Associations between Aortic Calcification and Components of Body Composition in Elderly Men

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Abstract

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Objective: To investigate associations among body composition, cardiovascular risk factors, and atherosclerosis in middle-aged and elderly men for the identification of potential pathogenic links.

Research Methods and Procedures: The study included 168 white men 44 to 86 years old. Severity of aortic calcification (AC) was graded on lateral radiographs, and body fat and lean mass were measured by DXA. Information on demographic and lifestyle characteristics also was gathered.

Results: A strong and independent inverse association was found between AC and peripheral lean mass (PLM), even after adjusting for age and BMI ($p < 0.05$). Independently of the influence of PLM, AC was directly correlated with truncal fat mass ($p < 0.05$). Furthermore, AC was inversely associated with tertiles of the free androgen index ($p < 0.05$). In a multiple regression model, age and serum cholesterol ($p < 0.01$) contributed directly, and truncal fat mass tended also to contribute directly ($p = 0.09$), whereas PLM contributed borderline inversely ($p = 0.06$) to the variation of AC ($R = 0.635$, $p < 0.0001$).

Discussion: Severity of AC is strongly dependent on age and further modulated by an array of traditional cardiovascular risk factors. Sarcopenia and truncal fat mass are reciprocal correlates of atherosclerosis of borderline statistical significance in multivariate models. To clarify whether sarcopenia is an atherogenic risk factor or rather a parallel consequence of low-grade inflammation also promoting atherogenic trends, further longitudinal studies in larger sample sizes of men and women are needed.

Key words: men, atherosclerosis, lean body mass, truncal fat mass, adipocytokines

Introduction

Coronary heart disease (CHD)[1] continues to be responsible for more deaths and disability than any other disease in industrialized countries (1). Male gender is an independent risk factor for CHD (2), as illustrated by the fact that CHD is more prevalent in men than in age-matched premenopausal women. Obesity has been implicated in the pathogenesis of CHD (2); however, the significance of body composition is not well understood. Body composition, rather than obesity per se, has been demonstrated to influence serum lipids and lipoprotein metabolism in healthy men (3), but whether this translates into a modulating effect of atherogenesis has not been systematically addressed.

Sarcopenia (i.e., age-related loss in skeletal mass) is implicated in an array of associated pathological conditions, including CHD (4,5). The important age-related decline in male gonadal function and several other endocrine organs, such as decreases in growth hormone and adrenal androgen secretion, are likely contributors to the loss of lean body

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[1] Nonstandard abbreviations: CHD, coronary heart disease; T, testosterone; CVD, cardiovascular disease; BP, blood pressure; HR, heart rate; TC, total cholesterol; WBC, white blood count; CV, coefficient(s) of variation; SHBG, sex hormone binding globulin; E_2, estradiol; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; PLM, peripheral lean mass; SEE, standard error of estimate; AC, aortic calcification; SBP, systolic BP; FAI, free androgen index.

mass. In addition to a likely contribution to the development of sarcopenia, testosterone (T) deficiency in the aging male has been suggested to contribute to the development of central obesity, insulin resistance, and alterations in lipid profile, and, ultimately, atherosclerosis (6–8). In a recent study, Villareal et al. (9) classified a group of elderly people into: "non-obese, non-frail" (control) subjects, "non-obese but frail" subjects, and "obese and frail" subjects (the majority of obese subjects being frail). The authors found that "obese and frail" subjects were significantly more disabled than "non-obese but frail" and control subjects. Although several likely mechanisms have been proposed, the etiopathogenic links among obesity, sarcopenia, and frailty remain poorly understood (10), and their relation to atherosclerosis and CHD is still obscure. In the present study, we investigated components of soft body composition (lean and fat mass) as evaluated by DXA and an array of cardiovascular risk factors in relation to direct measures of atherosclerosis in 168 middle-aged and elderly community-dwelling men.

Research Methods and Procedures

Population

The study population consisted of 168 community-dwelling white men 50 to 83 years old from the city of Aalborg, Denmark. The National Registration Office contacted citizens living in the city of Aalborg, Denmark, by mail, at the request of Center for Clinical and Basic Research, and the study population was recruited by questionnaire survey. Inclusion criteria were age $\geq$ 50 years and living in the city of Aalborg. All men signed an approved informed consent for participation. The study was carried out according to the principles outlined in the Declaration of Helsinki II and European Guidelines for Good Clinical Practice.

