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The relationship between serum adiponectin and inflammatory cytokines in obese Korean juveniles

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Purpose: Obesity is related to systemic inflammatory processes causing cardiovascular complications. Intercellular adhesion molecule-1 (ICAM-1), CD40 ligand (CD40L), P-selectin are newly described mediators of inflammation and have a significant effect in atherosclerosis. Adiponectin has shown anti-inflammatory effects in adults. The aim of this study was to evaluate the relationship between adiponectin and inflammatory mediators in children and adolescents.

Methods: Fifty children or adolescents, twenty two with a body mass index (BMI) over 95th percentile, and twenty eight with a BMI below 75th percentile were included in the study. Serum soluble ICAM-1 (sICAM-1), P-selectin, CD40L, lipid profiles, aspartate aminotransferase, alanine aminotransferase, glucose and insulin were measured to evaluate associations with adiponectin. Comparison of these variables was performed between the obese and the nonobese group.

Results: We found a adiponectin to be significant lower and sICAM-1 significant higher in the obese group compared to the nonobese group, but there were no significant differences in P-selectin and soluble CD40L. Adiponectin was negatively associated with ICAM-1 and P-selectin in the obese group.

Conclusion: Negative associations of adiponectin with ICAM-1 and P-selectin in obese children and adolescents suggest that serum adiponectin level may represent the inflammatory status.

Key words: Adiponectin, Intercellular adhesion molecule-1, CD40 ligand, P-selectin

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Received: 9 March, 2011
Revised: 26 January, 2012
Accepted: 21 May, 2014

Introduction

The rapid increase of obesity in children and adolescents has become a major health problem in many countries. In Korea, the estimated prevalence of overweight children increased from 15.1% in boys and 17.8% in girls, in 1998, to 26.8% in boys and 21.7% in girls¹.

Obesity in children and adolescents leads to an increased risk of cardiovascular disease. Overweight adolescents were more likely to have increased blood pressures or low high-density lipoprotein (HDL) cholesterol and high low-density lipoprotein (LDL) cholesterol, triglycerides and glucose intolerance as adults, increasing cardiovascular disease risk^{2,3}.

Adipose tissue is regarded as a paracrine and endocrine organ, acting as the dominant controller in systemic inflammation caused by obesity. Increased inflammation is associated with higher levels of tumor necrosis factor (TNF)- α and interleukin (IL) 6, but lower levels of adiponectin and IL-10⁴.

Adiponectin is an adipocyte-derived hormone. Known functions of adiponectin include increase of insulin sensitivity in the liver, anti-inflammatory and protective effect on atherosclerosis. Studies have found negative associations between adiponectin and insulin resistance, medium chain lipids and LDL cholesterol. Positive associations were found with HDL cholesterol^{5,6}.

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Systemic inflammation in obesity is essential in the process of atherosclerosis. Atherosclerosis involves a combination of endothelial dysfunction and inflammation, which disrupts the vascular homeostasis maintained by endothelium-derived relaxing and contracting factors. Atherosclerosis begins with endothelial dysfunction where nitric oxide lacks in production or availability. Initiation of inflammation involves increased expression of selectins, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) which promotes the adherence of monocytes. This cascade is induced by TNF- α or C-reactive protein (CRP). CD40/CD40 ligand (CD40L and CD154) interactions also trigger inflammatory processes⁷⁻¹².

There are many studies confirming early progression of atherosclerotic changes in overweight children and adolescents but few studies regarding inflammatory cytokine changes related to adiponectin.

In this study, we investigated whether the initiation of inflammatory changes in overweight children and adolescents is related to adiponectin. We compared serum adiponectin levels with ICAM-1, P-selectin, CD40L, and CRP in this age group.

Materials and methods

1. Subjects

Fifty participants who were admitted for evaluation purposes of stature, obesity or followed for stature, obesity without evidence of endocrinologic problems in Bundang Jaesaeng Pediatric Department were enrolled. They were divided into two groups by their body mass indexes (BMIs). Twenty-two subjects (nine female, thirteen male) with a BMI over 95th percentile were grouped as obese. Twenty-eight subjects (seventeen female, eleven male) who had a BMI below 75th percentile were grouped as nonobese control. All children had no history of chronic allergic or endocrinologic diseases.

