Clin Pediatr Endocrinol 2011; **20**(1), 1-6

Original Article

Insulin Resistance during Puberty in Non-obese Japanese Children

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Abstract. We examined whether non-obese Japanese children without diabetes exhibited insulin resistance during puberty. The study subjects were 201 Japanese school students, consisting 95 males and 106 females, aged 11.5 ± 2.6 yr. None of the subjects were obese, with the mean percent of overweight being 0.7 ± 10.5%, or had diabetes at the time of the study. Overnight fasting plasma values of insulin (FIRI) and HOMA-R were measured, with concomitant measurement of the plasma glucose (FPG) levels. The mean FPG, FIRI and HOMA-R values were 89.6 ± 7.3 (70–109) mg/dl, 9.0 ± 3.6 (1.7–24.4) μU/ml and 2.0 ± 0.9 (0.3–5.2), respectively. The mean FIRI value was significantly higher in females than in males (8.3 ± 3.4 vs. 9.6 ± 3.7 μU/ml, p=0.0060). The FIRI and HOMA-R values of the pubertal students were significantly higher compared with those of the prepubertal students (FIRI, 10.0 ± 3.4 vs. 6.5 ± 2.8 μU/ml; HOMA-R, 2.3 ± 0.8 vs. 1.4 ± 0.7; p<0.0001 for both). Similar trends were observed between the two genders. The mean FIRI levels and HOMA-R values were positively correlated with age (FIRI, r=0.280, p<0.0001; HOMA-R, r=0.300, p<0.0001). In conclusion, we demonstrated that the FIRI and HOMA-R values were significantly associated with pubertal development in non-obese Japanese children without diabetes, consistent with the results of studies in white and black children.

Key words: insulin resistance, insulin sensitivity, Japanese children, non-obese, puberty

Introduction

Hormonal and physical changes during puberty increase insulin resistance. Adolescents have been demonstrated to have higher insulin levels than prepubertal children. It has been reported that insulin sensitivity is decreased during puberty, and that this is associated with a compensatory increase of insulin secretion (1–6). However, most of these previously reported studies were conducted in white and black children, and there is a lack of corresponding data in Japanese adolescents. On the other hand, insulin sensitivity is also known to be deteriorated in obesity. Peripheral fat accumulation has been reported to increase insulin resistance through secretion of adipocytokines from fat cells (7, 8). Some Japanese studies have demonstrated insulin resistance associated with a compensatory increase of insulin secretion in obese children (9, 10).

To examine the effect of puberty on the insulin sensitivity without the influence of

Received: September 10, 2010
Accepted: October 22, 2010
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obesity, we examined the parameters reflecting insulin resistance in non-obese prepubertal and pubertal Japanese children.

Subjects and Methods

The study subjects were 201 Japanese school students, consisting 95 males and 106 females, aged 11.5 ± 2.6 (6–16) yr. There was no significant difference in mean age between genders (11.3 ± 2.8 vs. 11.7 ± 2.3, p=0.3932). The mean height and body weight were 144.0 ± 7.0 cm and 39.0 ± 8.9 kg in males and 147.5 ± 6.7 cm and 40.8 ± 8.5 kg in females, respectively. The mean height and weight in prepubertal students were 131.4 ± 6.0 cm and 29.8 ± 6.9 kg in males (mean age: 9.1 ± 2.8 yr) and 126.5 ± 5.7 cm and 26.8 ± 5.5 kg in females (mean age: 8.4 ± 2.3 yr), respectively. That in pubertal students were 159.0 ± 7.1 cm and 50.4 ± 10.5 kg in males (mean age: 13.4 ± 2.6 yr) and 155.3 ± 5.5 cm and 48.8 ± 8.4 kg in females (mean age: 13.7 ± 2.5 yr), respectively. None of the subjects were obese, with the mean percent of overweight being 0.7 ± 10.5% (–19.2–19.8) at the time of the study. There was no statistical difference in percent of overweight between the genders (males vs. females: 0.9 ± 10.5 vs. 0.5 ± 10.7, p=0.8450). The students participated in a urine glucose screening program at schools in the Tokyo Metropolitan Area (11) and exhibited no glucose intolerance.

Overnight fasting plasma values of insulin (FIRI) and HOMA-R were measured, with concomitant measurement of the plasma glucose (FPG) levels in the subjects at the time of the screening program. We examined the relation between insulin resistance assessed by FIRI levels and homeostasis model assessment insulin resistance (HOMA-R) and the parameters reflecting insulin resistance including sex, age and pubertal development among the subjects.

