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The Relationship of Body Mass and Fat Distribution With Incident Hypertension

Observations From the Dallas Heart Study

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ABSTRACT

BACKGROUND Obesity has been linked to the development of hypertension, but whether total adiposity or site-specific fat accumulation underpins this relationship is unclear.

OBJECTIVES This study sought to determine the relationship between adipose tissue distribution and incident hypertension.

METHODS Normotensive participants enrolled in the Dallas Heart Study were followed for a median of 7 years for the development of hypertension (systolic blood pressure [SBP] ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or initiation of blood pressure medications). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) was quantified by magnetic resonance imaging and proton-spectroscopic imaging, and lower body fat (LBF) was imaged by dual-energy x-ray absorptiometry. Multivariable relative risk regression was performed to test the association between individual fat depots and incident hypertension, adjusting for age, sex, race/ethnicity, diabetes, smoking, SBP, and body mass index (BMI).

RESULTS Among 903 participants (median age, 40 years; 57% women; 60% nonwhite; median BMI 27.5 kg/m^2), 230 (25%) developed incident hypertension. In multivariable analyses, higher BMI was significantly associated with incident hypertension (relative risk: 1.24; 95% confidence interval: 1.12 to 1.36, per 1-SD increase). However, when VAT, SAT, and LBF were added to the model, only VAT remained independently associated with incident hypertension (relative risk: 1.22; 95% confidence interval: 1.06 to 1.39, per 1-SD increase).

CONCLUSIONS Increased visceral adiposity, but not total or subcutaneous adiposity, was robustly associated with incident hypertension. Additional studies will be needed to elucidate the mechanisms behind this association.
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An epidemiological link between adiposity and hypertension development has been firmly established (1,2). However, many obese patients will remain normotensive despite significant adiposity. Differences in adipose tissue distribution may contribute to the heterogeneity of clinical and biological manifestations of obesity (3,4).

Under conditions of inadequate subcutaneous adipose tissue (SAT) (e.g., nutrient overload or lipodystrophy), excess triglyceride is stored ectopically

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BP = blood pressure

DBP = diastolic blood pressure

DEXA = dual-energy x-ray absorptiometry

hs-CRP = high-sensitivity C-reactive protein

LBF = lower body fat

MRI = magnetic resonance imaging

SAT = subcutaneous adipose tissue

SBP = systolic blood pressure

VAT = visceral adipose tissue

in other depots, such as visceral adipose tissue (VAT), muscle, and liver. Whereas SAT is relatively metabolically inert, VAT is associated with increased cytokine production (5) and insulin resistance (4).

SEE PAGE 1003

The question remains whether the association between obesity and hypertension is influenced by site-specific adipose tissue accumulation. We hypothesized that VAT mass, rather than SAT or the degree of overall adiposity, would be associated with the development of hypertension.

METHODS

STUDY POPULATION. The DHS study (Dallas Heart Study) is a multiethnic, probability-based cohort study of Dallas County adults (age 18 to 65 years), with deliberate oversampling of African-American participants (6). The study schema is summarized in Figure 1. The current study population was drawn from 2,716 participants who completed all 3 visits of DHS phase 1 (DHS-1) from 2000 to 2002, which included blood pressure (BP) measurements, laboratory testing, abdominal magnetic resonance imaging (MRI), and dual-energy x-ray absorptiometry (DEXA) scan. Of these participants, those with baseline hypertension (systolic blood pressure [SBP] ≥140 mm Hg, diastolic blood pressure [DBP] ≥90 mm Hg, or on antihypertensive medications) were excluded, as were participants with borderline BP elevations at baseline (SBP ≥130 or DBP ≥85 mm Hg) to preclude minimal increases in BP meeting the incident hypertension definition. After these exclusions, 1,306 participants were eligible for follow-up.

Of these, 903 participants completed all 3 visits of DHS-1 and returned for DHS phase 2 (DHS-2), which consisted of follow-up studies during a single visit between 2007 and 2009. This comprised the current study population. There were no significant differences in medical history, demographics, or biomarker data between eligible participants who did and did not complete DHS-2 (4). All participants provided written informed consent, and the University of Texas-Southwestern Medical Center institutional review board approved the protocol.

HYPERTENSION DEFINITION. Trained professionals took BP measurements after 5 min of rest in the seated position using an automated oscillometric device (Series #52,000, Welch Allyn, Arden, North Carolina). Five measurements were taken, and the last 3 readings were averaged. Antihypertensive medications were defined as any diuretic, alpha-blocker, beta-blocker, calcium channel blocker, angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker, nitrate, and hydralazine. Participants were asked to bring all their medications to their visit, and a trained professional examined all of the medications thoroughly. In both phases of the DHS, hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or the participant taking any antihypertensive medications.

