Low Serum Adiponectin Levels in Korean Children with a Family History of Type 2 Diabetes Mellitus

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Key Words

Family history of type 2 diabetes mellitus · Adiponectin · Korean children

Abstract

Background/Aims: The current worldwide increases of type 2 diabetes mellitus (T2DM) in children coincide with increases in the prevalence of obesity. We investigated the insulin resistance and adiponectin levels of children and adolescents with a family history of T2DM (FHD). **Methods:** Our sample included 131 children and adolescents aged 8–15 years. Fasting plasma glucose, lipids, fasting insulin, adiponectin levels and HOMA-IR were analyzed according to FHD and obesity. Oral glucose tolerance tests were performed in all subjects except non-obese subjects without FHD. **Results:** Adiponectin levels of subjects with FHD were significantly lower than those of subjects without FHD in both the obese and nonobese groups. HOMA-IR was significantly higher in obese subjects with FHD than in those without FHD. Adiponectin levels were found to be independently associated with FHD and Matsuda index. The frequency of impaired glucose tolerance in obese subjects with FHD was more than four times higher compared to obese subjects without FHD. **Conclusion:** Our results suggest that FHD could be a risk factor of T2DM in obese Korean children, especially with low serum levels of adiponectin.

Introduction

In concurrence with the increased prevalence of obesity worldwide [1], the incidence of metabolic syndrome and type 2 diabetes mellitus (T2DM) have also increased in children and adolescents [2, 3]. In South Korea, obesity has steadily increased among children and adolescents during the last few decades [4], and the prevalence of T2DM is therefore expected to become higher. Risk factors of T2DM include obesity, race, adolescence, birth weight [5], and a family history of T2DM (FHD). The morbidity of those who have lifetime diabetes are as high as 40% in first-degree relatives of T2DM patients [6, 7].

Insulin resistance and the relative decrease in beta-cell function are major factors in the pathogenesis of T2DM [7]. Insulin resistance is defined by abnormal insulin signaling in target tissues and this increases the likelihood of T2DM. Although the pathogenesis of T2DM in children and adolescents remains unclear, obesity and FHD are reported to be possible risk factors [8–10]. Therefore, it is important to investigate the risk factors of T2DM in children and adolescents, and to identify metrics to use in screening tests.

Adiponectin is an adipokine consisting of four 30-kDa domains secreted by adipose tissues [11], and serum adiponectin levels exhibit relationships to insulin resistance and obesity [12–14]. A number of studies have addressed

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Table 1. Clinical and auxological characteristics of all subjects according to family history of T2DM

	FHD(+) group (n = 61)	FHD(-) group (n = 70)
Age, years	11.2 ± 2.3	11.7 ± 2.0
Height, cm	149.2 ± 15.5	150.5 ± 12.7
Weight, cm	52.0 ± 15.2	50.6 ± 15.9
Male/female	38/23	38/32
BMI, kg/m ²	22.9 ± 3.8	21.8 ± 4.2
SMR		
I	27	26
II–III	24	35
IV–V	10	9

FHD(+/-) = Group with/without family history of T2DM. There were no significant differences between two groups.

the relationship between insulin resistance and adiponectin in obese children and adolescents [15–17]. However, there are only a few studies about the correlation between adiponectin levels and family history of T2DM in children and adolescents [18].

This study aims to evaluate changes of adiponectin level and insulin resistance according to FHD and to investigate impact of serum adiponectin level and FHD in the pathophysiology of T2DM in children and adolescents.

Materials and Methods

Subjects and Classification Criteria

The study subjects included 131 children and adolescents 8–15 years of age, who visited the pediatric endocrinology clinic of the Department of Pediatrics at Korea University Anam Hospital from July 2009 to June 2010 or those who were recruited through health examinations provided by hospital programs. All subjects were assessed by history and physical examination and were determined to be in good health. They had no prior history of medication and had to be free from disease. A positive family history of T2DM was defined as having one or more first- or second-degree relatives who were diagnosed with T2DM. Height, body weight and body mass index (BMI) were measured for all subjects. Subjects with BMI greater than the 95th percentile for their age and sex based on 2007 Korean national growth charts were labeled as obese. Subjects with BMI less than the 85th percentile for their age and sex were designated as nonobese. We enrolled 61 subjects with FHD and 70 without FHD, and divided them furthermore into four subgroups according to obesity: 36 obese subjects with FHD, 25 nonobese subjects with FHD, 36 obese subjects without FHD, and 34 nonobese subjects without FHD. Pubertal

development was assessed by physical examination and graded according to the Tanner criteria (SMR). This study was approved by the institutional review board of Korea University Anam Hospital, and written informed consent was obtained from all participating parents and subjects (IRB No. AN09093).

