Visceral Fat in Hypertension
Influence on Insulin Resistance and β-Cell Function

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Abstract—Preferential visceral adipose tissue (VAT) deposition has been associated with the presence of insulin resistance in obese and diabetic subjects. The independent association of VAT accumulation with hypertension and its impact on insulin sensitivity and β-cell function have not been assessed. We measured VAT and subcutaneous fat depots by multiscan MRI in 13 nondiabetic men with newly detected, untreated essential hypertension (blood pressure=151±2/94±2 mm Hg, age=47±2 years, body mass index [BMI]=28.4±0.7 kg · m^{-2}) and 26 age-matched and BMI-matched normotensive men (blood pressure=123±1/69±2 mm Hg). Insulin secretion was measured by deconvolution of C-peptide data obtained during an oral glucose tolerance test, and dynamic indices of β-cell function were calculated by mathematical modeling. For a similar fat mass in the scanned abdominal region (4.8±0.3 versus 3.9±0.3 kg, hypertensive subjects versus controls, $P=0.06$), hypertensive subjects had 60% more VAT than controls (1.6±0.2 versus 1.0±0.1 kg, $P=0.003$). Intrathoracic fat also was expanded in patients versus controls (45±5 versus 28±3 cm^2, $P=0.005$). Insulin sensitivity was reduced (10.7±0.7 versus 12.9±0.4 mL · min^{-1} · $kg_{ffm}{}^{-1}$, $P=0.006$), and total insulin output was proportionally increased (64 [21] versus 45 [24] nmol · m^{-2} · h, median [interquartile range], $P=0.01$), but dynamic indices of β-cell function (glucose sensitivity, rate sensitivity, and potentiation) were similar in the 2 groups. Abdominal VAT, insulin resistance, and blood pressure were quantitatively interrelated (ρ's of 0.39 to 0.47, $P<0.02$ or less). In newly found, untreated men with essential hypertension, fat is preferentially accumulated intraabdominally and intrathoracically. Such visceral adiposity is quantitatively related to both height of blood pressure and severity of insulin resistance, but has no impact on the dynamics of β-cell function. **(*Hypertension*. 2004;44:127-133.)**

Key Words: insulin resistance ■ obesity ■ adipose tissue ■ hypertension, essential

Epidemiological studies have documented the association between severe obesity, diabetes, and mortality caused by increased rates of cardiovascular and cerebrovascular disease.[1] In moderate obesity, regional fat distribution appears to be an important indicator of metabolic and cardiovascular risk.[2] Several prospective studies have shown that excess fat in the upper body (android or male-type obesity) correlates with increased mortality and risk for diabetes, hyperlipidemia, hypertension, and atherosclerosis of coronary, cerebral, and peripheral vessels.[3] The intraabdominal fat depots appear to mediate the detrimental influence of abdominal obesity on metabolic processes. Thus, visceral fat (VAT) was associated with glucose intolerance in the presence of hyperinsulinemia during an oral glucose tolerance test, suggesting an insulin-resistance state.[4] This effect of VAT accumulation on glucose tolerance was independent of total adiposity and subcutaneous abdominal adipose tissue.[5,6] Although the cause–effect relationship has not been established, the available evidence indicates that VAT may be a common element linking the many facets of the metabolic syndrome: glucose intolerance, hypertension, dyslipidemia, and insulin resistance.[7]

Studies in children have found that blood pressure is associated with hyperinsulinemia and VAT excess.[8] In centrally obese hypertensive women, accumulation of fat in the abdominal viscera, a process accelerated by menopause, has been found to be associated with higher blood pressure levels and insulin resistance.[9] Implementation of a strategy to prevent obesity, especially visceral obesity, has been advocated for the primary prevention of hypertension.[10] Whether VAT excess is present in untreated adult subjects with essential hypertension independent of obesity and diabetes has not been established. Aims of this study therefore were to determine whether VAT accumulation is quantitatively related to high blood pressure independently of obesity, diabetes, and pharmacological treatment, and to explore the relation of VAT accumulation to insulin resistance and β-cell function in untreated subjects with essential hypertension.

