p=0.047).

Serum IGFBP-3

The serum IGFBP-3 levels after 3 visits were significantly lower than that of the control. The 1st visit, 3464±305 and 5020±415 ng/mL p= 0.007. The 2nd visit, 3376±252 and 5020±415 ng/mL p=0.002. The 3rd visit, 2406±247 and 5020± 415 ng/mL $p < 0.001$. (Fig. 2)

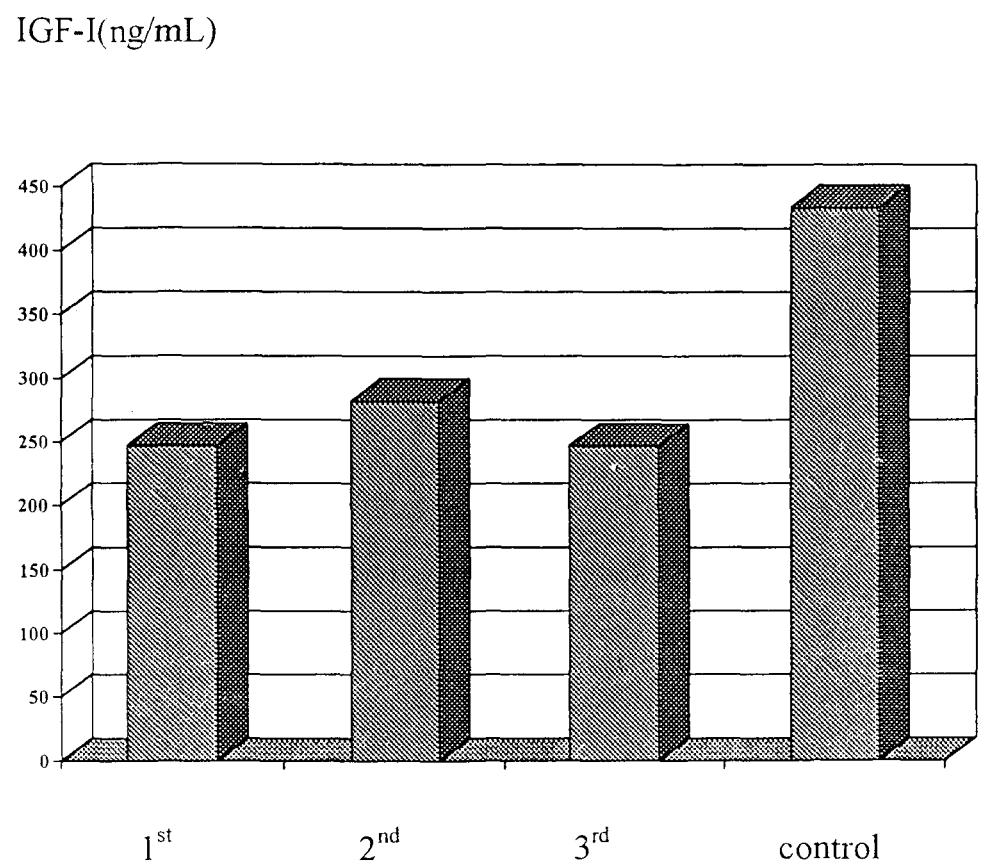

Fig. 1. Mean IGF-I level at the 1st, 2nd, 3rd visit and control.

