Insulin-like growth factor binding protein-1 as a predictor of glucose-stimulated hyperinsulinemia in prepubertal obese children

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Abstract

Objective: The present study was undertaken to examine the association of a glucose-stimulated insulin response with the fasting insulin-like growth factor-binding protein (IGFBP)-1 concentration in prepubertal obese children.

Subjects and methods: The fasting levels of serum insulin and IGFBP-1 were measured in 17 obese and 16 control children. Furthermore, we performed an oral glucose tolerance test in obese children and examined the association of the area under the curve (AUC) for insulin with the fasting IGFBP-1 level.

Results: The mean serum level of IGFBP-1 was significantly lower in obese children (41.0 ± 4.8 mg/l, P < 0.005) than in controls (91.2 ± 9.9 mg/l). Although there was an inverse relationship between the fasting levels of serum insulin and IGFBP-1 in all subjects (r = -0.42, P < 0.05), no significant correlation between these two parameters was observed in the obese group alone. In obese children, the fasting IGFBP-1 level correlated inversely with AUC-insulin (r = -0.70, P < 0.005), whereas there was no significant relationship between the fasting insulin level and AUC-insulin.

Conclusion: The present study suggests that the serum level of IGFBP-1 may be an early predictor of insulin resistance in prepubertal obesity.

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Introduction

It is well known that the fasting plasma level of insulin is significantly higher in obese children compared with non-obese children and it is one of the most useful indices for predicting the development of obesity-associated complications such as non-insulin dependent diabetes mellitus, hypertension and hyperlipidemia (1). However, prepubertal obese children do not always show fasting hyperinsulinemia as found in adult obesity, because such hyperinsulinism may not become manifest until a later age (2).

On the other hand, insulin-like growth factor (IGF)-binding protein (IGFBP)-1 is believed to play an important role in glucose regulation and is regulated directly by insulin, which suppresses IGFBP-1 production in the liver (3). In obese subjects, the serum IGFBP-1 level was low and correlated inversely with serum insulin (4). Recently, Mogul et al. (5) have demonstrated that the fasting level of IGFBP-1 is a useful marker of the future development of diabetes in obese adults. We have also reported that the serum IGFBP-1 level is suppressed in prepubertal obese children with fasting normoinsulinemia, suggesting that the reduced IGFBP-1 level may reflect potential hyperinsulinemia (6). The objective of this study was to examine the association of a glucose-stimulated insulin response with the fasting IGFBP-1 level in prepubertal obese children.

Subjects and methods

Subjects

Seventeen Japanese children with simple obesity and 16 control children were included in the study. Both obese and control children were prepubertal (Tanner stage 1). Boys had testes volumes less than 4 ml, and pubic hair stage P1. No breast or pubic hair development was seen in girls. The obese children, who weighed 20% or more

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above the expected weight for age, sex and height, were
diagnosed as having simple obesity with the absence of
 genetic or endocrinological abnormalities. With growth
curve charts recorded from the children’s birth, the
onset of obesity was dated from when the patient fulfilled
the criteria for simple obesity mentioned above. The mean
(±S.E.M.) duration of obesity in the children studied was 5.1±0.4 years. The obese children were all
free of clinically or biochemically apparent disease other
than obesity and were not taking any medication.
Informed consent was obtained from the parents of all
the children and the study was approved by the local
ethics committee.

**Methods**

An oral glucose tolerance test (OGTT: 1.75 g glucose/kg
body weight; maximum, 75 g) was performed after an
overnight fast in obese children. Blood samples were
obtained to assay blood glucose and serum insulin in the
fasting state and 30, 60, 90 and 120 min after
Glucose intake. All obese children had normal glucose
tolerance (7). The serum insulin was also measured in
controls. IGFBP-1 assays were performed on fasting serum
samples in both obese and control subjects. The glucose-
stimulated area under the curve (AUC) for insulin in the
studied is 5.1

**Coefficients of variation were 3.5–6.0% and
2.7–5.2% respectively, and a lower detection limit of
0.33 µg/l and inter- and intra-assay coefficients of
variation were 3.5–6.0% and 2.7–5.2%
respectively.**