Cardiovascular Risk Factors

All participants underwent an interview for collection of information regarding prevalent diseases, including type 2 diabetes, treated cardiovascular disease (CVD) (angina pectoris, myocardial infarction, or peripheral vascular disease), and treated hypertension [i.e., anti-hypertensive therapy given for blood pressure (BP) >140/90 mm Hg, regardless of the actual pressure)], smoking habits (never, past, or current smokers), and other lifestyle factors including daily coffee and alcohol consumption (yes/no), and a complete physical examination including assessment of arterial BP and heart rate (HR) (in a sitting position after at least 20 minutes of rest) using a digital BP monitor according to a standard protocol. Height and body weight were measured to the nearest centimeter and 100 grams, respectively, in men wearing light indoor clothing and no shoes. BMI was then calculated as weight (in kilograms) divided by height (in meters) squared. Blood samples were collected after an overnight (>12 hours) fasting and tobacco abstinence, and serum total cholesterol (TC), blood glucose, and total white blood count (WBC) were determined using enzymatic assays performed by a Vitros 250 automatic analyzer (Johnson & Johnson, Taastrup, Denmark). Coefficients of variation (CV) for these analyses (TC and glucose) were both <5%, respectively.

Hormones and Serum Proteins

We determined 17β-estradiol (E_2; intra-assay and inter-assay CV were 7% and 6%, respectively) and T (intra-assay and inter-assay CV were 6% and 10%, respectively), both by automated immunofluorescent assays (Brahms AG, Hennigsdorf, Germany), and androstenedione (intra-assay and inter-assay CV were 6% and 8%, respectively) and sex hormone binding globulin (SHBG; intra-assay and inter-assay CV were 9% and 12%, respectively), both by enzyme-linked immunosorbent assays (ELISAs) (Brahms). For the E_2/T ratio, which is frequently regarded as an index of aromatase activity in the aging male, 75% to 90% of circulating estradiol comes from peripheral aromatization, primarily from adipose tissue, whereas the remaining 10% to 25% of estrogen is synthesized in the testes (11).

Adipocytokines and Other Markers of Inflammation

An array of adipocytokines and biochemical markers of inflammation was determined in this population. Adiponectin, a plasma protein originating from adipose tissue and known to exhibit potent anti-inflammatory and anti-atherosclerotic effects (12), was measured by ELISA (B-Bridge International, Inc., Mountain View, CA) (intra-assay and inter-assay CV were 4% and 7%, respectively). Furthermore, we determined C-reactive protein (CRP) by automated immunofluorescent assay (Brahms), tumor necrosis factor (TNF)-α by ELISA (Quantine High Sensitivity; R&D Systems Europe, Oxford, United Kingdom), and interleukin (IL)-6 by ELISA (Quantine High Sensitivity, R&D Systems Europe) as additional inflammatory markers. The intra-assay and inter-assay CV percentage for these inflammatory markers were 5% and 14%, respectively (CRP), <9% and <17%, respectively (TNF-α), and <8% and <10%, respectively (IL-6).

Body Composition and Estimates of Fat Mass and Lean Body Mass

Total body fat mass and lean body mass were determined by DXA using a QDR4500 scanner (Hologic Inc., Waltham, MA). Vertical boundaries were used to separate arms and oblique boundaries to separate the legs from the trunk. Lean tissue mass is estimated by addition of peripheral lean mass (PLM) (legs + arms combined) and truncal lean mass, the former as a marker of skeletal muscle mass. Analogously, total fat tissue mass is estimated by addition of the mea-

surement of fat originating from two compartments: peripheral fat mass (legs + arms combined) and truncal fat mass, the latter including both the visceral fat mass and subcutaneous abdominal fat mass of the trunk.

Direct estimation of the amount of visceral fat mass in an individual is technically challenging. The DXA methodology for this purpose is limited because it cannot differentiate between peripheral fat and truncal fat tissue, which are metabolically very different and may possess opposite properties on risk of type II diabetes (12). However, truncal fat as measured by DXA correlates directly with waist circumference and with visceral fat tissue as assessed by computerized tomography (13).