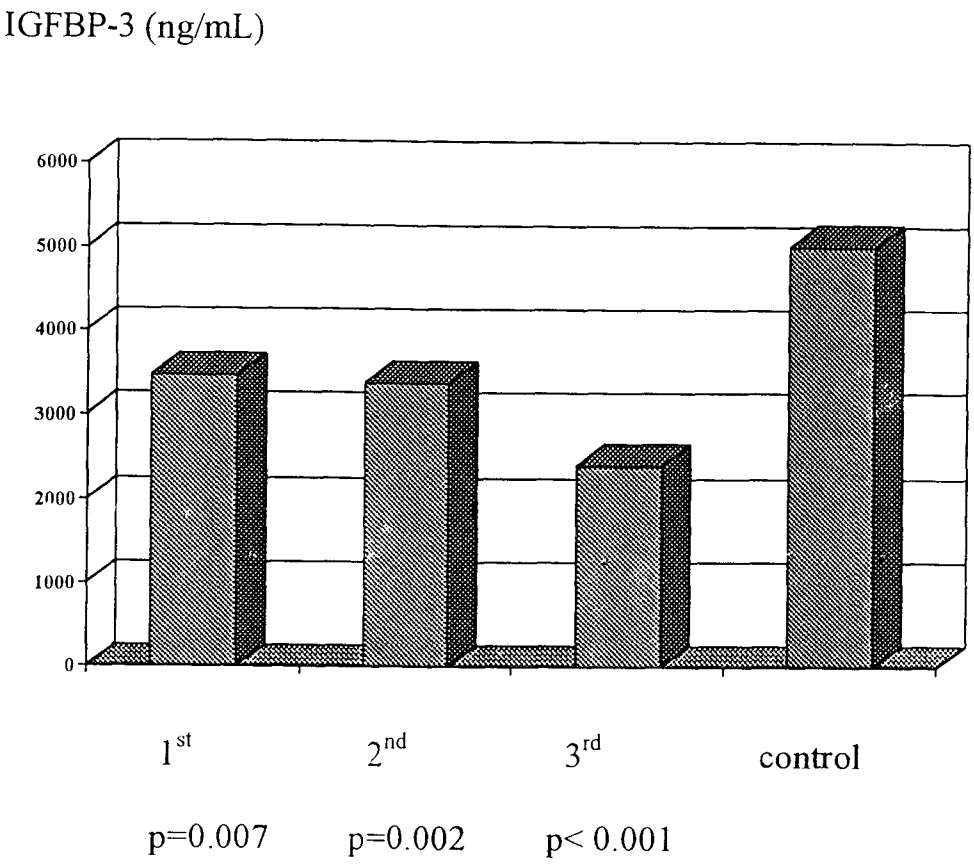

Fig. 2. Mean IGFBP-3 level at the 1st, 2nd, 3rd visit and control.

Serum IGFBP-1

The serum IGFBP-1 levels at the 1st and 2nd visit (102.1±12.9 and 114.1±14.5 ng/mL) were significantly higher than that of the control group (60.1 ±15.2 ng/mL) with the p value of 0.03 and 0.01 respectively but not at the 3rd visit (92.5±13.3 ng/mL). (Fig. 3)

Plasma free IGF-I

The plasma free IGF-I levels after 3 visits (0.62±0.11, 0.62±0.12, 0.54±0.37 ng/mL respectively) were not significantly different from that of the control (1.02±0.8 ng/mL). (Fig. 4)

Correlations between IGFs, IGFBPs and metabolic index

IGF-I level had a positive correlation with IGFBP-3 (R=0.56, p=0.01) (Fig. 5) and free IGF-I (R=0.53, p=0.01) (Fig. 6) and a negative correlation with IGFBP-1. (R=-0.38 p=0.01)

Free IGF-I had a negative correlation with IGFBP-1 (R=-0.64, p=0.01) (Fig. 7) However, all these growth factors had no correlation with the metabolic index including HbA1c, fructosamine, cholesterol and triglyceride.

IGFs and their binding proteins related to HbA1c

If the IGFs and their binding proteins were analysed according to the HbA1c levels, (Table 1), it was found that, only IGFBP-3 and cholesterol in the group with HbA1c<10 per cent were significantly different from that in the group with HbA1c ≥ 10 per cent. However, the correlations between IGF-I, IGFBP-3, IGFBP-1 and free IGF-I were still the same as mentioned above in both groups.

