



Central and peripheral fat mass have contrasting effect on the progression of aortic calcification in postmenopausal women

László B. Tankó^{a*}, Yu Z. Bagger^a, Peter Alexandersen^a, Philip J. Larsen^b, Claus Christiansen^b, for the PERF study group

^aCenter for Clinical and Basic Research A/S, Ballerup, Denmark

^bRheoscience, Rødovre A/S, Denmark

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Aim To investigate the long-term effects of central fat mass (CFM) and peripheral fat mass (PFM) on atherogenic risk profile and the progression of aortic calcification (AC) in postmenopausal women.

Methods and results Participants were 316 women aged 50–76 years, who were followed for 7.7 years. CFM and PFM were measured at baseline by DXA and related to follow-up measures of atherogenic metabolites, blood pressure, and the progression of AC assessed on lateral radiographs. CFM and PFM independently of each other exhibited contrasting influence on follow-up measures of atherogenic risk factors and the progression of AC. In a multiple regression model, the negative contribution of PFM ($P<0.05$), but not the adverse contribution of CFM, was independent of confounders. When comparing different extreme forms of obesity, women with central obesity showed the greatest (2.36 ± 0.60 , $n=11$), whereas those with peripheral obesity the smallest changes in AC (0.50 ± 0.34 , $n=10$) over the study period. Women with general obesity also tended to show less progression of AC compared with women with central obesity (1.23 ± 0.42 , $n=21$).

Conclusions This study provides direct support for the independent anti-atherogenic influence of PFM and calls on further research to define the adipocyte-derived factors involved in this favourable effect.

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Introduction

Obesity is often associated with co-morbidities such as hypertension, diabetes, atherogenic dyslipidaemia, and chronic inflammation, thereby constituting an important risk factor for cardiovascular disease and mortality.^{1,2} However, the contribution of body fatness per se to atherosclerosis is still under debate, particularly when regarding postmenopausal women. Two recent prospective studies provided direct support that high body mass index (BMI) accelerates the progression of atherosclerosis in young and adolescent men.^{3,4} This association, how-

ever, could not be confirmed in women, except for a slight trend in those with increased visceral fat mass.⁴ Absent association between overall measures of obesity and atherosclerosis was also observed in cross-sectional settings^{5,6} and in autopsy studies.^{7,8} Since the relative contribution of CFM and PFM to overall body fat mass differs significantly between men and women,^{9,10} the differences seen in the importance of BMI as a disease predictor could be due to differences in the contribution of CFM and PFM to atherogenesis.

A recent cross-sectional study on postmenopausal women indicated that indirect measures of CFM and PFM showed contrasting association with atherogenic lipid and glucose metabolites; CFM showing positive, whereas PFM negative correlations.¹¹ Two other groups confirmed these findings and reported strong negative associations

* Corresponding author. László B. Tankó MD, PhD, Center for Clinical and Basic Research, Ballerup byvej 222, DK-2750 Ballerup, Denmark. Tel.: +45-44684600; fax: +45-44684220.
E-mail address: lbt@ccbr.dk (L.B. Tankó).

between fat mass on the legs measured by DXA and atherogenic lipid and glucose metabolites.^{12,13} Moreover, large hip circumference was found to be a strong predictor of health and longevity in women providing a dominant protection against cardiovascular disease and diabetes-related morbidity and mortality.^{14,15} In line with these findings, we have recently observed in a cross-sectional setting an independent inverse correlation of PFM with insulin resistance and the severity of AC.¹⁶ These observations suggested an independent anti-atherogenic influence of this fat depot in elderly women. However, to obtain ultimate answers, long-term prospective studies relating direct measures of CFM and PFM to the progression of atherosclerosis are needed.

Therefore, the primary objective of the present study was to investigate how baseline measures of CFM and PFM influence the progression of AC, an established surrogate of atherosclerosis,^{17–19} in postmenopausal women over a 7.7-year observation period.