The validity of lean mass determination by DXA has been established from clinical studies (14–16) but may be limited in subjects with a body weight >100 kg. Accuracy of the DXA with respect to lean mass and fat mass has been shown. Regression lines demonstrated that total fat mass and lean tissue mass did not differ from the identity line when DXA in vivo results were compared with chemical composition of fat and lean mass ex vivo, respectively, from cadaver analysis [standard error of estimate (SEE) = 1.9 (fat mass) and 2.7 (lean mass) kg]. Part of the accuracy error was found to be related to incomplete homogenization of the cadavers (17).

Assessment of Aortic Calcification (AC)

AC was visualized and graded on lateral radiographs of the lumbar spine as originally described by the Framingham Study group (18). Briefly, the evaluation focused on calcified plaques present in the anterior and posterior wall of the lumbar aorta adjacent to the lumbar vertebrae L1 to L4. The plaques were scored separately for the anterior and posterior wall for each of the four segments and summed, thereby obtaining the anteroposterior severity score. Because one wall of each segment may receive a score on a 0 to 3 scale, the maximum score assigned to the aorta for a subject is $4 \times 2 \times 3 = 24$. The same investigator, who was blinded for all other results of the subject, carried out the scoring. Intrarater correlations were in the range of $r = 0.92$ to 0.98, similar to published results (19).

Statistical Methods

Characteristics are expressed as mean ± standard deviation unless otherwise indicated. Because values of AC (being a categorical variable) were not normally distributed, Spearman's ρ was used to assess bivariate correlations with the various risk factors or study parameters were analyzed with respect to tertiles of AC. Adjusted correlations between the severity of AC and risk factors were evaluated by partial correlation analysis. To isolate independent contributors to the variation in AC, we established multiple linear regression models including logarithmically transformed AC as a dependent variable and the various risk factors as independent variables, allowing step-wise backward model reductions ($p < 0.1$ as statistical default significance model criterion). The SPSS data analysis software (version 10.01, SPSS Inc., Chicago, IL) was used for the statistical analysis. Differences and associations were considered statistically significant if $p < 0.05$.

Results

Characteristics of the Study Population

Demographic characteristics and the frequency of various traditional risk factors are indicated in Table 1. This male population was 58.9 ± 10.3 years old with a BMI of 26.2 ± 3.6 kg/m^2 (Table 1). Thirteen men (7.7%) of the population were treated for hypertension, 17 (10.1%) for hyperlipidemia, and only two (1.2%) had type 2 diabetes; however, when considering men with a fasting blood sugar >7.0 mM, this was found in 11% of the population. Forty-three subjects (25.6%) consumed alcohol (≥1 drink) on a daily basis, and 51 subjects (30.4%) were current cigarette smokers at the time of examination.

Classic Cardiovascular Risk Factors and AC

A severity score of AC was obtained in 160 (95.2%) of the 168 men. A score of 0 was observed in 80 (47.6%) of the population. For the remaining 80 men (score >0), the scores distributed with 25.6% of the men with a score ≥1 but <5, 12.5% having a score ≥5 but <10, 4.2% having a score ≥10 but <15, and 5.3% having a score ≥15 (the maximal calcification score obtained being 17 in this population).

Severity score of AC showed a significant linear relationship with increasing age across the age range from 40 to 80 years, characterized by a Spearman's ρ of $r = 0.522$ ($p < 0.001$). In men 75 years old or more, mean severity of vascular calcification (score 7.6) was, thus, approximately twice the mean severity found in men 60 to 64 yeas old (mean score, 3.7). In addition to age, severity of AC was also directly correlated with IL-6, WBC, systolic BP (SBP), hyperlipidemia, serum TC, type 2 diabetes, resting HR, and SHBG (all $p < 0.05$) (Table 2). Interestingly, however, in this population, we found no direct correlation of AC with CRP ($r = 0.063$, $p = 0.440$).

Because of the non-normal distribution of the data for AC, the same risk factors were also analyzed with respect to tertiles of AC; we found linearity ($p < 0.05$) for all factors (as listed in Table 2), except for SHBG, which showed only borderline linearity ($p = 0.064$) with tertiles of AC.