**Hormone assays**

The serum insulin level was determined with an RIA kit
(Diagnostic Products Co., CA, USA), with inter- and
intra-assay coefficients of variation of 4.9–10% and
2.5–6.5% respectively, and a lower detection limit of
6 pmol/l. Serum IGFBP-1 was determined with an RIA
kit (Diagnostic System Laboratories, Inc., TX, USA)
which is not affected by the state of IGFBP-1
phosphorylation and quantifies total IGFBP-1 in serum.
The lower detection limit was 0.33 µg/l and inter- and
intra-assay coefficients of variation were 3.5–6.0%
and 2.7–5.2% respectively.

**Statistical analysis**

All results were expressed as means±S.E.M. unless
otherwise stated. Student’s unpaired t-test or the
Mann–Whitney U test was used to determine statistical
significance. Relationships between parameters were
evaluated by linear regression analysis. All analyses
were performed using Stat View 4.02 software (Abacus
Concepts, Inc., CA, USA). Statistical significance was
defined as a P value of less than 0.05.

**Results**

The fasting level of insulin was significantly higher in
obese subjects (62.5±8.0 pmol/l, P<0.005) than in
controls (34.5±4.1 pmol/l; Table 2). In contrast, the
serum level of IGFBP-1 was significantly lower in obese
subjects (41.0±4.8 µg/l, P<0.005) than in controls
(91.2±9.9 µg/l; Table 2). The mean AUC-insulin level
in the obese group was 629.1±62.1 pmol/l.

Although there was an inverse relationship between
the fasting levels of serum insulin and IGFBP-1 in all
subjects (r=−0.42, P<0.05; Fig. 1), no significant
correlation between these two parameters was observed
in the obese group alone (r=−0.17, P=0.52). In obese
children, the fasting IGFBP-1 level correlated inversely
with AUC-insulin (r=−0.70, P<0.005; Fig. 2), whereas
there was no significant relationship between the
fasting insulin level and AUC-insulin (r=0.31, P=0.22).

The mean (±S.D.) concentration of fasting serum
insulin in control children was 34.5±16.6 pmol/l.
Using the mean±2S.D. (67.7 pmol/l) of the fasting
insulin in controls as a cut-off point, we divided the
obese subjects into two groups. Twelve out of 17 obese
children were considered to be normoinsulinemic in the
fasting state, their IGFBP-1 levels remaining signifi-
cantly low (42.4±4.8 µg/l, P<0.01) compared with
those in controls.

**Discussion**

We selected prepubertal children for the present study,
because several studies had demonstrated that puberty
was associated with decreased insulin sensitivity (9, 10).
Traverse et al. (11) showed that the pubertal
changes in insulin sensitivity were related to changes in
body composition. Additionally, by studying prepubertal
children it is possible to eliminate the confounding

**Table 1** Characteristics of obese and control children. Values are
means±S.E.M. with the ranges in parentheses.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese (n = 17)</th>
<th>Control (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.3±0.3</td>
<td>8.3±0.6</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>9:8</td>
<td>9:7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3±0.7</td>
<td>16.1±0.4</td>
</tr>
<tr>
<td>Ideal body weight (%)</td>
<td>156.9±4.0</td>
<td>100.5±2.6</td>
</tr>
</tbody>
</table>

**Table 2** Mean serum concentrations of insulin and IGFBP-1 in
obese and control children. Values are means±S.E.M.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese (n = 17)</th>
<th>Control (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (pmol/l)</td>
<td>62.5±8.0</td>
<td>34.5±4.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>IGFBP-1 (µg/l)</td>
<td>41.0±4.8</td>
<td>91.2±9.9</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>
hormonal and metabolic effects of puberty per se on insulin action and secretion.