Methods

The study population consisted of 316 postmenopausal women who were recruited to randomized clinical trials on the prevention of osteoporosis during 1993 and 1994. In 2000, these women were invited for a follow-up examination—Prospective Epidemiological study focusing on Risk Factors for osteoporosis and cardiovascular disease (the PERF study). None of the participants had any chronic disease known to influence body composition. Demographic characteristics and cardiovascular risk profile of the participants at baseline and at the follow-up visit are indicated in Fig. 1. Those who were receiving on-going therapy with HRT ($n=20$) or lipid-lowering drugs ($n=19$) were excluded from the statistical analyses.

All women gave informed consent to participation and the study was carried out in accordance with the Helsinki Declaration II and the European Standards for Good Clinical Practice. The Ethical Committee of Copenhagen County approved the study protocol.

Estimates of body fat mass and fat distribution

Body composition at baseline and the follow-up visit was measured by DEXA using a Hologic QDR2000 scanner (Hologic Inc., Waltham, MA, USA, software version 9.03D).²⁰ Vertical boundaries separated the arms from the trunk at the shoulders, and angled boundaries separated the legs. Fat mass of the trunk (in kg), including both the subcutaneous and the visceral fat of this anatomical region, was termed as central fat mass (CFM). The sum of fat mass on the legs and arms (in kg) was termed as peripheral fat mass (PFM). In analogy with the well-known waist-to-hip ratio expressing the relative presence of the two types of fat mass was expressed by the CFM/PFM ratio. Lean tissue mass in the same compartments was also determined. Furthermore, when used for comparative purposes, CFM and PFM were expressed as the percentage of total soft tissue mass, i.e. sum of total body fat and lean tissue mass.

Grading of aortic calcification

AC at baseline and the end of the follow-up period was assessed on lateral radiographs as previously described by Kauppila et al.²¹ Briefly, calcified deposits in the lumbar aorta adjacent

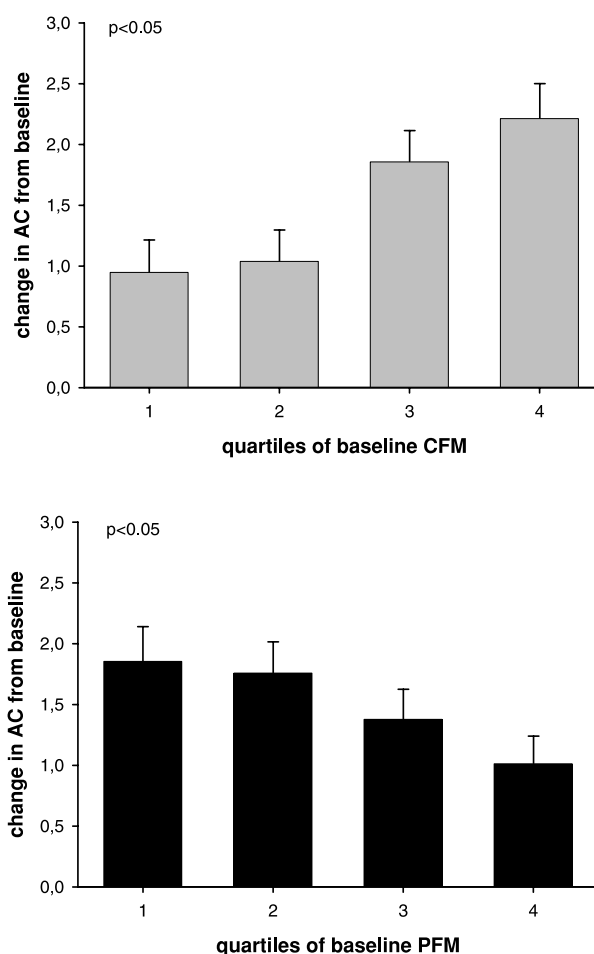


Fig. 1 The association between quartiles of central (CFM, upper panel) and peripheral fat mass (PFM, lower panel) with the 7.7-year progression of aortic calcification (AC) in postmenopausal women after adjustment for PFM and CFM, respectively.

