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Significance of leptin and high–molecular weight adiponectin in the general population of Japanese male adolescents

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Abstract

Adipokines play crucial roles in obesity-related insulin resistance in adults, but little is known in the general adolescent population. This study was designed to investigate the relationships between adipokines and metabolic parameters, the insulin resistance index, and proinflammatory cytokines in the general population of Japanese male adolescents. We studied 662 Japanese male high school students aged 16 to 17 years and 282 healthy Japanese male adults aged 30 to 61 years who received annual health checkups. High–molecular weight (HMW) adiponectin levels were significantly lower in adolescents (4.18 ± 2.24 μg/mL) than in adults (4.84 ± 3.20 μg/mL), despite body mass index (BMI) being significantly lower in adolescents. The HMW adiponectin levels correlated negatively with BMI and the homeostasis model assessment of insulin resistance index (HOMA-IR) in adults. In adolescents, HMW adiponectin correlated negatively with BMI and waist circumference, but not with HOMA-IR or other metabolic parameters except high-density lipoprotein cholesterol. Leptin levels correlated positively with HOMA-IR, triglycerides, tumor necrosis factor α, interleukin 6, and monocyte chemoattractant protein 1 and negatively with high-density lipoprotein cholesterol even after adjustment for BMI. These findings suggest that serum leptin is a more useful biomarker of fat accumulation–related insulin resistance, inflammation, and metabolic abnormalities than HMW adiponectin in the general population of male adolescents. The inverse correlation between adiponectin and insulin resistance may manifest in the later phase of obesity development.

1. Introduction

Obesity is the most common cause of metabolic syndrome, type 2 diabetes mellitus, and long-term vascular complications. In recent years, the prevalence of obesity has increased dramatically and has become a major health problem worldwide. Accumulating evidence has revealed that adipose tissue is not only an energy storage organ, but also a highly active endocrine organ [1]. Moreover, it is well established that adipokines, a variety of biologically active peptides secreted from adipose tissue, play crucial roles in the pathophysiology of obesity-related insulin resistance and complications.

Among the many known adipokines, adiponectin and leptin have attracted considerable attention. Adiponectin was shown to be an antidiabetic, anti-inflammatory, and antiatherogenic cytokine. We [2] and other groups [3,4] have reported that serum adiponectin levels correlate inversely with adiposity variables and insulin resistance. Prospective studies have shown that low adiponectin levels predict the progression to type 2 diabetes mellitus [5,6] and cardiovascular diseases [7]. In addition, adiponectin exists in a variety of multimer complexes in circulating blood, that is, low–molecular weight trimer, middle–molecular weight hexamer, and high–molecular weight (HMW) 12- to 18-mer. Recent studies have revealed that the HMW form is the active form of adiponectin and the useful biomarker for insulin resistance [6,8].

Leptin is elevated in obesity and controls food intake and energy expenditure. High leptin levels are usually accompanied by leptin resistance, and some epidemiological studies have demonstrated high leptin levels to be associated

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Table 1
Clinical characteristics of the 662 male adolescents and correlation coefficients (r) for HMW adiponectin or leptin

	Mean ± SD	r vs HMW adiponectin	Adjusted for BMI	r vs leptin	Adjusted for BMI
Height (cm)	171.2 ± 5.5	0.051		0.000	
Weight (kg)	61.1 ±8.5	−0.214 ***	0.037	0.494 ***	0.021
BMI (kg/m^2)	20.8 ± 2.6	−0.262 ***	–	0.551 ***	–
Waist (cm)	72 ± 7	−0.236 ***	−0.010	0.592 ***	0.267 ***
SBP (mm Hg)	115.9 ± 12.1	−0.054		0.202 ***	0.042
DBP (mm Hg)	63.7 ± 8.0	−0.058		0.123 **	0.065
HR (beats/min)	66.8 ± 12.4	−0.029		0.279 ***	0.296 ***
TC (mg/dL)	171 ± 27	0.051		0.040	
TG (mg/dL) [a]	52 ± 26	−0.056		0.275 ***	0.213 ***
HDL-C (mg/dL)	67 ± 13	0.200 ***	0.165 ***	−0.233 ***	−0.174 ***
FPG (mg/dL)	86 ± 6	−0.012		0.125 ***	0.131 **
IRI (μU/mL) [a]	4.8 ± 3.3	−0.063		0.437 ***	0.361 ***
HOMA-IR [a]	1.04 ± 0.73	−0.061		0.435 ***	0.363 ***
TNF-α (pg/mL) [a]	2.50 ± 1.19	−0.071		0.127 **	0.133 **
IL-6 (pg/mL) [a]	40.96 ± 41.98	−0.028		0.202 ***	0.233 ***
MCP-1 (pg/mL)	199.56 ± 65.75	0.020		0.107 ***	0.094 *
Leptin (ng/mL) [a]	1.57 ± 1.48	−0.158 ***	−0.017	–	–
Adiponectin (μg/mL) [a]	4.18 ± 2.24	–	–	−0.158 ***	−0.017

