

# Sex-Related Differences Between Adiponectin and Insulin Resistance in Schoolchildren

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**OBJECTIVE** — To study the effect of body composition and adiponectin on insulin resistance and  $\beta$ -cell function in schoolchildren during puberty.

**RESEARCH DESIGN AND METHODS** — Plasma adiponectin level and its relationships with insulin sensitivity and  $\beta$ -cell function were analyzed in 500 randomly recruited nondiabetic Taiwanese schoolchildren (245 boys and 255 girls) aged 6–18 years in a national survey program for diabetes in 1999. Insulin resistance and  $\beta$ -cell function were evaluated by homeostasis model assessment (HOMA). Plasma adiponectin concentrations were determined with radioimmunoassay.

**RESULTS** — Plasma glucose levels remained stable, whereas insulin resistance increased with a compensatory rise in  $\beta$ -cell function during this period. A transient drop of adiponectin level with a trough at 10–12 years was found in boys but not in girls. This pubertal drop of adiponectin levels in boys coincides with the sharp rise in testosterone concentration. A negative correlation between testosterone levels and adiponectin concentration was also noted in boys ( $r = -0.142$ ,  $P = 0.032$ ). Plasma adiponectin levels correlated inversely with relative body weight, fasting insulin concentrations, and insulin resistance index by HOMA in boys aged 15–18 years and in girls aged 11–14 years. No association was observed between adiponectin levels and  $\beta$ -cell function by HOMA.

**CONCLUSIONS** — There is a transient drop in the level of adiponectin during male puberty, correlated with the increase in testosterone level in boys. Plasma adiponectin levels were inversely correlated with obesity and insulin resistance in boys and girls during the pubertal period.

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Type 2 diabetes, once considered to be a disease of adults, is now emerging in children and adolescents worldwide (1,2). In adults, both insulin sensitivity and  $\beta$ -cell function decline

with aging. According to both cross-sectional and longitudinal studies (3–5), these abnormalities are always found in the pre-diabetic state during development of type 2 diabetes. However, little is

known about the evolution of the insulin resistance and  $\beta$ -cell function of children who are “growing” rather than “aging.”

Although children in their pre-diabetic state might share common pathogenesis in terms of insulin resistance and  $\beta$ -cell deterioration, the etiology of insulin resistance and the pattern of islet compensation under various stimuli for growth and development may differ markedly from those of adults. Much effort for elucidating transient insulin resistance during puberty has focused on sex steroids (6–8), which, however, fail to explain the restoration of insulin sensitivity after puberty, when sex hormones have achieved and maintain adult levels. On the other hand, the growth hormone/IGF-1 axis, a chronologically plausible culprit, is still controversial in its insulin-antagonizing effects in children of different ages and sexes (9–11). Given the tight, temporal coupling between growth and reproductive development, some common signals regulating adolescent growth and the initiation of puberty might contribute to pubertal insulin resistance.

During puberty, body composition, especially fat distribution, causes a remarkable sex-specific change (12–13), which, in addition to the evolution of various adipocytokines, may play a role in pubertal insulin resistance. Adiponectin is an adipose-specific protein abundantly present (0.01%) in the circulatory system. It is composed of 244 amino acid residues, homologous to collagens VIII and X and to complement factor C1q (14). Adiponectin has been shown to decrease cytokine production from macrophages (15) and to attenuate the biological effects of tumor necrosis factor- $\alpha$  by the interference of its signaling (16). Circulating levels of adiponectin are known to be lower in individuals with obesity, type 2 diabetes, and coronary artery disease (17–19). Hypoadiponectinemia, therefore, is considered as a new biomarker for metabolic syndrome (20). The physiological functions of adiponectin in humans are pri-

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**Abbreviations:** CFH, Chinese Foundation of Health; FAI, free androgen index; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; RBW, relative body weight; SHBG, sex hormone-binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical and hormonal characteristics of subjects