Laboratory Sample Analysis

Blood was drawn from all subjects after 10 h or more of fasting and then centrifuged. The plasma was separated and stored at -80°C prior to examination. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assayed and total cholesterol, triglyceride, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) were measured by enzymatic colorimetric method (Roche). Serum glucose was assayed by glucose oxidase method and serum insulin was measured using immunoradiometry assay (IRMA, DAsource). Serum adiponectin level was measured via enzyme linked immunosorbant assay (ELISA, Human Adiponectin, AdipoGen, Inc.). Insulin resistance was measured using homeostasis model assessment insulin resistance (HOMA-IR) index and Matsuda index. The homeostasis model assessment insulin resistance (HOMA-IR) index was calculated for each sample according to the following formula: (fasting insulin level × fasting glucose level)/22.5. Oral glucose tolerance tests (OGTT) were conducted for subjects with FHD or obesity by administering glucose 1.75 g/kg (maximum dose 75 g) orally and then glucose and insulin levels were measured 0 and 2 h after administration. Impaired glucose tolerance (IGT) was defined as a blood glucose level over 140 mg/dl and less than 200 mg/dl when measured 2 h after meals. The Matsuda index was proposed by Matsuda and DeFronzo, USA, in 1999 and indicates insulin sensitivity. This index is obtained using the following formula: 10,000/square root of [(fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT)] [19].

Statistical Analysis

All statistical analyses were performed using SPSS version 12 software. All data are presented as mean ± SD. Comparisons between the two groups with and without FHD were conducted by independent t test, Mann-Whitney test and χ^2 test. Comparisons among the four subgroups were conducted by analysis of variance (ANOVA) and Mann-Whitney tests. Pearson's correlation coefficients were calculated to evaluate the relationships between serum adiponectin level, HOMA-IR and Matsuda index. Multiple linear regression analysis was performed to investigate whether family history of T2DM, age, sex, pubertal stage, BMI, Matsuda index or HOMA-IR independently determine adiponectin levels. $p < 0.05$ was considered to be statistically significant.

Results

Serum Adiponectin Levels and Insulin Resistance According to Family History of T2DM

General characteristics of the study population are shown in table 1. There were no significant differences in age, BMI and Tanner stage between the two groups defined by the presence or absence of FHD. The anthro-

Table 2. Anthropometry and laboratory findings of 4 groups according to family history of T2DM and obesity

Variables	Obese group		Nonobese group	
	FHD(+) group (n = 36)	FHD(-) group (n = 36)	FHD(+) group (n = 25)	FHD(-) group (n = 34)
Age, years	10.9 ± 1.9	11.9 ± 2.2	11.6 ± 2.9	11.4 ± 1.7
Height, cm	149.6 ± 12.8	154.7 ± 11.8	148.4 ± 19.9	145.8 ± 12.2
Weight, kg	57.0 ± 13.1 ^{†,‡}	60.9 ± 11.8 ^{†,‡}	42.4 ± 14.6	39.3 ± 11.4
BMI, kg/m ²	25.1 ± 2.1 ^{†,‡}	25.2 ± 1.9 ^{†,‡}	18.6 ± 2.2	18.1 ± 2.5
ALT, IU/l	22.4 ± 8.5	21.9 ± 6.9	19.2 ± 7.0	21.6 ± 7.5
ALT, IU/l	23.3 ± 17.5	18.8 ± 10.2	11.6 ± 5.2	14.5 ± 7.3
HDL-C, mg/dl	46.9 ± 12.3	47.0 ± 10.7	53.4 ± 11.9 [‡]	39.4 ± 14.4
LDL-C, mg/dl	88.6 ± 31.0 [‡]	92.5 ± 23.9 ^{†,‡}	68.5 ± 21.4	64.5 ± 20.6
Triglyceride	106.6 ± 63.2	94.4 ± 46.6	75.7 ± 41.4	92.0 ± 52.3
FI, µIU/ml	26.0 ± 17.1 ^{†,‡}	16.7 ± 9.8 [‡]	11.6 ± 3.6	10.5 ± 3.7
FG, mg/dl	91.5 ± 21.8	89.1 ± 9.4	87.1 ± 11.3	88.2 ± 11.5
HOMA-IR	5.7 ± 3.6 ^{†,‡}	3.6 ± 2.0 ^{†,‡}	2.1 ± 0.4	2.2 ± 0.8
Matsuda index	2.8 ± 2.4 [†]	3.2 ± 1.9 [†]	5.8 ± 2.8	NA
Adiponectin, ng/ml	4.8 ± 3.0 ^{*,†,‡}	10.4 ± 8.2	7.1 ± 3.9 [‡]	13.8 ± 4.1

