Journal of Atherosclerosis and Thrombosis Vol. 11, No. 3

Original Articles

The Relationship of Abdominal Fat Mass Assessed by Helical or Conventional Computed Tomography to Serum Leptin Concentration

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In the present study, we focused on the relationship of intra-abdominal visceral fat (VF) or subcutaneous fat (SF) mass to serum leptin levels, and also on the relationship of leptin to serum lipid and lipoprotein concentration. Subjects with obesity (26 men, 26 women) were recruited for this study. We obtained helical CT scans with a tube current of 150 mA, voltage of 120 kV and 2:1 pitch (table speed in relation to slice thickness), starting at the upper edge of the liver and continuing to the pelvis. The intra-abdominal visceral fat (VF) volume was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal SF volume was calculated by subtracting the VF volume from the total abdominal fat volume. By comparison, the abdominal VF and SF areas were determined at the umbilical level by the established slice-by-slice CT scanning technique. We found: 1) abdominal SF mass, either as volume or area, was a more important determinant of serum leptin than was VF mass; 2) among TC, TG, HDL-C and LDL-C, only TG had a positive correlation to serum leptin levels in men, whereas in women no lipid parameters had any relationship with leptin; and 3) VF mass had a positive correlation to serum TC and TG in men, whereas SF did not.

The present study provides considerable evidence on the relationship between abdominal fat mass and serum leptin, and shows that the relationships between serum leptin and serum lipids and lipoproteins are not straightforward. We also suggest that fat area measured by conventional CT is a better indicator than its corresponding volume assessed by helical CT, based on the present results showing its closer association to serum lipids. ***J Atheroscler Thromb, 2004; 11: 173–179.***

Key words: Subcutaneous fat, Visceral fat, Helical CT, Leptin

Introduction

Adiposities have been found to be responsible for the secretion of various kinds of hormones and cytokines (1), in contrast to the previous notion. Leptin, a cytokine identified and cloned by Zhang *et al.* (2), which is produced and secreted mainly in adiposities (3), is known to be involved in the neuroendocrine regulation of adiposity and its metabolic sequelae (4–6). In recent years, the clinical significance of measuring serum (or plasma) leptin levels has been increasingly clarified since the introduction of the method for its assessment by radioimmunoassay (7). Leptin plasma concentrations have been reported to be associated with body mass index (BMI), percent fat (8, 9) and total body fat mass by dual energy X-ray absorptiometry (10). Subsequently, there has been a considerable number of researchers involved in determining which component of body fat mass, or how body fat distribution, affects serum leptin concentrations, using various methods (11–21). These methods are conventional computerized tomography (CT)(22) and mag-

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Received January 5, 2004.
Accepted for publication March 19, 2004.

netic resonance imaging (MRI)(23), the latter of which made it possible to assess subcutaneous fat (SF) and visceral fat (VF) volume. Moreover, in 1992, the method using abdominal ultrasonography for the assessment of subcutaneous and preperitoneal fat thickness was reported, which made it possible to assess abdominal fat distribution in each individual frequently and repeatedly (24).

Helical CT is an other technique used for diagnosing several disorders (25, 26). However, until recently, there had been few reports (27) describing its application in the assessment of intra-abdominal body fat distribution.

In this study, we investigated how abdominal SF or VF mass, as either area or volume measured by conventional CT or helical CT, affects serum lipid and leptin levels.

Materials and methods

Subjects

Subjects with obesity (26 men aged 48 ± 15, 26 women aged 56 ± 12) were recruited for this study (Table 1). Obesity was defined as individuals having a BMI greater than 25 kg/m^2, according to the definition established by the Japan Society for the Study of Obesity (28). Individuals with hypertension (HT) were defined as individuals having systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (29) or those being treated with anti-hypertensive medication. Seven men and two women were smokers. Fourteen men and fifteen women had HT. Three men and two women had a history of coronary artery disease. Venous blood was drawn from the forearm after 12 hours of fasting for assay of serum lipid and lipoprotein levels. The serum levels of TC and TG were determined by an enzymatic method, and that of HDL-C by a precipitation method. The LDL-C level was determined using the Friedewald formula. Clinical profiles of the subjects with or without HT are shown in Table 2. The men with HT tended to have a smaller SF mass and larger VF mass than those without HT.

