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ORIGINAL ARTICLE

Study of the Correlation Between IGF-I and Glycaemic Control in Type 1 Diabetes

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Diabetes is a common endocrine disease and its complications are major stimuli for the enhancment of efforts towards its control. At present, glycosylated hemoglobin (HbA1c) is used for long term control of glucose levels in diabetic patients, but due to lack of availability of a standard control method, recent findings suggest that insulin-like growth factor-I (IGF-I) may be used as a biomarker for glycaemic control. The aim of this study was to examine the correlation between IGF-I and glycaemic control measured as fasting plasma glucose (FPG) and HbA1c in Type 1 diabetes.

Materials and Methods: We designed a cross-sectional case-control study with systematic random sampling. The study included 26 newly diagnosed patients with Type 1 diabetes (15 male and 11 female; mean age 23.7±9.1 years) and 26 healthy controls (9 male and 17 female; mean age 24.1±4.4 years). The concentrations of FPG, IGF-I, HbA1c and IGF-binding protein-3 (IGFBP-3) were measured in both groups. FPG was measured by the enzymatic glucose oxidase method and the colorimetric method was used to measure HbA1c. Determination of serum IGF-I and IGFBP-3 total levels was carried out using immunoassay. P<0.05 was considered as statistically significant.

Results: The mean value of IGF-I concentration in Type 1 diabetics was significantly lower than in controls (p<0.05). No correlation was found between IGF-I and HbA1c in the patients.

Conclusion: Our data shows that total IGF-I levels are low in patients with Type 1 diabetes. No relationship was found between IGF-I and glycaemic control. However, more detailed intensive studies to further investigate this relationship are recommended.

Key Words: Type 1 diabetes, IGF-I, HbA1c, FPG

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Introduction

Diabetes is a common endocrine disease and its complications are major stimuli for the enhancement of efforts towards its control. At present, measurement of glycosylated hemoglobin (HbA1c) is used for long term control of glucose levels in diabetic patients. However, its application is limited due to the lack of availability of an internationally accepted standard method for its measurement and also to the interfering effects of the other forms of hemoglobin such as HbF and HbS. Current methods for measuring HbA1c present different results, the coefficients of variation of which range from 3.5% to 16.5%.[1] Recent findings suggest that insulin-like growth factor-I (IGF-I) may be used as a

biomarker for glycemic control in diabetes patients.[1,2] IGF-I is a polypeptide hormone that has 48% aminoacid sequence identity with proinsulin. Although the affinity of IGF-I for the insulin receptor is 0.5% that of insulin in vitro, when infused into animals and human subjects, IGF-I has approximately one twelfth the glucose-lowering capacity of insulin.[3,4] Most of the circulating IGF-I is derived from its synthesis in the liver, regulated by the growth hormone (GH), insulin, and nutritional intake. It has profound effects on the regulation of proliferation and differentiation of many cell types, as well as metabolic effects, which are similar to those of insulin, including actions on glucose metabolism.[5-7] It has been hypothesized that IGF-I, working through its own receptor, functions to enhance insulin sensitivity and that this accounts for part of its glucose-lowering activity.[7] Further verification of this hypothesis has come from studies in patients with extreme insulin resistance and in patients with Type 2 diabetes, demonstrating that there is a substantial improvement in insulin sensitivity during recombinant human IGF-I administration.[8,9] Patients with extreme insulin resistance, treated for periods as long as 12 months, have shown substantial reduction in HbA1c, indicating that IGF-I not only improves insulin sensitivity but also improves glycemic control.[10] Large trials of several hundred patients with Type 2 diabetes show that when IGF-I is given for 3 months, either as monotherapy or with insulin, there is substantial improvement in HbA1c. Administration of IGF-I to patients with Type 1 diabetes resulted in a 10% reduction in mean daily glucose levels, while reducing required insulin dosage by 28%.[11]

IGF-I binds to specific binding proteins in circulation known as IGF-binding proteins (IGFBPs). The IGFBPs family controls IGF access to receptors and modulates IGF-I action. IGFBP-3 appears to be the primary regulator of IGF levels in response to changes in circulating growth hormone levels and serves as a storage pool for IGF-I, whereas IGFBP-I appears to be the primary regulator of IGF-I levels in response to changes in circulating insulin levels.[3,4]

Studies that examined IGF-I and glycaemic control, as measured by HbA1c, have had conflicting findings. IGF-I has been found to be negatively correlated with HbA1c,[12] negatively correlated only in pubertal children,[13] and not correlated to HbA1c.[2,14] Because of controversial findings regarding the relationship between IGF-I concentration and glycaemic control, we designed a cross-sectional case-control study using systematic random sampling to show whether there is a relationship between serum levels of total IGF-I and glycaemic control in newly diagnosed patients with Type 1 diabetes.