FHD(+/-) = Group with/without a family history of T2DM; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; FI = fasting insulin; FG = fasting glucose. NA = not available.

* p < 0.05 compared with obese group without family history of T2DM. † p < 0.05 compared with nonobese group with family history of T2DM. ‡ p < 0.05 compared with nonobese group without family history of T2DM.

pometry and laboratory data of the 4 subgroups according to family history and obesity are presented in table 2. Obese groups with and without FHD did not differ in age, height, BMI and these were also similar among non-obese groups. Adiponectin levels of the group with FHD were significantly lower than those of the group without FHD in both the obese and non-obese groups. Comparisons of the obese groups by FHD revealed that the HOMA-IR of the subjects with FHD were significantly higher than those of the subjects without FHD. There was no difference in HOMA-IR between the two nonobese groups, regardless of FHD. The Matsuda index was significantly lower in the obese group compared to that of the nonobese group. Fasting glucose levels were similar among the 4 subgroups, while fasting insulin levels were significantly higher in the obese group with FHD compared to those of the nonobese group regardless of FHD. Serum AST, ALT and TG levels also did not differ significantly among the four groups.

Impaired Glucose Tolerance in Children with a Family History of T2DM

Of the 36 obese subjects with FHD, 8 had IGT, while 2 of the 36 obese subjects without FHD and none of the 25 non-obese subjects with FHD had IGT. The frequency of

Table 3. Results of multiple linear regression analysis to assess relationships between adiponectin level and other variables

	Adiponectin level	
	β	p value
FHD	-4.885	0.003
Sex	0.210	0.899
Age	0.063	0.897
BMI	-0.092	0.719
SMR	-1.020	0.219
Matsuda index	0.828	0.032
HOMA-IR	-0.132	0.658

Unstandardized coefficients (β) and p values are presented. SMR = Sexual maturity rate.

IGT was significantly higher in obese subjects with FHD than in obese subjects without FHD, at a prevalence of 22.2 and 5.5%, respectively (p < 0.05, table was not shown).

Relationships of Adiponectin with HOMA-IR and Other Variables

In the univariate analysis, adiponectin levels exhibited significant inverse relationships with HOMA-IR (r =

-0.424, $p < 0.01$) and positive correlation with Matsuda index ($r = 0.399$, $p < 0.01$). In the multiple linear regression analysis, adiponectin levels were found to be independently associated with FHD ($\beta = -4.855$, $p = 0.003$) and Matsuda index ($\beta = 0.828$, $p = 0.032$), whereas adiponectin levels demonstrated no significant correlation to sex, age, BMI, SMR and HOMA-IR, as shown in table 3.

Discussion

To the best of our knowledge, this study is the first attempt to compare serum adiponectin levels according to family history of T2DM in Asian children and adolescents. Our study showed that Korean obese children and adolescents with FHD were more insulin resistant and had lower serum adiponectin levels compared to the obese group without FHD. We also found that a family history of T2DM was an independent factor in determining serum adiponectin level.