2. Methods

1) Body measurements

Height and weight of all participants were measured. BMI was obtained by the following equation [BMI=weight (kg)/height (m²)]. The BMI percentile was calculated based on the 2007 Korean Pediatrics Society survey.

2) Sampling and lab measurements

After a minimum of ten hours overnight fasting, blood samples were obtained from every participant. The blood samples were centrifuged at 3,400 rounds per minute for ten minutes in 4°C. The serum was stored at -70°C.

The serum was melted at room temperature and prepared for enzyme-linked immunosorbent assay tests of serum adiponectin

(R&D systems, Minneapolis, MN, USA), ICAM-1 (R&D systems), CD40 (R&D systems), and P-Selectin (R&D systems). Total cholesterol, HDL, LDL, triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CRP, fasting glucose and serum insulin (Toshiba TBA 200FR, Toshiba Medical Systems, Tokyo, Japan) were also measured. Homeostasis model assessment (HOMA-IR) was calculated by the following equation (fasting serum insulin (mU/L)×fasting glucose (mmol/L)/22.5).

3. Statistics

Pearson correlation analysis and Kendall-tau analysis was used for comparing the relationship between serum adiponectin and other variables. The differences between the variables of obese and nonobese group were compared by Student *t* test. All statistics were calculated with IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA).

Table 1. Clinical and laboratory characteristics in obese and control subjects

Characteristic	Control (n=28)	Obese (n=22)	P value
Gender			
Female/male	17/11	9/13	
Age (y)	10.9±2.4	10.4±2.6	0.49
Range	7–15	7–16	
Height (cm)	140.8±17.0	144.5±16.8	0.44
Weight (kg)	36.9±11.4	55.6±21.4	<0.05
Body mass index (kg/m ²)	18.0±1.9	25.6±4.0	<0.05
Adiponectin (µg/mL)	12.7±10.4	6.3±3.8	<0.05
sCD40L (ng/mL)	7.0±4.40	4.3±3.3	<0.05
siCAM-1 (µg/mL)	0.27±0.1	0.33±0.1	<0.05
p-Selectin (pg/ml)	0.99±0.41	0.93±0.37	0.65
HsCRP (mg/dL)	0.01±0.03	0.13±0.3	0.06
AST (IU/L)	23.7±5.1	28.2±14.8	0.12
ALT (IU/L)	13.0±3.6	29.1±27.1	<0.05
Fasting glucose (mg/dL)	82.8±12.0	87.6±6.0	0.11
Insulin (µIU/mL)	8.6±7.5	38.9±51.3	<0.05
HOMA-IR	1.6±1.4	8.5±11.6	<0.05
total Cholesterol (mg/dL)	176.9±23.0	184.0±25.6	0.31
LDL (mg/dL)	101.0±27.6	107±20.7	0.39
Triglyceride (mg/dL)	91.2±46.8	131.5±70.2	<0.05
HDL (mg/dL)	69±22.7	49.7±11.5	<0.05

Values are presented as mean±standard deviation. sCD40L, soluble CD40 ligand; siCAM, soluble intercellular adhesion molecule; HsCRP, human soluble C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Results

1. Comparison by BMI percentiles.

The mean age was 10.9 ± 2.4 years in the control group compared to 10.4 ± 2.6 years in the obese group with no significant differences (Table 1).

Serum adiponectin was significantly lower in (control, 12.7 ± 10.4 $\mu\text{g/mL}$ vs. obese, 6.3 ± 3.8 $\mu\text{g/mL}$; $P < 0.05$) the obese group compared to the nonobese control group. Soluble ICAM-1 (control, 0.27 ± 0.1 $\mu\text{g/mL}$ vs. obese, 0.33 ± 0.1 $\mu\text{g/mL}$; $P < 0.05$) was significantly higher in the obese group. P-selectin (control, 0.99 ± 0.41 pg/mL vs. obese, 0.93 ± 0.37 pg/mL ; $P = 0.65$), sCD40L (control, 6.76 ± 4.30 ng/mL vs. obese, 4.57 ± 3.51 ng/mL ; $P = 0.09$) and CRP (control, 0.01 ± 0.03 mg/dL vs. obese, 0.13 ± 0.3 mg/dL ; $P = 0.06$) did not differ between groups.