Body Composition, Severity of AC, and Insulin Resistance

In this population, total lean mass comprised 69.4 ± 6.6% and total fat mass 21.4 ± 4.7% of the body weight, and the relative contribution of these components did not change significantly across age groups (data not shown). When investigating association of AC with the different components of soft body composition, an inverse association with components of lean body mass was noted ($p <$

Table 1. Characteristics of the male population

	Mean ± SD	Range
N	168	
Age (years)	58.8 ± 10.3	44 to 86
BMI (kg/m^2)	26.2 ± 3.6	18.9 to 49.6
TC (mM)	5.87 ± 1.10	3.62 to 9.70
White blood cell count ($\times 10^9$/L)	7.16 (4.39 to 9.03)*	2.60 to 119.8
Glucose (mM)	5.58 ± 1.21	2.90 to 11.80
SHBG (nM)	44.7 (26.9 to 65.9)*	12.9 to 115.8
Total T (nM)	15.9 (11.7 to 21.6)*	6.6 to 33.2
FAI†	0.430 ± 0.162	0.150 to 0.950
E_2 (pM)	41.7 (20.9 to 83.1)*	3.9 to 160.9
Free E_2 index‡	0.834 ± 0.670	0.070 to 4.270
Androstenedione (ng/mL)	1.68 (0.98 to 2.89)*	0.16 to 5.92
Adiponectin (mg/L)	12.0 (7.7 to 18.6)*	5.1 to 51.2
CRP (μg/mL)	1.09 (0.34 to 3.51)*	0.07 to 27.8
IL-6 (pg/mL)	1.78 (0.85 to 3.75)*	0.4 to 56.6
TNFα (pg/mL)	2.30 (1.56 to 3.38)*	1.19 to 10.06
SBP (mm Hg)	143 ± 23	103 to 216
DBP (mm Hg)	83 ± 11	60 to 160
HR (min^{-1})	64 ± 10	44 to 89
Central fat mass (g)	8555 ± 3640	2184 to 24914
[% of total soft tissue mass]	11.4 ± 3.8	3.4 to 11 to 4
Total lean mass (g)	56479 ± 6522	38250 to 72093
[% of total soft tissue mass]	77.4 ± 5.5	60.7 to 93.0
Treated hypertension (%)	13 (7.7%)	
Treated hyperlipidemia (%)	15 (8.9%)	
Glucose >7.0 mM	16 (9.5%)	
Treated diabetes (%)	2 (1.2%)	
Prevalent CVD	15 (8.9%)	
Smokers		
Current	51 (30.4%)	
Past	69 (41.1%)	

SD, standard deviation; TC, total cholesterol; SHBG, sex hormone-binding globulin; T, testosterone; FAI, free androgen index; E_2, estradiol; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; SBP, systolic blood pressure; DSP, diastolic blood pressure; HR, heart rate; CVD, cardiovascular disease.

* Geometric mean (geometric mean − SD, geometric mean + SD).

† FAI was calculated as total T/SHBG.

‡ Free E_2 index was calculated as E_2/SHBG.

0.001 for both) (Table 3). The inverse correlation between severity of AC and lean mass remained statistically significant after adjusting for differences in age and BMI ($r = -0.20$ to -0.22, $p < 0.05$). In contrast, with regard to fat mass, no significant association was apparent with total fat mass, central fat mass, or peripheral fat mass ($p > 0.05$ for all). However, after adjusting for differences in PLM, the direct correlation between obesity and the severity of AC became evident. Thus, under these boundaries, there was a weak but statistically significant direct correlation between severity of AC and total fat mass ($r = 0.16$, $p = 0.05$) and between AC and truncal fat mass ($r = 0.17$, $p < 0.05$).

Table 2. Significant bivariate non-parametric correlation coefficients (Spearman's ρ) of various risk factors and severity of AC in 168 community-dwelling white men

Age	IL-6	WBC	SBP	Smoking	TC	Type 2 diabetes	HR	SHBG	Androstenedione	FAI
0.582†	0.543†	0.365†	0.344†	0.311†	0.254‡	0.177*	0.172*	0.171*	−0.195*	−0.228§
	−0.120	0.209*	0.103	0.243*	0.263‡	0.197*	0.104	−0.097	−0.048	0.027

AC, aortic calcification; IL, interleukin; WBC, white blood count; SBP, systolic blood pressure; TC, total cholesterol; HR, heart rate; SHBG, sex hormone-binding globulin; FAI, free androgen index.
Top row, unadjusted correlation coefficients; bottom row, adjusted for age.
* $p < 0.05$.
† $p < 0.0001$.
‡ $p = 0.002$.
§ $p = 0.004$.

