Original Article

Relationships between Circulating Adiponectin Levels and Fat Distribution in Obese Subjects

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***Aim*: Most studies have reported that circulating levels of adiponectin are negatively correlated with the body mass index (BMI), and hypoadiponectinemia is related to cardiometabolic disorders; however, not all obese subjects have hypoadiponectinemia. The present study investigated circulating adiponectin levels and fat distribution, i.e. subcutaneous fat area (SFA) and visceral fat area (VFA), in obese subjects.**

***Methods*: Sixty-eight obese Korean subjects underwent fat distribution by computed tomography (CT) scan and laboratory tests including circulating total adiponectin levels (APN) and circulating high molecular weight adiponectin levels (HMW-APN).**

***Results*: Log-APN and log-HMW-APN did not correlate with log-BMI either in obese males or females in this study; however, log-APN significantly and negatively correlated with log-VFA both in obese males ($r=-0.691$, $p=0.009$) and females ($r=-0.319$, $p=0.002$), and log-HMW-APN also correlated negatively with log-VFA both in obese males ($r=-0.650$, $p=0.016$) and females ($r=-0.370$, $p=0.005$). Log-VFA was a significant determinant of log-APN and log-HMW-APN in obese subjects. In contrast, neither log-APN nor log-HMW-APN was significantly correlated with log-SFA in obese males and females.**

***Conclusions*: The present study demonstrated that APN and HMW-APN correlated with VFA, but not BMI and SFA, in obese subjects, and suggest that hypoadiponectinemia may represent dysfunction of adipose tissue in obesity.**

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Key words; Adiponectin, Fat distribution, Visceral obesity

Obesity is a world-wide health problem and is a common cause of cardiovascular diseases in industrialized countries. Adiponectin, which we identified as an adipocytokine in the human adipose tissue cDNA project, had anti-atherosclerotic, anti-diabetic and anti-inflammatory properties in experimental studies. We and others demonstrated that circulating levels of adiponectin are negatively correlated with the body mass index (BMI), and hypoadiponectinemia is related to cardiometabolic disorders[1)]; however, not all obese subjects have hypoadiponectinemia[1)]. Some obese people show normal or even high adiponectin levels even though they are morbidly obese. Both genetic and environmental factors affect circulating adiponectin levels. Several reports have demonstrated single nucleotide polymorphisms in the adiponectin gene that influence adiponectin levels. Body fat distribution may be related to the adiponectin level. Substantial evidence suggests that intra-abdominal visceral fat accumulation rather than BMI is related to the dysfunction of adipocytes and cardiometabolic disorders in obesity[2-4)]. The relationship between the circu-

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lating adiponectin level and precise evaluation of fat distribution by computed tomography (CT) scan has not been explored in obese subjects. The present study investigated circulating adiponectin levels and fat distribution, i.e. subcutaneous fat area (SFA) and visceral fat area (VFA), in obese subjects.

The present study included 68 obese Korean subjects (male/female: 13/55), who visited the hospital and were not taken on medications for diabetes, hypertension or dyslipidemia. This present study defined obesity as BMI ≥25 kg/m^2. **Table 1** summarizes the profiles of all subjects. All subjects were briefed on the research procedures, and written consent for participation was obtained from each subject. The registration number of the trial at the UMIN is 000002997. Height, weight and waist circumference were measured in a standing position, and blood pressures were measured with a standard mercury sphygmomanometer after the subjects had rested in a sitting position for at least 5 minutes. BMI was calculated using the formula [weight (kg)/height (m)^2]. To measure abdominal fat, after obtaining a single tomographic slice at the L4-L5 level by CT scanning, SFA and VFA were determined using a Hounsfield unit (HU) range for adipose tissue of -190 to -30 HU. After an overnight fast, venous blood samples were collected for measurements of glucose, total cholesterol, triglyceride high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and adiponectin in blood while the subject was in a sitting position. Circulating total adiponectin levels (APN) and circulating high molecular weight adiponectin levels (HMW-APN) were measured using a sandwich enzyme-linked immunosorbent assay system[1, 5]. Since BMI, VFA, SFA, APN and HMW-APN showed non-Gaussian skewed distribution, they were log-transformed before analysis. Data are presented as the mean ± SD (range). A p value <0.05 was considered significant. Pearson's correlation coefficient was used to examine the relationship between APN, HMW-APN, and fat distribution. Stepwise multiple regression analysis was conducted to identify the parameters that significantly contributed to log-APN and log-HMW-APN. Parameters with an F value >4.0 were subsequently entered into the regression analysis as independent variables. All statistical analyses were performed with StatView-J 5.0 (HULINKS, Inc., Tokyo).

