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Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men

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Abstract

Abdominal obesity increases the risk of clinical atherosclerotic diseases, but whether it accelerates the progression of preclinical atherosclerosis is unknown. We studied whether waist-to-hip ratio (WHR) and waist circumference are associated with 4-year increase in indicators of common carotid atherosclerosis, assessed by B-mode ultrasonography, in 774 Finnish men aged 42–60 years without atherosclerotic diseases. Men with WHR of < 0.91, 0.91–0.96 and > 0.96 (thirds) had increase in maximal intima-media thickness (IMT) of 0.230, 0.255 and 0.281 mm/4 years ($P = 0.007$ for linear trend; $P = 0.025$ for difference) and plaque height of 0.241, 0.254 and 0.291 mm/4 years ($P = 0.005$, $P = 0.013$) adjusting for age, body mass index and technical covariates. Men with waist circumference of < 85, 85–93 and > 93 cm (thirds) had increase in maximal IMT of 0.227, 0.251 and 0.290 mm/4 years ($P = 0.011$, $P = 0.035$) and plaque height of 0.229, 0.263 and 0.296 mm/4 years ($P = 0.003$, $P = 0.013$). These associations were stronger in men with high (≥ 3.8 mmol/l) than lower serum LDL cholesterol ($P < 0.05$ for interaction). This is the first documentation that abdominal obesity is associated with accelerated progression of atherosclerosis, and supports the view that it is an important cardiovascular risk factor. This study emphasizes the role of avoiding abdominal obesity to prevent atherosclerotic diseases. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

1. Introduction

Obesity is a widespread disease of increasing prevalence, which is associated with a number of comorbidities including atherosclerotic diseases. Overall obesity, high body weight and weight gain have been related to increased risk of clinical events of atherosclerotic diseases, e.g. acute coronary events and stroke, in prospective population-based studies [1–6]. Interestingly, there is some evidence that abdominal obesity, as indicated by high waist-to-hip circumference ratio (WHR) or high waist circumference, is even a stronger predictor of atherosclerotic diseases than overall obesity, as indicated by high body mass index (BMI), and that abdominal obesity is associated with increased cardiovascular risk independent of overall obesity [7–9].

Atherosclerosis in the human arteries develops from an asymptomatic phase to manifest diseases over decades. The occurrence of clinically significant atherosclerotic lesions and consequent symptomatic atherosclerotic diseases increases progressively at middle-age. Ultrasonography of the arteries has made it possible to investigate noninvasively preclinical stages of atherosclerosis in unselected human populations [10,11]. Ultrasonographically-assessed carotid intima-media thickening is regarded as a valid indicator of generalized atherosclerosis, because it has been related to an atherogenic risk factor profile, increased prevalence of coronary and peripheral atherosclerosis and increased risk of acute coronary events and stroke [10–13].

Abdominal obesity has been independently associated with increased risk of clinical events of atheroscle-

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rotic diseases [7–9], but there is no prospective evidence that it could accelerate the progression of preclinical atherosclerosis. We therefore studied whether WHR and waist circumference are directly related to 4-year increase in the indicators of common carotid atherosclerosis independent of BMI and other risk factors for atherosclerosis in a population-based sample of middle-aged men.

2. Methods

2.1. Subjects

The subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), which is an ongoing population-based study designed to investigate risk factors for atherosclerotic diseases and related outcomes in middle-aged men from eastern Finland [14], an area which is known for its high prevalence and incidence of atherosclerotic diseases [15]. The recruitment of the subjects has been explained in detail previously [14]. The KIHD was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each subject gave written informed consent to participate in the study.

The initial study population of the KIHD consisted of 2682 men aged 42, 48, 54 or 60 years living in the town of Kuopio and neighbouring rural communities. A total of 1229 men who had undergone ultrasound examination of the carotid arteries at the KIHD baseline between August 1986 and December 1989 were invited to participate in a 4-year follow-up study, which was conducted between March 1991 and December 1993. Of these men, 1038 (88.2%) participated, 107 refused, 52 could not participate because of death, severe illness or relocation and 32 could not be contacted. Average time to follow-up was 4.2 years (range 3.8–5.2 years).