Due to the marked lack of normality of the data for AC, the associations of aspects of body composition were also investigated for tertiles of AC. Body weight was linearly associated with tertiles of AC ($p = 0.008$), and the same was also found for total lean mass and PLM (Figure 1) ($p < 0.0001$ for both). In contrast, neither total fat mass nor truncal fat mass showed any association with tertiles of vascular calcification.

Implications of Sex Steroids

SHBG was directly associated with the severity of AC, whereas the free androgen index (FAI) was inversely correlated to AC (Table 2). Both total fat mass ($r = -0.18$, $p = 0.036$) and central fat mass ($r = -0.22$, $p = 0.008$) showed a statistically significant inverse association with SHBG, which was apparent even after adjusting for age and BMI ($r = -0.18$, $p < 0.05$ and $r = -0.22$, $p < 0.01$, respectively). Furthermore, when stratifying the population into tertiles of PLM, there was a clear inverse association with FAI ($p < 0.0001$), which remained statistically significant ($p < 0.0001$) even after adjustment for age.

In this population, severity of AC was furthermore inversely associated with tertiles of the FAI ($p < 0.05$). Tertiles of the ratio tended to be directly associated with serum fasting glucose concentrations ($p = 0.069$) and was linearly associated with the frequency of impaired fasting glucose concentrations (>7 mM) or prevalent diabetes, even after adjusting for age and BMI ($p < 0.05$). However, no association of the ratio with PLM, serum glucose concentrations, or with severity of AC was found ($p > 0.05$ for all).

Implications of Adipokines

Adiponectin was inversely associated with tertiles of truncal fat mass both before ($r = -0.42$, $p < 0.001$) and after ($r = -0.23$, $p < 0.01$) adjusting for age and BMI. In contrast, no apparent correlation between adiponectin and peripheral fat mass was found ($p > 0.05$). In line with the established anti-inflammatory characteristics of this adipokine (20), adiponectin was inversely associated with CRP ($r = -0.17$, $p < 0.05$). At the same time, IL-6 correlated directly with tertiles of truncal fat mass ($r = 0.21$, $p <$

Table 3. Non-parametric correlation coefficients (Spearman's ρ) of aspects of body composition and severity of AC in 168 community-dwelling elderly men

Body weight	Total fat mass	Truncal fat mass	Total lean mass	PLM
−0.184*	−0.008	−0.001	−0.290†	−0.336‡

AC, aortic calcification; PLM, peripheral lean mass.
* $p < 0.05$.
† $p < 0.001$.
‡ $p < 0.0001$.

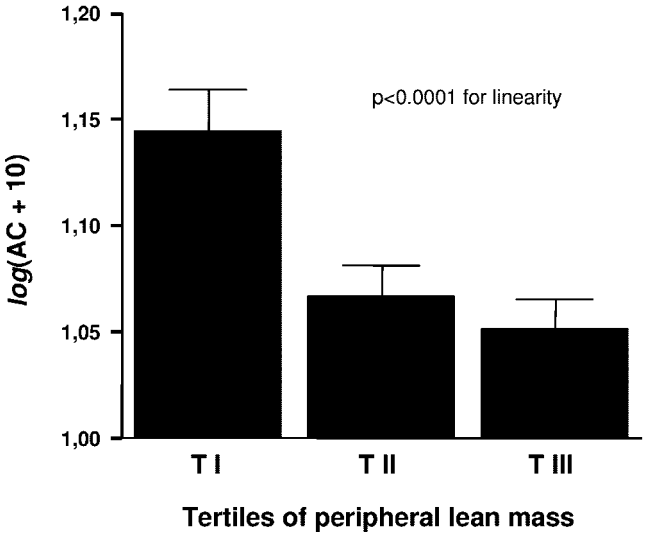

Figure 1: Linear inverse relationship ($p < 0.0001$ for linearity) of severity of AC (logarithmic values) across tertiles of PLM in 168 middle-aged and elderly men. Mean + standard error. After antilogarithmic transformation, the values (mean; mean − standard error to mean + standard error) of severity of AC with respect to the three tertiles were: Tertile I, 3.94 (3.33 to 4.58); Tertile II, 1.64 (1.25 to 2.05); and Tertile III, 1.25 (0.91 to 1–61), respectively.