to each lumbar vertebra (L1–L4) were assessed separately for the anterior and posterior wall of the aorta using the midpoint of the inter-vertebral space as the boundaries. Each wall of each segment was graded for the presence of calcified deposits with a score from 0 to 3 (0: no deposits, 1: less than 1/3 of the aortic wall, 2: 1/3 to 2/3 of the aortic wall, 3: more than 2/3 of the aortic wall covered with calcified deposits). The sum of the scores of individual aortic segments both for the anterior and posterior walls, termed as anterior–posterior severity score and was used to describe the overall severity of AC in the lumbar aorta. Maximum score possibly given was $4 \times 2 \times 3 = 24$. The relative increases from baseline ($\text{score}_{\text{follow-up}} - \text{score}_{\text{baseline}}$) were defined as the progression of AC. The same investigator, who was blinded for all other results of the individual participants, carried out the evaluations. Intra-rater correlations between repeated measurements were in the range of $r=0.92–0.98$ ($n=50$), similarly to published results.²¹

Cardiovascular risk factors

In women wearing light indoor clothes and no shoes, body weight and height were measured to the closest 0.1 kg and 0.001 m, respectively. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Arterial blood pressure and

Table 1 Baseline and follow-up characteristics of the study population (*n*=316)

	Baseline	Follow-up	<i>r</i>
Age (years)	62.3±5.8	70.0±5.6	
Age at menopause (years)	48.1±4.5	—	
BMI (kg/m ²)	25.5±3.8	26.0±4.3	0.857 ^a
TFM (kg)	26.73±0.83	28.31±0.92	0.785 ^a
PFM (kg)	13.89±0.38	14.71±0.46	0.801 ^a
CFM (kg)	12.05±0.50	12.89±0.51	0.778 ^a
CFM/PFM ratio	0.85±0.26	0.87±0.23	0.799 ^a
Systolic BP (mmHg)	136±26	148±23	0.483 ^a
Diastolic BP (mmHg)	83±15	82±11	0.415 ^a
Glucose (mmol/l)	5.55±0.98	5.55±1.40	0.419 ^a
Triglyceride (mmol/l)	1.30±0.53	1.29±0.56	0.692 ^a
Cholesterol (mmol/l)	6.95±1.07	6.30±0.99	0.633 ^a
WBC count (×10 ⁹ /l)	5.44±1.65	5.60±1.60	0.723 ^a
Current smoking (%)	26.6	20.3	
Former smoking (%)	23.7		
Regular alcohol (%)	54.7	57.0	
Daily coffee (%)	96.8	96.2	
No fitness activity (%)	23.7	25.4	
Current HRT (%)	0	6.0	
Treated hyperlipidaemia (%)	1.9	6.0	
Treated hypertension (%)	13.9	25.5	
Treated diabetes (%)	1.3	2.8	
Severity of AC	1.38±2.41	2.99±3.72	

^aCorrelation significant at *P*<0.001. Results shown are mean±SD.

heart rate at baseline and at the follow-up was measured using digital blood pressure monitor. Information on level of education (primary/secondary/university), smoking habits (never/current/past), daily alcohol and coffee consumption (yes/no), weekly fitness activities (1: never; 2: once weekly; 3: twice weekly; 4: more than twice weekly), presence of treated diabetes mellitus, treated hypertension or cardiovascular disease (treated angina pectoris, myocardial infarction, intermittent claudication, and stroke) were gathered during personal interviews using standardized questionnaires. Serum glucose, total cholesterol, triglycerides were determined from fasting (>12 h) blood samples using enzymatic assays performed by a Cobas Mira Plus (Roche Diagnostic Systems, Hoffmann-La Roche, Basel, Switzerland) at baseline Vitros-250 analyser (Johnson & Johnson, Taastруп, Denmark) at follow-up. Correlation between the two analysers was found excellent (*r*=0.98).²²

Data analysis

Results were expressed as means ± SD unless otherwise indicated. Statistical analysis was carried out using the SPSS data analysis software (version 10.01, SPSS Inc, Chicago, IL, USA). Spearman's rho was used to establish the bivariate correlates of the change in AC. General linear model adjusting for the other compartment of fat mass was used to establish the association between quartiles of CFM or PFM and the progression of AC over the 7.7 years. Linear relationship between these variables were tested with chi-square test. Backward stepwise multiple regression models were established to determine the independent contributors to the variation in the progression of AC.