This study is based on data from the 774 men who participated in the KIHD 4-year follow-up study, did not have prior atherosclerotic disease, e.g. coronary heart disease, stroke or claudication, and had complete information on obesity and carotid atherosclerosis. Of these men, 57 were in the pravastatin treatment group in the Kuopio Atherosclerosis Prevention Study (KAPS) between 1990 and 1993 [16].

2.2. Assessment of obesity

BMI was used as a measure of overall obesity and WHR and waist circumference were used as measures of abdominal obesity. BMI was calculated by dividing body weight in kg by the square of body height in meters. Waist circumference was calculated as an average of one measurement taken after inspiration and one taken after expiration at the level of mid-distance between the bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of the trochanter major. WHR was calculated as the ratio of the circumference of the waist to the hip.

2.3. Assessment of carotid atheroselerosis

Carotid atherosclerosis was assessed at the baseline and 4 years later by high-resolution B-mode ultrasonography of the right and left common carotid artery (CCA) of a 1.0–1.5 cm section at the distal end of the CCA proximal to the carotid bulb, as explained in detail previously [10]. The maximal IMT was calculated as the average of the points of maximal thickness from the right and left CCA and was used as an indicator of the depth of intima-media protrusion into the lumen. Plaque height was calculated as the average of the differences between the maximal and minimal IMT of the right and left CCA and was used as an indicator of how steeply atherosclerotic lesions protruded into the lumen. The mean IMT was calculated as the mean of approximately 100 IMT values from the right and left CCA and was used as an overall indicator of atherosclerosis.

2.4. Assessment of covariates

The examination protocol [14] and the assessment of medical history, medications, cigarette smoking, hair mercury content [17], BMI and blood pressure [18] have been described in detail previously. The collection of blood specimens and the measurement of serum lipids, plasma fibrinogen [17], blood glucose and serum insulin [18] have been presented previously.

2.5. Statistical methods

The heterogeneity of the means of baseline variables between the thirds of WHR and waist circumference (Table 1) was tested using variance analysis. The strongest baseline risk factors for the four-year increase in the indicators of carotid atherosclerosis (Table 2) were determined by forcing a number of variables which could be associated with the progression of carotid atherosclerosis individually into a multivariate linear regression model with age, technical covariates (examination years, baseline zooming depth separately for right and left side, baseline indicator of carotid atherosclerosis, baseline sonographer, follow-up time and pravastatin treatment in the KAPS) and BMI. The heterogeneity of the means of the 4-year increase in the indicators of carotid atherosclerosis between the thirds

of WHR and waist circumference (Table 3) was tested using covariance analysis, and the linear trend across these thirds (Table 3) was tested using multivariate linear regression analysis. Age, the technical covariates and BMI were forced into these models with WHR or waist circumference. All other baseline variables which were associated with either WHR, waist circumference (Table 1) or the 4-year increase in any of the indicators of carotid atherosclerosis (Table 2) were entered into multivariate linear regression models using step-wise method ($P < 0.050$ as a selection criterion). Statistical analyses were performed using SPSS 9.0 for Windows.

3. Results

3.1. Abdominal obesity and other baseline characteristics

The unadjusted associations of WHR and waist circumference with other baseline characteristics are shown in Table 1. WHR was directly associated with body weight, BMI, systolic and diastolic blood pressure, serum LDL cholesterol, triglycerides and apolipoprotein B, diabetes, fasting serum insulin, plasma fibrinogen and the mean IMT, and inversely associated with body height and serum HDL cholesterol. Waist

Table 1
Baseline characteristics in the thirds of waist-to-hip circumference ratio and waist circumference[a]