Data are expressed as means ± SD.
[a] These parameters were analyzed after logarithmic transformation.
* $P < .05$ by Pearson correlation coefficient.
** $P < .01$ by Pearson correlation coefficient.
*** $P < .001$ by Pearson correlation coefficient.

with increased risks of developing type 2 diabetes mellitus and insulin resistance [9-11], although a recent prospective study revealed that high leptin levels predict a decreased risk of diabetes independently of adiponectin, after adjustment for obesity, hyperinsulinemia, inflammation, and other metabolic components [12].

The purpose of the present study was to clarify the associations of HMW adiponectin and leptin with anthropometric and metabolic parameters, insulin resistance, and proinflammatory cytokines in the general population of Japanese male adolescents, who might still be in the development stage in terms of their adipose tissues and would be less affected by environmental factors, such as medications, smoking, and alcohol consumption, than adults. We compared the results of these adolescents with those of healthy Japanese male adults.

2. Subjects and methods

2.1. Subjects

This study included 662 Japanese male adolescents at Keio high school, 16 to 17 years (16.1 ± 0.2) of age, and 282 Japanese male teachers and employees at Keio university, 30 to 61 years (46.4 ± 9.2) of age, who received annual health checkups. All subjects were asked to fast overnight. None of the adolescents had been prescribed medications for diabetes, hypertension, or dyslipidemia. The proportion of adolescents whose body mass index (BMI) was more than 25.0 kg/m^2 was only 6.0% (40 subjects). Adult subjects with cardiovascular disease, endocrine disease, or significant renal or hepatic disease and those who were taking medications for diabetes, hypertension, or dyslipidemia were excluded from the analyses.

The present study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject after a full explanation of the purpose, procedures, and risks of the study. The protocol was approved by the ethics review committees of the Health Center and the Department of Internal Medicine, Keio University School of Medicine (Tokyo, Japan).

2.2. Clinical variables

Height was measured to the nearest 0.1 cm. Weight was measured in light indoor clothing with shoes removed. Body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference was obtained at the navel level while standing with slight expiration.

2.3. Biochemical measurements

Plasma glucose and lipids were assayed by routine automated laboratory methods. The serum insulin concentration was measured by an enzyme immunoassay using a commercially available kit (Tosoh, Tokyo, Japan) with intra- and interassay coefficients ranging from 2.9% to 4.6% and from 4.5% to 7.0%, respectively [2]. The insulin resistance index was calculated based on homeostasis model assessment (HOMA-IR). The serum HMW adiponectin level was measured with an enzyme-linked immunosorbent assay kit (Fujirebio, Tokyo, Japan) [13] with intra- and interassay coefficients ranging from 4.8% to 4.9% and from 3.3% to 6.8%, respectively, as described previously [2]. The serum