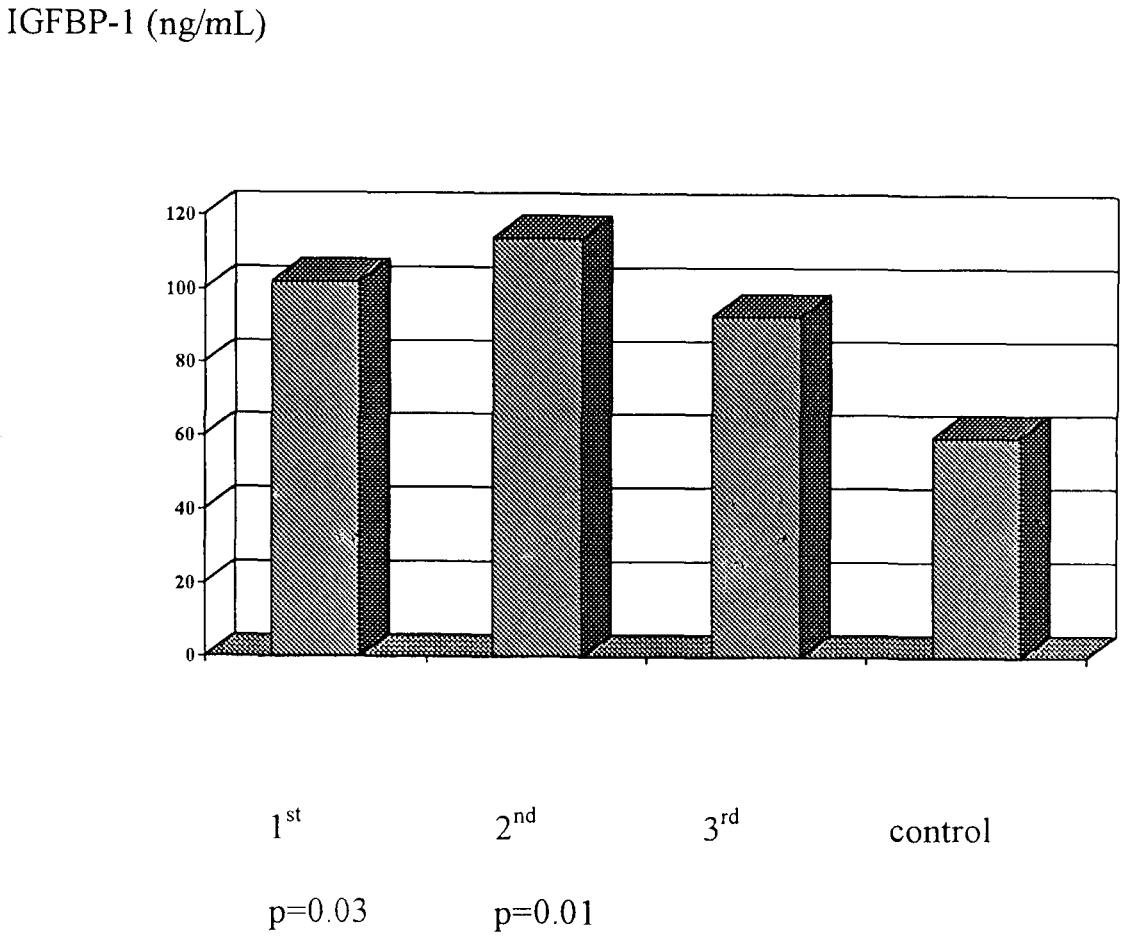

Fig. 3. Mean IGFBP-1 level at the 1st, 2nd, 3rd visit and control.

DISCUSSION

In diabetic children, IGF-I had a positive correlation with IGFBP-3 as seen in normal children. However, their serum levels were lower than that of the normal control, especially the IGFBP-3. This was similar to previous studies which showed the IGF-I and IGFBP-3 were low or in the low/normal range in adolescents with IDDM[9-11]. This supported that insulin had an influence on IGF-I production. The diabetic children in the present study still had a low insulin level even though they had had insulin treatment as could be seen from the high HbA1c in our patients. A previous study showed that the serum IGF-I and IGFBP-3 levels increased with intensified insulin treatment[14]. In another direction, a decrease in the insulin requirement was reported in diabetic adolescents treated with recombinant IGF-I[15]. This suggested that both insulin and IGF-I exerted the interaction on their receptors. However, the IGF-I levels and actions were regulated by IGFBPs. The changes of serum IGF-I and IGFBP-3 in children with IDDM showed the different results in many previous studies[11,14,16]. The age of patients might have an affect on this according to a previous study which showed a normal serum IGF-I and IGFBP-3 level in diabetic children younger than 6 years of age but a lower IGF-I and IGFBP-3 in those older than 6 years of age[16]. In the present study, the mean CA was 10.8 years and they had low IGF-I and IGFBP-3 levels.