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TABLE 1. Clinical Characteristics

Clinical Data	Normotensives	Hypertensives	*P**
N	26	13	NS
Age, y	41±2	47±2	NS
BMI, kg · m^{-2}	27.0±0.5	28.4±0.7	NS
Fat mass, %	25±1	26±1	NS
Waist circumference, cm	94±2	101±2	0.02
Waist-to-hip ratio	0.92±0.01	0.93±0.02	NS
Leptin, ng/mL	3.6±0.5	4.3±0.7	NS
Adiponectin, μg/mL	6.6±0.4	5.2±0.7	0.06
HbA_{1c}, %	4.8±0.1	5.0±0.1	NS
Serum LDL cholesterol, mmol/L	3.33±0.17	3.34±0.21	NS
Serum HDL cholesterol, mmol/L	1.11±0.04	1.02±0.06	NS
Serum triglycerides, mmol/L	0.82 [0.56]	1.28 [1.52]	0.01
Systolic BP, mm Hg	123±1	151±2	<0.0001
Diastolic BP, mm Hg	69±2	94±2	<0.0001
Mean blood pressure, mm Hg	87±1	113±2	<0.0001
Heart rate, bpm	64±2	68±3	NS

Entries are mean±SE or median [interquartile range].

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

*Mann–Whitney *U* test.

Materials and Methods

Subjects

From subjects attending our clinics, we selected men with the following characteristics: (1) age between 25 and 70 years; (2) body mass index (BMI) between 20 and 35 kg · m^{-2}; (3) no diabetes (defined as a fasting plasma glucose <7.0 mmol/L and a 2-hour plasma glucose concentration <11.1 mmol/L on a 75-g oral glucose tolerance test [OGTT], see later)[11,12]; and (4) no previous treatment with antihypertensive or antidiabetic drugs or any other drug known to affect glucose metabolism. Subjects (n=13) with confirmed systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and a negative workup for secondary hypertension were considered to have essential hypertension and were recruited into the study.[13] These subjects were matched by age and BMI to normotensive subjects in a ratio of 2:1. The clinical characteristics of the resulting study groups are shown in Table 1. The study protocol was approved by the Institutional Review Board of the University of Pisa, and each subject gave informed written consent to participate.

Study Protocol

All subjects received a 3-hour, 75-g OGTT with frequent blood sampling and MRI multiscan study for the quantitation of abdominal, subcutaneous, and VAT mass and intrathoracic fat area.

Anthropometrics Measurements

The waist-to-hip circumference ratio was determined by measuring the waist circumference at the narrowest part of the torso and the hip circumference in a horizontal plane at the level of the maximal extension of the buttocks. Fat-free mass was measured by electrical bioimpedance, as previously described;[14] fat mass was then obtained as the difference between body weight and fat-free mass. After an overnight (10 to 14 hours) fast and a 30-minute acclimation period, arterial blood pressure was measured 3 times to the nearest 2 mm Hg in the sitting position using appropriately sized cuffs, and the mean of the 2 closest values was recorded. Mean blood pressure was calculated as the diastolic value plus one third of the pulse pressure value.

Metabolic Measurements

The OGTT was performed in the morning (8:00 AM) after a 10- to 14-hour overnight fast. Blood samples were collected at −15, 0, 15, 30, 60, 90, 120, 150, and 180 minutes for the measurement of plasma glucose, free fatty acids (FFA), C-peptide, glucagons, and insulin concentrations. Leptin and adiponectin were assayed on fasting serum samples. Plasma glucose was measured by the glucose oxidase reaction (Beckman Glucose Analyzer). Plasma insulin, glucagons, and C-peptide concentrations were measured by radioimmunoassay using specific kits (Linco Research). Enzyme-linked immunosorbent assays were used to measure leptin and adiponectin (respectively, DRG and Linco Research). Serum FFA was measured spectrophotometrically (Wako).

Adipose Tissue Compartmentation

Abdominal VAT and subcutaneous fat depots (SAT) were measured by MRI, using imaging procedures that have been published previously.[15] Briefly, images were acquired on a GE Signa Horizon LX System 1.5T scanner (slew rate: maximum 150 mT/m per second) that operates with a 40-mT/m gradient using a body coil. A sagittal localizing image was used to center transverse sections on the line through the space between L4 and L5. Thirty-two transverse, T1-weighted 256×256 images (repetition time [TR]=135, echo time [TE]=4.2, flip angle=90°, field of vision=50 cm, pixel size 1.875×1.875 mm) were acquired in breath-hold with a slice thickness of 5 mm with no overlap. Data were transferred to a dedicated workstation and analyzed by an *ad hoc* developed software[16] to determine abdominal subcutaneous and VAT areas and volumes. The SAT area was analyzed by automatic detection of the outer and inner margins of subcutaneous adipose tissue as region of interest from the cross-sectional images, and by counting the number of pixels between the outer and inner margins of subcutaneous adipose tissue. The VAT (intraabdominal) area was determined using histograms specific to the visceral regions. The histograms were summed over the range of pixel values designated as fat by fitting 2 normal analysis distribution curves to them. A factor of 0.92 was use to convert adipose tissue volume into adipose tissue mass.[17]