	All	Age-group			P	
		6–10	11–14	15–18	ANOVA	Trend
<b>Boys</b>						
n	245	35	121	89		
Height (cm)	157 ± 16.1	127.7 ± 8.3	155.7 ± 9.9	170.3 ± 6.1	<0.001	<0.001
Weight (kg)	49.1 ± 13.7	29.5 ± 7.3	48.1 ± 10.0	58.1 ± 11.3	<0.001	<0.001
BMI (kg/m <sup>2</sup> )	19.55 ± 3.21	17.91 ± 2.92	19.72 ± 3.11	19.95 ± 3.28	0.004	0.001
Systolic BP (mmHg)	112 ± 15	99 ± 11	112 ± 14	117 ± 14	<0.001	<0.001
Diastolic BP (mmHg)	69 ± 11	64 ± 10	68 ± 10	73 ± 11	<0.001	<0.001
Fasting glucose (mmol/l)	4.44 ± 0.39	4.50 ± 0.44	4.44 ± 0.39	4.39 ± 0.39	0.221	0.092
Fasting insulin (pmol/l)	73.2 ± 57.4	59.6 ± 42.3	67.4 ± 44.5	86.1 ± 73.9	0.020	0.019
Adiponectin (μg/ml)	6.54 ± 3.16	7.0 ± 2.8	5.9 ± 3.2	7.3 ± 3.0	0.005	0.631
Ln HOMA-IR	0.472 ± 0.685	0.261 ± 0.763	0.435 ± 0.641	0.604 ± 0.691	0.003	0.012
Ln HOMA-β	5.255 ± 0.674	4.932 ± 0.668	5.196 ± 0.651	5.462 ± 0.647	<0.001	<0.001
TTE (nmol/l)	11.24 ± 7.51	6.88 ± 6.65	11.91 ± 7.72	11.90 ± 7.06	0.002	0.002
FAI	38.4 ± 34.5	17.7 ± 20.6	41.5 ± 37.3	41.7 ± 32.1	0.003	0.001
<b>Girls</b>						
n	255	54	136	65		
Height (cm)	150.0 ± 11.9	133.4 ± 10.6	152.3 ± 7.6	158.9 ± 5.0	<0.001	<0.001
Weight (kg)	43.1 ± 10.8	32.0 ± 9.9	43.8 ± 8.9	51.0 ± 7.0	<0.001	<0.001
BMI (kg/m <sup>2</sup> )	18.89 ± 3.12	17.67 ± 3.44	18.76 ± 3.05	20.18 ± 2.47	<0.001	<0.001
Systolic BP (mmHg)	107 ± 14	102 ± 12	109 ± 14	107 ± 13	0.007	0.073
Diastolic BP (mmHg)	68 ± 11	64 ± 10	70 ± 11	69 ± 9	0.001	0.015
Fasting glucose (mmol/l)	4.39 ± 0.39	4.33 ± 0.33	4.44 ± 0.33	4.39 ± 0.33	0.374	0.742
Fasting insulin (pmol/l)	75.3 ± 45.2	57.4 ± 40.9	81.1 ± 46.6	76.1 ± 41.6	0.004	0.026
Adiponectin (μg/ml)	6.94 ± 2.98	6.94 ± 2.70	6.85 ± 2.92	7.14 ± 3.35	0.816	0.726
Ln HOMA-IR	0.545 ± 0.609	0.241 ± 0.650	0.653 ± 0.572	0.574 ± 0.571	<0.001	0.002
Ln HOMA-β	5.359 ± 0.637	5.112 ± 0.716	5.440 ± 0.580	5.397 ± 0.640	0.005	0.014

Data are means ± SD. BP, blood pressure; TTE, total testosterone.

marily related to insulin sensitivity and atherosclerosis.

Recently, adiponectin was reported to be strongly and independently associated with a reduced risk of type 2 diabetes in adults (21). Similarly, adipocytokine levels are correlated with fat mass, insulin sensitivity, and cardiovascular risk factors in children (22). However, little is known about its change in plasma levels during puberty and whether adiponectin plays any role in pubertal insulin resistance. The present study was designed to examine the serial changes of plasma adiponectin levels and its relationship with insulin resistance and β-cell function in school-children throughout puberty.

## RESEARCH DESIGN AND METHODS

Subjects comprised 500 randomly selected Taiwanese school students (245 boys and 255 girls) aged 6–18 years without diabetes, according to the 1997 ADA criteria (23), in a nationwide survey program for diabetes in 1999 (24). Basic demographic data, anthropometric measurement, and fasting venous

blood sampling were obtained. This program was approved by the Ministry of Education of Taiwan and conducted by the Chinese Foundation of Health (CFH) with support from the Taiwan Provincial Department of Health. Written informed consent was obtained for each participant before blood was drawn.