IGFBP-1, a peptide predominantly of hepatic origin, is one of six binding proteins which regulate IGF-I bioavailability, and is believed to play an important role in glucose counter-regulation (12). The serum level of IGFBP-1 is regulated directly by insulin, which suppresses IGFBP-1 production in the liver (3). Conover et al. (4) showed that the serum IGFBP-1 level was low and correlated inversely with the serum level of insulin in obese adults. We also observed the decreased level of IGFBP-1 in prepubertal obese children with fasting normoinsulinemia. However, the low level of IGFBP-1 could not be explained by the fasting insulin level alone, since no inverse correlation existed between these two parameters in the study. Brismar et al. (13) reported that no correlation was found between basal levels of insulin and IGFBP-1 in non-obese healthy adults, but the basal IGFBP-1 level correlated inversely with the integrated 2 h insulin release during the hyperglycemic clamp. We therefore hypothesized that the hyperinsulinemia which could not be detected in the fasting state might have suppressed hepatic production of IGFBP-1. Thus, we performed an OGTT to examine the association of a glucose-stimulated insulin response with the fasting IGFBP-1 level in obese children. Consequently, in obese children, the fasting IGFBP-1 level correlated inversely with AUC-insulin, whereas there was no significant relationship between fasting insulin and AUC-insulin. Therefore, it is suggested that the fasting IGFBP-1 may be a better predictor of AUC-insulin than the fasting insulin. This finding is similar to the previous report by Helle´nius et al. (14), who showed that the basal IGFBP-1 level correlated inversely with AUC-insulin in normo-glycemic healthy men. Furthermore, Mogul et al. (5) also demonstrated that the fasting level of IGFBP-1 was a useful marker of the future development of diabetes in obese menopausal women.

Since no OGTT was performed in our control children, we could not determine whether the AUC-insulin level was abnormally high in obese children compared with controls. However, several studies have demonstrated a hyperresponse of insulin to glucose in obese subjects regardless of the fasting insulin level. Le Stunff & Bougnères (2) studied the development of hyperinsulinemia in obese children with a recent onset of obesity, and showed that postprandial hypersecretion of insulin was one of the earliest metabolic alterations, followed by fasting hyperinsulinemia. Similarly, Reaven et al. (15) reported that moderately obese adults with normal glucose tolerance and fasting normoinsulinemia have an exaggerated insulin response to OGTT compared with the non-obese individuals. Thus, it is conceivable that the AUC-insulin level in OGTT is increased in our obese children, which in turn may reflect the decreased IGFBP-1 level.

Brismar et al. (13) investigated a role of insulin in the regulation of IGFBP-1 in healthy adults, who were classified as high insulin responders or low insulin responders on the basis of their insulin response to a standardized glucose infusion test, and showed that the fasting level of IGFBP-1 was significantly lower in high insulin responders than in low insulin responders, although the fasting insulin level did not differ between the two groups. Furthermore, they demonstrated that the fasting level of IGFBP-1 correlated inversely with the integrated insulin and positively with insulin sensitivity, whereas it did not correlate with the fasting insulin level (13). In addition, Morris & Falcone (16) showed that, in women with polycystic ovary syndrome, both insulin sensitivity and the IGFBP-1 level were significantly lower than in controls and the IGFBP-1 level correlated positively with insulin sensitivity. Therefore, the reduced IGFBP-1 level may be explained by impaired insulin sensitivity and may predict insulin resistance in obese subjects. In our study, the serum level of IGFBP-1 was significantly decreased even in the obese children with fasting normoinsulinemia, suggesting that impaired
insulin sensitivity had already developed. Since it is difficult and time consuming to evaluate insulin resistance by an OGTT in prepubertal children, a single measurement of IGFBP-1 may be a better method for screening potential insulin resistance. Alternatively, the reduced level of IGFBP-1 allows greater fractions of IGF-I to be unbound and increases the tissue availability of IGF-I, which in turn stimulates glucose uptake in patients with impaired insulin sensitivity. Therefore, the low IGFBP-1 level may be a compensatory response to decreased insulin sensitivity.

In conclusion, our results suggest that the fasting level of IGFBP-1 may be a useful predictor for early identification of the development of insulin resistance in prepubertal obese children.

References


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