0.05), with IL-6 being a strong correlate of CRP ($r = 0.54$, $p < 0.0001$). In contrast, TNF-α did not show any correlation with either fat depots or CRP. Interestingly, there was a significant inverse association between CRP and the two measures of lean mass, total lean mass and PLM ($r = -0.18$, $p < 0.05$ for both), independently of age and BMI.

Determinants of AC

To identify independent correlates of AC, we established multiple regression models including the severity score of AC as the dependent variable and potential contributors as independent variables. The analysis indicated that PLM ($p = 0.06$) and truncal fat mass ($p = 0.09$) were marginally significant correlates of AC (multiple regression Model I, Table 4).

When including further cardiovascular risk factors into the multivariate model (i.e., hypertension drug treatment, cholesterol lowering drug treatment, and prevalent CVD), we found that age, serum TC, prevalent CVD, truncal fat mass ($p = 0.031$), and peripheral lean mass ($p = 0.049$) were all significant correlates of AC (multiple regression Model II, Table 5).

Discussion

The major and novel finding of the present study was the marginally significant associations of PLM and truncal fat mass with severity of AC. Our findings suggest that low-grade inflammation induced by proinflammatory adipokines deriving from truncal (visceral) fat mass could be a common driving force underlying the parallel progression of atherogenesis and skeletal muscle loss. Prospective studies are needed to clarify the causal links underlying these associations.

Table 4. Multiple regression Model I of the severity of AC ($N = 168$)

AC ($R = 0.642$, SEE = 0.099, $p < 0.0001$)	β (standardized coefficient)	p (significance)
Age	0.489	<0.0001
Serum TC	0.196	0.008
Truncal fat mass	0.172	0.089
PLM	−0.156	0.064

AC, aortic calcification; SEE, standard error of estimate; TC, total cholesterol; PLM, peripheral lean mass; FAI, free androgen index; CRP, C-reactive protein; SBP, systolic blood pressure.
Other variables included in the multiple regression model were current smoking, FAI, CRP, peripheral fat mass, and SBP. Factors with $p < 0.10$ were considered as significant contributors to the variation in the severity of AC.

Table 5. Multiple regression Model II of the severity of AC ($N = 168$)

AC ($R = 0.676$, SEE = 0.096, $p < 0.0001$)	β (standardized coefficient)	p (significance)
Age	0.481	<0.0001
Serum TC	0.209	0.002
Prevalent CVD	0.208	0.003
Truncal fat mass	0.151	0.031
PLM	−0.153	0.049

AC, aortic calcification; SEE, standard error of estimate; TC, total cholesterol; CVD, cardiovascular disease; PLM, peripheral lean mass; FAI, free androgen index; SBP, systolic blood pressure; HR, heart rate; CRP, C-reactive protein.
Other variables included in the multiple regression model were current smoking, treated hyperlipidemia, FAI, peripheral fat mass, SBP, treated hypertension, glucose above 7 mM or known type 2 diabetes, HR, adiponectin, and CRP. Factors with $p < 0.10$ were considered as significant contributors to the variation in the severity of AC.

The present study revealed an interesting inverse relationship between circulating levels of IL-6 and PLM. Although this might imply an anti-inflammatory impact of skeletal muscle mass, it seems more likely that the association reflects a catabolic effect of low-grade inflammation on muscle mass, as recently suggested by Roubenoff (21). Increased secretion of IL-6 and, consequently, the increase in CRP could act by direct catabolic effects on skeletal muscle, or indirectly by causing reduced dietary energy intake (the anorexia of aging), or by inducing insulin resistance or lowering growth hormone-insulin-like growth factor I concentrations (21).

In addition, the study documented a direct association between severity of AC and IL-6, further reiterating the direct effects of proinflammatory cytokines on atherogenesis (22). It is probable that an increased catalytic signal conveyed by low-grade inflammation also contributes to the development of sarcopenia. Thus, in the present population of middle-aged and elderly men, the marginally significant inverse association between PLM and AC could be explained by combined implications of truncal obesity and sarcopenia for low-grade inflammation. A strong direct association between IL-6 and severity of AC emphasizes the likely atherogenic role of inflammatory adipokines.