Pubertal development was assessed by Tanner stage ranging from I to V (12). Prepubertal children were in Tanner stage I, and pubertal children were beyond Tanner stage II. According to the Tanner stage, 142 children were in prepubertal and 59 were in pubertal. Percent of overweight was calculated as (current weight – sex-, age- and height-matched ideal weight) / sex-, age- and height-matched ideal weight × 100 (%). Subjects with a percent of overweight exceeding 20% were judged to be obese (13). HOMA-R was an acceptable alternative for estimating insulin resistance and was calculated by FPG (mg/dl) × IRI (μU/ml) / 405. HOMA-R exceeding 2.5 was judged to be insulin resistant (14). PG was measured by a glucose oxidase method, and IRI was measured using a radioimmunoassay.

Statistical Analysis

The results were expressed as the mean values ± SD. The Mann-Whitney U test was used to detect differences between the two groups. Analysis of correlation was performed by Pearson and Spearman correlation coefficients. $p<0.05$ was considered to be statistical significant.

Results

The mean values of FPG, FIRI and HOMA-R among the subjects were 89.6 ± 7.3 (70–109) mg/dl, 9.0 ± 3.6 (1.7–24.4) μU/ml and 2.0 ± 0.9 (0.3–5.2), respectively. Figure 1 shows the distribution of these values.

Figure 2 shows a comparison of FIRI and HOMA-R between genders. The mean value of FIRI was significantly higher in females than in males (8.3 ± 3.4 vs. 9.6 ± 3.7 μU/ml, p=0.0060). There was no statistical deference in HOMA-R between genders (2.1 ± 0.9 vs. 1.9 ± 0.9, p=0.0547).

Figure 3 shows a comparison of FIRI and HOMA-R between prepubertal and pubertal students. There was no significant difference in percent of overweight between prepubertal and pubertal students (prepubertal, –0.9 ± 9.4; pubertal, 1.4 ± 11.0; p=0.1638). Pubertal students showed significantly higher values of FIRI and

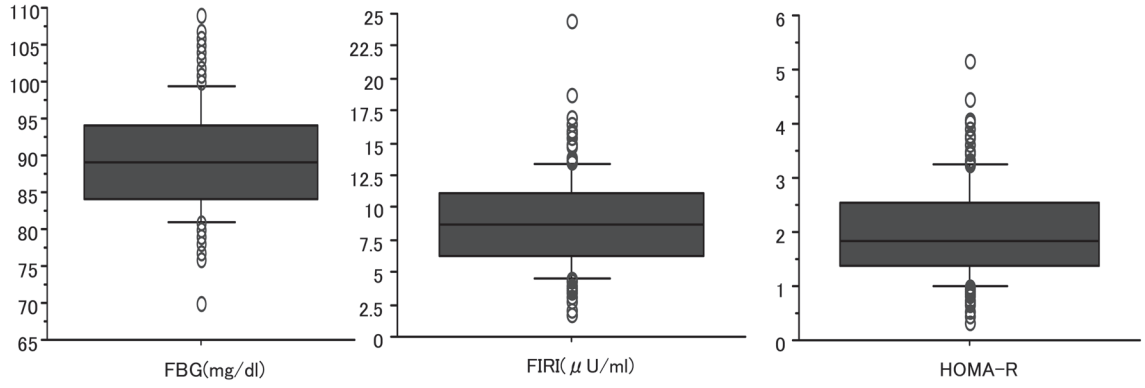

Fig. 1 Distribution of FBG, IRI and HOMA-R among the subjects.