To isolate subjects with four extremes of body fat distribution, women were stratified into percentiles, first according to percentage of CFM, then the percentage of PFM. Extremes of body fat distribution were defined as previously described in detail.¹⁵ Briefly, 1-1: lean women, 1-4: peripheral obesity, 4-1:

central obesity, 4-4: overall obesity; where 1 denotes the <25th and 4 the >75th percentiles. Comparison of the progression of AC between women with different extremes of body fat distribution was performed by Kruskal–Wallis test. Significance level used for the statistical testing was *P*<0.05.

Results

Body fat mass, body fat distribution, and risk factors at baseline and follow-up

There was a slight trend toward increasing BMI, total fat mass, and more central body fat distribution. There was a high degree of correlation between baseline and follow-up measures of body fatness and body fat distribution indicating, on average, minor variations over the observation period. Baseline and follow-up measures of major metabolic risk factors and blood pressure also showed significant correlation (Table 1).

Significant baseline correlates of the progression of AC

The 7.7-year progression of AC showed significant bivariate correlation with baseline age, systolic blood pressure and total cholesterol, smoking, and prevalent diabetes mellitus (all *P*<0.05). Body height was a significant inverse correlate of the progression of AC (*P*<0.05).

The long-term impact of CFM and PFM on cardiovascular risk factors

Baseline measures of CFM, independently of PFM, showed consistent positive correlation with all cardiovascular

Table 2 Associations of baseline measures of central and peripheral fat mass and their ratio with follow-up measures of major cardiovascular risk factors ($n=277$)

Risk factors at follow-up	Body fat mass at baseline		
	Central ^a	Peripheral ^b	CFM/PFM
Triglyceride	0.37 ^c	-0.18 ^c	0.43 ^c
White blood cell count	0.16 ^c	-0.19 ^c	0.25 ^c
Glucose	0.26 ^c	-0.05	0.20 ^c
Cholesterol	0.04	-0.08	0.04
Systolic BP	0.27 ^c	-0.12 ^c	0.24 ^c
Diastolic BP	0.20 ^c	0.01	0.19 ^c
Heart rate	0.17 ^c	-0.09	0.14 ^c

^aCorrected for peripheral fat mass.^bCorrected for central fat mass.^cCorrelation significant at $P<0.01$.

risk factors, except for serum cholesterol (Table 2). In contrast, baseline PFM was negatively correlated with triglyceride, WBC, and systolic pressure ($P<0.05$, Table 2). Other correlations were also negative, but did not reach statistical significance. The CFM/PFM ratio was the strongest correlate of triglyceride and WBC count, while it did not add to the predictive value of CFM when concerning blood pressure, glucose, or resting heart rate.

The independent contribution of CFM and PFM to the progression of AC

Baseline measures of body weight, BMI, and total body fat mass showed no significant correlation with the progression of AC over the observation period ($r=0.020-0.060$, $P>0.05$). Baseline CFM, independently of PFM, showed, a significant direct correlation ($r=0.190$, $P<0.001$), whereas baseline PFM, independently of CFM, was inversely correlated with the progression of AC ($r=-0.189$, $P<0.001$). Fig. 1 shows the association between quartiles of the baseline measures of CFM (upper panel) and PFM (lower panel) and the progression of AC after adjustment for PFM and CFM, respectively. As indicated by the figure, the two compartments exhibited contrasting influence on atherogenesis. The correlation between body fat distribution (CFM/PFM ratio) and the progression of AC remained statistically significant even after adjustment for BMI ($r=0.159$, $P=0.009$).

To address the contribution of the two fat depots to the progression of AC independently of traditional cardiovascular risk factors, we established a multiple regression model including the 7.7-year change in AC as dependent variable, and all potential contributors as independent variables. Included variables are shown in Table 3 and the corresponding legend. Results of the analysis indicated that baseline PFM, but not CFM, was an independent negative contributor to the variation in the change in AC ($P<0.05$).