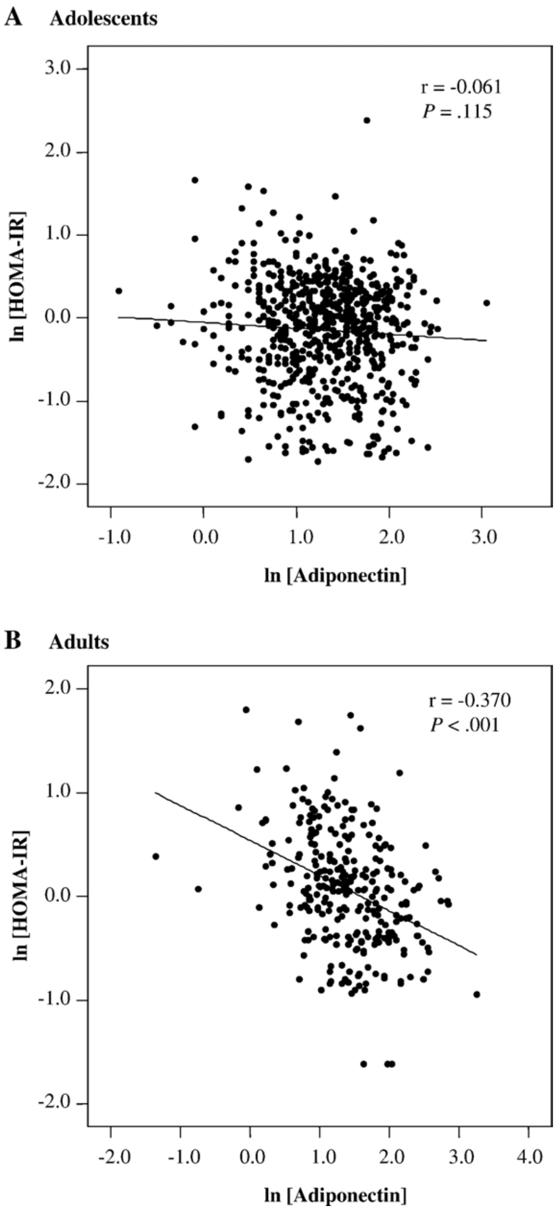

Fig. 1. Relationships between serum HMW adiponectin levels and HOMA-IR in male adolescents (n = 662, A) and male adults (n = 282, B). The HMW adiponectin and HOMA-IR values were log-transformed for statistical analysis. Statistical significance was evaluated by Pearson correlation coefficients.

leptin, tumor necrosis factor (TNF) α, interleukin (IL) 6, and monocyte chemoattractant protein (MCP) 1 levels were measured in adolescent subjects using a LINCOplex kit (Linco Research, St Charles, MO) with intra- and interassay coefficients of 1.4% to 7.9% and <21%, respectively.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS program for Windows (version 12.0; SPSS, Chicago, IL). Relationships between adipokines, HOMA-IR, and other parameters were analyzed by simple and multiple correlations and by stepwise linear regressions. Because serum insulin, HOMA-IR, triglycerides (TG), HMW adiponectin, leptin, TNF-α, and IL-6 were normally distributed after log transformation, the logarithm of these parameters was used for the analyses. All data are expressed as mean ± SD, and $P < .05$ was considered statistically significant.

3. Results

3.1. Relationships between adiponectin and metabolic parameters in adolescents

The anthropometric and metabolic parameters and the proinflammatory cytokine and adipokine levels in male adolescents are shown in Table 1. The serum adiponectin level in adolescents was 4.18 ± 2.24 μg/mL (range, 0.4-21.0 μg/mL). Adiponectin levels in adolescents correlated negatively with BMI and waist circumference. Among metabolic parameters, only high-density lipoprotein cholesterol (HDL-C) correlated significantly with adiponectin ($r = 0.200$, $P < .001$). This correlation was significant even after adjustment for BMI ($r = 0.165$, $P < .001$) or waist circumference ($r = 0.167$, $P < .001$). Adiponectin levels did not correlate with HOMA-IR in adolescents (Fig. 1A).

When we separated 171 adolescents (25.8%) whose BMI were more than 22.0 kg/m^2, there was a weak but significant inverse correlation between HMW adiponectin and HOMA-IR ($r = -0.152$, $P = .047$). However, this was not significant after adjustment for BMI.

3.2. Relationships between leptin and metabolic parameters in adolescents

As shown in Table 1, serum leptin levels correlated positively with BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate

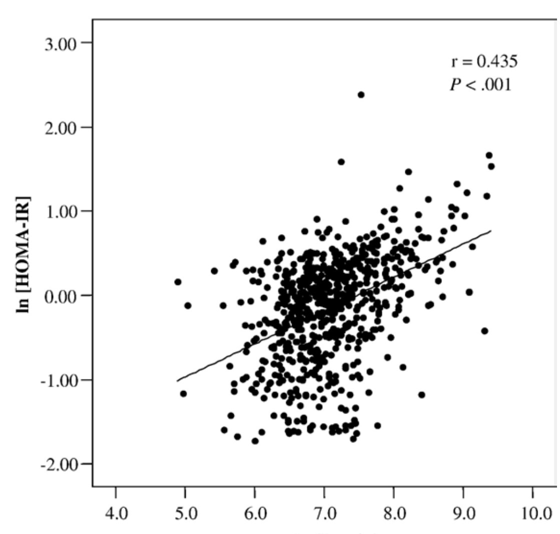

Fig. 2. Relationship between serum leptin levels and HOMA-IR in 662 male adolescents. Leptin and HOMA-IR values were log-transformed for statistical analysis. Statistical significance was evaluated by Pearson correlation coefficients.