In addition to the abdominal region, in 24 subjects (14 normotensive subjects and 10 hypertensive subjects) the thoracic region was also imaged by combined echo and MRI. MRI acquisition involved a standardized protocol. Cardiac coil and electrocardiogram triggering was used for the sequences; during the acquisition time, patients were in breath-hold (10 to 12 seconds). Mediastinal[18] adipose tissue scans were obtained by fast-spin echo T_1-weighted sequences with oblique axial orientation, for a correct study of horizontal long axes of the heart[19] (TE, 42 ms; echo train length, 23; bandwidth, 62.50; slice thickness, 8 mm; slice gap, 0 mm; field of vision, 38 cm; matrix, 288×224; phase field of vision, 0.75; NEX 1; Trigger delay=minimum 8-mm-thick section with 0-mm intersection gap, field of view, and a 256×256 matrix) (Figure 1). Mediastinal and intrapericardial fat areas were measured using a semiautomatic program.

Insulin Secretion

Insulin secretion rates were calculated from plasma C-peptide concentrations by deconvolution, as previously described.[20] Fasting plasma insulin clearance rate was then calculated as the ratio of fasting insulin secretion rate and fasting plasma insulin concentration. Parameters of β-cell function were derived from mathematical analysis of plasma glucose and C-peptide concentrations during the OGTT according to a previously developed model.[21,22] The model describes the relationship between insulin secretion, S(t), and glucose concentration. Insulin secretion consists of 2 components, according to the equation:

$$S(t) = S_g(t) + S_d(t)$$

The first component, $S_g(t)$, represents the dependence of insulin secretion on the absolute glucose concentration (G) at any time point, and is characterized by a dose–response function, f(G), relating these variables. A characteristic parameter of the dose–response is its

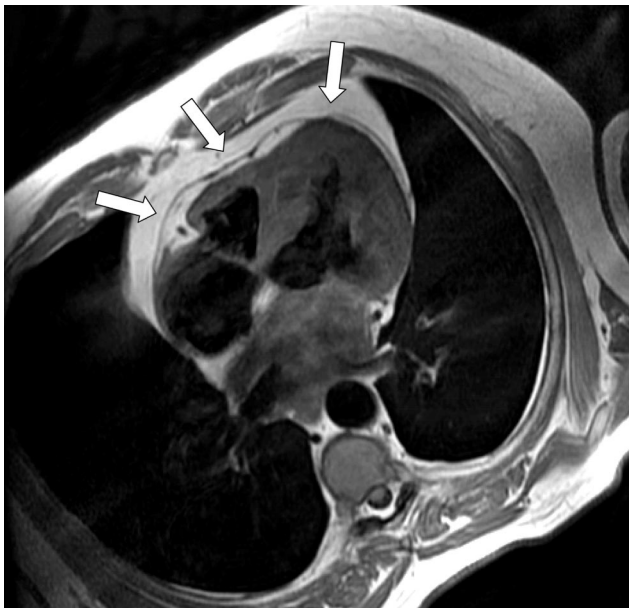

Figure 1. Mediastinal fat. Arrows indicate the pericardium separating intrapericardial and extrapericardial adipose tissue on a gated cardiac image.

mean slope (in the observed glucose range), denoted as β-cell glucose sensitivity. The dose–response is modulated by a potentiation factor, P(t), which incorporates glucose-mediated and nonglucose-mediated potentiation (ie, by nonglucose substrates, gastrointestinal hormones, and neurotransmitters):

$$S_g(t) = P(t)\, f(G)$$

Potentiation is a time-dependent phenomenon.[23] The potentiation factor is therefore modeled as a positive function of time and averages one during the experiment. The potentiation parameter used for the present analysis is the ratio of the potentiation factor at the end of the OGTT (160 to 180 minutes) to the one at the beginning of the OGTT (0 to 20 minutes).