Characteristic	Third of waist-to-hip circumference ratio			P for difference between groups
	<0.91 Mean (95% CI[b])	0.91–0.96 Mean (95% CI[b])	>0.96 Mean (95% CI[b])	
Age (years)	50.3 (49.5, 51.1)	51.0 (50.2, 51.8)	51.5 (50.7, 52.4)	0.109
Height (cm)	174.4 (173.6, 175.1)	174.3 (173.6, 175.1)	173.2 (172.4, 173.9)	0.040
Weight (kg)	73.8 (72.7, 74.9)	80.1 (79.1, 81.2)	87.1 (85.7, 88.6)	<0.001
BMI[b] (kg/m^2)	24.2 (24.0, 24.5)	26.3 (26.1, 26.6)	29.0 (28.6, 29.4)	<0.001
Cigarette smoking (pack-years)	6.5 (4.7, 8.4)	6.6 (5.0, 8.2)	9.1 (7.0, 11.2)	0.086
Hair mercury content (µg/g)	1.39 (1.21, 1.57	1.52 (1.32,1.72)	1.60 (1.40,1.79)	0.328
Systolic blood pressure (mmHg)	128.2 (126.4,130.0)	132.1 (130.3, 134.0)	136.2 (134.3, 138.1)	<0.001
Diastolic blood pressure (mmHg)	84.4 (83.2, 85.6)	87.7 (86.6, 88.9)	91.6 (90.4, 92.8)	<0.001
Serum LDL[b] cholesterol (mmol/l)	3.74 (3.62, 3.85)	3.84 (3.73, 3.96)	3.93 (3.83, 4.04)	0.047
Serum HDL[b] cholesterol (mmol/l)	1.41 (1.37, 1.45)	1.29 (1.26, 1.33)	1.23 (1.20,1.26)	<0.001
Serum triglycerides (mmol/l)	1.15 (1.07,1.23	1.35 (1.25,1.44)	1.61 (1.51, 1.71)	<0.001
Serum apolipoprotein B (g/l)	0.95 (0.92, 0.97)	1.00 (0.97,1.03)	1.07 (1.04,1.09)	<0.001
Diabetes (%)	1.6	2.3	5.8	0.015
Fasting serum insulin (mU/l)	8.2 (7.8, 8.6)	10.2 (9.6,10.8)	12.9 (12.1, 13.7)	<0.001
Plasma fibrinogen (g/l)	2.87 (2.80,2.94)	2.92 (2.86, 2.97)	3.09 (3.02, 3.16)	<0.001
Maximal IMT[b] (mm)	0.916 (0.891, 0.942)	0.914 (0.891, 0.936)	0.946 (0.921, 0.972)	0.111
Plaque height (mm)	0.390 (0.371, 0.409)	0.357 (0.339, 0.374)	0.372 (0.354, 0.390)	0.038
Mean IMT[b] (mm)	0.727 (0.709, 0.745)	0.740 (0.724, 0.756)	0.769 (0.749, 0.788)	0.005
	Third of waist circumference (cm)			P for difference between groups
	<85 Mean (95% CI[b])	85–93 Mean (95% CI[b])	>93 Mean (95% CI[b])	
Age (years)	50.5 (49.7, 51.3)	51.1 (50.2,51.9)	51.4 (50.5, 52.2)	0.314
Height (cm)	172.5 (171.7, 173.2)	174.4 (173.7, 175.1)	175.0 (174.3, 175.8)	<0.001
Weight (kg)	70.4 (69.7, 71.2)	79.5 (78.8, 80.2)	91.7 (90.5, 92.9)	<0.001
BMI[b] (kg/m^2)	23.7 (23,5, 23.9)	26.1 (26.0, 26.3)	29.9 (29.6, 30.2)	<0.001
Cigarette smoking (pack-years)	7.8 (6.0,93)	6.8 (5.1, 8.6)	7.6 (5.7,9.5)	0.746
Hair mercury content (µg/g)	1.50 (1.32,1.68)	1.49 (1.28,1.70)	1.51 (1.34,1.69)	0.984
Systolic blood pressure (mmHg)	128.1 (126.2, 129.9)	131.8 (130.0, 133.6)	137.0 (135.1, 138.9)	<0.001
Diastolic blood pressure (mmHg)	83.9 (82.7, 85.0)	87.8 (86.7, 89.0)	92.2 (91.1, 93.4)	<0.001
Serum LDL[b] cholesterol (mmol/l)	3.77 (3.65, 3.89)	3.96 (3.85, 4.07)	3.79 (3.69. 3.90)	0.031
Serum HDL[b] cholesterol (mmol/l)	1.41 (1.37,1.44)	1.28 (1.25,1.32)	1.23 (1.20,1.26)	<0.001
Serum triglycerides (mmol/l)	1.09 (1.01, 1.17)	1.39 (1.29,1.48)	1.65 (1.54,1.75)	<0.001
Serum apolipoprotein B (g/l)	0.95 (0.92, 0.98)	1.01 (0.99,1.04)	1.05 (1.03,1.08)	<0.001
Diabetes (%)	1.9	3.1	4.7	0.184
Fasting serum insulin (mU/l)	7.9 (7.6, 8.3)	9.8 (9.2, 10.3)	13.7 (12.9, 14.6)	<0.001
Plasma fibrinogen (g/l)	2.90 (2.83, 2.96)	2.96 (2.89, 3.03)	3.03 (2.96, 3.10)	0.022
Maximal IMT[b] (mm)	0.915 (0.890, 0.939)	0.933 (0.908, 0.957)	0.930 (0.905, 0.954)	0.539
Plaque height (mm)	0.388 (0.369, 0.408)	0.371 (0.354, 0.388)	0.359 (0.341, 0.377)	0.082
Mean IMT[b] (mm)	0.724 (0.707,0.741)	0.755 (0.736, 0.773)	0.758 (0.739, 0.777)	0.016

