Obesity, Adipokines, and Abdominal Aortic Aneurysm
Health in Men Study

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Background—Obesity is associated with occlusive artery disease but is not considered a risk factor for abdominal aortic aneurysm (AAA). We investigated the association between anthropometric measures of obesity, serum adipokines, and AAA.

Methods and Results—As part of a population study, we screened 12 203 men 65 to 83 years of age for AAA using ultrasound; 875 had an AAA (≥30 mm). Cardiovascular risk factors and waist and hip circumference were recorded. Serum adipokines were measured in 952 men, 318 of whom had an AAA. Waist circumference (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.06 to 1.22) and waist-to-hip ratio (OR, 1.22; 95% CI, 1.09 to 1.37) were independently associated with AAA after adjustment for other known risk factors. The association was stronger for AAA ≥40 mm (waist-to-hip ratio: OR, 1.53; 95% CI, 1.26 to 1.85). Serum resistin concentration was strongly independently associated with AAA (OR, 1.53; 95% CI, 1.32 to 1.76) and aortic diameter (β=0.19, P<0.0001). Serum adiponectin was associated with AAA ≥30 mm (OR, 1.26; 95% CI, 1.07 to 1.50) but not AAA ≥40 mm (OR, 1.03; 95% CI, 0.77 to 1.39). Serum leptin was not associated with AAA.

Conclusions—Measures of obesity are independently associated with AAA. Serum resistin concentrations were more strongly associated with aortic diameter than adipokines that are more intimately associated with adiposity. Further studies are required to investigate the mechanisms linking resistin and AAA. **(*Circulation*. 2007;116:2275-2279.)**

Key Words: aortic aneurysm, abdominal ■ obesity ■ resistin

Obesity, particularly when measured by central adipose deposition, has been independently related to the severity and prognosis of occlusive coronary and peripheral arterial disease.[1–5] Abdominal aortic aneurysm (AAA) is associated with some but not all of the risk factors for atherosclerosis; thus, its origin is believed to be different from that of occlusive arterial disease.[6,7] For example, a number of population-based studies have demonstrated that diabetes mellitus is negatively associated with AAA.[8,9] Insulin resistance is believed to be one of the main mechanisms by which central obesity predisposes to atherosclerosis. This may explain why the association of anthropometric measures and AAA has been little investigated.[8]

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Besides insulin resistance, another mechanism believed to be important in the association between obesity and occlusive arterial disease is the ability of adipose tissue to release cytokines.[10] These adipokines, including adiponectin, leptin, and resistin, have been shown to modulate inflammation, an integral mechanism in the pathogenesis of AAA.[11–13] The aim of this study was to examine the association between obesity, adipokines, and AAA.

Methods

Study Design

We tested the association of the following markers of obesity with AAA: (1) central obesity measured by waist circumference and waist-to-hip ratio and (2) serum concentrations of adiponectin, leptin, and resistin. The Health in Men study is based on the follow-up of a cohort of men who were originally participants of a population-based randomized controlled trial of screening for AAA. Details of the design of these studies have been reported elsewhere.[14–17] For aim 1, anthropometric data were available for 12 203 men (875 had an AAA ≥30 mm, 268 had an AAA ≥40 mm, and 87 had an AAA ≥50 mm). For aim 2, archived serum was available from 318 subjects with AAA. We randomly selected 634 control subjects from men with a normal aortic diameter (19 to 22 mm).[15]

Anthropometric Measurements, Clinical Data, and Aortic Assessment

All men completed a cardiovascular risk factor questionnaire used to define dyslipidemia, coronary heart disease (CHD), hypertension,

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smoking, and diabetes mellitus.[15] Dyslipidemia and hypertension were defined by a history of diagnosis or treatment of hyperlipidemia or hypertension. CHD was defined by a history of myocardial infarction, angina, or treatment for coronary artery disease. Smoking was defined by history as past smoker, current smoker, or never smoker. Subjects' weight, height, waist, and hip circumference were measured in accordance with guidelines of the International Society for the Advancement of Kinanthropometry.[18] The American Heart Association/National Heart, Lung, and Blood Institute classifications of obesity (a waist circumference of ≥102 cm) and metabolic syndrome were used.[19] Body mass index was calculated as weight in kilograms divided by height in meters squared. The maximum diameter of the infrarenal aorta was measured with a Toshiba Capasee ultrasound machine with a 3.75-MHz probe (Toshiba Australia, North Ryde, New South Wales).[14–17] Assessment of intraobserver and interobserver reproducibility in aortic diameter measurement was carried out every 4 months on 10 randomly selected subjects, including obese subjects, as previously reported.[14] No significant differences were found between observers. The 95% confidence intervals (CIs) for anteroposterior and transverse aortic diameters were <3 mm and not influenced by the presence of obesity.[14]