The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration. This component is called the derivative component and is described by a single parameter, denoted as rate sensitivity.

Data Analysis

Data are given as the mean±SEM; because of their skewed distribution, serum triglyceride concentrations and all insulin parameters are given as median and interquartile range. Areas under glucose and insulin concentration curves were calculated by the trapezoidal rule. Insulin sensitivity, as the average metabolic clearance rate of glucose during the OGTT (expressed in mL/min per kg of fat-free mass), was calculated from the plasma glucose and insulin values during the OGTT according to the method of Mari et al,[24,25] which has been validated against the euglycemic insulin clamp technique. Power analysis of the main outcome variable (VAT mass) showed that the sample size could detect (with a 2-tailed α value of 0.05 and a 10% risk of making a type II error) a minimum difference of 79 mL (or 7% of the mean value of the control group). Group values were compared by the Mann–Whitney *U* test; adjustment for confounders was performed with the use of ANCOVA. Categorical variables were compared by the χ^2 test. Univariate associations were tested with the use of Spearman rank correlations. The contribution of multiple factors to blood pressure was assessed by multivariate analysis.

Results

Hypertensive subjects and normotensive subjects were matched by age, BMI, and total fat mass (as a percentage of body weight); however, waist circumference (but not the waist-to-hip circumference ratio) was slightly higher in hypertensive subjects than controls (Table 1). Fasting and postglucose plasma FFA levels were super imposable (Figure 2), as were plasma glucagon and aldosterone concentrations (data not shown). Whereas leptin levels were similar in the 2 groups, adiponectin levels were lower in hypertensive subjects than normotensive subjects, particularly when normalized for percent body fat.

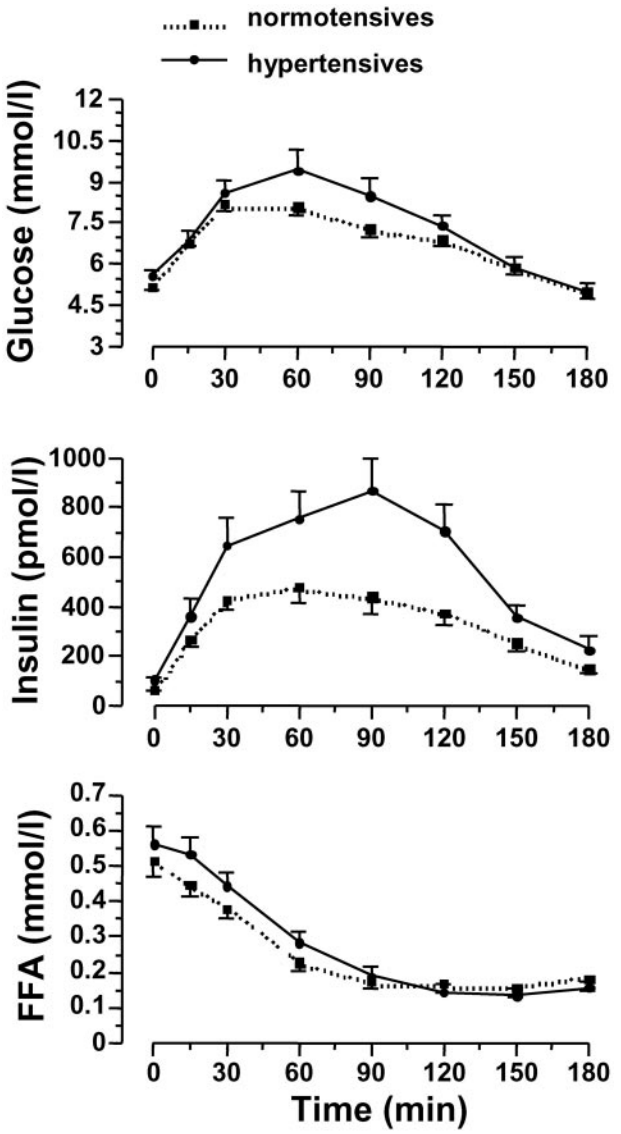

Figure 2. Time-course of plasma glucose, insulin, and FFA concentrations in hypertensive and normotensive men. Values are mean±SEM.