ABDOMINAL FAT QUANTIFICATION. Participants were scanned at their baseline exam by a 1.5-T MRI scanner (Intera, Philips Healthcare, Best, the Netherlands). Retroperitoneal, intraperitoneal, and SAT abdominal fat masses were quantified by a single MRI slice taken at the L2-L3 level using manual contours, as previously validated against cadaveric samples (7). Areas were converted to mass (kg) using previously determined regression equations (8). VAT was then defined as the combination of both retroperitoneal and intraperitoneal fat masses to express the total intra-abdominal fat mass (4,9). Subjects also underwent ^{1}H-magnetic resonance spectroscopy for hepatic triglyceride quantification, as previously described (10).

LOWER BODY FAT QUANTIFICATION. Participants were scanned by DEXA, which was performed with a

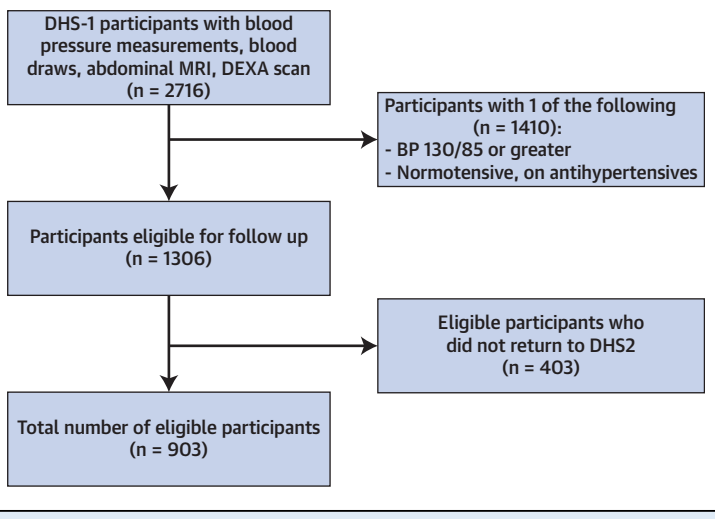


FIGURE 1 Flow Diagram of the DHS Study Cohort

BP = blood pressure; DEXA = dual-energy x-ray absorptiometry; DHS = Dallas Heart Study; MRI = magnetic resonance imaging.

Delphi W scanner (Hologic, Bedford, Massachusetts) with a fan beam to determine fat and lean mass (11). Lower body fat (LBF) was quantified from the total fat mass from the lower extremities, and it was reported in kilograms.

BIOMARKER ANALYSIS. Venous blood was collected in tubes containing EDTA and was maintained at 4°C for <4 h. Plasma was then removed and frozen at −80°C until assays were performed. Samples were analyzed for high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, cystatin-C, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), adiponectin, leptin, fasting glucose, and insulin levels (Online Appendix).

STATISTICAL ANALYSIS. Baseline demographic, clinical, laboratory, and imaging variables are expressed as median (25th, 75th percentile) or proportions, as appropriate. Differences in variables between normotensive participants and those with incident hypertension were compared using chi-square tests or the Wilcoxon rank sum test. Multivariable relative risk regression models with a log link and binomial error distribution were created to analyze associations between individual measures of adiposity and incident hypertension while adjusting for age, sex, race/ethnicity, history of smoking, diabetes mellitus, and baseline SBP. Correlation coefficients and variance inflation factors for adiposity measures are shown in the Online Appendix. Interactions were also tested in the fully adjusted model to assess for differential relationships between body mass index (BMI)/VAT on incident hypertension by sex, age, and race (black vs. non-black). Two-sided p values <0.05 were considered significant. All analyses were performed using SAS version 9.2 (SAS Corporation, Cary, North Carolina).

RESULTS

The study cohort consisted of 903 initially normotensive (SBP <130 mm Hg and DBP <85 mm Hg) participants. Their clinical characteristics are shown in Table 1.

INCIDENT HYPERTENSION. After a median of 7 years of follow-up, 230 participants (25%) developed hypertension. As shown in Table 1, those who developed hypertension were older, more commonly black, had a higher prevalence of diabetes, and had a higher baseline BP at the baseline examination ($p < 0.01$ for each). They also had higher measures of adiposity, including higher BMI, VAT (including retroperitoneal and intraperitoneal fat), SAT, and LBF (Table 1). Although the baseline BMI was higher among participants who developed hypertension than those who did not (29.9 kg/m^2 vs. 26.8 kg/m^2, $p < 0.0001$), the median interval weight increase between groups was essentially identical (3.5 kg vs. 3.6 kg, $p = 0.70$).