Serum Assays

Blood was collected from subjects after an overnight fast as previously described.[17,20] Serum was stored at −80°C until later batch assessment of adipokine concentrations using ELISA according to the manufacturer's instructions and expressed as microgram per milliliter (adiponectin) or nanogram per milliliter (leptin and resistin) (R&D Systems, Minneapolis, Minn). These assays were selected because a previous study demonstrated excellent recovery and intra-assay and interassay reproducibility in our laboratory.[5] Fasting serum glucose was measured by an automated assay as previously described.[17] C-reactive protein (CRP) was measured by a high-sensitivity assay with a particle-enhanced immunonephelometry system on the BNII analyzer. The interassay coefficient of variation was 4% to 7%.[14]

Statistical Analyses

The associations between anthropometric measures and serum adipokines with aortic diameter, obesity, and AAA were examined with Spearman's rank-order correlation and the Mann-Whitney *U* test. Mean concentrations of serum adipokines, glucose, and CRP adjusted for age and body mass index were estimated with ANCOVA. The associations between anthropometric measures and serum adipokines and AAA or aortic diameter, with adjustment for other known correlates of AAA, were assessed using multiple logistic or linear regression analysis. Serum adipokines were not normally distributed and were logarithm transformed for incorporation into linear regression analysis. The following risk factors were adjusted for in regression analyses: age, dyslipidemia, hypertension, smoking, CHD, and diabetes mellitus. In the adjustment of analyses that assessed the association of serum adipokines with AAA, waist-to-hip ratio and serum glucose also were included. Odds ratios (ORs) reflected the presence or absence of categorical variables or change in units for continuous variables (eg, waist circumference and height were expressed in decameters; age, per 4 years; and waist-to-hip ratio, per 0.1 unit on the basis of approximate SDs). The ability of serum adipokines to distinguish the patients with AAA was investigated with receiver-operating characteristic curves and area under the curve.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Relationship Between Anthropometric Measures and AAA

Obesity was present in 4714 men (39%) at baseline (Table 1), of whom 386 had an AAA (OR, 1.28; 95% CI, 1.11 to 1.47).

Table 1. Characteristics of Men in Relation to Aortic Diameter

	Aortic Diameter, mm		
Variable	<30	≥30*	≥40
n	11 328	875	268
Age, y	72.0±4.4	73.5±4.4	73.4±4.4
Hypertension, n (%)	4823 (43)	488 (56)	157 (59)
Diabetes mellitus, n (%)	1354 (12)	99 (11)	33 (12)
Dyslipidemia, n (%)	3875 (34)	377 (43)	102 (38)
Smoking, n (%)	7880 (70)	758 (87)	238 (89)
CHD, n (%)	2796 (25)	364 (42)	117 (44)
Aortic diameter, mm	21.7±2.7	38.2±4.4	49.1±9.0
Waist circumference, cm	98.9±10.4	100.7±10.2†	102.4±10.7†
Hip circumference, cm	103.2±7.1	103.8±7.8	104.4±7.8
Waist-to-hip ratio	0.95±0.06	0.97±0.06†	0.98±0.06†
BMI, kg/m^2	26.8±3.7	27.1±3.8‡	27.5±3.9‡
Height, cm	171.0±6.8	171.9±6.5	172.0±6.8
Obesity, n (%)§	4328 (38)	386 (44)†	143 (53)†

Continuous variables are given as mean±SD; nominal variables, as numbers and percentages. BMI indicates body mass index.

*Includes all subjects with aortic diameter ≥30 mm.

†$P<0.0001$, ‡$P<0.05$ vs group with aortic diameter <30 mm.

§Defined by AHA criteria as waist circumference ≥102 cm.