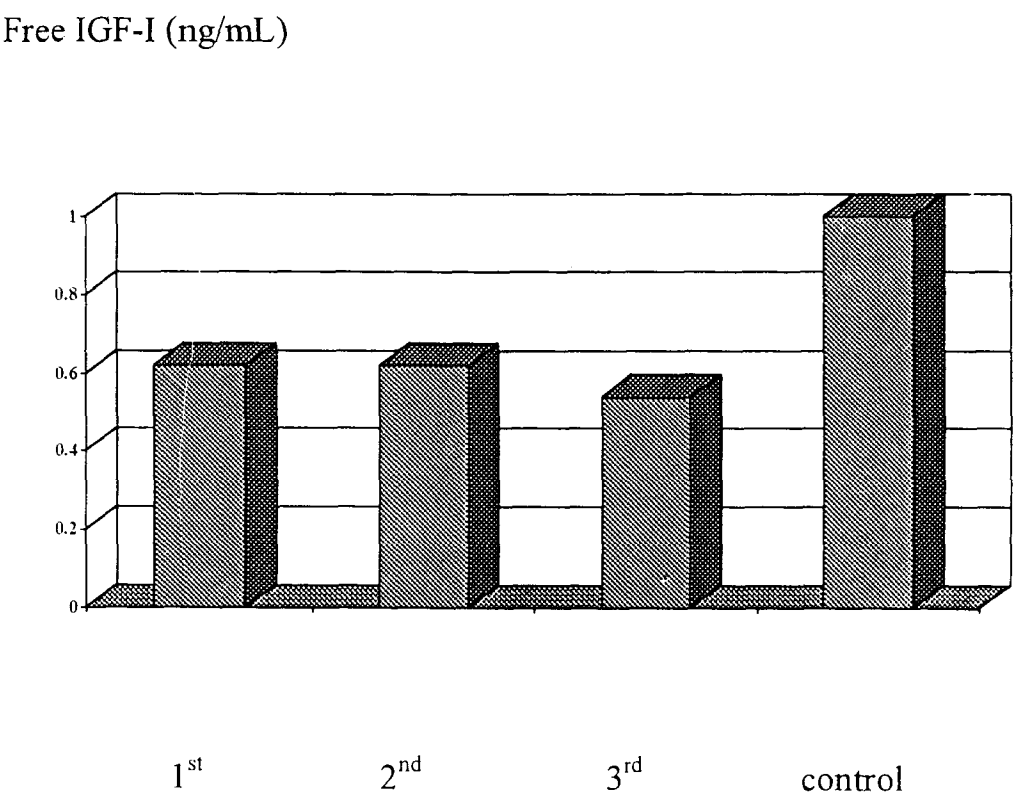

Fig. 4. Mean free IGF-I level at the 1st, 2nd, 3rd visit and control.

Therefore, insulin may show different predominant effects on IGF-I and IGFBP-3 production depending on the CA of the patients. Relative insulin resistance in adolescents with diabetes has already been documented[17] and this may be one reason for decreased IGF-I and IGFBP-3 production in older diabetic children.

Free IGF-I, representing the active fraction of IGF-I, exerts both tonic hypoglycemic effect and stimulant DNA synthesis and its effects would be attenuated by IGFBP-1 and IGFBP-3 administration. Cotterill et al suggested that the dawn phenomenon seen in adolescents with diabetes was due to elevated IGFBP-1 and this could suppress free IGF-I level[18] but they didn't measure the serum free IGF-I level. However, a previous study showed the reduced free IGF-I level measured by IRMA in 16 children and adolescents with newly diagnosed and untreated IDDM and this could be restored progressively within 1 month[12]. In the present study, the authors measured the free IGF-I in diabetic children who had been treated with insulin for a period of time and their levels were found to be stable and not statistically different from the controls. This suggested the adaptive mechanism in diabetic children to maintain metabolic status and, possibly, normal growth. This could also explain why the patients in the present study had normal height potential when compared to the genetic height.

Very few studies in the literature measured the IGF-II level in IDDM and the results were not conclusive[19,20]. The authors measured the serum IGF-II at the first visit, and the result showed that it had a significant positive correlation with IGF-I and IGFBP-3, but it had no correlation with IGFBP-1 and free IGF-I level. However, it was found that there was a positive correlation between IGF-II and HbA1c. This finding was similar to a previous study by Hall et al which showed the elevated IGF-II levels correlated with prevailing