### Anthropometric Measurement

BMI (in kg/m<sup>2</sup>) and relative body weight (RBW), the ratio of each child's weight to a predicted weight, expressed as a percentage, were calculated (25). Based on chronological age, prepubertal (6–10 years old), pubertal (11–14 years old), and late pubertal (15–18 years old) periods were stratified to study the pubertal change of various metabolic variables.

### Biochemical assays

All blood samples were transferred to the central laboratory at the CFH headquarters and were aliquoted and stored at –70°C until use. Blood glucose levels were measured using an automatic analyzer (Technician RA 2000 serum auto-

analyzer; Bayer Diagnostic, Tarrytown, NY), and insulin concentration was determined by microparticle enzyme immunoassay on an Abbott AxSYM automatic analyzer (Abbott Laboratories, North Park, IL). Plasma adiponectin levels were determined by radioimmunoassay (Linco Research, St. Charles, MO). The sensitivity of this assay was 0.78 ng/ml. The coefficients of variation for intra- and interassay were 9.3 and 15.3%, respectively. Testosterone and sex hormone-binding globulin (SHBG) were determined by competitive immunoassay and immunometric assay on a DPC Immulite automatic analyzer (Los Angeles, CA). The sensitivity was 0.3467 nmol/l for testosterone and 0.2 nmol/l for SHBG.

The indexes of β-cell function and insulin resistance were calculated according to the homeostasis model assessment (HOMA) as follows: HOMA-IR = FIRI × FPG/22.5, HOMA-β = 20 × FIRI/(FPG – 3.5), where HOMA-IR is HOMA of insulin resistance, FIRI is fasting immunoreactive insulin (μU/ml), and FPG is fasting plasma glucose levels (mmol/l)

(26). Log-transformed HOMA-IR was used because it provided better correlation with insulin sensitivity indexes as assessed by glucose clamp or minimal model analysis (27). The free androgen index (FAI) was obtained as the quotient of (testosterone/SHBG)  $\times$  100 (28).

### Statistical analyses

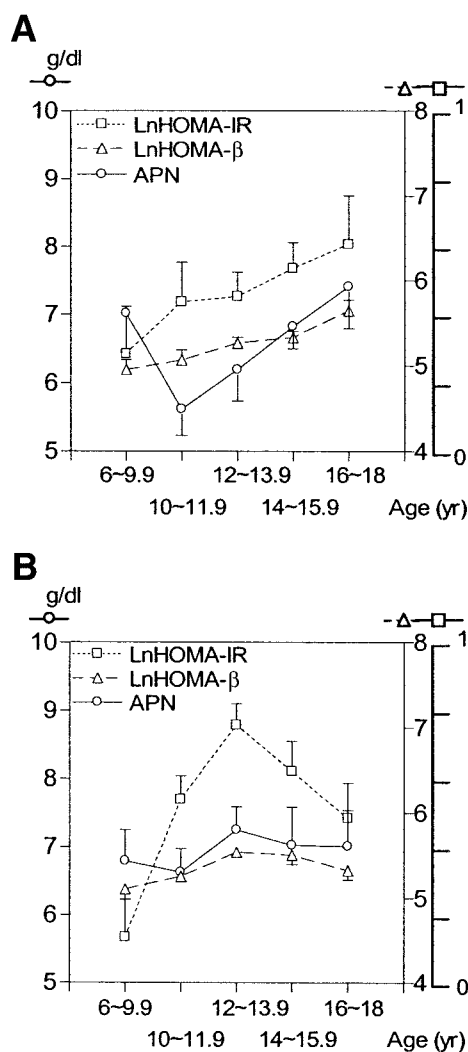
Data were presented as arithmetic means  $\pm$  SD. For variables with skewed distribution, logarithm (insulin and glucose) or square root (adiponectin) transformation to normality were made before analysis. Differences in continuous variables among the groups of subjects were tested with one-way ANOVA and trend analysis. Pearson's correlation was used to check the relationships between adiponectin levels and selected anthropometric or metabolic parameters. A nominal *P* value of  $<0.05$  was considered significant, whereas that between 0.05 and 0.1 was considered borderline in significance. Statistical analysis was performed using SPSS software version 8.0 (SPSS, Chicago, IL).

## RESULTS

### Evolution of plasma adiponectin levels, insulin resistance, and $\beta$ -cell function throughout puberty in schoolchildren

As shown in Table 1, height, weight, BMI, and blood pressure increased steadily with age during pubertal periods in both girls and boys. Although fasting plasma glucose levels remained relatively stable during this age range, there was an increase in the fasting insulin concentration, the index of insulin resistance (HOMA-IR), as well as in  $\beta$ -cell function (HOMA- $\beta$ ) with advancing ages (Table 1).