Obesity also was associated with aortic diameter ≥40 mm; the OR was 1.84 (95% CI, 1.44 to 2.35). Waist circumference ($r=0.14$, $P<0.0001$) and waist-to-hip ratio ($r=0.10$, $P<0.0001$) both were correlated with aortic diameter (by comparison, $r=0.11$, $P<0.0001$ for age) and were significantly greater in patients with AAA (Table 1). Waist circumference (OR, 1.14; 95% CI, 1.06 to 1.22; $\beta=0.10$, $P<0.0001$) and waist-to-hip ratio (OR, 1.22; 95% CI, 1.09 to 1.37; $\beta=0.07$, $P<0.0001$) were independently associated with AAA and aortic diameter after adjustment for other known risk factors (Table 2). The ORs for waist (OR, 1.09; 95% CI, 1.01 to 1.17) and waist-to-hip ratio (OR, 1.22; 95% CI, 1.09 to 1.37) were little altered by inclusion of height in the model and were greater in terms of association with AAAs measuring ≥40 mm (Table 2) or ≥50 mm (waist-to-hip ratio: OR, 1.62; 95% CI, 1.17 to 2.25; waist: OR, 1.46; 95% CI, 1.20 to 1.78).

Relationship Between Adipokines and AAA

Adipokines were measured in 318 men in whom AAAs were detected and serum was available. For comparison, serum was assessed in 634 randomly selected men in whom aortic diameter was normal (19 to 22 mm). The characteristics of these men were similar to those of the total cohort (online-only Data Supplement Table I). Obesity was present in 382 of these 952 men (40%). Serum resistin (24.5±12.7 compared with 22.1±10.6 ng/mL; $P=0.006$), leptin (20.1±16.6 compared with 9.8±6.7 ng/mL; $P<0.0001$), and glucose (5.9±1.4 compared with 5.6±1.4 mmol/L; $P<0.0001$) concentrations were higher in obese men. Serum concentrations of resistin were better correlated with CRP ($r=0.21$) than anthropometric measures such as waist circumference ($r=0.13$). Serum concentrations of leptin were associated with waist circumference ($r=0.60$) more than CRP ($r=0.23$).

Table 2. Independent Correlates of AAAs and Large AAAs in 12 203 Men

	AAA ≥30 mm		AAA ≥40 mm		AAA ≥30 mm		AAA ≥40 mm	
Characteristic	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age per 4 y*	1.33	1.25–1.42	1.26	1.13–1.40	1.34	1.25–1.42	1.27	1.14–1.42
Hypertension	1.41	1.22–1.63	1.54	1.19–2.00	1.40	1.21–1.62	1.52	1.17–1.97
Diabetes mellitus	0.75	0.60–0.94	0.79	0.55–1.16	0.75	0.60–0.94	0.79	0.54–1.16
Dyslipidemia	1.22	1.04–1.42	0.88	0.67–1.15	1.22	1.05–1.42	0.88	0.67–1.15
CHD	1.73	1.49–2.01	1.91	1.47–2.48	1.74	1.49–2.02	1.92	1.48–2.50
Current or past smoker	2.63	2.15–3.21	2.99	2.04–4.39	2.63	2.15–3.22	3.00	2.05–4.41
Waist-to-hip ratio per 0.1*	1.22	1.09–1.37	1.53	1.26–1.85	...	...	...	...
Waist circumference per 10 cm*	...	...	...	...	1.14	1.06–1.22	1.30	1.16–1.46

Left side of the model includes waist-to-hip ratio; the right side of the model includes waist circumference. For nominal variables, the comparisons are to subjects without the risk factor.

*Approximately 1 SD.

Serum adiponectin concentrations (9.3±4.2 compared with 10.8±4.9 μg/mL; $P<0.0001$) were lower in obese men. The serum concentrations of all 3 adipokines correlated with aortic diameter (resistin: $r=0.26$, $P<0.0001$; leptin: $r=0.11$, $P=0.001$; adiponectin: $r=0.11$, $P=0.001$). Unadjusted concentrations of all 3 serum adipokines were elevated in men with AAA (resistin: 27.6±12.1 and 20.7±10.5 ng/mL, $P<0.0001$; leptin: 16.5±16.7 and 12.6±9.9 ng/mL, $P<0.0001$; adiponectin: 10.8±4.7 and 9.9±4.7 μg/mL, $P=0.001$, in men with and without AAA, respectively). Mean concentrations of adipokines, glucose, and CRP adjusted for age and body mass index are shown for men with and without AAA in Table 3. Adjusted concentrations of all 3 serum adipokines were elevated in men with AAA (Table 3). Only resistin was present at greater concentrations in the serum of men with larger AAAs (Table 3). Both resistin and adiponectin but not leptin were independently associated with AAA allowing for other risk factors, including waist-to-hip ratio (Table 4). Only resistin was associated with large AAAs after adjustment for other risk factors (Table 4). Serum resistin concentration also was independently associated with aortic diameter with adjustment for other risk factors (resistin: $\beta=0.19$, $P<0.0001$; leptin: $\beta=0.03$, $P=0.33$; adiponectin: $\beta=0.06$, $P=0.07$; waist-to-hip ratio: $\beta=0.14$, $P<0.0001$). Receiver-operating characteristic curves demonstrated that serum resistin concentration predicted the presence of AAA better than other adipokines, CRP, and anthropometric measures. The areas under the curve were 0.69 (95% CI, 0.66 to 0.73), 0.59 (95% CI, 0.55 to 0.63), 0.56 (95% CI, 0.53 to 0.60), 0.59 (95% CI, 0.55 to 0.63), and 0.58 (95% CI, 0.54 to 0.62) for resistin, leptin, adiponectin, CRP, and waist-to-hip ratio, respectively. A serum resistin concentration of 21 ng/mL had a sensitivity and specificity of 69% and 60%, respectively, in predicting the presence of AAA. A similar accuracy in our total cohort would have been associated with positive and negative predictive values of only 12% and 96%, respectively.