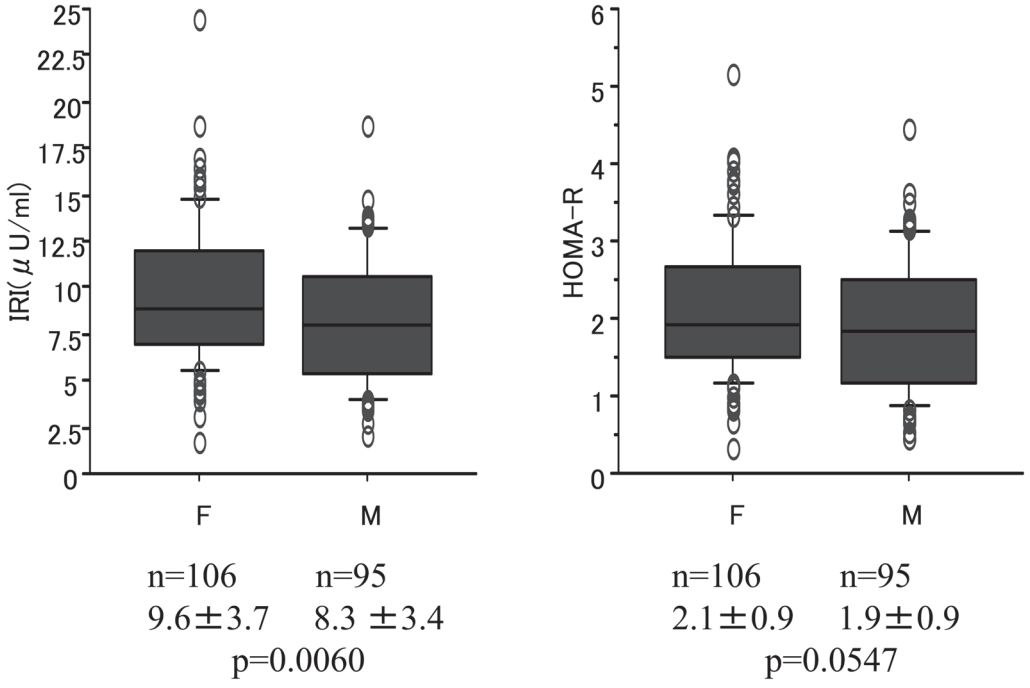

Fig. 2 Comparison of IRI and HOMA-R between sex.

HOMA-R as compared with prepubertal students (FIRI and HOMA-R: 10.0 ± 3.4 vs. 6.5 ± 2.8 μU/ml, and 2.3 ± 0.8 vs. 1.4 ± 0.7, $p<0.0001$, respectively). A similar relationship was also seen for males (FIRI and HOMA-R: 9.5 ± 3.1 vs. 6.3 ± 2.8 μU/ml and 2.2 ± 0.8 vs. 1.4 ± 0.7, $p<0.0001$, respectively) and females (FIRI and HOMA-R: 10.3 ± 3.5 vs. 6.9 ± 2.8 μU/ml and 2.3 ± 0.8 vs. 1.5 ± 0.6, $p<0.0001$, respectively).

Figure 4 shows the correlation between age at the time of study and FIRI and HOMA-R. Both the FIRI levels and HOMA-R were positively

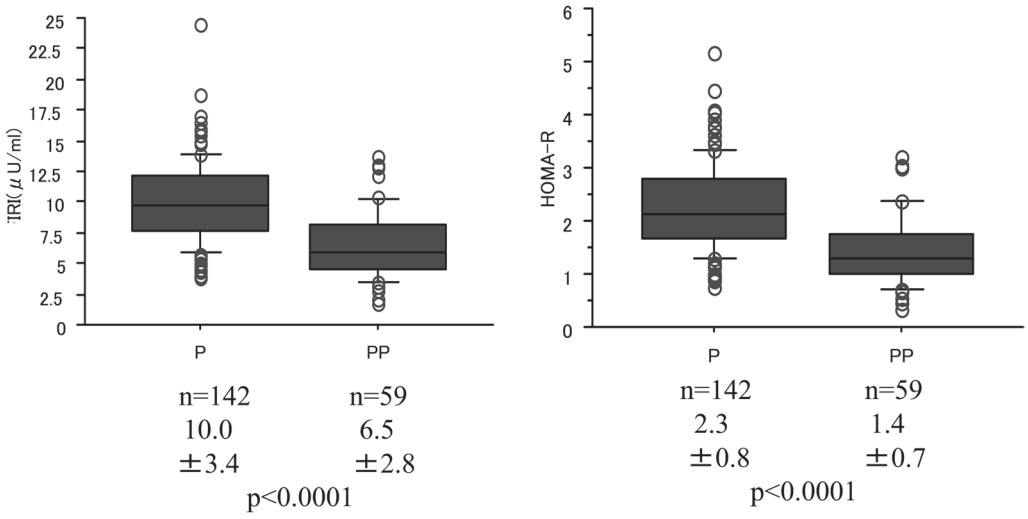

Fig. 3 Comparison of IRI and HOMA-R between pubertal (P) and prepubertal (PP) subjects.