A significant change in plasma adiponectin levels was found in boys ( $P = 0.005$  by ANOVA) but not in girls (Table 1). For illustrating the age-related evolution in plasma adiponectin levels and its relationship with insulin sensitivity during puberty, these children were further subdivided into five different age-groups as depicted in Fig. 1. The adiponectin levels exhibited a V shape with a remarkable trough in boys aged 10–12 years (Fig. 1A). No significant fluctuation of adiponectin levels was observed in girls (Fig. 1B). We then examined the relationship between the plasma level of total testosterone and the derived FAI to investigate



**Figure 1**—Evolutions of mean plasma adiponectin (APN) levels, Ln HOMA-IR, and Ln HOMA- $\beta$  in nondiabetic boys (A) and girls (B) by age-groups. Data are means  $\pm$  SE. The case numbers for age 6–9.9, 10–11.9, 12–13.9, 14–15.9, and 16–17.9 years old are 32, 38, 70, 78, and 27 for boys, respectively (A), and 38, 72, 72, 37, and 36 for girls, respectively (B).

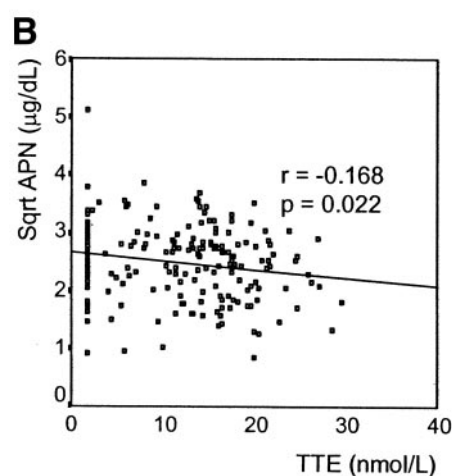
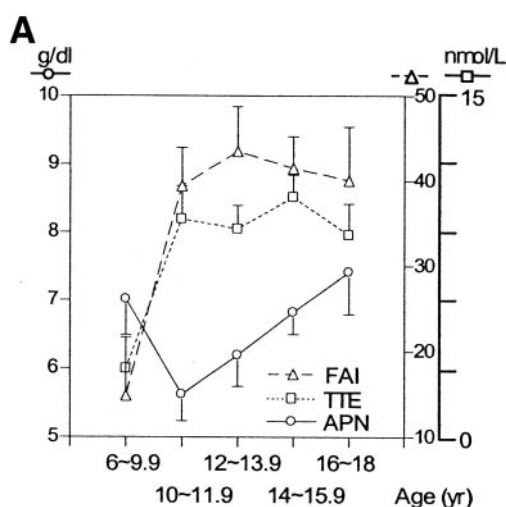
the effect of male puberty on the plasma level of adiponectin. As shown in Table 1, the levels of total testosterone and FAI had a great jump after age 11–14 years in boys. This increase in testosterone level associated with the occurrence of a remarkable drop in adiponectin levels (Fig. 2A). There was a significant inverse relationship between adiponectin concentrations and testosterone levels in boys of all ages (Table 2). By excluding boys  $<10$  years old, in whom the testosterone level was mostly below the detection limit, this negative correlation became even stronger ( $r = -0.168$ ,  $P = 0.022$ ) (Fig. 2B).

### Correlation of plasma adiponectin levels and anthropometric parameters and glucose homeostasis

The univariate correlation between plasma adiponectin levels and selected

anthropometric and metabolic parameters are shown in Table 2. A significant inverse relationship between plasma adiponectin concentrations and BMI or RBW was noted in schoolchildren  $>10$  years old.

To further understand the role of plasma adiponectin levels on insulin sensitivity, we used fasting insulin levels and the derived HOMA-IR as indicators for insulin resistance. In girls, plasma adiponectin levels were inversely related to fasting insulin concentrations ( $r = -0.162$ ,  $P < 0.01$ ) and HOMA-IR ( $r = -0.180$ ,  $P < 0.01$ ) (Table 2), mainly during mid-puberty (11–14 years old). In contrast, negative correlations between adiponectin levels and both fasting insulin concentrations ( $r = -0.221$ ,  $P = 0.039$ ) and HOMA-IR ( $r = -0.228$ ,  $P = 0.032$ ) were only found in late-pubertal



**Figure 2**—Relationship between adiponectin and testosterone levels in boys. A: Evolution of mean plasma adiponectin (APN) levels and the mean total testosterone (TTE) concentrations and FAI by age-groups. Data are means  $\pm$  SE. B: Correlations between total testosterone and adiponectin levels (in square root [Sqrt]) in boys  $>10$  years old.

boys after adiponectin returned from trough level.

