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Is there any association between subcutaneous adipose tissue area and plasma total and high molecular weight adiponectin levels?

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Abstract

This study was conducted for the purpose of clarifying the correlations between the subcutaneous adipose tissue area and plasma total and high–molecular weight (HMW) adiponectin levels. The subjects of this study comprised 359 men and 142 women who underwent general health examinations from October 2005 to December 2006. The abdominal subcutaneous and visceral adipose tissue areas were measured using low-dose x-ray computed tomography. Total and HMW adiponectin levels were measured using the enzyme-linked immunosorbent assay system based on a monoclonal antibody to humans. There were negative correlations between the plasma total and HMW adiponectin levels and visceral and subcutaneous adipose tissue areas using simple correlation analysis. Multiple linear regression analysis clearly indicated that the subcutaneous adipose tissue area was independently correlated with the HMW adiponectin levels in men and closely related in women. Many studies reported that only the visceral adipose tissue area showed a significant correlation with metabolic syndrome. However, these results clearly indicate that it is also important to consider the subcutaneous adipose tissue area in metabolic syndrome.

1. Introduction

The prevalence of obesity has increased in recent years [1]. It is commonly associated with type 2 diabetes mellitus, coronary artery disease, and hypertension, and the coexistence of these diseases has been termed *metabolic syndrome* [2-4]. It was reported that those who have visceral adipose tissue areas of 100 cm^2 or more at the umbilical level are at a markedly increased risk of *obesity-related disorders*, which were defined as hyperglycemia, dyslipidemia, and hypertension [5]. Otherwise, there have been no studies analyzing the features of subcutaneous adipose tissue accumulation.

On the other hand, adiponectin has recently attracted much attention because of its antidiabetic and antiatherogenic effects [6]. Furthermore, it has been reported that lower levels of adiponectin are associated with adverse outcomes [7,8].

Adiponectin combines to 3 major oligomeric forms: a low molecular weight trimer, a middle molecular weight hexamer, and high molecular weight (HMW) 12- to 18-mer adiponectin. The HMW form of adiponectin has been reported to be the most active form of this protein and has a more important role in insulin sensitivity and protecting against diabetes [9]. A negative correlation between the visceral adipose tissue area and plasma total adiponectin was reported [10]. Adiponectin is secreted by adipose tissue [6]. However, there have been no studies analyzing the correlations between the subcutaneous adipose tissue area and adiponectin. Therefore, it is meaningful to clarify their correlation.

This study was conducted for the purpose of clarifying the correlations between the subcutaneous adipose tissue area and plasma total and HMW adiponectin levels.

2. Materials and methods

2.1. Subjects

The subjects of the study comprised 359 men and 142 women who underwent general health examinations from October 2005 to December 2006 at Grand Tower Medical

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Court and who wanted to undergo examination of their abdominal fat areas, measured by low-dose x-ray computed tomography (CT), and the plasma adiponectin levels. The study subjects were all Japanese. This study was approved by the Medical Ethics Committee of the Grand Tower Medical Court Life Care Clinic. All subjects provided written informed consent before their inclusion in the study.

2.2. Methods

After an overnight fast, fasting blood samples were obtained, and blood pressure (BP) was measured in the sitting position with the right arm. The waist circumference was measured according to the World Health Organization method at a level midway between the lower rib margin and the iliac crest [11]. Measurements of the abdominal subcutaneous and visceral adipose tissue areas were undertaken using low-dose x-ray CT with a HITACHI ROBUSTO (HITACHI Medical, Tokyo, Japan). Serum lipids were measured using an enzymatic method with a HITACHI 7080 analyzer. The serum glucose levels were measured using the hexokinase method. Serum insulin was measured using a chemiluminescent enzyme immunoassay. Total and HMW adiponectin levels were measured using the enzyme-linked immunosorbent assay system (Daiichi Pure Chemicals, Tokyo, Japan) based on a monoclonal antibody to humans [12]. For total adiponectin, the intraassay CV was 4.5% and the interassay CV was 3.0%. For HMW adiponectin, the intraassay CV was 7.7% and the interassay CV was 9.1%. Total and HMW adiponectin levels were measured in 184 men and 120 women.

2.3. Statistical analysis

In this study, data on men and women were analyzed independently. All data are expressed as the means ± standard deviations. The continuous variables of men and women were compared using Student unpaired *t* test. Because insulin, triglycerides, and total and HMW adiponectin did not show normal distributions, the data were analyzed after logarithmic transformation. All analyses were performed using JMP statistical software (SAS Institute, Cary, NC).

3. Results

The clinical and biochemical characteristics of the study subjects are shown in Table 1. Body mass index, waist circumference, systolic and diastolic BP, triglycerides, fasting plasma glucose, and fasting insulin were significantly higher in men than in women. The visceral adipose tissue area was significantly larger in men than in women. High-density lipoprotein (HDL) cholesterol and the plasma total and HMW adiponectin levels were significantly lower in men than in women.