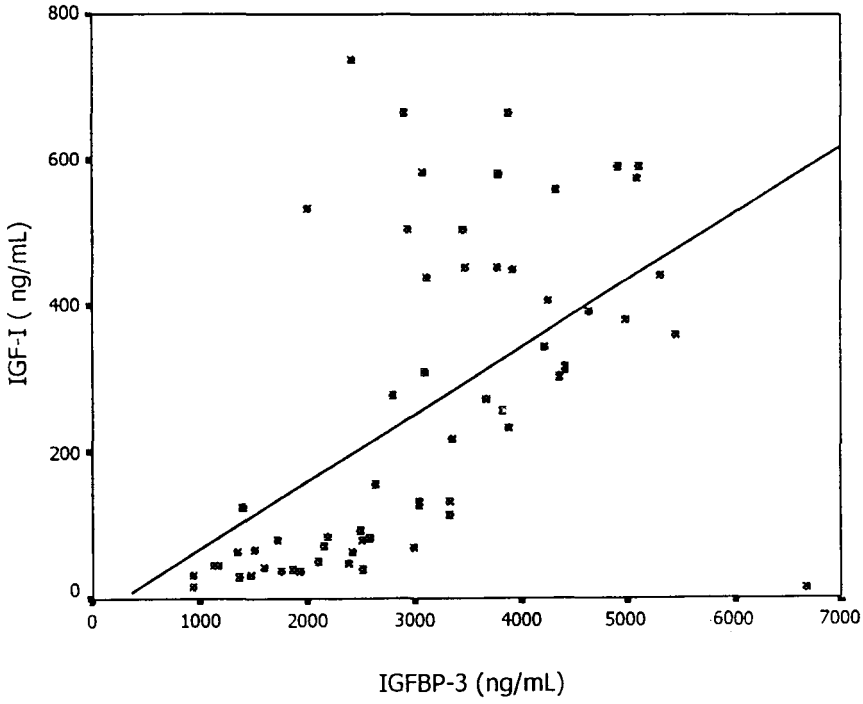

Fig. 5. Correlation between IGF-I and IGFBP-3 in children with IDDM.

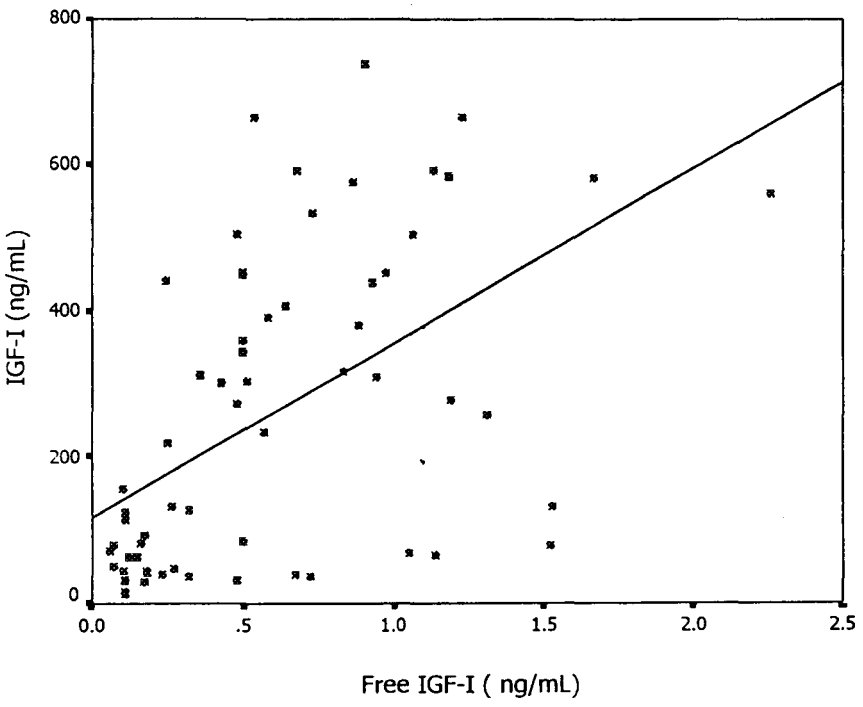

Fig. 6. Correlation between IGF-I and free IGF-I in children with IDDM.

