A Role of Free Insulin-Like Growth Factor-I in Dawn Phenomenon in Children and Adolescents with TYPE 1 Diabetes Mellitus

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Abstract. It has been hypothesized that a decreased amount of the free form of insulin-like growth factor-I (fIGF-I) results in morning hyperglycemia in patients with type 1 diabetes mellitus. In this study, we attempted to clarify the role of fIGF-I in relation to total IGF-I (tIGF-I) and its related peptides or proteins in type 1 diabetes. Forty-seven patients with type 1 diabetes, mean age 13.7 years, were evaluated. Blood samples were obtained for the measurement of BG at 0200, 0400 and 0700, and of insulin, total IGF-I (tIGF-I), fIGF-I, IGFBP-1 and IGFBP-3 at 0700. The SD scores (SDS) were determined for the levels of tIGF-I, fIGF-I, IGFBP-1 and IGFBP-3 by using Japanese reference data. The morning increase in BG (Δ BG(4-7)) correlated significantly with fIGF-I SDS ($r = -0.352$, $p = 0.0152$) and IGFBP-1 SDS ($r = 0.438$, $p = 0.0021$), but did not correlate significantly with the fIGF-I level itself or the ratio of fIGF-I to tIGF-I (f/t IGF-I ratio). Hereupon, the f/t IGF-I ratio correlated positively with fIGF-I SDS ($r = 0.541$, $p = 0.0003$). The mean $\pm$ SD in the f/t IGF-I ratio was $0.94 \pm 0.43\%$, and that in fIGF-I SDS was -0.50 ± 1.32 . The level of IGFBP-1 SDS correlated negatively with fIGF-I SDS ($r = -0.472$, $p = 0.0008$) and insulin ($r = -0.365$, $p = 0.0116$). We suggest that the morning level of fIGF-I SDS, rather than the fIGF-I level itself, may be a useful marker of decreased insulin-like bioactivity in the dawn phenomenon in type 1 diabetes mellitus.

Key words: Type 1 diabetes mellitus, Free IGF-I, IGFBP-1, Dawn phenomenon, Puberty

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CHILDREN and adolescent patients with type 1 diabetes mellitus have often shown unstable morning blood glucose levels. They have also shown a high level of growth hormone (GH), a low level of insulin-like growth factor-I (IGF-I) and a high level of IGF binding protein (IGFBP)-1 [1–3]. We have therefore speculated that a decreased amount of free form of IGF-I (fIGF-I) due to an increase in IGFBP-1 may be involved in the dawn phenomenon. Recently, some reports have discussed relationships between somatic growth and fIGF-I or the ratio of fIGF-I to total IGF-I (f/t IGF-I ratio) [4, 5]. Whereas IGFBP-3, a major stabilizer of the IGF-I, is

of a far higher serum level than IGFBP-1, it has been demonstrated that a phosphorylated form of IGFBP-1 has a higher affinity than that of IGFBP-3 [6]. In this study, we attempted to clarify the involvement of fIGF-I in relation to IGF-I and its related peptides or proteins in the dawn phenomenon of type 1 diabetes mellitus.

Patients and Methods

We evaluated 47 Japanese patients with type 1 diabetes mellitus, 16 male and 31 female, mean age 13.7 years. Blood samples were obtained for the measurement of blood glucose (BG) at 0200, 0400 and 0700, and of insulin (IRI), total IGF-I (tIGF-I), fIGF-I, IGFBP-1, IGFBP-3 and HbA_{1C} only at 0700 before insulin injection and breakfast.

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The serum levels of tIGF-I, IGFBP-1 and IGFBP-3 were measured as previously reported [3]. The levels of fIGF-I were measured by means of a two-site immunoradiometric assay (IRMA) kit (Diagnostic Systems Laboratories, Texas, USA).

Data are expressed as the mean $\pm$ SD. The SD scores (SDS) for tIGF-I, fIGF-I and IGFBP-3 were determined by using reference data in Japanese for corresponding ages by sex to neglect the pubertal effects. The SDS for IGFBP-1 were calculated after log transformation from our data for control subjects [3]. The Mann-Whitney test was applied to analyze the differences between two groups. Correlations between variables were examined by least-squares linear regression analysis. $P < 0.05$ was accepted as statistically significant.