Table 3 Multiple regression model of the progression of aortic calcification ($n=277$)^a

Baseline	Beta	P-value
Age	0.110	0.081
Body mass index	0.221	0.058
Systolic blood pressure	0.167	0.010
Current smoking	0.181	0.003
All diabetes mellitus	0.135	0.023
Peripheral lean mass	-0.125	0.079
Peripheral fat mass	-0.233	0.026

^a $R=0.369$, $SEE=2.00$, $P<0.0001$. Other variables included in the model were baseline age, years since menopause, level of education, coffee and alcohol consumption, weekly fitness activity, serum cholesterol, white blood cell count, and glucose reported or found at baseline, and all cases of treated hypertension (baseline+follow-up). Factors with a $P<0.10$ were considered as significant contributors to the variation in the progression of AC.

Interactions between CFM and PFM in different forms of body fat distribution

In attempting to obtain further insights into the simultaneous contribution of CFM and PFM to atherogenesis, we isolated small sub-groups of women with different extremes of body fat distribution.

The upper panel of Fig. 2 illustrates means of CFM, PFM, and total fat mass in the four subgroups expressed as percentage of total body soft tissue mass. Lean and peripheral obese women had the same low percentage of CFM, but they differed in PFM. Similarly, central and general obese women had the same high percentage of CFM, but they were different in terms of PFM. Percentage of PFM was the same low in lean and central obese women, and the same high in peripheral and general obese women.

Demographic characteristics and cardiovascular risk profile of the four groups did not reveal differences except for current smoking ($P=0.036$). Thus, there were no differences in terms of age or prevalence of treated diabetes mellitus, hyperlipidaemia, or hypertension either at baseline or at the follow-up visit (all $P>0.05$). Of the various metabolic risk factors measured at follow-up, only serum triglycerides showed statistically significant differences ($P<0.001$). Thus, triglycerides were significantly higher in central obesity (1.99 ± 1.09 mmol/L, $n=11$) compared to both lean (1.03 ± 0.35 , $n=34$) and peripheral obese women (0.98 ± 0.71 mmol/L, $n=10$). Women with general obesity had significantly higher triglyceride (1.51 ± 0.59 mmol/L, $n=21$), but comparable with that in women with peripheral obesity ($P>0.05$).

The lower panel of Fig. 2 indicates the progression of AC in the same groups before and after adjustment for smoking habits. Although, the power to detect differences was low due to the small number of subjects, the progression from baseline was apparently more rapid in women with central compared to peripheral obesity. Furthermore, in women with the same percentage of CFM but significantly higher PFM, the progression of AC was slower rather than more rapid compared to that in