In multivariable risk regression models, increasing BMI was significantly associated with the development of incident hypertension (Table 2). However, when both VAT and SAT were added to the model, increasing VAT was the only fat parameter independently associated with incident hypertension (relative risk: 1.22 [95% confidence interval 1.07 to 1.39] per 1-SD increase in VAT; $p = 0.004$), whereas BMI and SAT were no longer significant. LBF was not associated with incident hypertension nor attenuated the association of VAT with incident hypertension. There was no difference noted in the relationship

TABLE 1 Demographic, Clinical, Imaging, and Biochemical Characteristics of the Study Population at Baseline Examination

	Entire Cohort (N = 903)	No Hypertension (n = 673)	Hypertension (n = 230)	p Value
Age, yrs	40 (34, 47)	39 (33, 46)	43 (37, 49)	<0.0001
Men	388 (43)	299 (44)	89 (39)	0.13
Black	349 (39)	221 (33)	128 (56)	<0.0001
White	364 (40)	298 (44)	66 (29)	<0.0001
Hispanic	172 (19)	137 (20)	35 (15)	0.09
Smoking	208 (23)	141 (21)	67 (29)	0.01
Prevalent DM	32 (4)	15 (2)	17 (7)	0.0003
Systolic BP, mm Hg	117 (109, 125)	114 (107, 122)	124 (117, 130)	<0.0001
Diastolic BP, mm Hg	74 (69, 79)	72 (67, 77)	79 (75, 83)	<0.0001
Cholesterol, mg/dl	175 (153, 202)	174 (152, 201)	180 (157, 204)	0.13
HDL, mg/dl	48 (40, 59)	48 (41, 59)	48 (40, 59)	0.66
Triglyceride, mg/dl	86 (62, 124)	84 (61, 121)	96 (64, 140)	0.02
LDL, mg/dl	104 (83, 125)	103 (82, 125)	109 (88, 125)	0.35
GFR, ml/min	98 (86,112)	97 (86,109)	100 (88,116)	0.02
HOMA-IR	2.2 (1.3, 3.9)	2.0 (1.2, 3.5)	3.3 (1.6, 5.2)	<0.0001
BMI, kg/m^2	27.5 (23.8, 32.0)	26.9 (23.3, 30.7)	29.9 (26.1, 36.5)	<0.0001
VAT, kg	1.8 (1.2, 2.5)	1.7 (1.2, 2.4)	2.0 (1.5, 2.8)	<0.0001
RP fat, kg	0.7 (0.5, 1.0)	0.6 (0.5, 0.9)	0.7 (0.6, 1.0)	<0.0001
IP fat, kg	1.1 (0.7, 0.9)	1.0 (0.7, 1.5)	1.3 (0.9, 1.7)	<0.0001
SAT, kg	3.7 (2.4, 5.5)	3.4 (2.4, 5.1)	4.8 (3.1, 7.1)	<0.0001
LBF, kg	8.3 (5.9, 11.5)	7.9 (5.8, 10.8)	9.8 (6.9, 13.1)	<0.0001
Liver fat, %	3.0 (1.9, 5.2)	2.8 (1.8, 4.7)	3.8 (2.6, 6.6)	<0.0001
Cystatin C	0.79 (0.72, 0.88)	0.79 (0.71, 0.87)	0.81 (0.72, 0.91)	0.04
hs-CRP, mg/dl	1.9 (0.8, 4.7)	1.7 (0.7, 4.2)	2.6 (1.1, 7)	0.0001
Leptin, ng/l	9.9 (4.5, 22.8)	9.0 (3.9, 19.4)	16.7 (6.1, 30)	<0.0001
Adiponectin, µg/ml	7.4 (4.8, 10.4)	7.8 (5.1, 10.7)	6.7 (4.4, 8.9)	0.0002
IL-6, pg/ml	16.5 (0, 34.5)	16.9 (0, 36.0)	15.0 (0, 29.4)	0.11
NT-proBNP, pg/ml	26.4 (12.7, 49)	26.8 (12.6, 49)	26.0 (13.1, 50)	0.87

Values are median (25th, 75th percentiles) or n (%).

BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; IP = intraperitoneal; LBF = lower body fat; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RP = retroperitoneal; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

TABLE 2 Results of the Multivariate Risk Regression of Measures of Adiposity on Incident Hypertension

	RR (95% CI)	p Value
Model 1*		
BMI	1.24 (1.12–1.36)	<0.0001
Model 2*		
BMI	1.14 (0.90–1.43)	0.27
VAT	1.22 (1.07–1.39)	0.003
SAT	0.97 (0.78–1.20)	0.78
Model 3*		
BMI	1.16 (0.89–1.52)	0.27
VAT	1.22 (1.06–1.39)	0.004
SAT	0.95 (0.75–1.20)	0.66
LBF	1.01 (0.83–1.23)	0.91

Relative risk of developing hypertension per 1-SD increase in adiposity measure. *Models adjusted for age, baseline systolic BP, sex, race/ethnicity, history of smoking, and diabetes mellitus.

CI = confidence interval; RR = relative risk; other abbreviations as in Table 1.

between VAT and hypertension based on gender, age, or race (interaction p value >0.1 for each).

The association between VAT and incident hypertension remained significant after further adjusting for levels of inflammatory markers (hs-CRP, IL-6), adipokines (adiponectin, leptin), insulin-resistance (homeostatic model assessment of insulin resistance), renal function (cystatin-C), or NT-proBNP (Online Figure 1).

SUBDIVISION OF INTRA-ABDOMINAL FAT. The results of the multivariate model were qualitatively similar when either liver fat or retroperitoneal fat, but not intraperitoneal fat, were tested in place of VAT as a marker of ectopic fat (Table 3). In quartile analysis, there was a graded dose-response observed between retroperitoneal fat and the risk of developing hypertension (Figure 2). This association was seen even among those with the lowest quartile of baseline SAT (Online Figure 2). After simultaneously adjusting for each intra-abdominal fat depot, only retroperitoneal fat was significantly associated with incident hypertension in the fully adjusted multivariable model (Table 3).

TABLE 3 Results of the Multivariate Risk Regression of Specific Measures of Intra-Abdominal Adiposity on Incident Hypertension

	RR (95% CI)	p Value
Model 1*		
Liver fat	1.13 (1.02–1.25)	0.02
Model 2*		
IP fat	1.09 (0.84–1.40)	0.51
Model 3*		
RP fat	1.09 (1.05–1.13)	<0.0001
Model 4*		
IP fat (kg)	1.10 (0.98–1.23)	0.12
RP fat (kg)	1.12 (1.02–1.23)	0.02
Liver fat (%)	1.10 (0.99–1.22)	0.08

Relative risk of developing hypertension per 1-S.D. increase in adiposity measure. *Models adjusted for age, baseline systolic BP, sex, race/ethnicity, history of smoking, diabetes mellitus, BMI, SAT, and LBF.

Abbreviations as in Tables 1 and 2.

DISCUSSION

In this probability-based cohort study, among individuals who were initially normotensive, a greater amount of visceral adiposity was associated with an increased risk for the development of hypertension after a median of 7 years of follow-up (Central Illustration). Addition of VAT to the multivariable model attenuated the association of BMI with incident hypertension, suggesting that visceral adipose, rather than total adiposity, is more important in this relationship.

A prior study reported an association between VAT and incident hypertension in a cohort of Japanese Americans. Similar to our study, intra-abdominal fat by computed tomography was independently associated with incident hypertension (9). Our study extends these observations and highlights the possible specific pathological role of retroperitoneal fat.

There is growing evidence that VAT represents a pathological adipose tissue depot, which accumulates when subcutaneous depots are overwhelmed or otherwise unavailable for storage. Relative to SAT, visceral fat is more sensitive to lipolysis and secretes

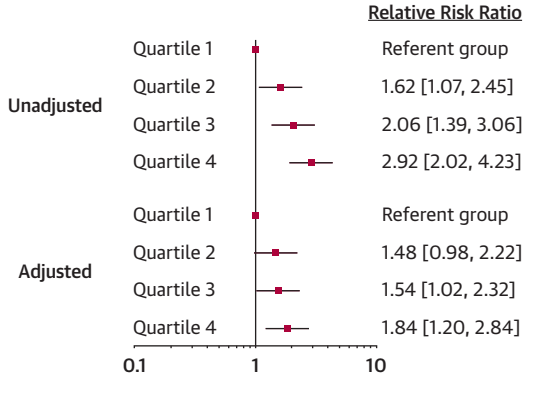


FIGURE 2 Incidence of Hypertension Increases With RP Fat

Forest plot of the graded risk for incident hypertension across sex- and race-specific quartiles of retroperitoneal fat (RP), before and after adjustment for clinical and demographic variables.