Results

The mean blood glucose levels at 0200, 0400 and 0700 were 125 ± 69 , 139 ± 58 and 178 ± 75 (mg/dl), respectively, and the mean amounts of increase in BG (Δ BG [2–4] and Δ BG [4–7]) were 14 ± 56 and 39 ± 50 (mg/dl), respectively. The mean SDS values for tIGF-I, fIGF-I, IGFBP-1 and IGFBP-3 were -2.13 ± 1.48 , -0.50 ± 1.32 , $+1.70 \pm 0.96$ and $+0.45 \pm 1.26$, respectively. The mean f/t IGF-I ratio was $0.94 \pm 0.43\%$.

The levels of Δ BG [4–7] correlated significantly with IRI ($r = -0.297$, $p = 0.0426$), fIGF-I SDS ($r = -0.352$, $p = 0.0152$) (Fig. (a)) and IGFBP-1 SDS ($r = 0.438$, $p = 0.0021$), but did not correlate signifi-

cantly with the fIGF-I level itself, the f/t IGF-I ratio or $\text{HbA}_{1\text{C}}$.

The levels of IGFBP-1 SDS correlated significantly with IRI ($r = -0.365$, $p = 0.0116$) and fIGF-I SDS ($r = -0.472$, $p = 0.0008$) (Fig. (b)), but not with tIGF-I SDS, IGFBP-3 SDS or the f/t IGF-I ratio.

The levels of fIGF-I SDS correlated significantly with tIGF-I SDS ($r = 0.521$, $p = 0.0008$), f/t IGF-I ratio ($r = 0.541$, $p = 0.0003$) (Fig. (c)), IGFBP-1 SDS ($r = -0.472$, $p = 0.0008$) and IGFBP-3 SDS ($r = 0.316$, $p = 0.0305$).

Discussion

There have been some recent reports regarding the role of fIGF-I [4–8]. An increase in the f/t IGF-I ratio was noted in early infancy and in pregnant women [4, 7]. This could contribute to the rapid somatic growth. On the other hand, a fIGF-I level itself in precocious and normal puberty was related to pubertal growth, but the f/t IGF-I ratio was not related to it [8]. The evaluation in normal children and children with growth hormone deficiency also confirmed a high f/t IGF-I ratio in infancy, and the relationship between the increase in height velocity and the serum fIGF-I level [5]. From another point of view, we may have to pay an attention to the insulin-like metabolic effect of fIGF-I. Children and adolescent patients with type 1 diabetes mellitus often suffer from dawn phenomenon. We have demonstrated that their IGFBP-1 levels are higher than those in healthy subjects [3]. Westwood *et al.* [6]

Fig. 1. Correlations between fIGF-I SDS and (a) Δ BG(4–7), (b) IGFBP-1 SDS, and (c) the f/t IGF-I ratio

reported that an affinity of phosphorylated IGFBP-1 for the free form of IGF-I is higher than that of IGFBP-3, whereas that of nonphosphorylated IGFBP-1 is lower than that of IGFBP-3. Because there has been shown a relationship between morning hyperglycemia and IGFBP-1 [3, 9], we speculate that a decrease in the free form of IGF-I causes dawn phenomenon. The levels of ΔBG [4–7] actually correlated negatively with fIGF-I SDS, and positively with IGFBP-1 SDS. One of the reasons why the IGFBP-1 level increases in type 1 diabetes is related to how therapeutic insulin is administered. The exogenous insulin administered by subcutaneous injection may cause a relative shortage insulin in the liver. Since lowering the serum level and/or unstable absorption of insulin during the night results in a greater deficiency in the liver, the IGFBP-1 level often increases inappropriately. The latter consequently makes the fIGF-I level drop due to its binding. The low fIGF-I causes dawn phenomenon because of the disruption of insulin-like bioactivity, and causes the GH level to increase due to the feed-

back mechanism. It is highly likely that the fIGF-I levels are altered in type 1 diabetes, whereas short-term overnight fasting does not alter the circulating fIGF-I levels in normal human serum [10].

We have demonstrated that the morning level of fIGF-I SDS, rather than the fIGF-I level itself, may be a useful marker of decreased insulin-like bioactivity in the dawn phenomenon. Since increased binding of a free fraction of IGF-I with IGFBP-1 may occur during the early morning in type 1 diabetes, the fIGF-I SDS or f/t IGF-I ratio may be decreased in fasted blood samples, although each marker remains stable in a non-diabetic subject. Nevertheless, the overnight change in f/t IGF-I in type 1 diabetes remains to be examined.

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