[a] From variance analyses.

[b] BMI, denotes body mass index; CI, confidence interval; LDL, low density lipoprotein; HDL, high density lipoprotein; and IMT, intima-media thickness.

Table 2
The strongest baseline risk factors for the progression of carotid atherosclerosis[a]

Risk factor	Four-year increase in the indicators of carotid atherosclerosis					
	Four-year increase in the maximal IMT[b]		Four-year increase in plaque height		Four-year increase in the mean IMT[b]	
	B[b]	P-value	B[b]	P-value	B[b]	P-value
Waist circumference (cm)	0.139	0.011	0.152	0.003	0.088	0.101
Waist-to-hip circumference ratio	0.116	0.007	0.113	0.005	0.097	0.021
Systolic blood pressure (mmHg)	0.098	0.006	0.062	0.066	0.118	0.001
Plasma fibrinogen (g/l)	0.088	0.012	0.064	0.049	0.078	0.022
Diastolic blood pressure (mmHg)	0.072	0.050	0.057	0.101	0.065	0.072
Cigarette smoking (pack-years)	0.058	0.116	0.051	0.144	0.060	0.096
Serum triglycerides (mmol/l)	0.043	0.237	0.057	0.098	0.020	0.578
Hair mercury content (μg/g)	0.012	0.735	−0.018	0.584	0.065	0.056

[a] From linear multivariate regression models including age, the technical covariates (examination years, the zooming depth at baseline for right and left side, the baseline indicator of carotid atherosclerosis, sonographer, follow-up time and pravastatin treatment in the Kuopio Atherosclerosis Prevention Study [KAPS]) and body mass index.
[b] B denotes standardized multivariate regression coefficient and IMT intima-media thickness.