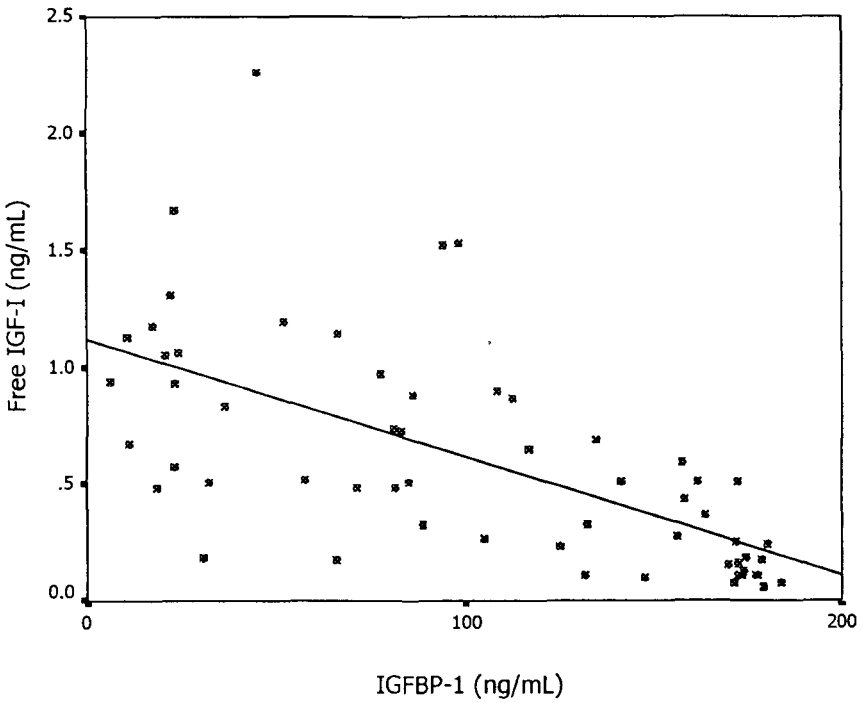

Fig. 7. Correlation between free IGF-I and IGFBP-1 in children with IDDM.

Table 1. The IGF/IGFBP levels according to HbA1c levels.

	HbA1c<10	HbA1c≥10	
HbA1c (%)	7.1±0.4	12.8±0.4	P<0.001
Cholesterol (mg/dL)	182.1±6.7	215.3±8.1	P=0.005
TG (mg/dL)	98.2±13.8	120.2±16.4	P=0.6
IGF-I (ng/mL)	246.5±46.5	276.4±35.2	P=0.47
IGFBP-3 (ng/mL)	2,793.2±289.7	3,528.4±212.4	P=0.024
IGFBP-1 (ng/mL)	89.5±14.1	110.5±10.4	P=0.23
Free IGF-I (ng/mL)	0.59±0.09	0.65±0.09	P=0.87

HbA1c[21]. The authors postulated that IGF-II had no important role in controlling the growth factors related to carbohydrate metabolism but their level may be influenced indirectly by GH resistant which was shown in poorly controlled diabetes mellitus. The longitudinal data of IGF-II in IDDM may give more conclusions.

The IGFBP-1, which had the opposite action to that of insulin, had a high serum level in diabetic children. Because of the high IGFBP-1 level, this can inhibit the IGF bioactivity. The free IGF-I representing the most active biological activity of IGF-I in the present study was lower than the normal control. Nevertheless, this was not significantly different. This is probably due to the low level of IGFBP-3 in diabetic children and, therefore, can increase the free form of IGF-I. Another possibility that was not proved in this study was due to the enhancing IGFBP-3 protease enzyme activity and then release of the free IGF-I as seen in other previous studies [22]. Insulin, therefore, may be one of the IGFBP-3 protease regulators. The trend of serum IGFBP-1 was

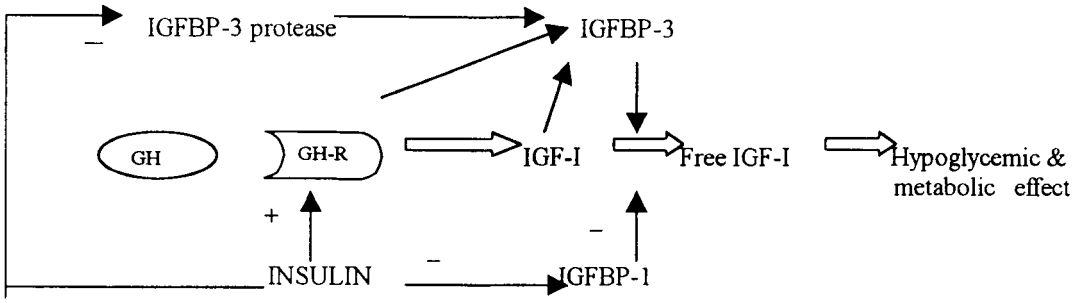

Fig. 8. The influences of insulin on IGF-I and IGFBPs productions and net metabolic status. GH=growth hormone, GH-R=GH receptor, - = inhibit, + = stimulate.

decreased if the HbA1c was near normal as shown at the 3rd visit. The present study was too short to evaluate the impact of HbA1c on the growth factors and HbA1c was still high at the 3rd visit. If HbA1c was normalized as much as possible, there might have been more conclusive data.