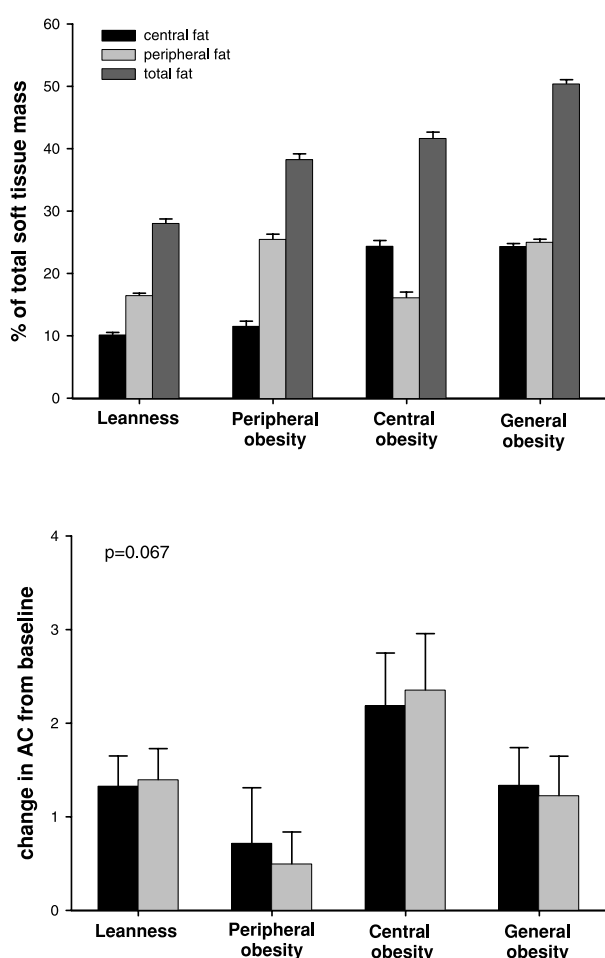


Fig. 2 The upper panel shows central fat mass (CFM), peripheral fat mass (PFM) and total fat mass expressed as percentage of total body soft tissue mass in women with various extremes of body fat distribution. Lean and peripheral obese women had the same low percentage of CFM, but they differed in terms of PFM. Central and general obese women had the same high percentage of CFM, but they differed in PFM. Percentage of PFM was the same low in lean and central obese women, and the same high in peripheral and general obese women. The lower panel shows the 7.7-year progression of aortic calcification (AC) in the same groups before (black bars) and after (grey) adjustment for smoking habits.

women with central obesity. Adjustment for smoking did not change these results considerably.

Discussion

The present study is the first to analyse longitudinal associations between direct measures of CFM and PFM and the progression of AC in a long-term prospective study on postmenopausal women. In line with our previously reported cross-sectional results,¹⁶ the present findings further support the independent anti-atherogenic effect of PFM and emphasize that in postmenopausal women distribution of fat mass rather than obesity per se has critical implications for atherogenesis.

Although there was a trend toward increasing body fatness, the strong correlation between baseline and

follow-up measures of different indices of body fatness indicated relatively moderate fluctuations over the observation period. Baseline measures of CFM and PFM showed significant correlations with major cardiovascular risk factors assessed 7.7 years later. As expected, CFM exhibited a consistent adverse influence on atherogenic metabolites, blood pressure, and heart rate. In contrast, PFM exhibited a favourable long-term influence on several components of the metabolic syndrome, particularly on systolic blood pressure, serum triglyceride, and the crude marker of inflammation, WBC. These observations, thus, confirm previous cross-sectional observations^{11–13,16} that suggested a contrasting influence of CFM and PFM on major cardiovascular risk factors.

In accordance with the contrasting influence on atherogenic risk factors, CFM showed positive, whereas PFM showed an inverse correlation with the long-term progression of AC. Since the correlation of CFM with the progression of AC was not independent of other cardiovascular risk factors included in the multiple regression model, the adverse influence of this fat depot appears to be mainly attributable to the metabolic syndrome.^{23,24} On the contrary, PFM independently contributed to the progression of AC indicating that the anti-atherogenic influence of PFM is mediated by other fat-derived factors or fat-related mechanisms.

Results of this study showed that overall measures of body fatness (weight, BMI, total fat mass) do not have considerable predictive value for the long-term progression of AC. In contrast, high CFM/PFM ratio, independently of BMI or total fat mass, was associated with accelerated atherogenesis. Our findings are in accordance with previous studies on women that indicated that large waist circumference or high waist-to-hip ratio had a greater predictive value for cardiovascular morbidity and mortality compared with body weight and BMI.^{6,25–27} Collectively, these results strongly support the concept that in women the relative distribution of fat mass rather than obesity per se is important for atherogenesis and related cardiovascular risk.

In attempting to further analyse the relative importance of CFM and PFM to atherogenesis, we also compared the progression of AC in four subgroups of women representing different extremes of body fat distribution. Due to the relatively small number of women with extreme peripheral and central obesity, the power to detect differences was very low. However, the results suggest that in women with peripheral obesity, AC progresses more slowly than in women with central obesity. Furthermore, the progression of AC was apparently more rapid in lean women compared to peripheral obese women and seemed to be comparable with that in women with general obesity. These observations were independent of confounding with smoking. The significantly better cardiovascular profile and less progressive AC of general versus central obese women is strongly supported by our previous cross-sectional observation obtained on larger groups of such women.¹⁶ In addition, it is tempting to speculate that the relative lack of PFM and concomitant protective effects contribute to the understanding of the greater mortality rate observed among the elderly with

low compared to high BMI, a phenomenon that cannot be ascribed to confounding with smoking.^{28–32}