Table 3
The progression of carotid atherosclerosis in the thirds of waist-to-hip circumference ratio and waist circumference[a]

	Four-year increase in the indicators of carotid atherosclerosis		
	Increase in the maximal IMT[b] Mean (95% CI[b])	Increase in plaque height Mean (95% CI[b])	Increase in the mean IMT[b] Mean (95% CI[b])
Waist-to-hip circumference ratio			
<0.91	0.230 (0.207, 0.254)	0.241 (0.218, 0.263)	0.095 (0.078, 0.111)
0.91–0.96	0.255 (0.234, 0.276)	0.254 (0.235, 0.274)	0.109 (0.095, 0.124)
>0.96	0.281 (0.258, 0.305)	0.291 (0.269, 0.314)	0.126 (0.109, 0.143)
P-value for linear trend	0.007	0.005	0.021
P-value for difference between thirds	0.025	0.013	0.069
Waist circumference (cm)			
<85	0.227 (0.200, 0.254)	0.229 (0.204, 0.254)	0.098 (0.079, 0.117)
85–93	0.251 (0.230, 0.273)	0.263 (0.243, 0.283)	0.104 (0.089, 0.119)
>93	0.290 (0.260, 0.319)	0.296 (0.269, 0.324)	0.128 (0.107, 0.149)
P-value for linear trend	0.011	0.003	0.101
P-value for difference between thirds	0.035	0.013	0.167

[a] From covariance models including age, the technical covariates (examination years, the zooming depth at baseline separately for right and left side, the baseline indicator of carotid atherosclerosis, sonographer, follow-up time and pravastatin treatment in the Kuopio Atherosclerosis Prevention Study [KAPS]) and body mass index.
[b] CI denotes confidence interval; and IMT intima-media thickness.

circumference was directly related to body height and weight, BMI, systolic and diastolic blood pressure, serum triglycerides and apolipoprotein B, fasting serum insulin, plasma fibrinogen and the mean IMT and inversely related to serum HDL cholesterol.

3.2. The strongest baseline risk factors for the progression of carotid atherosclerosis

The strongest baseline risk factors for the progression of carotid atherosclerosis adjusting for age, the technical covariates and BMI are shown in Table 2. WHR and waist circumference in thirds, systolic blood pres-

sure, plasma fibrinogen and diastolic blood pressure were statistically significantly associated with the 4-year increase in the maximal IMT, waist circumference and WHR in thirds and plasma fibrinogen with the 4-year increase in plaque height and WHR in thirds, systolic blood pressure and plasma fibrinogen with the 4-year increase in the mean IMT.

3.3. Abdominal obesity and the progression of carotid atherosclerosis in all subjects

The associations of WHR and waist circumference with the 4-year increase in the indicators of carotid

atherosclerosis adjusting for age, the technical covariates and BMI are shown in Table 2. There was a statistically significant linear trend across the thirds of WHR in the 4-year increase in the maximal IMT, plaque height and the mean IMT. Men with the WHR of > 0.96 (the highest third) had a 22% greater increase in the maximal IMT, a 21% greater increase in plaque height and a 33% greater increase in the mean IMT than men with the WHR of < 0.91 (the lowest third). There also was a statistically significant linear trend across the thirds of waist circumference in the 4-year increase in the maximal IMT and plaque height, but a borderline statistically significant linear trend in the 4-year increase in the mean IMT. Men with the waist circumference of > 93 cm (the highest third) had a 28% greater increase in the maximal IMT, a 29% greater increase in plaque height and a 31% greater increase in the mean IMT than men with the waist circumference of < 85 cm (the lowest third).
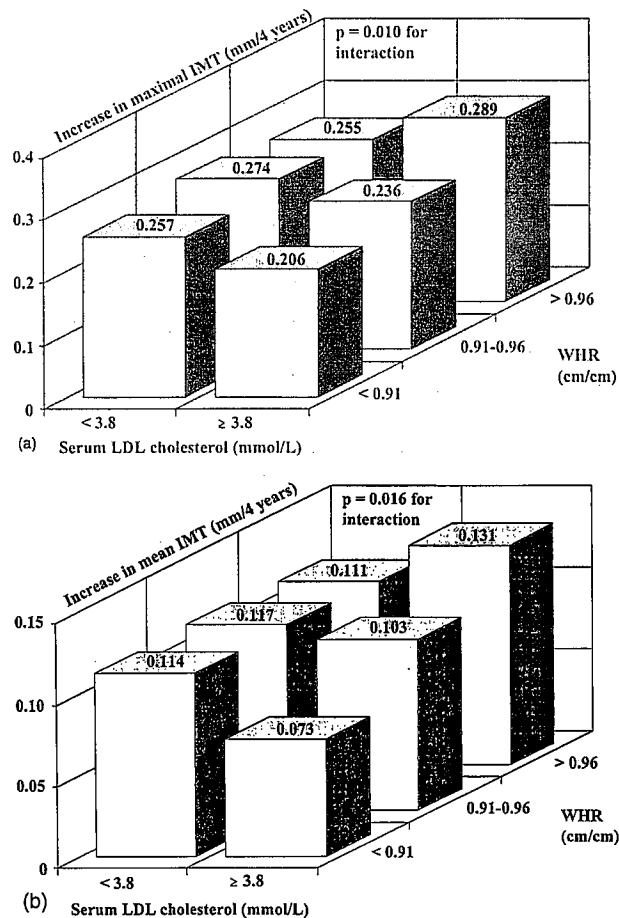