Discussion

This study of >12 000 men demonstrates an independent association between central obesity and AAA. In a smaller population of these men, we also have identified an association between serum concentrations of the adipokine resistin and AAA.

Obesity is not generally considered a risk factor for AAA. The association between self-reported anthropometric measures and aortic diameter has been assessed previously in a large screening study.[8,21] The authors concentrated on the relationship between body size and normal aortic diameter. In the present study in which accurate anthropometric measures were obtained, a number of findings support an association between obesity and AAA. Waist circumference and waist-to-hip ratio were independently associated with both AAA and aortic diameter in 12 203 men. The association was not influenced by other measures of body size such as height and

Table 3. Serum Adipokine Concentrations in Relation to Aortic Diameter

	≥30 mm		<30 mm		≥40 mm		<40 mm	
Aortic Diameter	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
n	318	...	634	...	67	...	885	...
Aortic diameter, mm	35.8	35.3–36.3	21.1	20.8–21.4	47.1	45.7–48.5	24.4	24.0–24.8
Adiponectin, μg/mL	10.89	10.39–11.39	9.82	9.46–10.18	10.22	9.12–11.32	10.18	9.87–10.48
Leptin, ng/mL	15.38	14.18–16.57	13.16	12.31–14.01	15.38	12.78–18.00	13.80	13.08–14.52
Resistin, ng/mL	27.43	26.22–28.65	20.79	19.92–21.67	28.55	25.82–31.28	22.61	21.86–23.37
Glucose, mmol/L	5.64	5.49–5.80	5.72	5.61–5.83	5.91	5.58–6.25	5.67	5.58–5.77
CRP, mg/L	4.77	3.78–5.76	4.16	3.46–4.86	4.60	2.44–6.76	4.34	3.75–4.93

Serum adipokines were measured in 634 men with normal aortic diameter (19 to 22 mm) and 318 men with AAAs (≥30 mm), of which 67 had aortic diameters ≥40 mm (see Methods for selection). Shown are mean and 95% CIs adjusted for age and body mass index estimated with ANCOVA.

Table 4. Serum Concentration of Resistin Is Independently Associated With AAA

	AAA ≥30 mm		AAA ≥40 mm	
Characteristic	OR	95% CI	OR	95% CI
Age per 4 y*	1.17	1.00–1.38	1.23	0.94–1.60
Hypertension	1.03	0.74–1.42	1.19	0.68–2.06
Diabetes mellitus	1.41	0.74–2.67	1.42	0.55–3.65
Dyslipidemia	1.49	1.07–2.06	0.60	0.33–1.04
CHD	2.46	1.72–3.51	3.03	1.72–5.35
Current or past smoker	2.88	1.96–4.24	2.26	1.08–4.73
Waist-to-hip ratio per 0.1*	1.50	1.13–1.99	2.10	1.33–3.31
Resistin per 10 ng/mL*	1.53	1.32–1.76	1.32	1.10–1.58
Leptin per 10 ng/mL*	1.13	0.99–1.28	1.00	0.82–1.21
Adiponectin per 5 μg/mL*	1.26	1.07–1.50	1.03	0.77–1.39
Glucose per 1 mmol/L*	0.94	0.83–1.06	1.07	0.91–1.26

This analysis includes the 952 men in whom serum adipokines were measured (see online-only Data Supplement Table I). For nominal variables, the comparisons are to subjects without the risk factor.