Materials and Methods

Subjects

The study group consisted of 26 randomly selected patients, newly diagnosed with Type 1 diabetes (15 male and 11 female; mean age, 23.7±9.1 years), with no diabetic complications such as nephropathy, neuropathy, and retinopathy, as confirmed by an experienced internal medicine specialist. The patients were diagnosed according to 1985 World Health Organization (WHO) criteria.[15] The control group included 26 non-diabetic healthy individuals (9 male and 17 female; mean age 24.1±4.4 years). Neither group had any clinical conditions threatening normal GH production (i.e. malnutrition, chronic diseases states or excess production of GH and acromegaly).

Laboratory assessments

Blood samples were collected from both patients and controls between 08:00-09:00 after an overnight fast. The last insulin injection for type 1 diabetics was administered the day prior to blood sampling.

Total IGF-I was measured by a commercially available radioimmunoassay (RIA) kit (BioSource, Eroupe).[4] Intra- and inter-assay coefficients of variation for serum total IGF-I were 6.1% and 9.9%, respectively. The immunoradiometric assay (IRMA) kit (BioSource, Euroupe) was used for the measurement of IGFBP-3.[4] Intra- and inter-assay coefficients of variation for serum IGFBP-3 were 0.56% and 1.9%, respectively. Hemoglobin A1c (HbA1c) was measured by the WHO colorimetric method[16] (Mahsayaran Kit, Iran, normal rang 5.0-7.5%). Fasting plasma glucose (FPG) concentration was measured using the enzymatic glucose oxidase method (Pars Azmun, Iran). Intra- and inter-assay coefficients of variation for FPG were 1.74% and 4.9%, respectively.

Statistical Analysis

Differences between quantitative variables were tested with Student's t-test. Correlations were measured by Pearson's correlation coefficient. A two-sided p value <0.05 was considered statistically significant. All data are presented as mean±SD. Statistical analysis was done using SPSS 9.0 for windows software.

Results

Initially, we measured biochemical markers including FPG, HbA1c, and serum levels of total IGF-I and IGFBP-3 in 26 patients newly diagnosed with Type 1 diabetes and in 26 non-diabetic healthy controls, the results of which are presented in Table 1. Mean levels of both FPG and HbA1c in the case group were significantly higher than in the control group ($p<0.001$). Mean IGF-I levels in the patients were found to be significantly lower than in the control group ($p<0.05$), but the difference between mean IGFBP-3 levels in these groups was not significant. Mean IGF-I levels in male subjects did not differ significantly from those of the female subjects, both within and between groups. Following this, we examined correlation of total IGF-I levels with HbA1c and FPG concentrations. HbA1c was correlated directly with FPG in the patients ($r= 0.826$, $p<0.05$) and controls ($r = 0.413$, $p<0.05$). No correlation was found between IGF-I and HbA1c in the patients, nor was any observed between IGF-I and FPG in this group. IGF-I correlated inversely with age in the patient group ($r = -0.47$, $p<0.05$; Fig. 1), but not in the control group.

Table 1. Characteristics of FPG, HbA1c, IGF-I, and IGFBP-3 in case and control groups.

Variables	Case (N=26)	Control (N=26)
FPG (mg/dL)	187±97*†	95±11
HbA1c (%)	9.69±1.59†	4.63±1.28
IGF-I (ng/mL)	221±111‡	274±74
IGFBP-3 (ng/mL)	3496±1017	3335±534

* Mean±SD

† $P< 0.001$; ‡ $P<0.05$ as compared with the control group

Discussion

This study showed that serum total IGF-I levels in newly diagnosed patients with Type 1 diabetes were significantly lower than in the control group. IGFBP-3 total levels however did not show any significant difference between the two groups. Our study also showed no correlation between IGF-I and glycaemic control in patients with Type 1 diabetes. One limitation of our study was that the criteria to include Type 1 diabetes and to exclude Type 2 were based on clinical judgment according to 1985 WHO criteria, without measurement of other markers such as glutamic acid decarboxylase autoantibodies and islet cell autoantibodies.

Dills et al. investigated the relationship between IGF-I and glycaemic control in 137 subjects aged 17 years and younger with recently diagnosed insulin-dependent diabetes mellitus in a population-based cohort study conducted between 3 and 11 months after diagnosis.[12]