Table 1
Clinical and biochemical characteristics of the study subjects

Variable	Men	Women	*P***
n	359	142	
Age (y)	45.7 ± 10.5	44.6 ± 12.0	.320
BMI (kg/m^2)	24.5 ± 3.5	20.9 ± 3.4	<.0001
Waist circumference (cm)	85.3 ± 9.7	69.5 ± 9.1	<.0001
Systolic BP (mm Hg)	126.8 ± 14.9	118.2 ± 6.2	<.0001
Diastolic BP (mm Hg)	79.8 ± 10.2	73.2 ± 10.4	<.0001
Total cholesterol (mg/dL)	204.4 ± 33.8	200.6 ± 41.8	.292
Triglycerides (mg/dL)[a]	125.5 (82.0-207.3)	67.5 (49.0-96.3)	<.0001
HDL cholesterol (mg/dL)	55.8 ± 14.7	69.3 ± 17.8	<.0001
LDL cholesterol (mg/dL)	120.4 ± 31.1	115.3 ± 35.6	.129
Fasting plasma glucose (mg/dL)	108.6 ± 24.1	93.5 ± 19.1	<.0001
Fasting insulin (μU/mL)[a]	6.1 (4.1-10.2)	4.6 (3.5-6.2)	<.0001
Visceral adipose tissue area (cm^2)	96.0 ± 48.9	37.9 ± 33.1	<.0001
Subcutaneous adipose tissue area (cm^2)	133.7 ± 66.1	139.3 ± 66.4	.393
Total adiponectin (μg/mL)[a,b]	4.40 (3.00-5.70)	6.95 (5.20-10.00)	<.0001
HMW adiponectin (μg/mL)[a,b]	1.60 (0.90-2.60)	3.60 (2.30-5.55)	<.0001

Data are expressed as means ± SD or medians (interquartile range). BMI indicates body mass index; LDL cholesterol, low density lipoprotein cholesterol.

[a] Log-transformed value.

[b] Men, n = 184; women, n = 120.

The correlations between total and HMW adiponectin levels and clinical parameters were analyzed using simple correlation analysis (Table 2). Among men, there were positive correlations between total adiponectin levels and HDL cholesterol, and there were negative correlations between total adiponectin levels and the subcutaneous and visceral adipose tissue areas, systolic BP, triglycerides, low-density lipoprotein cholesterol, and fasting insulin. As for HMW adiponectin levels, for men, there were negative correlations between HMW adiponectin levels and the subcutaneous and visceral adipose tissue areas, systolic BP, total cholesterol, triglycerides, and fasting insulin. Among women, there were positive correlations between total and HMW adiponectin levels and HDL cholesterol, and there were negative correlations between total and HMW adiponectin levels and the subcutaneous and visceral adipose tissue areas, total cholesterol, triglycerides, and fasting insulin.

Multiple linear regression analysis was performed to evaluate whether there were correlations between visceral and subcutaneous adipose tissue areas and the plasma total and HMW adiponectin levels (Table 3). Among men, the model including visceral adipose tissue area, age, systolic BP, triglycerides, and HDL cholesterol (model 1) demonstrated that the visceral adipose tissue area was not correlated with the total adiponectin levels. When the subcutaneous adipose tissue area was added (model 2), visceral and subcutaneous adipose tissue areas were also not correlated. As for HMW adiponectin, model 1

Table 2
Linear regression analysis of relationships between the total and HMW adiponectin levels and clinical parameters

Variable	Men				Women			
	Total adiponectin[a]		HMW adiponectin[a]		Total adiponectin[a]		HMW adiponectin[a]	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Visceral adipose tissue areas (cm^2)	−0.209	.0044	−0.199	.0073	−0.256	.0047	−0.212	.0204
Subcutaneous adipose tissue area (cm^2)	−0.311	<.0001	−0.334	<.0001	−0.283	.0018	−0.261	.0040
Age (y)	0.248	.0007	0.168	.0242	0.179	.0506	0.130	.1579
Systolic BP (mm Hg)	−0.190	.0096	−0.200	.0072	−0.068	.4581	−0.058	.5258
Diastolic BP (mm Hg)	−0.059	−.059	0.4284	.1205	−0.047	.6065	−0.051	.5837
Total cholesterol (mg/dL)	−0.099	.1803	−0.206	.0056	−0.180	.0486	−0.150	.1014
Triglycerides (mg/dL)[a]	−0.349	<.0001	−0.363	<.0001	−0.244	.0072	−0.224	.0140
HDL cholesterol (mg/dL)	0.382	<.0001	0.347	<.0001	0.314	.0005	0.299	.0009
Fasting plasma glucose (mg/dL)	−0.119	.1164	−0.069	.3726	−0.055	.5632	−0.094	.3191
Fasting insulin (μU/mL)[a]	−0.369	<.0001	−0.371	<.0001	−0.334	.0005	−0.277	.0045

[a] Log-transformed value.

demonstrated that the visceral adipose tissue area was not correlated. Furthermore, model 2 demonstrated that the subcutaneous adipose tissue area was independently correlated with the HMW adiponectin levels but the visceral adipose tissue area was not. Among women, model 1 demonstrated that the visceral adipose tissue area was independently correlated with the total adiponectin levels. As for model 2, visceral and subcutaneous adipose tissue areas were not correlated. Regarding HMW adiponectin levels, model 1 demonstrated that the visceral adipose tissue area was independently correlated. As for model 2, the subcutaneous adipose tissue area was closely correlated with the HMW adiponectin levels, but the visceral adipose tissue area was not.