T2DM in children and adolescents is characterized by a combination of insulin resistance and relative beta-cell secretory dysfunction, similar to adults. Insulin resistance and beta-cell secretory dysfunction each independently increase the risk of T2DM [20] and are related to genetic and environmental factors such as race, obesity, lifestyle, FHD, adolescence, low birth weight and gender [5]. Several studies have shown that insulin resistance is present before the eventual development of hyperglycemia [21–23]. Based on previous adult studies, it is generally hypothesized that obesity leads to insulin resistance, which eventually leads to type 2 diabetes [10, 24, 25]. However, only a few prior studies have examined the underlying factors that could contribute to insulin resistance in children at risk. Despite lack of detailed information of insulin resistance and T2DM, there are some known factors for insulin resistance in childhood. According to the statement of the consensus conference group for insulin resistance in children, two important factors are ethnicity and puberty [26]. African-American, Hispanic, Pima Indian and Asian children have lower insulin sensitivity levels compared with Caucasian children and such insulin sensitivity decreases during puberty. Obesity is a well-known risk factor for T2DM, as well as the predominant cause of insulin resistance [26]. Previous studies have shown that a family history of T2DM in children was associated with decreases in insulin sensitivity [10, 27]. According to studies conducted among African-American children and Caucasian families, FHD attributes to increases in insulin resistance and decreases

in insulin secretion [28, 29]. Recent studies also reported FHD as a risk factor of diabetes and correlations with insulin resistance in children and adolescents were noted. In the Bogalusa Heart Study, parental diabetes was an independent predictor of longitudinal changes in adiposity, glucose, insulin and HOM-IR in the offspring, regardless of race and gender [9]. The offspring of diabetic parents displayed excess body fatness beginning in childhood and had an accelerated progression of insulin resistance syndrome from childhood to young adulthood. Liu et al. [30] showed that the children with a family history of T2DM and obesity were predisposed to diabetes, and had insulin resistance in adolescence. Our study found that HOMA-IR was higher in Korean obese children with FHD than in those without FHD, and that obese subjects with FHD had higher IGT rates than obese subjects without FHD. These findings were consistent with those of previous studies and suggested that children and adolescents with FHD accordingly are more insulin resistant and susceptible to development of T2DM.

Adipose tissues secrete tumor necrosis factor- α (TNF- α), plasminogen activator inhibitor-1, leptin, resistin, angiotensinogen and various adipokines including adiponectin, all of which plays a key role in monitoring and controlling metabolism. Some hinder insulin signaling to provoke insulin resistance and hamper glucose transport [31, 32]. Adiponectin Acrp30 is a protein secreted during the differentiation of adipocytes, it acts as an adipokine which consists of four domains [11]. Acrp30 is related to obesity and insulin resistance [12, 13, 15] and also suppresses vasculitis by anti-inflammatory and anti-arteriosclerotic effects [14, 33]. Low serum adiponectin level has been suggested to be an independent risk factor for progression of T2DM [34, 35]. In adults, adiponectin is positively correlated with age, insulin sensitivity and high-density lipoprotein cholesterol (HDL-C) while negatively correlated with BMI, subcutaneous adipose tissue, visceral adipose tissue, and serum triglyceride (TG) [36]. A previous study has shown that serum adiponectin level is lower in obese adults than in non-obese adults [13], and serum adiponectin levels declined in adults with T2DM [12, 37]. In a study of Taiwanese children, plasma adiponectin levels were negatively associated with BMI, insulin, insulin resistance but positively correlated with HDL-C [38]. Negative correlations between adiponectin levels and insulin resistance have been observed in Korean obese children [15]. However, there are no studies about changes in adiponectin level amongst non-obese children with a family history of T2DM. Our study investigated correlation between adiponectin levels and FHD in obese

and nonobese children. We found that adiponectin levels were significantly lower in children with FHD than in children without FHD regardless of obesity. We also found that a family history of T2DM was an independent factor in determining serum adiponectin levels. From the results of our study, it can be suggested that children with FHD have a higher risk of developing T2DM.

This study has some limitations. Our sample sizes were small, and insulin secretion was investigated only indirectly to examine β cell function because direct assays such as euglycemic hyperinsulinemic clamps could not be conducted. In addition, this was a cross-sectional rather than a longitudinal study, so the actual incidence of T2DM could not be accurately determined.

In summary, we found that adiponectin levels were significantly lower in subjects with FHD than in those without FHD, regardless of obesity, and a positive family

history and Matsuda index were independent factors which determined adiponectin levels. We could infer that children and adolescents with a family history of T2DM were thought to be more susceptible to T2DM and low adiponectin levels may play some role in the pathogenesis of T2DM in children with FHD. Therefore, even more active screening programs and regular follow-up are required for children and adolescents with FHD to prevent T2DM.

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