Although glucose tolerance, as the glucose area under curve, was similar between the 2 groups, hypertensive subjects have slightly higher plasma glucose concentrations in the fasting state (Table 2) and at 60 minutes during the OGTT (Figure 1). Both fasting and postglucose plasma insulin levels were markedly elevated in the hypertensive subjects (Figure 2 and Table 2). The corresponding insulin secretory rates, as calculated by C-peptide deconvolution, were also higher, with total insulin output over the 3 hours of the OGTT being

TABLE 2. Metabolic Characteristics

Metabolic Data	Normotensives	Hypertensives	*P*
Fasting plasma glucose, mmol/L	5.2±0.1	5.6±0.2	<0.05
AUC_G, mol · L^{-1} · h	1.25±0.03	1.35±0.08	NS
Fasting plasma insulin, pmol/L	70 [29]	96 [74]	0.02
AUC_I, nmol · L^{-1} · h	59 [24]	120 [77]	0.01
Insulin sensitivity, mL · min^{-1} · kg_{ffm}^{-1}	12.9±0.4	10.7±0.7	0.006
Basal insulin secretion, pmol · min^{-1} · m^{-2}	67 [45]	96 [36]	0.07
Basal insulin clearance, L · min^{-1} · m^{-2}	1.17±0.11	0.86±0.07	0.05
Total insulin output, nmol · m^{-2} · h	45 [24]	64 [21]	0.01
Glucose sensitivity, pmol · min^{-1} · m^{-2} · mM^{-1}	82 [66]	89 [70]	NS
Rate sensitivity, nmol · m^{-2} · mM^{-1}	0.99 [0.69]	1.18 [1.14]	NS
Potentiation factor (fold)	1.33 [0.79]	1.70 [0.79]	NS

Entries are mean±SE or median [interquartile range].
AUC_G indicates glucose area under curve; AUC_I, insulin area under curve.

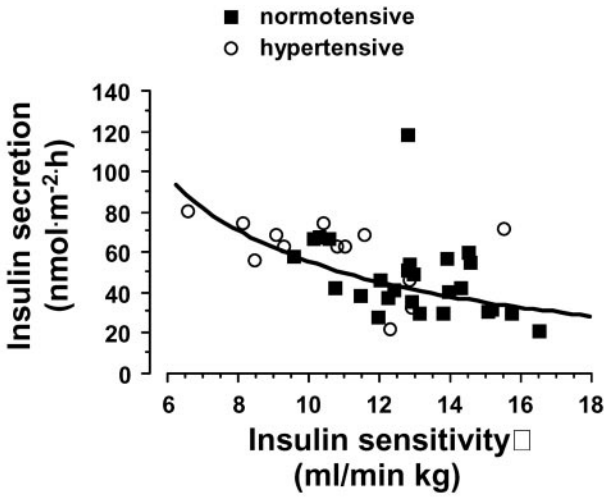

Figure 3. Relationship between total insulin output during the OGTT and insulin sensitivity.

40% higher in hypertensive subjects than in normotensive subjects. The dynamic parameters of β-cell function (glucose sensitivity, rate sensitivity, and the potentiation factor) were superimposable between the 2 groups. Fasting insulin clearance was reduced in the hypertensive subjects by 26%. Insulin sensitivity, as the average metabolic clearance rate of glucose during the OGTT, was 17% lower in hypertensive subjects than in controls. In the whole group, total insulin output and insulin sensitivity were significantly related to one another (ρ=0.59, P<0.0001) in an inverse manner, with hypertensive and normotensive subjects being categorized in the same regression line (P=NS for the difference in slope) (Figure 3). Insulin sensitivity and adiponectin levels were directly related to one another (ρ=0.41, P<0.01).

Total fat mass in the abdominal region averaged 3.9±0.3 kg and 4.8±0.3 kg, in normotensive subjects and hypertensive subjects, respectively (P=0.06), and represented similar proportions of total fat mass (20±1 and 22±1%, respectively, P=NS). However, VAT mass was 60% larger (P<0.003) in hypertensive subjects than normotensive subjects, whereas SAT mass was not significantly different (Figure 4). Thus, VAT comprised 24±2% of abdominal fat mass in normotensive subjects and 33±2% in hypertensive subjects (P=0.007). Intrapericardial fat area was similar in hypertensive subjects and normotensive subjects (10±1 and 9±1 cm^2, respectively, P=NS), whereas mediastinal fat area (Figure 5) was considerably larger in the former than the latter (45±5 versus 28±3 cm^2, P=0.005). Mediastinal and abdominal VAT were positively related to one another (ρ=0.66, P<0.0006) (Figure 6).