Scanning for intra-abdominal fat volume in helical CT

The subjects were examined in a supine position with both arms stretched above the head using a Toshiba X-VISION GX (Tokyo, Japan). We obtained helical CT scans with a tube current of 150 mA, voltage of 120 kV and 2:1 pitch (table speed in relation to slice thickness), starting

Table 1. Clinical profile of the study subjects.

	Men	Women
n (total)	26	26
n (BMI > 25 kg/m^2)	24	24
n (VFA ≥ 100 cm^2)	21	20
Age (yr)	48 ± 15	56 ± 12
Body mass index	30 ± 5.0	29 ± 3.8
Fat area (cm^2)		
subcutaneous	236 ± 108	293 ± 112
visceral	169 ± 65	134 ± 40
Fat volume (*l*)		
subcutaneous	6.6 ± 3.2	8.3 ± 3.8
visceral	4.9 ± 2.0	3.7 ± 1.0
Serum leptin (ng/ml)	6.5 ± 3.4	15 ± 7.8
Total cholesterol (mg/dl)	199 ± 39.6	231 ± 29.2
Triglycerides (mg/dl)	150 ± 99.8	108 ± 38
HDL-cholesterol (mg/dl)	48 ± 10.7	54.5 ± 9.44
FPG (mg/dl)	111 ± 23.8	108 ± 19.9
HbA1c (%)	5.49 ± 1.45	4.99 ± 1.14
Hypertension	14 (54%)	15 (58%)
Smoker	7 (27%)	2 (7.7%)
Coronary heart disease	3 (12%)	2 (7.7%)

HDL: high density lipoprotein
FPG: fasting plasma glucose
VFA: visceral fat area

Table 2. Abdominal fat mass in individuals with or without hypertension.

Men

	HT (+)	HT (–)	*p*
n	14	12	
Body mass index	30 ± 5.1	31 ± 4.9	0.62
Fat area (cm^2)			
subcutaneous	205 ± 86	285 ± 124	0.065
visceral	183 ± 65	146 ± 62	0.152
Fat volume (*l*)			
subcutaneous	5.7 ± 2.5	8.0 ± 3.7	0.072
visceral	5.1 ± 2.3	4.5 ± 1.5	0.45

Women

	HT (+)	HT (–)	*p*
n	15	11	
Body mass index	29 ± 3.8	29 ± 4.8	1
Fat area (cm^2)			
subcutaneous	284 ± 127	302 ± 90	0.69
visceral	135 ± 32	131 ± 45	0.79
Fat volume (*l*)			
subcutaneous	8.4 ± 4.4	8.2 ± 3.0	0.9
visceral	3.7 ± 1.1	3.8 ± 1.4	0.84

HT: hypertension

at the upper edge of the liver and continuing to the pelvis. The intra-abdominal VF volume was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal SF volume was calculated by subtracting the VF volume from the total abdominal fat volume. The abdominal VF and SF areas were determined at the umbilical level by the previously reported CT scanning technique (22, 30).

Measurement of serum leptin

Measurement of serum leptin was performed by radioimmunoassay as previously described (7). This assay measures the total (free plus bound) leptin in the blood. Sensitivity was 0.5 ng/ml, and the intraassay and interassay coefficients of variation were less than 3% and 8%, respectively.

Statistical analysis

StatView-J 5.0 software was used for all statistical analysis in this study. Values are shown as mean ± sd. Simple linear correlations, Pearson's correlation coefficients and partial correlation analysis were performed. A difference with a p value < 0.05 was considered to be significant.