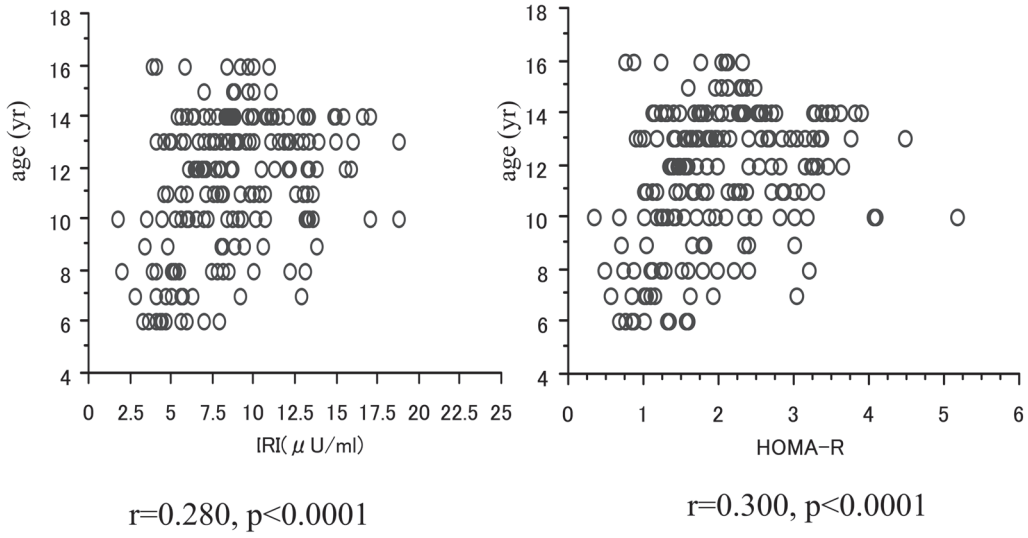

Fig. 4 Correlation between age and IRI and HOMA-R in the subjects.

correlated with age (r=0.280 for FIRI, r=0.300 for HOMA-R, p<0.0001, respectively).

Discussion

The present study demonstrated significantly higher FIRI and HOMA-R values in pubertal subjects than prepubertal subjects among non-obese Japanese children without diabetes. These results are consistent with those reported previously among white and black children (1–6). Thus, a decrease in insulin sensitivity during puberty, generally associated with a compensatory increase in insulin secretion, is seen not only in Caucasians and Blacks, but also in the Japanese. Bloch *et al.* (2) demonstrated that the insulin

resistance level in pubertal children was approximately 30% higher than that in prepubertal children, as assessed by the euglycemic-hyperinsulinemic clamp technique. However, the mechanisms underlying insulin resistance during puberty have not yet been clearly elucidated. A selective effect of sex hormones appears to be unlikely because the concentrations of sex hormones would be even higher in adults, who show a higher sensitivity to insulin than adolescents. Furthermore, Yki-Järvinen (15) showed that insulin-mediated glucose metabolism in normal women was not affected during the menstrual cycle, despite the different levels of sex hormones during this period. On the other hand, the insulin resistance during puberty is most likely explained by the increased secretion of growth hormone (GH) during puberty. Several studies have shown that hypersecretion of GH deteriorates insulin sensitivity in normal adolescents (1, 2, 5, 16, 17). Amiel *et al.* (1) demonstrated an inverse correlation between the mean 24-h levels of GH and insulin-stimulated glucose metabolism, and Bloch *et al.* (2) showed a negative correlation between insulin sensitivity and IGF-1 levels in white children.

The present study also demonstrated that females exhibited higher levels of insulin resistance than males during puberty, despite the absence of any significant difference in percent of overweight between the genders. This difference is likely to be due to the difference in body composition, that is, the percent body fat, between male and female adolescents. Females, especially during adolescence, show a higher body fat mass than males (18, 19). Nakanishi *et al.* (19) reported that the increased body fat mass and enhanced insulin resistance in pubertal females were associated with higher leptin levels in these subjects.

In recent years, the prevalence of obese children in Japan has been increasing, and childhood type 2 diabetes is detected at a relatively high frequency by a urine glucose screening programs at schools (11). Obesity is known to be one of the major factors predisposing to the development of type 2 diabetes. Puberty is also considered to be a risk factor because of increased insulin resistance, as demonstrated in the present study. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has proposed that obese adolescents in high-risk ethnic groups with a family history of type 2 diabetes should be screened for glucose intolerance (20). It is very important to screen children with risk factors for type 2 diabetes to prevent the onset and progression of the disease.

Conclusions

We demonstrated a significant increase of the insulin resistance during puberty in Japanese children without diabetes, which is consistent with the results of previous studies in white and black children. The decreased insulin sensitivity observed during puberty in normal adolescents is compensated for by an increase of the insulin secretion. Further studies using special techniques, such as the insulin clamp technique (2, 21), may be necessary to endorse the findings of the present study.

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