Recent clinical observations suggest that sarcopenia and decreased muscle quality [defined as the relationship between muscle strength and muscle mass (9)] in the elderly often may be present in combination with obesity (sarcopenic obesity) (9), suggesting pathogenic links. Adipokines, which are circulating hormones deriving from adipose tissue, are important modulators of low-grade inflammation (23). IL-6 exerts proinflammatory effects (24), whereas adiponectin exerts anti-inflammatory effects (20); these effects were reflected in a reciprocal association of IL-6 and adiponectin with CRP in this cross-sectional study. Conditions in elderly men that are associated with increased circulating concentrations of CRP and decreased levels of adiponectin contribute to atherogenesis due to reciprocal impact by CRP and adiponectin on atherosclerosis (25). The direct association of IL-6 with truncal fat mass in this population can be explained by increased low-grade inflammation in individuals with visceral fat. Moreover, Nasir et al. (26) recently reported that asymptomatic middle-aged men with increased waist circumference (truncal obesity) have increased coronary artery calcification compared with individuals with normal waist circumference, independently of BMI. Thus, the proinflammatory disequilibrium of adipokines accompanying truncal obesity is a plausible mechanism that might explain the link between truncal obesity and skeletal muscle loss leading to sarcopenia and atherosclerosis.

In the present study, we found a strong inverse association of severity of AC with androstenedione and with FAI (although not with T). The causal nature of the associations reported in the present study requires prospective observations, which, to date, are sparse. T replacement in aging men with sarcopenia and truncal obesity would theoretically provide metabolic benefits by increasing muscle mass and strength and decreasing fat tissue mass (8), thus preventing the sarcopenic obesity syndrome. Observations of improved insulin sensitivity described by recent studies might reflect these hypothetical changes in body composition to hormonal replacement with T (27,28). Interestingly, the effect of T replacement is not associated with improvement in systemic inflammation (29), suggesting modest countering of proinflammatory effects posed by truncal obesity. In line with this, to date, no clinical data demonstrate an antiatherogenic effect of exogenous T in middle-aged and elderly men or a reduction in cardiovascular/coronary events (6–8). Thus, it remains speculative whether a pathophysiological scenario exists in which PLM, truncal fat mass, low-grade inflammation, and alterations in glucose/insulin metabolism all contribute to the development of the sarcopenic obesity syndrome (9), which seems to be a critical component of men's risk for a more rapid development of CHD.

Our data revealed only marginally significant reciprocal associations of PLM and truncal fat mass with severity of AC in a linear regression model (Table 4). One possible explanation for this is the small sample size of this cohort of community-dwelling middle-aged and elderly men and the low prevalence of clinically apparent CVD. In patients with symptomatic CHD, the average severity of ACs and low-grade inflammation are both likely to be more pronounced than in asymptomatic and healthy community-dwelling subjects. However, prospective studies in various male populations with CHD, truncal obesity with or without type II diabetes, and sarcopenic obesity clearly are also needed to determine the relative contribution of PLM and truncal fat mass in the progression of atherogenesis.

The present study has some limitations. In addition to the well-known limitations associated with a cross-sectional study design, the present analysis was also limited by its relatively small sample size, limiting generalization to the elderly male population at large. Furthermore, although DXA is frequently used to determine body composition, the amount of visceral fat cannot be assessed directly using this methodology. Finally, with severity of AC being a categorical variable in this study, the likelihood of obtaining statistically significant associations with other (continuous) variables is obviously less than if it had been a continuous variable. Nevertheless, the novel associations described in this study still represent interesting hypothesis-generating results concerning the complex mechanism underlying the sarcopenic obesity phenotype, which also seems to be associated with cardiovascular risk.

In conclusion, the novel associations from this study provide reason to believe that the proinflammatory milieu

accompanying truncal obesity might have common implications for both atherogenesis and muscle loss in elderly men. This would explain the pathogenesis of sarcopenic obesity. To clarify the causality, we call on future prospective studies addressing the simultaneous predictive value of different pro-inflammatory adipocytokines for atherogenesis and progressive muscle loss and the parallel progression of atherogenesis and muscle loss in elderly men.

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