Results

Intra-abdominal VF volume, measured by helical CT, showed a positive correlation with VF area measured by conventional slice-by-slice CT in both genders (Men, $r = 0.837$, $p < 0.0001$ for VF area *vs* VF volume) (Women, $r = 0.899$, $p < 0.0001$ for VF area *vs* VF volume). SF volume also showed a positive correlation with SF area in both genders (Men, $r = 0.974$, $p < 0.0001$ for SF area *vs* SF volume) (Women, $r = 0.912$, $p < 0.0001$ for SF area *vs* SF volume). To determine how abdominal fat mass affects serum leptin levels, we then analyzed the correlations of BMI, SF, or VF mass to serum leptin levels in the study subjects. In both genders, BMI was positively correlated to serum leptin levels (Fig. 1). SF mass, either by volume or area, was correlated to serum leptin more strongly than BMI in both genders. In both genders, the correlation coefficient was almost the same for SF volume *vs* leptin as for SF area *vs* leptin (Fig. 2). In men, neither VF volume nor VF area showed a significant correlation with serum leptin, whereas in women, both VF volume and, to a slightly lesser degree, VF area had a positive correlation with serum leptin (Fig. 3).

The relationships of abdominal SF or VF mass with serum lipid and lipoprotein levels are shown in Tables 3 and 4.

SF, either as area or volume, did not have any relationship with TG, but had an inverse relationship with HDL-C in men, while in women, SF area, not volume, had an inverse relationship with TC and LDL-C (Table 3). VF

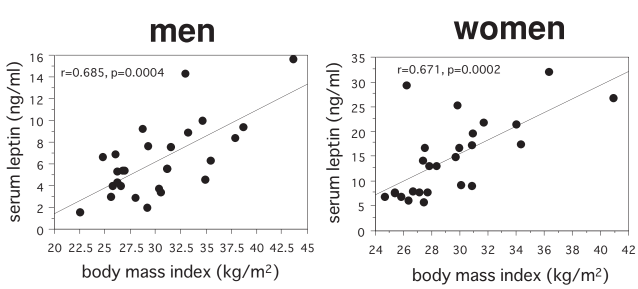

Fig. 1. Correlation between body mass index and serum leptin concentrations in men and women.

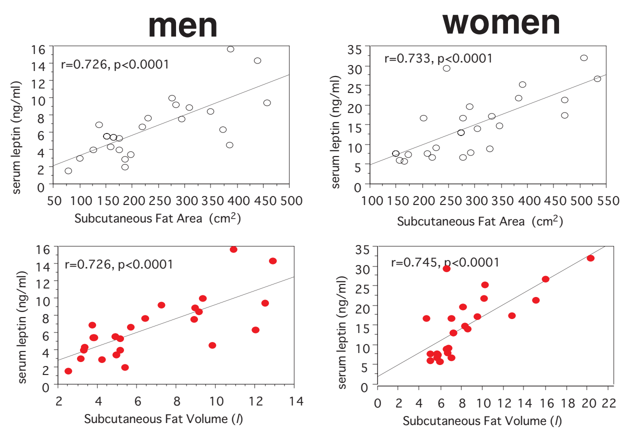

Fig. 2. Correlation between SF area measured by conventional CT, or SF volume measured by helical CT, and serum leptin concentrations in men and women.

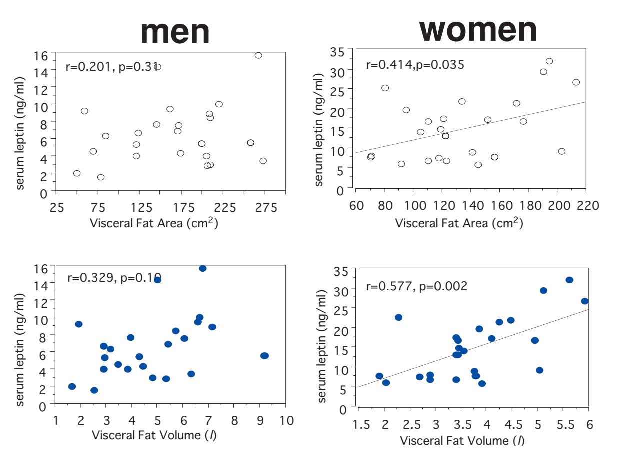

Fig. 3. Correlation between VF area measured by conventional CT, or VF volume measured by helical CT, and serum leptin concentrations in men and women.

mass, either as area or volume, had a positive relationship with TC, LDL-C and TG in men. In women, however, no association was observed except for the positive relationship between VF area, not volume, and LDL-C (Table 4). We then investigated the relationships of serum leptin levels with serum lipid and lipoprotein levels in the study subjects. None of the lipid parameters had a special relationship with serum leptin levels, except for TG, which had a positive relationship with serum leptin in men (Table 5).