(a)

(b)

Fig. 1. The increase in the maximal and mean carotid intima-media thickness according to serum LDL cholesterol level and waist-to-hip circumference ratio. Adjusted for age, examination years, the zooming depth at baseline for right and left side, the baseline maximal or mean carotid intima-media thickness, sonographer, follow-up time, pravastatin treatment in the Kuopio Atherosclerosis Prevention Study and body mass index.

Plasma fibrinogen had weak effects on the associations of WHR with the 4-year increase in the maximal IMT ($P = 0.014$ for linear trend across the thirds, $P = 0.049$ for difference between the thirds, 20% difference between the highest and lowest third), plaque height ($P = 0.009$, $P = 0.023$, 19%) and the mean IMT ($P = 0.037$, $P = 0.114$, 29%) and on the relationships of waist circumference with the 4-year increase in the maximal IMT ($P = 0.013$, $P = 0.041$, 27%), plaque height ($P = 0.004$, $P = 0.015$, 28%) and the mean IMT ($P = 0.113$, $P = 0.184$, 29%). Systolic and diastolic blood pressure had even weaker impacts on the associations of WHR with the 4-year increase in the maximal IMT ($P = 0.010$, $P = 0.038$, 21%), plaque height ($P = 0.008$, $P = 0.018$, 20%) and the mean IMT ($P = 0.025$, $P = 0.081$, 32%) and on the relationships of waist circumference with the 4-year increase in the maximal IMT ($P = 0.015$, $P = 0.046$, 26%), plaque height ($P = 0.005$, $P = 0.022$, 27%) and the mean IMT ($P = 0.107$, $P = 0.186$, 31%). Cigarette smoking, hair mercury content, serum LDL or HDL cholesterol, triglycerides or apolipoprotein B, fasting serum insulin or diabetes had no effect on these associations.

3.4. Abdominal obesity and the progression of carotid atherosclerosis in subgroups

WHR had even a stronger direct association with the progression of carotid atherosclerosis in men with serum LDL cholesterol of ≥ 3.8 mmol/l (above median, Fig. 1) and in men with serum apolipoprotein B of ≥ 1.010 g/l (above median, data not shown), while WHR was not related to the progression of carotid atherosclerosis in men with serum LDL cholesterol of < 3.8 mmol/l (below median, Fig. 1) and in men with serum apolipoprotein B of < 1.010 g/l (below median, data not shown) adjusting for age, the technical covariates and BMI. Waist circumference had similar interactions with serum LDL cholesterol and apolipoprotein B (data not shown). Age (42 and 48 years versus 54 and 60 years), BMI (below versus above median), cigarette smoking (yes versus no), systolic or diastolic blood pressure (below versus above median), dyslipidemia (serum HDL cholesterol above median and triglycerides below median versus HDL cholesterol below median or triglycerides above median), fasting serum insulin (below versus above median) or plasma fibrinogen (below versus above median) did not statistically significantly modify the associations of WHR or waist circumference with the progression of carotid atherosclerosis.