There were no significant differences in serum AST (control 23.7 ± 5.1 vs. obese 28.2 ± 14.8 , IU/L, $P = 0.18$) and fasting glucose (control, 82.8 ± 12.0 mg/dL vs. obese 87.6 ± 6.0 mg/dL ; $P = 0.11$) between groups. Serum ALT (control, 13.0 ± 3.6 IU/L vs. obese, 29.1 ± 27.1 IU/L; $P < 0.05$), serum insulin (control, 8.6 ± 7.5 $\mu\text{IU/mL}$ vs. obese, 38.9 ± 51.3 $\mu\text{IU/mL}$; $P < 0.05$) and HOMA-IR (control, 1.6 ± 1.4 vs. obese, 8.5 ± 11.6 ; $P < 0.05$) were significantly elevated in the obese group.

There were no significant differences in total cholesterol (control, 176.9 ± 23.0 mg/dL vs. obese, 184.0 ± 25.6 mg/dL ; $P = 0.31$)

Table 2. Correlation of serum adiponectin and other variables in the obese group (BMI over 95th percentile)

Variable	r value	P value
Body mass index (kg/m^2)	-0.24	0.28
Height (cm)	0.64	0.77
Weight (kg)	-0.92	0.68
AST (IU/mL)	-0.09	0.66
ALT (IU/mL)	-0.08	0.69
Total cholesterol (mg/dL)	0.28	0.27
Triglyceride (mg/dL)	-0.13	0.56
Glucose (mg/dL)	0.23	0.28
Insulin ($\mu\text{IU/mL}$)	-0.12	0.58
HOMA-IR	-0.10	0.63
HDL (mg/dL)	0.10	0.64
LDL (mg/dL)	0.13	0.55
sICAM-1 ($\mu\text{g/mL}$)	-0.49	<0.05
p-Selectin (pg/mL)	-0.50	<0.05
hsCRP (ng/mL)	0.05	0.82
sCD40L (ng/mL)	-0.13	0.56

Values are presented as mean \pm standard deviation. sCD40L, soluble CD40 ligand; sICAM, soluble intercellular adhesion molecule; HsCRP, human soluble C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

and LDL (control, 101.0 ± 27.6 mg/dL vs. obese, 107.0 ± 20.7 mg/dL ; $P = 0.18$). Triglyceride (control, 91.2 ± 46.8 mg/dL vs. obese, 131.5 ± 70.2 mg/dL ; $P < 0.05$) was higher and serum HDL (control, 69 ± 22.7 mg/dL vs. obese, 49.7 ± 11.5 mg/dL ; $P < 0.05$) lower in the obese group. No sexual differences were found in serum adiponectin, ICAM-1, P-selectin, and CD40L.

2. Correlation between serum adiponectin and other variables

In all subjects, serum adiponectin was negatively correlated with BMI ($r = -0.225$, $P = 0.047$) and Triglyceride ($r = -0.250$, $P = 0.028$). A positive correlation with adiponectin and HDL ($r = 0.225$, $P = 0.049$) was found but there was no significant correlation between serum adiponectin and inflammatory cytokines.

Correlation between adiponectin and other variables was obtained in the obese group (Table 2). Adiponectin was significantly negatively correlated with ICAM-1 ($r = -0.49$, $P < 0.05$) (Fig. 1) and P-selectin ($r = -0.50$, $P < 0.05$) (Fig. 2). CD40L and CRP were

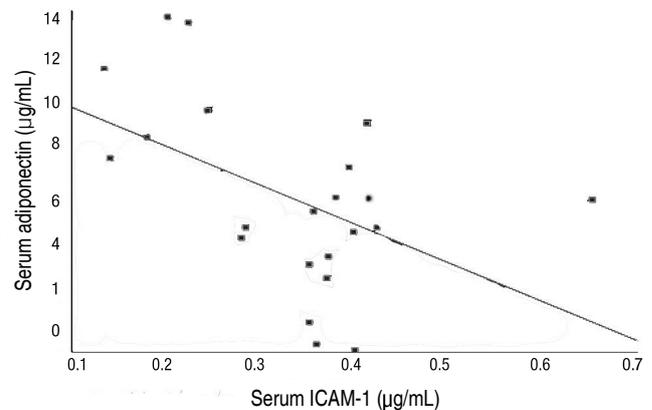


Fig. 1. Correlation of adiponectin and intercellular adhesion molecule (ICAM)-1 in the obese group (body mass index over 95th percentile). $P < 0.05$, $r = -0.49$.