Our cross-sectional findings, in line with previous reports, indicate that the protective influence of PFM can be, at least in part, explained by insulin sensitization.¹⁶ Longitudinal observations on rhesus monkeys have shown that plasma adiponectin, a recently discovered fat-cell derived hormone with putative insulin sensitizing³³ and anti-atherogenic effects,³⁴ decrease with increasing body weight and gradually drop with progression toward diabetes debut.³⁵ Humans undergoing weight loss respond with elevations in adiponectin,³⁶ but it is presently uncertain to what extent the different fat compartments contribute to these changes. It has recently been shown that adiponectin is significantly lower in visceral adipocytes of genetically obese Zucker rats compared to lean rats, and that expression is restored to normal levels after body weight reduction.³⁷ Given that these observations are directly applicable to humans, it seems evident that contribution of visceral adipocytes to plasma adiponectin is inversely correlated to their volume, this phenomenon, however, does not seem to apply to peripheral adipocytes. In support, our preliminary observations indicated that after adjustment for the negative influence of CFM, PFM showed a significant direct association with serum adiponectin (Tankó et al, unpublished observations). Furthermore, the significantly higher levels of adiponectin in women with general compared with central obesity (despite the same percentage of CFM and higher BMI) also seem to support the independent contribution of PFM to serum adiponectin. The autocrine/paracrine secretion of proinflammatory cytokines, first of all, IL-6 by visceral adipocytes with subsequent down regulation of adiponectin secretion in the same compartment but without major influence on production in PFM could explain our aforementioned observations.³⁸ Further research is warranted to clarify these important pathophysiological aspects of adipocytokine production.

In summary, the present study is the first to obtain direct support for the protective influence of PFM in atherogenesis in a long-term prospective setting and the results thus further emphasize that in postmenopausal women distribution rather than the excessive presence of body fat that has a dominant influence on atherogenesis. These findings call for targeted efforts to identify the genetic and environmental determinants of body fat distribution and the role of adipocytokines mediating the favourable metabolic effects of PFM.

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References

- Melanson KJ, McInnis KJ, Rippe JM et al. Obesity and cardiovascular disease risk: research update. *Cardiol Rev* 2001;9:202–7.
- Alexander JK. Obesity and coronary heart disease. *Am J Med Sci* 2001; 321:215–24.
- Lakka TA, Lakka HM, Salonen R et al. Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. *Atherosclerosis* 2001;154:497–504.
- McGill HC Jr, McMahan CA, Herderick EE et al. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation* 2002;105:2712–8.
- Tanaka K, Kodama H, Sasazuki S et al. Obesity, body fat distribution and coronary atherosclerosis among Japanese men and women. *Int J Obes Relat Metab Disord* 2001;25:191–7.
- Hodgson JM, Wahlqvist ML, Balazs ND et al. Coronary atherosclerosis in relation to body fatness and its distribution. *Int J Obes Relat Metab Disord* 1994;18:41–6.
- Kortelainen ML, Sarkioja T. Coronary atherosclerosis and myocardial hypertrophy in relation to body fat distribution in healthy women: an autopsy study on 33 violent deaths. *Int J Obes Relat Metab Disord* 1997;21:43–9.
- Kortelainen ML. Myocardial infarction and coronary pathology in severely obese people examined at autopsy. *Int J Obes Relat Metab Disord* 2002;26:73–9.
- Heitmann BL. Body fat in the adult Danish population aged 35–65 years: an epidemiological study. *Int J Obes* 1991;15:535–45.
- Lev-Ran A. Human obesity: an evolutionary approach to understanding our bulging waistline. *Diabetes Metab Res Rev* 2001; 17:347–62.
- Seidell JC, Perusse L, Despres JP et al. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001;74:315–21.
- Williams MJ, Hunter GR, Kekes-Szabo T et al. Regional fat distribution in women and risk of cardiovascular disease. *Am J Clin Nutr* 1997; 65:855–60.
- Tatsukawa M, Kurokawa M, Tamari Y et al. Regional fat deposition in the legs is useful as a presumptive marker of antiatherogenesis in Japanese. *Proc Soc Exp Biol Med* 2000;223:156–62.
- Lissner L, Björkelund C, Heitmann BL et al. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 2001;9:644–6.
- Snijder MB, Dekker JM, Visser M et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am J Clin Nutr* 2003; 77:1192–7.
- Tankó LB, Bagger YZ, Alexandersen P et al. Peripheral fat mass exhibits an independent dominant antiatherosclerotic effect in elderly women. *Circulation* 2003;107:1626–31.
- Iribarren C, Sidney S, Sternfeld B et al. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *JAMA* 2000;283:2810–5.
- Danielsen R, Sigvaldason H, Thorgeirsson G et al. Predominance of aortic calcification as an atherosclerotic manifestation in women: the Reykjavik study. *J Clin Epidemiol* 1996;49:383–7.
- Witteaman JC, Kok FJ, van Saase JL et al. Aortic calcification as a predictor of cardiovascular mortality. *Lancet* 1986;2:1120–2.
- Spector E, LeBlanc A, Shackelford L. Hologic QDR 2000 whole-body scans: a comparison of three combinations of scan-modes and analysis software. *Osteoporos Int* 1995;5:440–5.
- Kaupilla LI, Polak JF, Cupples LA et al. New indices to classify location, severity and progression of calcific lesions in the trunk aorta: a 25-year follow-up study. *Atherosclerosis* 1997;132:245–50.
- Tankó LB, Bagger YZ, Nielsen SB et al. Does serum cholesterol contribute to vertebral bone loss in postmenopausal women? *Bone* 2003;32:8–14.
- Lamarche B. Abdominal obesity and its metabolic complications: implications for the risk of ischaemic heart disease. *Coron Art Dis* 1998;9:473–81.
- Reeder BA, Senthilselvan A, Despres JP et al. The association of cardiovascular disease risk factors with abdominal obesity in Canada. Canadian Heart Health Surveys Research Group. *CMAJ* 1997; 157:539–45.