Table 3. Relationships of subcutaneous fat mass to lipid and lipoprotein levels.

To SF area	Men		Women	
	r	*p*	*r*	*p*
Total cholesterol	– 0.161	NS	– 0.505	0.01
Triglycerides	0.299	NS	– 0.23	NS
HDL-cholesterol	– 0.499	0.0132	– 0.318	NS
LDL-cholesterol	– 0.203	NS	– 0.409	0.042

To SF vol	Men		Women	
	r	*p*	*r*	*p*
Total cholesterol	– 0.119	NS	– 0.336	NS
Triglycerides	0.291	NS	– 0.251	NS
HDL-cholesterol	– 0.456	0.0252	– 0.318	NS
LDL-cholesterol	– 0.157	NS	– 0.189	NS

SF area: subcutaneous fat area, SF vol: subcutaneous fat volume.

Table 4. Relationships of visceral fat mass to lipid and lipoprotein levels.

To VF area	Men		Women	
	r	*p*	*r*	*p*
Total cholesterol	0.592	0.0023	0.364	NS
Triglycerides	0.543	0.0061	0.061	NS
HDL-cholesterol	– 0.204	NS	0.025	NS
LDL-cholesterol	0.446	0.0329	0.41	0.0419

To VF vol	Men		Women	
	r	*p*	*r*	*p*
Total cholesterol	0.564	0.0041	0.183	NS
Triglycerides	0.451	0.0271	– 0.008	NS
HDL-cholesterol	– 0.264	NS	– 0.034	NS
LDL-cholesterol	0.493	0.017	0.213	NS

VF area: visceral fat area, VF vol: visceral fat volume.

Table 5. Relationships of serum leptin levels to lipid and lipoprotein levels.

To lepin	Men		Women	
	r	*p*	*r*	*p*
Total cholesterol	0.189	NS	– 0.075	NS
Triglycerides	0.421	0.036	– 0.11	NS
HDL-cholesterol	– 0.218	NS	– 0.108	NS
LDL-cholesterol	0.045	NS	– 0.049	NS

We also subdivided the subjects into individuals with (VFA $\geq$ 100 cm^2) or without VF accumulation (VFA < 100 cm^2). In men, individuals with VFA $\geq$ 100 cm^2 had higher TC ($p < 0.05$) and TG ($p < 0.05$) than those with VFA < 100 cm^2, whereas in women lipid levels did not differ between these two subgroups. Serum leptin levels did not differ between these two subgroups in either gender.

Discussion

The main findings of this study are as follows: 1) abdominal SF mass, either as volume or area, was a more important determinant of serum leptin than was visceral fat mass; 2) among TC, TG, HDL-C and LDL-C, only TG had a positive correlation with serum leptin levels in men, whereas in women, there was no relationship between serum leptin levels and lipid parameters; and 3) VF mass had a positive relationship with serum TC and TG in men, whereas SF did not.