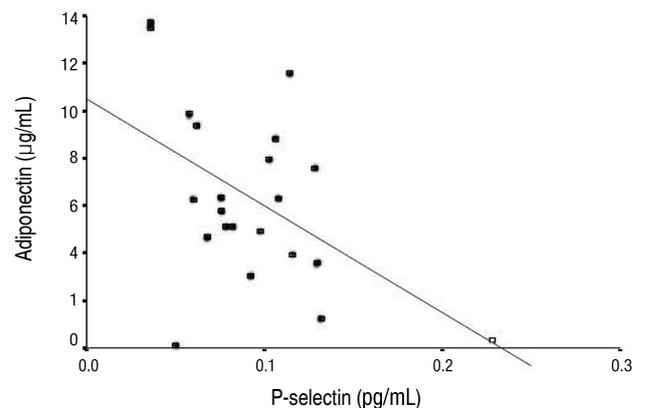


Fig. 2. Correlation of adiponectin and P-selectin in the obese group (body mass index over 95th percentile). $P < 0.05$, $r = -0.50$.

not associated with adiponectin.

Due to the sexual differences in the obese group and nonobese control group, another correlation analysis based on both sexes was performed. The results showed no significant correlations with adiponectin and other variables by sex.

Discussion

Adiponectin is a member of the complement 1q family and is known to form a homomultimer. Structurally, adiponectin belongs to the collagen-superfamily and its structure resembles collagen, complements and cerebellin. The adiponectin monomer has a molecular weight of 30 kDa and as a trimer it forms a low-molecular weight polymer. The monomer is only found in adipose tissues and all polymers exist in human circulation. Adiponectin is produced in both abdominal fat cells and nonadipose cells. The referential mean concentration of adiponectin is 5–10 µg/mL¹³.

The functioning form of adiponectin depends on the binding receptor. Two receptors, AdipoR1 and AdipoR2 are known. AdipoR1 exists in skeletal muscles and bind with high affinity globular adiponectin. AdipoR2 exist mostly in liver and binds with full-length adiponectin¹⁴.

In our study, due to limited numbers of study participants (obese 22), the correlation between adiponectin and glucose intolerance and lipid profiles was not significant. Adiponectin has been implicated in the pathophysiology of obesity related insulin resistance, glucose intolerance, insulin mediated lipoprotein metabolism, atherosclerosis, and coronary heart diseases¹⁵⁻¹⁸.

The negative correlation between adiponectin and ICAM-1, P-selectin showed known inflammatory aspects of adiponectin in the obese group, suggesting early initiation of atherosclerotic changes. Anti-inflammatory aspects of adiponectin involves preventing attachment of monocytes provoked by TNF- α from endothelial cells and suppression of TNF- α induced and endothelial cell derived VCAM-1, endothelial-leukocyte adhesion molecule-1 (E-selectin), and ICAM-1, IL-8. Proinflammatory cytokines like TNF- α and IL-6 suppress gene expression and protein synthesis of adiponectin¹⁹.

In our study, there were no significant differences between both sexes in serum adiponectin. Adiponectin seems to be higher in the lower ages and sexual differences were observed in many studies. Because of these differences, it is difficult to assess direct associations of serum adiponectin and cardiovascular risk factors in young age groups²⁰.

Simple weight or BMI in the obese group did not have any direct correlation with adiponectin in our study. BMI is a simple and effective of indicator of obesity but it does not represent the adipose tissue components of the subject. Some research has noted that a loss in weight caused an increase of

serum adiponectin^{21,22}. A negative feedback mechanism with adiponectin and adipose white tissue is currently suggested in humans²³.

Our result indicates that assessment of adiponectin level may be a proxy measure of inflammatory status in obese children and adolescents. Further studies regarding pubertal status and fat contents are needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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