Therefore, the picture of the relationship between insulin and IGFs/IGFBPs in IDDM children as in Fig. 8 can be drawn. The production of IGF-I, IGFBP-3 and, to a lesser extent, IGF-II depends on GH and insulin status. In an insulin deficient state, IGFBP-1 levels increase but IGFBP-3 levels decrease. Free IGF-I level depends on the balance between IGFBP-1 and IGFBP-3. However, the authors think that, IGFBP-1 production is influenced more by insulin level than IGFBP-3. Thereore, the net result causes the low free IGF-I and causes poor metabolic control. IGFBP-3 protease may be attenuated to keep the homeostasis of the patients.

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REFERENCES

1. Zapf J, Schoenle E, Froesch ER. Insulin-like growth factors-I and II, some biological actions and receptor binding characteristics of two purified constituents of non suppressible insulin-like activity of human serum. Eur J Biochem 1978; 87: 285-96.
2. Cohick WS, Clemmons DR. The insulin-like growth factors. Ann Rev Physiol 1993; 55: 131-53.
3. Menon RK, Arslanian S, May B, Cutfield WS, Sperling MA. Diminished growth hormone binding protein in children with insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1992; 74: 934-8.
4. Hochberg Z, Hertz P, Colin V, Ish-Shalon S, Youdim MBH, Amil T. The distal axis of growth hormone in nutritional disorders: GH binding protein, insulin-like growth factor-I (IGF-I) and IGF-I receptors in obesity and anorexia nervosa. Metabolism 1992; 41: 106-12.
5. Ballard J, Baxter RC, Binoux M, et al. Report on the nomenclature of the IGF binding protein. J Clin Endocrinol Metab 1992; 74: 15-6.
6. Daughaday WH, Ward AP, Goldberg AC, Trivedi B, Kapadia M. Characterization of somatomedin binding in human serum by ultracentrifugation and gel filtration. J Clin Endocrinol Metab 1982; 55: 916-21.
7. Roith DL, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis 2001. Endocrine Rev 2001; 22: 3-74.
8. Lewitt MS, Denyer GS, Cooney GJ, Baxter RC. Insulin-like growth factor binding protein-1 modulates blood glucose levels. Endocrinology 1991; 129: 2254-6.
9. Taylor AM, Dunger DB, Grant DB, Preece MA. Somatomedin-C/IGF-I measured by radioimmunoassay and somatomedin bioactivity in adolescents with insulin dependent diabetes compared with puberty matched controls. Diabetes Res 1988; 9: 177-81.
10. Batch JA, Baxter RC, Werther G. Abnormal regulation of insulin-like growth factor binding proteins in adolescent with insulin dependent diabetes. J Clin Endocrinol Metab 1991; 73: 964-8.
11. Munoz MT, Barrios V, Pozo J, Argente J. Insulin-like growth factor I, its binding protein 1 and 3, and growth hormone-binding protein in children and adolescents with insulin-dependent diabetes mellitus: clinical implications. Pediatr Res 1996; 39: 992-8.
12. Bereket A, Lang CH, Blethen SL, Ng LC, Wilson TA. Insulin treatment normalizes reduced free insulin-like growth factor-I concentrations in diabetes children. Clin Endocrinol (Oxf) 1996; 45: 321-6.
13. Eguchi T, Tokuyama A, Tanaka Y, et al. Hypoglycemia associated with the production of insulin-like growth factor II in adrenocortical carcinoma. Intern Med 2001; 40: 759-63.
14. Bereket A, Lang CH, Blethen SL, et al. Effect of insulin on the insulin-like growth factor system in children with new-onset insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1995; 80: 1312-7.
15. Cheetham TD, Clayton KL, Taylor AM, Holly J, Matthews DR, Dunger DB. The effects of recombinant human insulin-like growth factor I (rhIGF-I) on growth hormone secretion in adolescents with insulin dependent diabetes mellitus. Clin Endocrinol (Oxf) 1994; 40: 515-22.
16. Cianfarani S, Bonfanti R, Bitti MLM, et al. Growth and insulin-like growth factors (IGFs) in children with insulin-dependent diabetes mellitus at the onset of disease: evidence for normal growth, age dependency of the IGF system alterations, and presence of a small (approximately 18-kilodalton) IGF-binding protein-3 fragment in serum. J Clin Endocrinol Metab 2000; 85: 4162-7.
17. Moran A, Jacobs DR Jr, Steinberg J, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999; 48: 2039-44.
18. Cotterill AM, Daly F, Holly JM, et al. The "dawn phenomenon" in adolescents with insulin dependent diabetes mellitus: possible contribution of insulin-like growth factor binding protein-1. Clin Endocrinol (Oxf) 1995; 43: 567-74.
19. Amiel SA, Sherwin RS, Hintz RL, Gertner JM, Press CM, Tamborlane WV. Effects of diabetes and its control on insulin-like growth factors in young subject with type I diabetes. Diabetes 1984; 33: 1175-9.
20. Acerini CL, Clayton KL, Hintz R, et al. Serum insulin-like growth factor II levels in normal adolescents and those with insulin dependent diabetes mellitus. Clin Endocrinol (Oxf) 1996; 45: 13-9.
21. Hall K, Johansson BL, Povoa G, Thalme B. Serum level of insulin-like growth factor (IGF) I, II and IGF binding protein in diabetic adolescents treated with continuous subcutaneous insulin infusion. J Intern Med 1989; 225: 273-8.
22. Zachrisson I, Brismar K, Carlsson-Skwirut C, Dahlquist G, Wallensteen M, Bang P. Increased 24 hr mean insulin-like growth factor binding protein-3 proteolytic activity in pubertal type 1 diabetes boys. Growth Horm IGF Res 2000; 10: 324-31.