In the whole group of study subjects, abdominal VAT and SAT were positively related to one another (ρ=0.43, P<0.007). However, VAT, but not SAT, was directly related to age (ρ=0.56, P=0.0002) and to mean blood pressure (ρ=0.46, P=0.004) (Figure 7). A direct correlation with mean blood pressure was also found for mediastinal fat area (ρ=0.46, P<0.03) (Figure 7). Insulin sensitivity, however, was reciprocally related to both abdominal VAT and intrathoracic fat, and to mean blood pressure (Figure 7). In a multivariate regression model also adjusting for abdominal SAT, insulin sensitivity (partial r=−0.38, P=0.02) and VAT (partial r=0.42, P<0.01) were independent correlates of mean blood pressure, together explaining 36% (P=0.001) of its observed variability. This model predicted that an increase in VAT mass of 1 kg is associated with an increment in mean blood pressure of 10 mm Hg. This pattern of associations was essentially the same for systolic and diastolic blood pressure.

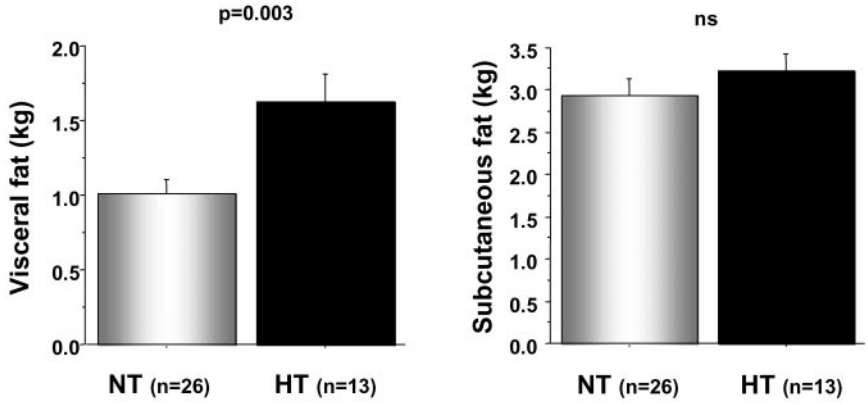

Figure 4. Visceral and subcutaneous fat mass in hypertensive and normotensive men.

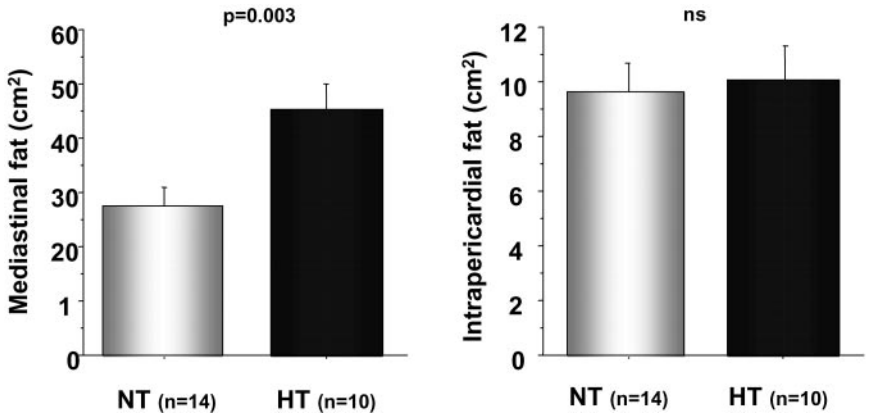

Figure 5. Mediastinal and intrapericardial fat area in hypertensive and normotensive men.

Discussion

The association of VAT accumulation with high blood pressure can be confounded by several factors, including age, gender, degree of obesity, and glucose tolerance status; each of these factors has been shown to be related to both abdominal obesity and hypertension. Also, drug treatment, for example, with thiazolidinediones,[26] may induce a shift in fat deposition from visceral to subcutaneous depots. To assess any independent association of fat distribution with blood pressure, we carefully selected newly detected, drug-naive men with high blood pressure and matched them with normotensive men of comparable age and body mass. Very obese (with a BMI >35 kg $\cdot$ m^{-2}) or diabetic subjects were excluded because marked obesity may obscure any specific effect of fat distribution, and diabetes is very often associated with hypertension and severe insulin resistance.[27,28] Thus, our findings are relevant to the nondiabetic untreated segment of the hypertensive male population.