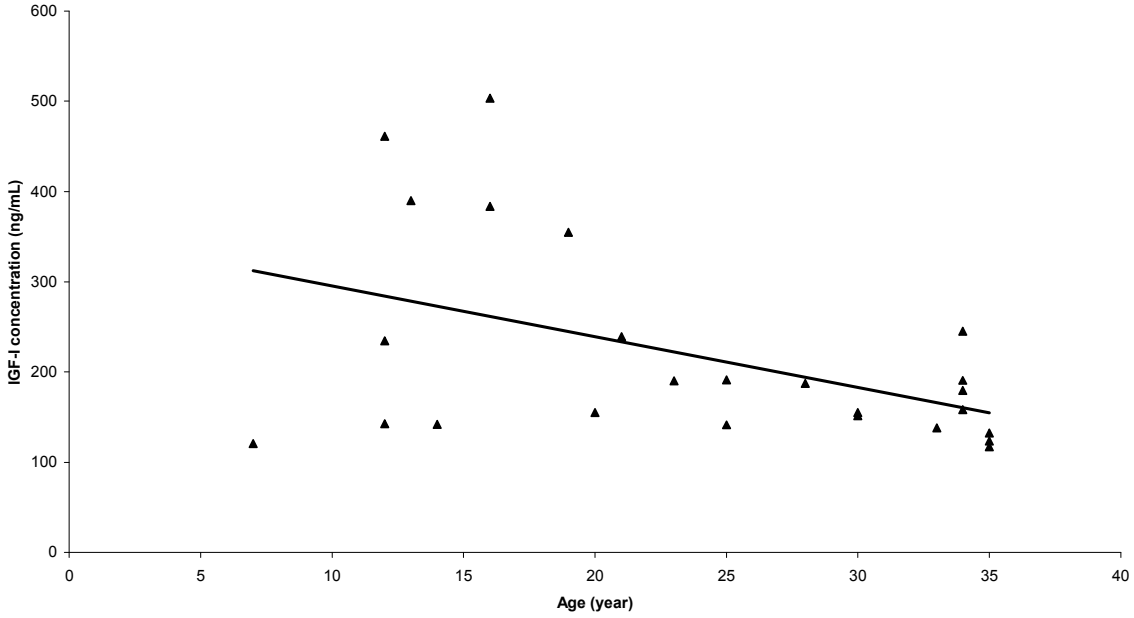

Fig. 1. Correlation between IGF-I concentration and age in the case group (P<0.05).

They found that IGF-I levels were strongly related to age (r=0.74, p<0.001) and glycosylated hemoglobin (r=-0.43, p<0.001) and also observed higher levels of IGF-I in females than males. Because in our study all subjects were adults, mean IGF-I level did not differ significantly between males and females. Growth hormone (GH) is the primary controlling factor of plasma IGF-I level, its concentration being dependent on age. Growth hormone deficiency in children is usually associated with declines in serum IGF-I levels.[17] Since GH secretion changes with age, IGF-I levels vary at different ages.[18] All subjects of the Dills study were children and adolescents (mean age 8.0±4.5yr) and IGF-I levels were correlated directly to age, but in our study because all subjects were adults this correlation was inverse.

Ekman et al. studied the correlation between circulating IGF-I concentration and glycaemic control in Type 1 diabetes.[2] Their case group consisted of 79 men and 55 women aged 20-60 years compared with 80 men and 83 women aged 20-60 years as a reference population. They found that mean IGF-I level was significantly lower in diabetics as compared to the controls. They also observed that IGF-I was negatively correlated with age in patients and controls. No correlation was found between IGF-I and glycaemic control measured as HbA1c in the patients. They concluded that subcutaneous insulin substitution is inefficient in normalizing circulating IGF-I concentrations in patients without endogenous insulin secretion. Our study results were very similar to these findings.

IGFBP-3 appears to be the primary binding protein of IGF-I in circulation and serves as a storage pool for IGF-I,[3,4] which is the reason why we measured its total circulating concentration. As there was no significant

difference in total IGFBP-3 between the two groups, decline in total IGF-I levels in patients could not be related to this binding protein.

Quattrin et al. conducted a 12-week trial comparing insulin and recombinant human IGF-I (rhIGF-I) to insulin and placebo in patients with Type 1 diabetes mellitus aged 11-66 years. The average decrease of HbA1c from baseline was higher in the rhIGF-I treated group as compared to the placebo group. They concluded that rhIGF-I cotherapy could play a role in adolescents and young adults with Type 1 diabetes mellitus.[19]

Insulin regulates hepatic IGF-I production and has an independent as well as an additive effect to that of GH.[20,21] As the major source of circulating IGF-I is the liver and IGF-I levels are inappropriately low for the higher GH levels seen in Type 1 diabetes, it is thought that there is an acquired state of hepatic GH resistance. Several days of rhGH treatment has little effect on IGF-I levels in patients with Type 1 diabetes. This points to the importance of portal insulin for hepatic IGF-I secretion.[22] The route of insulin administration in Type 1 diabetes appears important, as insulin delivered by the hepatic portal route (as occurs normally in vivo) is better at normalizing IGF-I levels and hepatic IGF-I expression in diabetic rats than subcutaneous insulin despite no difference in glycaemic control. When insulin is given to patients with Type 1 diabetes by continuous intraperitoneal infusion using an implantable pump (CPII), portal insulin levels increase and there is near-normalization of IGF-I levels.[23] Low circulating IGF-I may explain the increased GH secretion seen in Type 1 diabetes through reduced negative feedback control. rhIGF-I replacement therapy in adolescents and adults with Type 1 diabetes results in a reduction in overnight GH secretion, indicating restoration of the normal negative feedback on pituitary GH secretion. Thus IGF-I may exert its effect on glucose metabolism directly or indirectly by inhibiting GH secretion.[24]

In summary, our findings show that total IGF-I levels are low in patients with Type 1 diabetes and no relationship was found between IGF-I and glycaemic control. However, it is recommended that more comprehensive studies are needed to further investigate this relationship and verify these findings.

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