Insulin-like Growth Factors (IGFs) และ IGF-Binding Proteins ในผู้ป่วยเด็กเบาหวานชนิดพึ่งอินซูลิน

สุทธิพงศ์ วัชรสินธุ, M.R.C.P. (UK),*
สุมาลี ศรีวัฒนา, พ.บ., สุภาพ อรุณภาคมงคล, วท.บ.**

Insulin-like growth factor (IGF) โดยเฉพาะอย่างยิ่ง IGF-I และ IGF receptor มีโครงสร้างคล้ายคลึงกับ insulin และ insulin receptor ดังนั้นการเปลี่ยนแปลงของ IGFs และ IGF-binding proteins (IGFBPs) อาจมีความสัมพันธ์กับการเปลี่ยนแปลงระดับน้ำตาลในเลือดของผู้ป่วยเบาหวานเด็กชนิดพึ่งอินซูลิน คณะผู้วิจัยได้ศึกษาตัวอย่างเลือดจำนวน 63 ตัวอย่าง จากผู้ป่วยเบาหวานเด็กชนิดพึ่งอินซูลิน 21 คน ที่มารับการรักษาที่คลินิกเบาหวานจำนวน 3 ครั้งติดต่อกัน จากการศึกษาพบว่า ระดับ HbA1c ลดลงอย่างมีนัยสำคัญทางสถิติจากครั้งแรกจนถึงครั้งที่ 3 ระดับ IGF-I ทั้งชนิด bound และ free form มีค่าไม่ต่างจากเด็กปกติ ระดับ IGFBP-3 ทั้ง 3 ครั้ง (3406±305, 3376±252, และ 2406±247 ng/mL) มีค่าต่ำกว่าเด็กปกติ (5020±415ng/mL) อย่างมีนัยสำคัญทางสถิติ ที่ p value เท่ากับ 0.007, 0.002 และ < 0.001 ตามลำดับ ระดับ IGFBP-1 เฉพาะในครั้งที่ 1 และ 2 (102.1±12.9 และ 114.1±14.5 ng/mL) มีค่าสูงกว่าเด็กปกติ (60.1±15.2 ng/mL) ที่ p value เท่ากับ 0.03 และ 0.01 ตามลำดับ IGF-I มีความสัมพันธ์เชิงบวกกับ IGFBP-3 (R=0.56, p=0.01) และ free IGF-I (R=0.53, p=0.01) free IGF-I มีความสัมพันธ์เชิงลบกับ IGFBP-1 (R=-0.64, p=0.01) IGF-II ที่วัดในคลินิกเบาหวานครั้งที่ 1 มีความสัมพันธ์เชิงลบกับระดับ HbA1c (R=-0.49, p=0.047) จากการศึกษาครั้งนี้ไม่พบความสัมพันธ์ใดๆ ระหว่าง IGF-I, IGFBP-3, free IGF-I, IGFBP-1 กับ HbA1c ความสูงของเด็กเป็นไปตามความสูงตามพันธุกรรม คณะผู้วิจัยคาดว่าระดับ free IGF-I ที่เกือบปกติในเด็กเบาหวานเป็นผลรวมสุดท้ายระหว่าง IGFBP-1 และ IGFBP-3 ที่กระทำต่อ IGF-I เพื่อให้การทำงานของร่างกายเป็นไปโดยปกติ

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* หน่วยต่อมไร้ท่อ, ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330