The main finding is that hypertensive men had considerably more fat in the abdominal visceral region (and in the mediastinum) than did normotensive men for approximately the same amounts of fat in the abdominal subcutaneous depot and in the whole body. Furthermore both intrathoracic (ie, mediastinal) and intraabdominal (ie, visceral) adiposity was quantitatively related to both the height of blood pressure and the severity of insulin resistance across the respective ranges in the whole study group. These findings require specification.

First, we assessed abdominal fat distribution by 32-scan MRI, thereby providing estimates of fat content in a roughly cylindrical volume 16 cm in length centered at the L4–L5 interspace. This volume encloses $>50\%$ of the abdomen when compared with estimates obtained by helical computed tomography scans between the upper edge of the liver and the pelvis.[29] Therefore, by assuming a constant density of 0.92 for white adipose tissue and by extrapolating the scanned volume to the whole abdomen, we can calculate that, in men with a BMI <35 kg $\cdot$ m^{-2} total abdominal fat represents approximately one third of total body fat, and that abdominal VAT averages 10% of total body fat. The relatively small fraction of total fat that is located in abdominal viscera stresses the point that the impact of selective VAT accumulation on blood pressure or insulin sensitivity must reflect the biologic activity of such depot rather than its mass action. Thus, it should not be surprising that systemic FFA levels, which result from whole body lipolysis, were found to be only minimally elevated in the hypertensive subjects (Figure 1), despite their excess fat in the abdominal visceral region. In our subjects, we also found excess adipose tissue in the mediastinum in rough proportion to VAT mass. This finding indicates that ectopic fat deposition is not limited to the abdominal viscera, but may occur in the thorax as well as in atypical subcutaneous depots (the buffalo hump in Cushing disease). The factors that control the differentiation of preadipocytes and the "homing" of triglycerides into them in the various adipose tissue compartments are still largely unknown.

Second, from the linear relationship between visceral/mediastinal fat and blood pressure (Figure 7), one can speculate that the amount of adipose tissue accumulating in the abdominal viscera exerts a graded influence on blood pressure. This effect is compatible with the selective release of vasoactive adipocytokines (eg, angiotensinogen)[30,31] from VAT, or, alternatively, with a hepatic effect of adipocytokines reaching the liver at high concentrations from intraabdominal depots draining into the portal system.[32,33] The same paradigm applies to the observed linear association

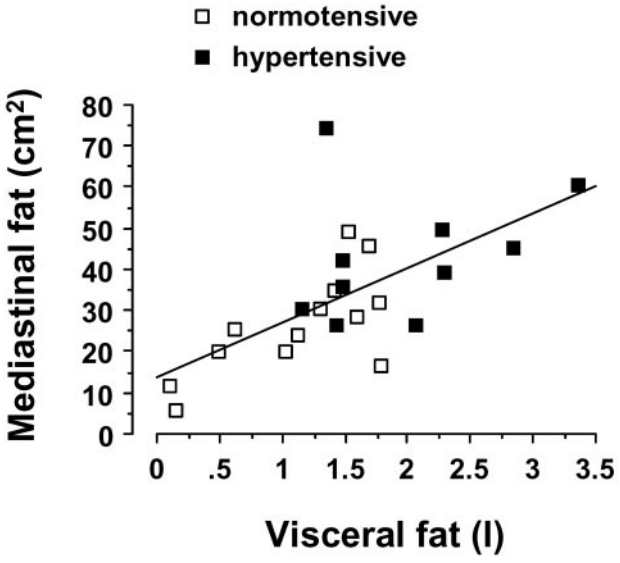

Figure 6. Relationship between mediastinal fat area and intraabdominal visceral fat mass.