Table 2
Clinical characteristics of the 282 male adults and correlation coefficients (r) for HMW adiponectin

	Mean ± SD	r	Adjusted for BMI
Age (y)	46.4 ± 9.2	−0.029	−0.036
Height (cm)	169.7 ± 6.1	−0.041	−0.065
Weight (kg)	66.7 ± 9.1	−0.357 **	−0.059
BMI (kg/m^2)	23.2 ± 2.7	−0.387 **	–
SBP (mm Hg)	122 ± 16	−0.160 **	−0.010
DBP (mm Hg)	77 ± 10	−0.134 *	0.035
HR (beats/min)	74 ± 11	−0.049	−0.033
TC (mg/dL)	201 ± 30	−0.090 **	−0.053
TG (mg/dL) [a]	122 ± 77	−0.358 **	−0.235 **
HDL-C (mg/dL)	54 ± 14	0.438 **	0.325 **
FPG (mg/dL)	94 ± 9	−0.097 *	−0.034
IRI (μU/mL) [a]	5.4 ± 3.5	−0.367 **	−0.222 **
HOMA-IR [a]	1.26 ± 0.83	−0.370 **	−0.223 **
Adiponectin (μg/mL) [a]	4.84 ± 3.20	–	–

Data are expressed as mean ± SD.
[a] These parameters were analyzed after logarithmic transformation.
* $P < .05$ by Pearson correlation coefficient.
** $P < .001$ by Pearson correlation coefficient.

(HR), TG, fasting plasma glucose (FPG), immunoreactive insulin (IRI), HOMA-IR, TNF-α, IL-6, and MCP-1 and correlated negatively with HDL-C. Correlation of leptin with HR, TG, HDL-C, FPG, IRI, HOMA-IR, TNF-α, IL-6, and MCP-1 was significant even after adjustment for BMI. The correlation between leptin and HOMA-IR was significant even after adjustment for both BMI and waist circumference ($r = 0.343$, $P < .001$) (Fig. 2). Tumor necrosis factor α, IL-6, and MCP-1 correlated with neither BMI nor HOMA-IR.

3.3. Relationships between adiponectin and metabolic parameters in adults

The anthropometric and metabolic parameters and the adiponectin levels in male adults are shown in Table 2. The serum adiponectin level in adults was 4.84 ± 3.20 μg/mL (range, 0.30-26.0 μg/mL). Adult serum adiponectin levels were significantly higher than those in adolescents (P = .026), despite adult BMI being significantly higher ($P < .001$). The serum adiponectin levels in adults correlated negatively with BMI, SBP, DBP, total cholesterol (TC), TG, FPG, IRI, and HOMA-IR and correlated positively with HDL-C. The correlations between adiponectin and TG, HDL-C, IRI, and HOMA-IR were significant even after adjustment for BMI.

Table 3A
Stepwise multiple regression analysis for HOMA-IR as the dependent variable in male adolescents (n = 662)

	Standardized β	P	Change in R^2 (%)
Leptin	0.333	<.001	18.8
HR	0.185	<.001	3.8
TG	0.181	<.001	2.6

Variables are shown in the order of entry. Entry of the following variables in regression mode was permitted: BMI, SBP, DBP, HR, TC, TG, HDL-C, HMW adiponectin, and leptin. The HOMA-IR, TG, HMW adiponectin, and leptin were analyzed after logarithmic transformation.

Table 3B
Stepwise multiple regression analysis for HOMA-IR as the dependent variable in male adults (n = 282)

	Standardized β	P	Change in R^2 (%)
BMI	0.320	<.001	25.0
HDL-C	−0.269	<.001	5.9
TC	0.151	<.001	2.9
HR	0.126	<.001	1.4
Adiponectin	−0.111	<.05	0.7

Variables are shown in the order of entry. Entry of the following variables in regression mode was permitted: BMI, SBP, DBP, HR, TC, TG, HDL-C, and HMW adiponectin. The HOMA-IR, TG, HMW adiponectin, and leptin were analyzed after logarithmic transformation.

3.4. Multiple regression analysis with HOMA-IR in adolescents and adults

As shown in Table 3A, stepwise multiple regression analysis revealed leptin, HR, and TG to be significantly correlated with HOMA-IR in adolescents ($R^2 = 0.252$). On the other hand, BMI, HDL-C, TC, HR, and HMW adiponectin correlated significantly with HOMA-IR in adults ($R^2 = 0.359$, Table 3B).

4. Discussion

In this study, we have shown that (1) serum HMW adiponectin levels are decreased and leptin levels are increased with adiposity variables in the general population of male adolescents; (2) HMW adiponectin significantly correlates with HOMA-IR in adults, but not in adolescents; (3) HMW adiponectin correlates positively with HDL-C in adolescents, but not with any other obesity-related metabolic parameters; and (4) leptin is closely associated with HOMA-IR, obesity-related metabolic parameters, and proinflammatory cytokines in adolescents.

It is particularly noteworthy that our observations were made in a general population of adolescents, most of whom were healthy and minimally affected by environmental factors, such as medication, smoking habit, and alcohol consumption.