Our findings suggest that SF mass, either as area or volume, has a stronger association than VF mass with serum leptin levels. There are conflicting reports as to whether plasma leptin is associated with total body, subcutaneous or visceral adipose tissue (11–21). A considerable amount of recent studies has suggested that it is SF, not VF, which shows a close association with serum (or plasma) leptin (11, 12, 14–16, 20). Studies by Cnop *et al.* (11) and Banerji *et al.* (12) have suggested, using conventional CT, that plasma leptin levels are highly associated with SF deposition. In accordance with these reports, a cohort study of 34 premenopausal African-American women showed that leptin is a significant indicator of total body fat, but not of VF or insulin insensitivity (13). Studies by Tai *et al.* (14) and Caprio *et al.* (15) showed by using magnetic resonance imaging (MRI) techniques, that abdominal SF is the most important determinant of plasma leptin. In line with these observations, it has been shown that leptin was influenced primarily by SF volume in both subject groups of 45 control women (aged 18–56) and 13 women with Prader-Willi syndrome (aged 20–38) (16). Recently, Minocci *et al.* (20) reported that, using an ultrasound assessment technique in 147 obese patients consisting of 77 men and 70 women, aged 45.1 ± 13.2 with a BMI of 42.3 ± 5.9 kg/m^2, leptin concentrations were directly and significantly related to subcutaneous but not preperitoneal fat. One possible explanation for the SF being more strongly associated with serum leptin than VF is that SF accounts for a much larger portion of abdominal adipose tissue than VF. A study using MRI techniques showed that intra-abdominal VF volume is relatively small, 0.5–8.5 l in men and 0.9–5.5 l in obese women, and accounts for only 6–20% of total adipose tissue volume in obese individuals (23). In contrast, Ronnemaa *et al.* (17) suggested that VF is of special importance in the regulation of leptin levels and is more so in men than in women, after investigating 23 healthy identical twin pairs (9 male pairs and 14 female pairs, aged 33 to 59). A study by Gower *et al.* (21) showed that in 54 postmenopausal women, VF was independently related to serum leptin levels after adjusting for SF, leg fat and lean mass. A cross-sectional study of 56 nondiabetic, elderly men and women aged 64–94 showed that leptin was significantly associated with both SF and VF in each gender (18). The main factors presumably contributing to these conflicting results, in which the abdominal fat component is a main determinant of serum leptin levels, could be related to the small sample size of those studies, including our study. Further studies with a larger sample size are required to give a more detailed answer to this question.

The relationship of serum leptin level to serum lipids does not appear to be well established. Silver *et al.* (31) reported that in leptin-deficient (ob/ob) mice, increased HDL levels due to a marked hepatic catabolic defect for apoA-I and apoA-II were observed. Hasty *et al.* (32) reported unexpectedly severe hyperlipidemia in ob/ob mice with low density lipoprotein receptor (LDLR) deficiency (-/-), while low-level leptin treatment significantly lowered TG levels, suggesting that leptin may have a favorable effect on lipid metabolism in LDLR-deficient (-/-) + mice. Aside from studies using mice, there have been very few reports showing how serum leptin affects serum lipid and lipoprotein metabolism. In the present study, no association was observed between serum leptin and several lipid and lipoprotein parameters, except for TG having a positive relationship with serum leptin level in men. This finding is surprising in view of the report showing that leptin increases LPL expression *in vivo* in mice (33). One mechanism for the positive relationship between leptin and TG could be related to the observation by Sweeney *et al.* (34) that leptin may be responsible for the development of glucose intolerance, possibly leading to insulin resistance.

There have been considerable numbers of reports on the relationship of abdominal fat and lipids (30, 35–37). It is generally believed that VF mass has a positive relationship with TG (30, 35–37) and an inverse relationship with serum HDL-C (36), while SF does not. It should be noted that in this study, VF mass, either as area or volume, had a positive relationship with serum TC and LDL-C in both genders, as well as with TG in men, which is in line with the previous findings (38, 39). It is also notable that in women the inverse relationship between SF area and TC (or LDL-C) (Table 3) and the positive relationship between VF area and LDL-C (Table 4) did not persist when those respective fat components were measured as volume. This fact suggests that measurement of fat area using conventional CT is a better indicator than that of fat volume using helical CT.

In conclusion, the present study provides considerable evidence on the relationship between abdominal fat mass and serum leptin, and shows that the relationships between serum leptin and serum lipids and lipoproteins are not straightforward.

Acknowledgments: We acknowledge the productive advice given by Dr. M. Shinomiya and Dr. N Tadokoro regarding this work.

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