Interestingly, log-APN and log-HMW-APN did not correlate with log-BMI either in obese males ($p=0.109$, $p=0.064$, respectively) or females ($p=0.064$, $p=0.055$, respectively) (**Fig. 1A** and **1B**) in this study; however, log-APN significantly and negatively correlated with log-VFA both in obese males ($r=-0.691$, $p=0.009$) and females ($r=-0.319$, $p=0.002$) (**Fig. 1C**), and log-HMW-APN also correlated negatively with log-VFA both in obese males ($r=-0.650$, $p=0.016$) and females ($r=-0.370$, $p=0.005$) (**Fig. 1D**). In contrast, neither log-APN nor log-HMW-APN was significantly correlated with log-SFA in obese males ($p=0.051$, $p=0.068$, respectively) and females ($p=0.070$, $p=0.133$, respectively) (**Fig. 1E** and **1F**). In obese males, log-APN and log-HMW-APN did not correlate with each metabolic parameter, such as systolic and diastolic blood pressures, total cholesterol, triglyceride, high density lipoprotein-cholesterol (HDL-C) and glucose (**Table 2**). In obese females, log-APN and log-HMW-APN correlated negatively with HDL-C only for the above metabolic parameters ($p<0.001$, $p<0.001$, respectively). Stepwise multiple regression analysis identified HDL-C and VFA as significant determinants of log-APN and log-HMW-APN (**Table 2**).

We have previously shown that APN is negatively correlated with BMI in the general population[1]. Fur-

Table 1. Clinical characteristics of all subjects

Number (males/females)	68 (13/55)
Age (year)	33.4 ± 8.4 (20-58)
Body mass index, BMI (kg/m^2)	
all	29.4 ± 3.0 (25.2-40.1)
males	28.9 ± 1.5 (26.4-31.0)
females	29.5 ± 3.2 (25.2-40.1)
BMI ≥25-<30 (%)	58.8
BMI ≥30-<35 (%)	36.8
BMI ≥35 (%)	4.4
Subcutaneous fat area (cm^2)	291.0 ± 76.9 (99.0-454.9)
Visceral fat area (cm^2)	99.3 ± 36.1 (40.7-218.7)
Systolic blood pressure (mmHg)	125.8 ± 13.4 (98-160)
Diastolic blood pressure (mmHg)	82.4 ± 11.9 (52-110)
Total cholesterol (mg/dL)	181.7 ± 32.2 (118-258)
Triglyceride (mg/dL)	138.9 ± 104.2 (49-622)
HDL-cholesterol (mg/dL)	52.4 ± 11.4 (31-89)
Glucose (mg/dL)	90.6 ± 11.4 (73-134)
Circulating total adiponectin (μg/mL)	
males	5.6 ± 2.6 (1.9-10.3)
females	7.4 ± 4.0 (2.2-24.9)
Circulating HMW-adiponectin (μg/mL)	
males	3.8 ± 2.5 (0.8-9.3)
females	6.0 ± 4.2 (0.7-23.5)
Smoking status	
Current smoker	$n=16$
Ex-smoker	$n=3$
Non-smoker	$n=49$

Data are the mean ± SD (range).
HDL, high density lipoprotein; HMW, high molecular weight