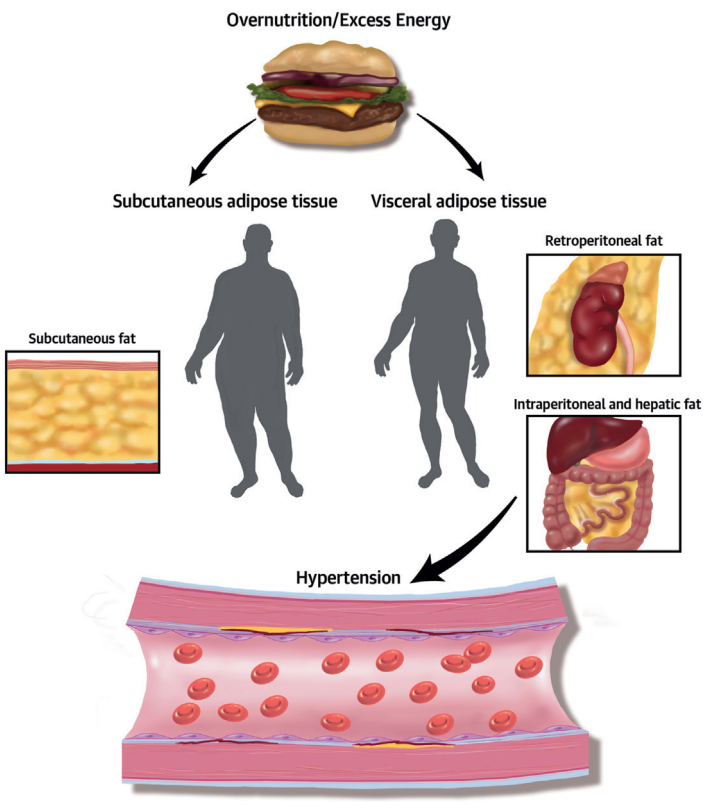
higher amounts of inflammatory cytokines (12). VAT is associated with insulin resistance (3,13) and predicts incident diabetes among obese adults (4). VAT is associated with a higher atherosclerotic risk profile (14) and also recently has been prospectively linked to adverse cardiovascular events (15). These results suggest that VAT may be the important link between BMI and cardiovascular disease, and that VAT may be acting in part by promoting the development of hypertension and insulin resistance (**Central Illustration**).

The specific mechanisms behind the association of VAT and hypertension are currently unknown, and it remains a matter of considerable interest as to the identity of the responsible drivers of hypertension in this context. We did not note any significant attenuation of the relationship of VAT with hypertension after adjusting for several biological pathways, suggesting that this relationship might be independent of these pathways.

Although our results from the specific intra-abdominal fat depots should be regarded as hypothesis-generating, it is nonetheless interesting that the most significant associations between visceral adiposity and hypertension were observed with retroperitoneal fat. To our knowledge, this observation has not been reported previously, but if validated, suggests that there may be local effects from fat surrounding the kidneys that influence the development of hypertension. Though this is a small fat mass in relative terms, similar paracrine effects have recently been suggested between epicardial fat and the occurrence of coronary artery disease (16,17).

In this study, we did not observe any protective effect of LBF on the future development of hypertension. This finding may suggest that LBF could have a less important role in preventing hypertension than it does in protecting against lipolysis and insulin resistance (11).

STUDY LIMITATIONS. Although prospective, this is still an observational study. Thus, we are unable to draw a causal relationship between VAT and hypertension. Approximately one-third of the eligible participants from DHS-1 did not return for the second phase of follow-up. Although we have previously not observed any significant clinical differences between those who did and did not return for DHS-2 (4), this remains a source of potential bias. Additionally, we did not have available measures of site-specific adiposity at follow-up, so we were unable to account for changes in adipose mass/distribution between examinations.



CENTRAL ILLUSTRATION Ectopic Fat Deposition Links Overnutrition With Hypertension Development

Excess energy can either be stored in subcutaneous fat depots or in ectopic locations, such as intrahepatic, periomental, or retroperitoneal. Such visceral fat depots, particularly retroperitoneal, are specifically associated with incident hypertension.

CONCLUSIONS

These data from a multiethnic, probability-based cohort demonstrate that the association between obesity and the development of hypertension is specifically accounted for by visceral adiposity. The strongest associations were observed with retroperitoneal fat. These data are consistent with a growing body of literature implicating VAT, rather than generalized adiposity, in the aggregation of cardiovascular risk factors that eventually drive adverse clinical events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Visceral adiposity is closely associated with the development of hypertension.

TRANSLATIONAL OUTLOOK: Identification of the paracrine mediators linking retroperitoneal fat to the development of hypertension may open new avenues for the prevention and management of hypertension.

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KEY WORDS body fat distribution, hypertension, obesity, visceral fat

APPENDIX For supplemental methods and figures, please see the online version of this article.