*Approximately 1 SD.

was stronger with larger AAAs. Among the men in our study, the degree of association was significantly less than that seen for CHD or smoking but similar to that of age (Table 2).

A recent study examined the association of obesity with AAA in a population of 104 813 male and female multiethnic subjects who were followed up over a 13-year period.[22] The authors reported no association between sagittal abdominal diameter and incidence of AAA.[22] In the study of Iribarren et al,[22] however, AAA was diagnosed only by clinical events on the basis of hospitalization or death certificates.[22] In the absence of imaging in their population, it is impossible to know the exact incidence of AAA in their affected and control populations. The authors also did not measure waist-to-hip ratios. In contrast, in the present study, we carried out accurate ultrasound measurement of maximum infrarenal aortic diameter and assessed a number of different measures of obesity.

The positive association of obesity with AAA is particularly interesting because some studies have demonstrated a negative association between diabetes mellitus and AAA.[8,9] In fact, we have previously found a negative correlation between aortic diameter and serum glucose in men who do not have diabetes mellitus.[17] Thus, it is not likely that insulin resistance, commonly demonstrated in obese subjects, is the reason for the association between obesity and AAA. We therefore centered further investigation between obesity and AAA on a number of adipokines. Serum resistin concentration was independently associated with the presence of both small and large AAAs (Table 4). Receiver-operating characteristic curve analysis suggested that although resistin concentration was more associated with the presence of AAA than other adipokines and CRP, serum resistin was unlikely to be useful for diagnostic purposes because of its low positive predictive value. A number of recent studies have associated circulating resistin concentrations with the presence of coronary artery disease.[23,24] In some investigations, however, resistin levels were more reflective of systemic inflammation than the degree of intimal expansion.[25,26] Resistin was initially demonstrated to be released in large amounts from adipocytes in mice.[27] Studies in humans suggest that resistin is expressed at low levels in adipose tissue but at higher concentrations in monocyte-macrophages.[12] Although AAA is known to be more common in patients with atherosclerosis such as those with CHD, a number of factors suggest that its pathogenesis is different from that of occlusive artery disease. For example, biopsies of human AAA demonstrate marked transmural inflammation rather than the intimal expansion typical of atherosclerosis.[6,7] Our finding of an independent association of serum resistin concentrations with AAA after controlling for other factors such as CHD suggests that this cytokine might play a role in the pathogenesis of AAA. The presence of resistin within macrophages identified within AAA has been confirmed recently both in our laboratory (data not shown) and by other investigators.[28] Given the demonstrated ability of resistin to modulate vascular smooth muscle cell and endothelial function in vitro, this cytokine may be a target for therapeutic intervention.[28,29] Studies to investigate this possibility will have to take into account the different role of resistin in humans and animal models.[12,26] Given the association between serum resistin and AAA that we have identified and the fact that serum resistin concentrations are genetically determined, further investigation of allelic variation centered on this gene may uncover determinants of AAA.[30]

The interpretation of our findings needs to recognize a number of study limitations. First, because we carried out blood assays on only a small percentage of our subjects, cardiovascular risk factors were defined mainly by history. Hence, the adjustment for other cardiovascular risk factors is less complete than if we had measured lipids and glucose on all 12 203 men. Second, serum adipokine analyses were carried out on only a proportion of our patients. We analyzed serum from 952 men representing 8% of the total population. This subgroup, however, was representative of the total population (online-only Data Supplement Table I). Confirmation of our serum findings in other populations is required.

In conclusion, this study demonstrates an independent association of obesity and serum concentrations of resistin with AAA. Additional animal and human cohort studies will be important in further examinations of this relationship.

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CLINICAL PERSPECTIVE

Obesity has been associated with occlusive arterial disease but not previously with abdominal aortic aneurysm. In a cross-sectional study of 12 203 men 65 to 83 years of age, we observed that higher waist circumference and greater waist-to-hip ratio were independently and positively associated with prevalence of abdominal aortic aneurysms. In a subset of 952 men, we also investigated the association of serum resistin, leptin, and adiponectin with prevalence of abdominal aortic aneurysm. Serum resistin was strongly and positively associated with both small and large abdominal aortic aneurysms. Our findings suggest the potential importance of excess adiposity in the development of abdominal aneurysms.

Obesity, Adipokines, and Abdominal Aortic Aneurysm: Health in Men Study

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