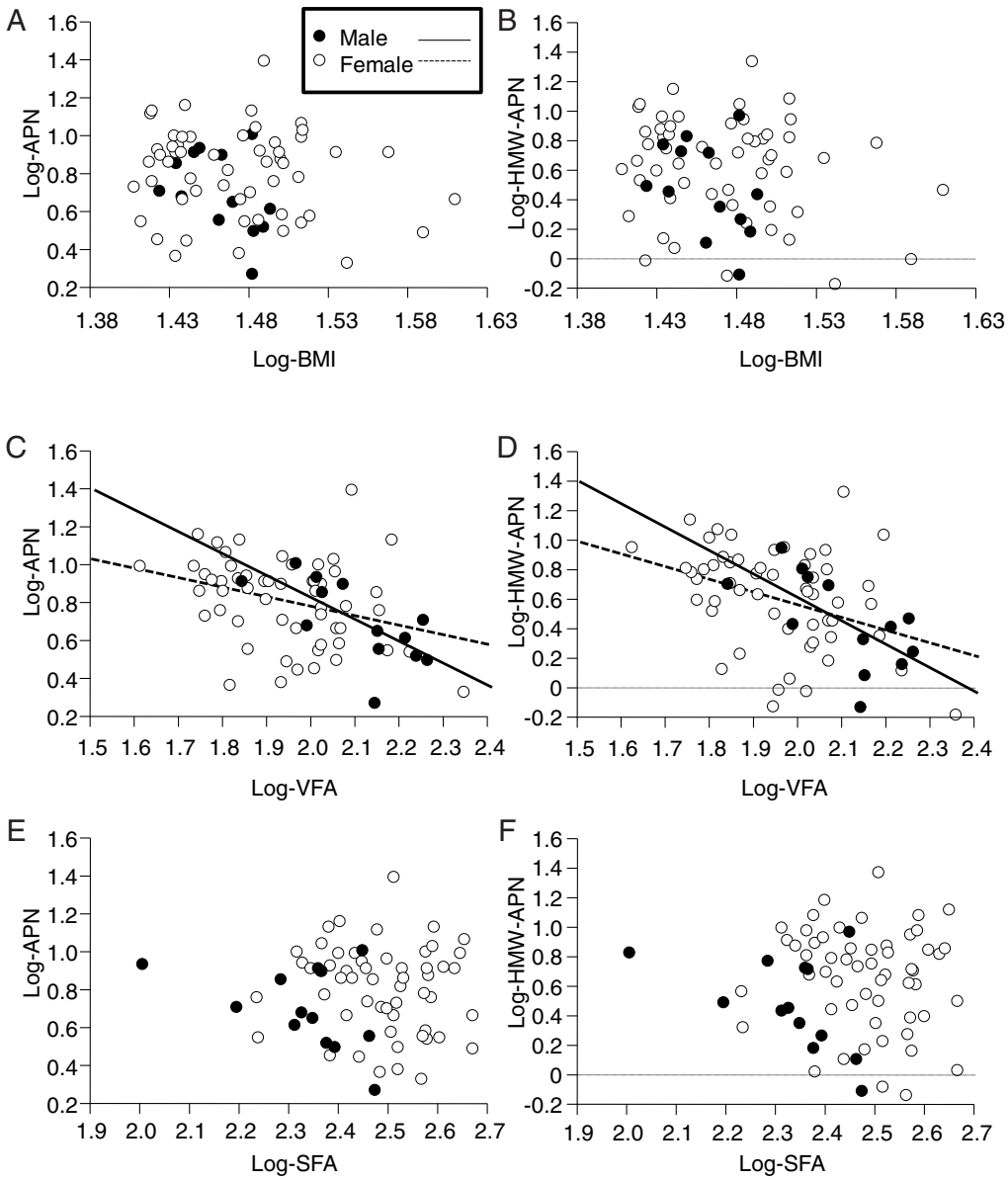

Fig. 1. Relationships between circulating total adiponectin levels (APN), circulating high molecular weight adiponectin levels (HMW-APN), and fat distribution, i.e. body mass index (BMI) (A, APN; B, HMW-APN), visceral fat area (VFA) (C, APN; D, HMW-APN) and subcutaneous fat area (SFA) (E, APN; F, HMW-APN) in males (closed circle) and females (open circle). Pearson's correlation coefficient was used to examine the relationships between APN, HMW-APN and fat distribution in males (solid line) and females (dotted line). In all cases, $p < 0.05$ was considered significant.

thermore, we and another author have shown that APN is negatively correlated with VFA and SFA as well as BMI in the general population[6] and young men[7]; however, there is a considerable variation in circulating adiponectin levels among subjects with a similar BMI, even in obesity[1]. The present study demonstrated that APN and HMW-APN correlated with VFA, but not BMI and SFA, in obese subjects, which is the first report to our knowledge. Taken together with substantial evidence showing a relationship between visceral adiposity and cardiometabolic disorders, the present results suggest the hypoadiponectinemia may represent the dysfunction of adipose tissue in obesity and is associated with atherosclerosis.

Table 2. Results of uni- and multivariate analyses of correlation between log-APN, log-HMW-APN and various parameters

	Log-APN			Log-HMW-APN		
	Males	Females		Males	Females	
	Univariate *p* value	Univariate *p* value	Multivariate *F* value	Univariate *p* value	Univariate *p* value	Multivariate *F* value
Log-BMI	0.109	0.064	–	0.064	0.055	–
Log-VFA	0.009	0.002	4.14	0.016	0.005	6.33
Log-SFA	0.051	0.070	–	0.068	0.133	–
Systolic blood pressure	0.877	0.779	–	0.496	0.868	–
Diastolic blood pressure	0.708	0.254	–	0.570	0.199	–
Glucose	0.158	0.409	–	0.338	0.331	–
Total cholesterol	0.517	0.596	–	0.710	0.477	–
Triglyceride	0.098	0.217	–	0.119	0.225	–
HDL-cholesterol	0.168	<0.001	10.75	0.109	<0.001	9.57

Univariate: Pearson's correlation analysis, Multivariate: Stepwise multiple regression analysis. Parameters with F value >4.0 were subsequently entered into the regression analysis as independent variables.

Reducing visceral fat accumulation to improve hypoadiponectinemia is a potential strategy to prevent atherosclerotic cardiovascular disease in obesity.

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