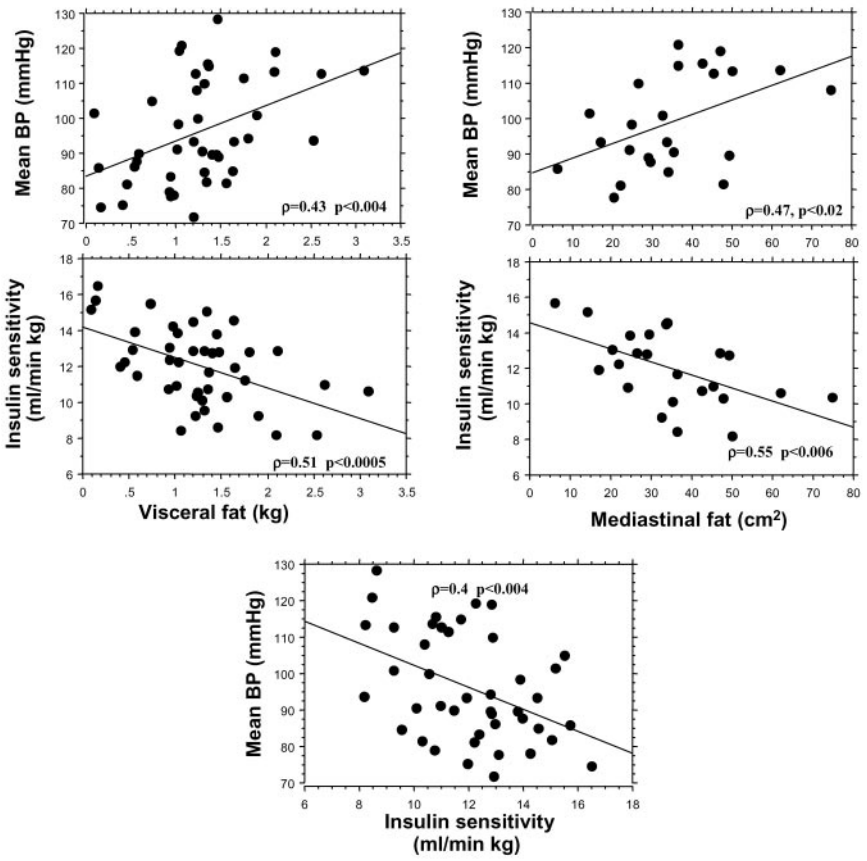

Figure 7. Interrelationships between mean blood pressure, insulin sensitivity, and visceral and mediastinal fat.

between VAT and insulin resistance (Figure 7): insulin antagonistic (eg, FFA,[32] tumor necrosis factor-α,[34,35] resistin[36]) or insulin agonistic molecules (adiponectin)[37,38] may be released with some selectivity from visceral adipose tissue or they may exert their effects selectively on the liver by virtue of its anatomical connection to abdominal viscera. Many of these biological phenomena are undergoing active investigation. Our results establish that in nondiabetic men, VAT excess, high blood pressure, and insulin resistance consistently form a triad of interconnected abnormalities.

Finally, whereas presence and mechanisms of insulin resistance in essential hypertension have been amply investigated,[39,40] the integrity of β-cell function in nondiabetic individuals with untreated hypertension has not been evaluated. In our untreated hypertensive men, fasting and postglucose insulin secretion was increased in proportion to the degree of insulin resistance, as expected from the inverse relationship linking the 2 variables. In contrast, model-derived parameters describing the ability of the β cell to acutely respond to a glucose challenge (namely, β-cell glucose sensitivity, rate sensitivity, and potentiation) all were similar in hypertensive and normotensive controls (Table 2). As recently discussed,[41] fasting and total insulin output represent the set point of the secretory machinery; these responses are reciprocally related to insulin sensitivity. However, glucose sensitivity, rate sensitivity, and potentiation are dynamic indices of β-cell function, which are only weakly linked with insulin sensitivity. Thus, in the present group of hypertensive men, β-cell function was perfectly normal and bore no relation to either insulin sensitivity or blood pressure.

Perspectives

In men with essential hypertension, fat is selectively accumulated in the visceral abdominal and intrathoracic region. This visceral adiposity appears to be an inherent feature of the hypertensive phenotype because it was found in newly diagnosed, untreated cases. It is quantitatively related to both height of blood pressure and degree of insulin resistance. β-cell function, however, is unaffected by VAT accumulation. Whether ectopic fat mass is causally related to insulin resistance and/or hypertension (through the release of hormones and vasoactive cytokines) or is just part of an inherited/acquired cluster of abnormalities remains matter for speculation. The observation that thiazolidinediones lower arterial blood pressure consistently, albeit slightly, at the same time as they induce a shift of fat distribution from visceral to subcutaneous depots[42] supports the notion that ectopic fat, blood pressure, and insulin action are linked traits in humans.

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Correction

In an article by Anna Maria Sironi et al in the August 2004 issue (*Hypertension*, 2004;44:127–133), Vincenzo Positano's name was spelled incorrectly. The authors regret the error.

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