Because both testosterone and RBW were negatively correlated with the level of adiponectin, we then compared the relationships between HOMA-IR and adi-

ponectin concentrations after adjustments with total testosterone and RBW. When adiponectin levels were corrected for both RBW and total testosterone, a borderline negative correlation between adiponectin and HOMA-IR was still ob-

served in boys  $>14$  years old ( $r = -0.199$ ,  $P = 0.069$ ) (Fig. 3). On the other hand, for girls of all age-groups, the association of adiponectin concentrations with HOMA-IR was abolished after adjusting either RBW or BMI (data not shown).

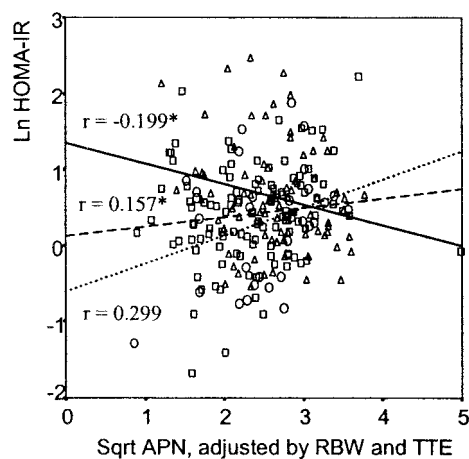
No correlation was found between adiponectin levels and  $\beta$ -cell function as measured by HOMA- $\beta$ . Besides, there was no significant association between adiponectin levels and either systolic or diastolic blood pressure in schoolchildren (Table 2), consistent with our previous observations in an adult population (20).

**CONCLUSIONS**— Adiponectin levels evolved in a sex-specific way throughout puberty. In boys, a striking V shape with a trough at  $\sim 10$ – $12$  years old was noted. What triggers the fall of adiponectin in boys during puberty is not known. One plausible explanation is gonad steroids. Indeed, we documented an inverse relationship between adiponectin levels and testosterone levels. Our data are consistent with the results published by Nishizawa et al. (29), who noticed an inhibitory effect by androgen on the production of adiponectin in cell lines and animal studies. Nevertheless, it is noteworthy that adiponectin concentrations are restored after puberty, and, at that point, androgens remain at adult levels. This indicates that other signals might play a role in the restoration of adiponectin after puberty. Interestingly, the study by Combs et al. (30) indicates that surgical excision of the testes or ovaries before puberty did not interfere with the rise of Acrp30, the human adiponectin homo-

**Table 2**—Correlations between adiponectin and selected anthropometric or metabolic variables in schoolchildren

Age-group	Boys				Girls			
	6–10	11–14	15–18	All	6–10	11–14	15–18	All
n	35	121	89	245	54	136	65	255
BMI	-0.115	-0.155*	-0.463†	-0.254†	-0.116	-0.186‡	-0.365†	-0.198†
RBW	0.016	-0.141	-0.401†	-0.219†	-0.144	-0.157*	-0.335†	-0.186†
SBP	0.215	0.047	-0.044	0.037	-0.029	0.002	-0.045	-0.020
DBP	0.263	0.013	-0.037	0.049	0.187	-0.093	-0.117	-0.050
Ln insulin	0.221	0.058	-0.221‡	0.002	-0.186	-0.187‡	-0.107	-0.162†
Ln HOMA-IR	0.226	0.064	-0.228‡	0.000	-0.207	-0.191‡	-0.149	-0.180†
Ln HOMA- $\beta$	0.165	0.013	-0.139	0.008	-0.057	-0.104	0.093	-0.039
TTE	-0.015	-0.044	-0.300†	-0.130‡	—	—	—	—
FAI	0.021	-0.021	-0.190*	-0.079	—	—	—	—

DBP, diastolic blood pressure; SBP, systolic blood pressure; TTE, total testosterone. \* $P < 0.10$ ; † $P < 0.01$ ; ‡ $P < 0.05$ .