The present study showed HMW adiponectin to be decreased in accordance with rising levels of adiposity variables while not being significantly associated with insulin resistance (Fig. 1A) or metabolic parameters except for HDL-C in adolescents, whereas a close negative correlation between adiponectin and insulin resistance was observed in adults (Fig. 1B), as we previously reported [2]. Many clinical studies have demonstrated adiponectin to correlate inversely with insulin resistance in adults. Recently, several pediatric studies have shown a negative correlation between total adiponectin and insulin resistance in obese children and adolescents [14-22] and in the general population of those [23-25], whereas negative data were reported only in 2 studies [26,27]. Our results are not in line with those of former reports. This discrepancy might be attributable to the characteristics of our study subjects. First, our study was performed in a general population in which mean BMI averaged 20.8 kg/m^2. Second, they were in the same grade at high school and their lifestyles were relatively uniform. Third, our subjects were all Japanese. Bush et al [24] reported a positive correlation between adiponectin and insulin sensitivity in adolescents from the general population. In their study, almost half of the subjects were African Americans. Another reason may be related to the form of adiponectin measured: we measured adiponectin by enzyme-linked immunosorbent assay without a denaturing step using a kit capable of detecting only HMW, the more active form of adiponectin [13]. Recently, Araki et al [22] reported that HMW, rather than total, adiponectin levels better reflect insulin resistance and visceral fat area even in obese children. To our knowledge, this is the first report to examine the relationship between HMW adiponectin and insulin resistance in adolescents from the general population.

Previously, we reported that both BMI and serum leptin levels were lower in adolescents than in adults [28], although the assay method used was different from that of the present study. Herein, we found adiponectin levels in adolescents to be significantly lower than those of adults, despite BMI being significantly lower in adolescents. This observation might be related to the difference in plasma testosterone concentrations because testosterone suppresses adiponectin levels [29] and free testosterone levels are known to increase dramatically during puberty and to decrease with aging.

The positive association between leptin and insulin resistance in adults has been confirmed by many epidemiological studies [30,31]. Whether this is true for adolescents has not been fully elucidated. Huang et al [32] showed plasma leptin levels to be positively associated with insulin resistance independently of BMI in nondiabetic male adolescents with a mean BMI of 26.6 kg/m^2. To our knowledge, there is only one study to find a positive correlation between leptin and insulin resistance in the general adolescent population [27]. Of note, the present study revealed a close positive association between leptin and HOMA-IR (Fig. 2) and many obesity-related metabolic parameters in a general population of Japanese adolescents with a mean BMI of 20.8 kg/m^2. Furthermore, stepwise multiple regression analysis revealed that leptin, but not BMI or waist circumference, significantly correlated with HOMA-IR. This finding suggests that leptin resistance may already exist in such adolescents.

In addition, we demonstrated positive correlations between leptin and proinflammatory cytokines even in this general population of adolescents, although r values were weak. This observation may be compatible with the results of experimental studies that showed that leptin increases the production of TNF-α and IL-6 in macrophages [33] and up-regulates MCP-1 expression in hepatic stellate cells [34]. Accumulating evidence suggests that obesity is associated with a state of chronic low-grade inflammation [35]. Cross-sectional studies have demonstrated elevated levels of TNF-α and IL-6 among individuals with obesity [36], and a prospective study has revealed IL-6 to be a determinant of risk for developing type 2 diabetes mellitus [37]. Positive correlations between leptin and proinflammatory cytokines, as observed in the present study, may provide at least one explanation for high leptin levels predicting an increased risk of developing type 2 diabetes mellitus [9-11].

Taken together, our findings suggest that leptin may be a more upstream molecule in the mechanism of fat accumulation–related insulin resistance than adiponectin, at least in male adolescents. Our hypothesis is mentioned below: With the development of adipose tissue, secretion of adiponectin and leptin may increase. In the general population of adolescents, however, only leptin may play a role in preventing fat accumulation–related insulin resistance, which was described in Schmidt et al [12]. In association with leptin resistance, leptin levels may further increase and accelerate the production of proinflammatory cytokines, although proinflammatory cytokine levels in adolescents were not associated with adiposity variables in the present study. In the latter phase of obesity, adiponectin may play an important role as an insulin sensitizer by inhibiting these proinflammatory cytokines, at least in part.

In conclusion, serum leptin is suggested to be a more useful biomarker of fat accumulation–related insulin resistance, inflammation, and metabolic abnormalities than HMW adiponectin in the general population of male adolescents. The inverse correlation between adiponectin and insulin resistance may manifest in the later phase of obesity development.

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