4. Discussion

The present 4-year follow-up study provides the first prospective evidence that abdominal obesity, as indi-

cated by high WHR and high waist circumference, is associated with accelerated progression of carotid atherosclerosis independent of overall obesity and other risk factors in middle-aged men with no prior atherosclerotic diseases. This finding agrees with the results of previous prospective studies concerning abdominal obesity and the risk of clinical events of atherosclerotic diseases [7–9].

Previous evidence of the association between abdominal obesity and atherosclerosis derives mainly from cross-sectional coronary angiographic studies [19–22] and autopsy studies [23,24]. Increased amount of visceral fat quantified by computed tomography (CT) was associated with more serious coronary stenoses independent of age, BMI and the amount of subcutaneous fat in men with heterozygous familial hypercholesterolemia [19]. In another study among men with heterozygous familial hypercholesterolemia, those who had waist circumference of >95 cm had a higher odds of having coronary stenoses, but this association was largely explained by plasma lipoproteins and insulin [20]. WHR was higher in patients with coronary atherosclerosis than in normal controls matched for age, sex and race [21]. WHR was also directly associated with the extent of coronary atherosclerosis and the amount of myocardium threatened by coronary lesions in patients with coronary heart disease, but these relationships were nonsignificant after controlling for other coronary risk factors [22]. In female forensic autopsy cases of sudden violent death without prior clinical atherosclerotic diseases, those who had WHR of >0.92 had more stenotic coronary arteries independent of age [23], and those with WHR of >0.87 and increased amount of intraperitoneal fat had thicker coronary intima media independent of age and BMI, the thickest coronary lesions containing the largest number of macrophage foam cells [24]. Inconsistently, however, WHR and waist circumference have not been associated with coronary atherosclerosis in some other studies [25].

The association between abdominal obesity and coronary atherosclerosis has been found in a number of studies [19–24], but only a few studies, all of which have had a cross-sectional study design [26–28], have demonstrated an association between abdominal obesity and carotid atherosclerosis. High WHR was related to increased carotid IMT in a population-based sample of middle-aged individuals free of atherosclerotic diseases [26] and in non-diabetic, but not in diabetic persons [27]. Increased amount of visceral fat quantified by ultrasonography was related to increased carotid IMT in non-obese, normoglycemic men [28]. On the basis of a cross-sectional study, however, it is impossible to draw a conclusion of the time order of the relationship, e.g. whether abdominal obesity is a true atherosclerotic risk factor or is a result of a pre-existing

atherosclerotic disease, which has predisposed to weight gain and abdominal fat accumulation. In our prospective study among men free of atherosclerotic diseases, WHR and waist circumference were directly associated with the progression of carotid atherosclerosis, which makes it unlikely that the observed relationship would be due to self-selection bias.

Visceral fat could cause atherosclerosis through its unfavorable metabolic effects, which have been reviewed in detail previously [29,30]. Shortly, visceral adipocytes have high lipolytic activity and they produce free fatty acids and glycerol, which are drained by the portal vein into the liver, where they increase triglyceride and glucose production, decrease insulin clearance and may cause hepatic steatosis. Visceral adipocytes continue to produce fatty acids postprandially despite hyperinsulinemia due to their resistance to the antilipolytic effects of insulin, and increase postprandial hyperlipidemia and hyperglycemia. In turn, excessive systemic lipid availability increases intramuscular lipid levels and causes peripheral insulin resistance. It may also increase β-cell fatty acyl coenzyme A levels and contribute to islet cell failure and diabetes. Moreover, visceral adipocytes increase circulating tumor necrosis factor α levels, which may contribute to adipose tissue insulin resistance. Omental tissue also produces plasminogen activator inhibitor 1, which may cause insulin resistance and suppress fibrinolysis. Although subcutaneous adipocytes have lower lipolytic activity than visceral adipocytes, they also are lipolytically active and may have atherogenic effects [30]. For example, in a previous study among men subcutaneous fat was more closely related to insulin resistance than visceral fat [31].