4. Discussion

In this study, there were positive correlations between total and HMW adiponectin levels and HDL cholesterol, and there were negative correlations between the plasma total and HMW adiponectin levels and the visceral and subcutaneous adipose tissue areas, systolic BP, total cholesterol, triglycerides, and fasting insulin using simple correlation analysis (Table 2). These correlated values were chosen as the predictive values in Table 3. Multiple linear regression analysis demonstrated that the addition of the subcutaneous adipose tissue area was significantly related to the strength of the model, especially regarding HMW adiponectin, and that the subcutaneous adipose tissue

Table 3
The relationship of the clinical parameters and the total and HMW adiponectin levels by multiple regression analyses

Independent variables	Men				Women			
	Total adiponectin[a]		HMW adiponectin[a]		Total adiponectin[a]		HMW adiponectin[a]	
	β	*P*	β	*P*	β	*P*	β	*P*
Model 1								
Visceral adipose tissue (cm^2)	−.001	.202	.004	.587	−.002	.009	−.003	.047
Age (y)	.005	.001	.005	.045	.006	.0004	.008	.008
Systolic BP (mm Hg)	−.002	.141	−.003	.109	−.001	.253	−.001	.476
Triglycerides (mg/dL)[a]	.118	.107	−.262	.026	−.104	.188	−.143	.280
HDL cholesterol (mg/dL)	.046	.005	.005	.027	.002	.043	.004	.038
R^2	.237		.195		.248		.185	
Adjusted R^2	.215		.172		.212		.147	
Model 2								
Visceral adipose tissue (cm^2)	.005	.529	.004	.607	−.001	.187	−.001	.571
Subcutaneous adipose tissue (cm^2)	.036	.219	−.001	.020	−.0005	.171	−.001	.076
Age (y)	.005	.006	.003	.043	.005	.002	.006	.036
Systolic BP (mm Hg)	−.002	.189	−.002	.400	−.001	.425	−.001	.777
Triglycerides (mg/dL)[a]	−.124	.090	−.287	.246	−.114	.150	−.164	.212
HDL cholesterol (mg/dL)	.003	.012	.003	.012	.002	.054	.003	.050
R^2	.243		.220		.261		.209	
Adjusted R^2	.217		.193		.219		.165	

Age: per year.
[a] Log-transformed value.

area exhibited a significant correlation with plasma HMW adiponectin levels in men and was closely related in women.

Adiponectin is secreted by adipose tissue [6]. Fat cell size is greater in obese than in lean subjects [13], and plasma adiponectin levels are also decreased in obese subjects [7]. Some articles have compared the cell size of adipose tissue from intraabdominal fat deposits (mainly the omentum) to that of adipocytes from other more peripheral areas. It was mostly reported that subcutaneous adipocytes were significantly larger than omental adipocytes [14-16]. Regional differences in lipoprotein lipase activity have also been examined in a number of studies [17-22]. These studies have shown a higher lipoprotein lipase activity in subcutaneous fat [17,18], higher activity in omental fat [19,20], and no difference [21,22].

Otherwise, there has been a previous demonstration of an inverse association of adiponectin with subcutaneous adipose tissue that includes trunk fat by dual-energy x-ray absorptiometry [23]. The association was even stronger than with total body fat. In this study measuring adipose tissue areas using low-dose x-ray CT, it is possible to separate visceral and subcutaneous adipose tissue areas and to clarify the correlations between the subcutaneous adipose tissue area and plasma total and HMW adiponectin levels.

Some articles have reported that plasma adiponectin levels showed a more significant correlation with the visceral adipose tissue area than the subcutaneous adipose tissue area [24-26]. These studies may have been affected by methodological limitations including a small sample size and combining men and women and obese and nonobese subjects.

A limitation of this study was that the women in our sample were not excessively obese, and we did not assess the associations of variants in adiponectin gene polymorphism. This study was a cross-sectional examination, and it is impossible to indicate the clinical impact of the subcutaneous adipose tissue area on diabetes or coronary heart disease. Some articles reported that fat accumulation differs according to race [4], so further studies are required to clearly elucidate this issue. There was no significant correlation between the plasma total and HMW adiponectin levels and plasma glucose possibly because diabetes subjects were on medication.

It is noteworthy that this study involved clarification of the correlations between the subcutaneous adipose tissue area and plasma total and HMW adiponectin levels. Multiple linear regression analysis clearly indicated that the subcutaneous adipose tissue area was independently correlated with the HMW adiponectin levels in men and closely related in women.

Many studies have reported that only visceral adipose tissue accumulation exhibited a significant correlation with metabolic syndrome. However, the present results clearly indicate that it is important to also consider the subcutaneous adipose tissue area in metabolic syndrome.

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