**Figure 3**—Correlations between insulin resistance (Ln HOMA-IR) and adiponectin levels (in square root [Sqrt]), adjusted by total testosterone (TTE) concentrations and RBW in boys.  $\circ$ , 6–10 years old;  $\square$ , 11–14 years old;  $\triangle$ , 15–18 years old. Regression lines were shown:  $r = -0.199$ ,  $P = 0.069$  for ages 15–18;  $r = 0.157$ ,  $P = 0.098$  for ages 11–14. \* $P < 0.10$  is marked on the graphs.

logue, in adult mice. Intriguingly, the pubertal change in concentrations of another adipocytokine, leptin, also shows a sex-dimorphic picture (31), a pattern like the mirror image of the evolution of adiponectin levels presented in this study.

The exact cause of pubertal insulin resistance is not fully understood, despite there being extensive experimental evidence that androgens act directly on peripheral tissues to promote insulin resistance (32). In our present study, we found that the pubertal rise of testosterone correlated with a sharp reduction in adiponectin levels that might contribute to insulin resistance in boys. Nonetheless, the negative correlations between adiponectin levels and both fasting insulin concentrations and HOMA-IR remain significant even after adjusting testosterone or FAI levels in older boys. These data suggest that androgens negatively regulate the adiponectin levels during pubertal and postpubertal ages in boys. However, the relationship between adiponectin levels and insulin resistance in older boys still exists even after adjustment with testosterone levels.

An inverse relationship between plasma adiponectin concentrations and both adiposity and fasting insulin levels was reported in both adults and children (18,20,33). Similarly, we observed a negative correlation between adiponectin levels and BMI or RBW, but not in younger children <10 years old. On the contrary, we found a positive correlation between plasma adiponectin concentrations and HOMA-IR in boys aged 6–10 years. No solid conclusions can be drawn with the limited case number, multiple comparisons, lack of pubertal staging,

and cross-sectional nature of this survey. Adjustment for pubertal stage might influence the results. However, there is a possibility that the lack of overweight and insulin resistance in the very young children before puberty (6–10 years old) contributed to the lack of a reverse relationship between adiponectin level and BMI/insulin resistance. On the other hand, the adiposity that developed in early puberty might disappear in late puberty in boys because testosterone decreases body fat. Regardless of whether and how these children experience a process of transition during puberty, turning this correlation from positive to negative merits further studies.

In adults, the relationship between plasma adiponectin concentrations and insulin sensitivity has been reported to be independent of BMI, percentage of body fat, and waist-to-hip ratio (34). However, we found that this relationship was abolished in schoolgirls after adjusting for RBW or BMI, and it was weakened in schoolboys >14 years old with adjustment for both RBW and total testosterone. This indicates that under respective physiological conditions across puberty, adiponectin, interacting with sex steroids and other complex hormones and factors, might play a different role in determining insulin sensitivity among boys and girls. As can be seen, the degree of insulin resistance measured with HOMA-IR increases steadily in boys aged 6–18 years. HOMA-IR increases with age in girls, peaking at age 12–14 years and declining gradually afterward. Further investigation of the etiological factors involved in insulin resistance in girls during this period

will be required to explain this transient rise of insulin resistance.

In schoolchildren, although fasting plasma glucose levels remained relatively stable, there was an increase in insulin resistance with age during this period, reflected by an increase in fasting insulin concentrations and HOMA-IR. In contrast with the steady decline in  $\beta$ -cell function with age observed in adults (4,5), the increasing insulin resistance in childhood could be well compensated by an increase in  $\beta$ -cell function, as measured with HOMA- $\beta$ , to maintain glucose homeostasis. Adiponectin level was not correlated with HOMA- $\beta$  in the schoolchildren.

Although the cross-sectional data are relatively preliminary, this finding may spark future research to establish the role of adipocytokines in pubertal insulin resistance by a longitudinal study. Our observation needs to be verified by further longitudinal studies to illuminate the role of adiponectin levels during the development of type 2 diabetes. In conclusion, plasma adiponectin level may be one of the factors of pubertal insulin resistance. However, significant inverse correlations (possibly mediated by the evolution of the body component) of adiponectin and insulin resistance can be observed in both mid-pubertal girls and late-pubertal boys. Interestingly, plasma adiponectin levels, insulin resistance,  $\beta$ -cell function, and correlation of adiponectin levels with insulin resistance all display a sex-specific picture throughout puberty. This dimorphism may herald different risks for developing type 2 diabetes and cardiovascular diseases and merits further study.

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