These metabolic effects of abdominal adiposity result in insulin resistance, glucose intolerance, type 2 diabetes, hypertriglyceridemia, low serum HDL cholesterol, high serum LDL cholesterol, predominance of small dense LDL particles, hypertension, hemostatic disorders and hyperandrogenicity, which have been suggested as mechanisms through which abdominal obesity could cause atherosclerosis [29,30]. Abdominal adiposity has been associated with insulin resistance and dyslipidemia independent of overall obesity, and these relationships have been found even in non-obese, healthy individuals [30]. Visceral adiposity has also been associated with impaired endothelial function independent of overall obesity [32,33], which suggests that it could be an important risk factor for early atherosclerosis. These findings partly explain why abdominal obesity has been more closely associated with atherosclerosis and its clinical manifestations than overall obesity, and why the associations have been independent of overall obesity [7–9,26–28]. In the present study, however, fasting serum insulin, diabetes, serum lipids, lipoproteins or apolipoproteins, systolic or diastolic blood pressure or plasma fibrinogen did not have

a marked effect on the association between abdominal obesity and the progression of carotid atherosclerosis.

Interestingly, in the present study the association between abdominal obesity and the progression of carotid atherosclerosis was stronger in men with increased serum LDL cholesterol or apolipoprotein B levels than in other men. Accordingly, abdominal obesity has been associated with coronary atherosclerosis in men with heterozygous familial hypercholesterolemia [19,20]. Abdominal obesity has been found to enhance the oxidizability of LDL and VLDL particles, as indicated by increased formation of thiobarbituric acid reactive substances and decreased antioxidant potential of lipid fractions [34], by increasing circulating free fatty acids, triglycerides, small and dense LDL particles and biological oxidants [32]. This has been suggested as one of the mechanisms through which abdominal obesity could cause atherosclerosis. Taken together with previous findings, the results of the present study suggest that a combination of an increased total number of LDL particles in circulation and a large proportion of small dense and oxidatively modified LDL, associated with abdominal obesity, could be especially harmful with respect to atherosclerosis.

There are several methodological reasons which weaken the observed association between abdominal obesity and the progression of carotid atherosclerosis, and consequently underestimate the true relationship. Since atherosclerosis is a slow process which develops over decades, no large differences in the progression of carotid atherosclerosis between the extremities of abdominal obesity would be expected during a follow-up period of 4 years. WHR and waist circumference are somewhat less reproducible measures of obesity than BMI due to their larger measurement variability [35]. Although WHR and waist circumference are strongly correlated with the amount of visceral fat, they are less precise in assessing visceral fat accumulation than CT and magnetic resonance imaging (MRI) [35]. However, WHR and waist circumference are cheap and easily available, and have been recommended as methods for assessing abdominal obesity in population studies [35]. One of the advantages of our study is that we were able to control for a number of risk factors for atherosclerosis. We cannot, however, exclude the possibility of residual confounding due to some unmeasured factors. For these reasons, a longer follow-up period, repeated measurements of obesity, a comprehensive set of other variables and, if possible, more accurate methods for assessing abdominal obesity such as CT or MRI, should be used in future studies. Ultimately, however, only a trial focused specifically on weight reduction and decrease in the amount of abdominal fat would prove a possible causal relationship between abdominal obesity and atherosclerosis.

The results of the present study are important from both a public health and a clinical viewpoint. This is the first documentation that abdominal obesity, especially when combined with increased serum LDL cholesterol level, is associated with accelerated progression of carotid atherosclerosis in men with no prior atherosclerotic disease, and supports the view that abdominal obesity is an important cardiovascular risk factor. Taken together with the previous evidence, this study emphasizes the role of avoiding abdominal obesity to prevent atherosclerotic diseases.

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