25. Van Gaal LF, Vansant GA, De Leeuw IH. Upper body adiposity and the risk for atherosclerosis. *J Am Coll Nutr* 1989;**8**:504–14.
26. Folsom AR, Kaye SA, Sellers TA et al. Body fat distribution and 5-year risk of death in older women. *JAMA* 1993;**269**:483–7.
27. Rexrode KM, Carey VJ, Hennekens CH et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;**280**:1843–8.
28. Miyazaki M, Babazono A, Ishii T et al. Effects of low body mass index and smoking on all-cause mortality among middle-aged and elderly Japanese. *J Epidemiol* 2002;**12**:40–4.
29. Vandenbroucke JP, Mauritz BJ, de Bruin A et al. Weight, smoking, and mortality. *JAMA* 1984;**252**:2859–60.
30. Singh PN, Lindsted KD, Fraser GE. Body weight and mortality among adults who never smoked. *Am J Epidemiol* 1999;**150**:1152–64.
31. Selmer R, Tverdal A. Body mass index and cardiovascular mortality at different levels of blood pressure: a prospective study of Norwegian men and women. *J Epidemiol Community Health* 1995;**49**:265–70.
32. Grabowski DC, Ellis JE. High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. *J Am Geriatr Soc* 2001;**49**:968–79.
33. Yamauchi T, Kamon J, Waki H et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;**7**:941–6.
34. Yamauchi T, Kamon J, Waki H et al. Globular adiponectin protected ob/ob mice from diabetes and apoE deficient mice from atherosclerosis. *J Biol Chem* 2003;**278**:2461–8.
35. Hotta K, Funahashi T, Bodkin NL et al. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 2001;**50**:1126–33.
36. Yang WS, Lee WJ, Funahashi T et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;**86**:3815–9.
37. Milan G, Granzotto M, Scarda A et al. Resistin and adiponectin expression in visceral fat of obese rats: effect of weight loss. *Obes Res* 2002;**10**:1095–103.
38. Bastard JP, Maachi M, Van Nhieu JT et al. Adipose tissue IL-6 content correlates with resistance to insulin. *J Clin Endocrinol Metab* 2002;**87**:2084–9.