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The association of pericardial fat with calcified coronary plaque

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Abstract

Background—Pericardial fat has a higher secretion of inflammatory cytokines than subcutaneous fat. Cytokines released from pericardial fat around coronary arteries may act locally on the adjacent cells.

Objective—We examined the relationship between pericardial fat and calcified coronary plaque.

Design—Participants in the community-based Multi-Ethnic Study of Atherosclerosis underwent a computed tomography scan for the assessment of calcified coronary plaque in 2001/02. We measured the volume of pericardial fat using these scans in 159 whites and blacks without symptomatic coronary heart disease from Forsyth County, NC, aged 55–74 years.

Results—Calcified coronary plaque was observed in 91 participants (57%). After adjusting for height, a one standard deviation increment in pericardial fat was associated with an increased odds of calcified coronary plaque (odds ratio (95% confidence interval): 1.92 (1.27, 2.90)). With further adjustment of other cardiovascular factors, pericardial fat was still significantly associated with calcified coronary plaque. This relationship did not differ by gender and ethnicity. On the other hand, body mass index and height-adjusted waist circumference were not associated with calcified coronary plaque.

Conclusions—Pericardial fat is independently associated with calcified coronary plaque.

Keywords

coronary heart disease; body mass index; waist circumference

Introduction

Obesity or excess body fat amount is a well established coronary heart disease risk factor (1). The distribution of body fat varies among individuals and may be as important as the amount of body fat in determining risk. In fact, excess accumulation of fat around the upper body is associated with a higher risk of coronary heart disease regardless of total body fat (2). Fat depots in various parts of the body have different properties which may underlie the importance of fat distribution. For example, pericardial fat, the fat depot around the heart, releases more inflammatory cytokines (3) than subcutaneous fat. Inflammation has been linked to coronary heart disease (4). Furthermore, inflammation due to fat depots tends to be localized in their surrounding tissues and organs (3). Therefore, pericardial fat may be the fat depot of principal interest with regard to coronary heart disease.

In the present study, we developed a method to measure the volume of pericardial fat from computed tomography (CT) scans used to quantify calcified coronary plaque. Although the relation between calcified coronary plaque and vulnerable plaque is unclear, the amount of calcified coronary plaque may reflect the overall burden of coronary atherosclerosis (5), which is the main cause of coronary heart disease. Furthermore, calcified coronary plaque predicts the risk of the future coronary heart disease events beyond the Framingham Risk Score (6). We hypothesized that pericardial fat is a correlate of calcified coronary plaque independently of body mass index and waist circumference, which have been used as indicators of obesity and fat distribution, respectively, in epidemiologic studies.

Research methods and procedures

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a community-based cohort study designed primarily to investigate prevalence, correlates, and progression of subclinical cardiovascular disease (7). A total of 6,814 whites, blacks, Hispanics, and Asian Americans, aged 45–84 years, were recruited from Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN in 2001/02. Individuals with physician-diagnosed cardiovascular disease or any related procedures were not eligible. The study was approved by institutional review boards of participating institutions. All MESA participants underwent a CT scan for the assessment of calcified coronary plaque at baseline, when information on anthropometry and other cardiovascular factors was collected. For the present study, we randomly selected 160 white and black MESA participants aged 55–74 years from Forsyth County, NC, 40 from each gender-ethnic group. The volume of pericardial fat was measured in these individuals using existing CT scans. One individual was excluded due to an unreadable CT scan, leaving a sample size of 159 for the present analysis.

Calcified coronary plaque

Calcified coronary plaque was determined with a LightSpeed Plus four-detector row CT system (GE Medical Systems, Milwaukee, WI) at Forsyth County site of MESA. Details of the method have been previously published (8). The CT has a minimum gantry rotation period of 0.5 second and an exposure time of 330 msec. The system is operated in the axial

scan mode (cine) with 120 kVp, and four 2.5-mm sections are acquired simultaneously. The ECG triggering was set at 50% of the R-R interval.

Experienced and trained technologists scanned the heart of each participant twice and transmitted the scans over the internet to the CT Reading Center (Harbor-UCLA Research and Education Institute in Torrance, CA). A cardiologist read all scans in a masked fashion. The Agatston score (9), averaged from the two scans, was used to quantify the amount of calcified coronary plaque. The presence of calcified coronary plaque was defined as Agatston score greater than 0. The agreement for the presence of calcified coronary plaque between duplicate scans (Kappa, 0.92) (10) as well as the reread agreement for the Agatston score (intraclass correlation coefficient, 0.99) (8) were excellent. The re-read agreement for the presence of calcified coronary plaque was also high (Kappa for intra-observer and inter-observer, 0.93 and 0.90, respectively) (11).

Pericardial fat

Two experienced CT readers blinded as to the measure of calcified coronary plaque measured pericardial fat volume on the CT scans used for quantifying calcified plaque. Although a previously published method used in the Diabetes Heart Study (DHS) to measure the volume of pericardial fat can be considered the “gold standard” (12), it is too time-intensive. Thus, for the present study, a new protocol was developed in which pericardial fat encasing coronary arteries was sampled. The superior extent of the left main coronary artery was identified in a cross-sectional scan. Slices within 15 mm above this slice and 30 mm below this slice were included in the new measure. This region of the heart was selected because it includes the pericardial fat located around the proximal coronary arteries (left main coronary, left anterior descending, right coronary, and circumflex arteries). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Volume Analysis software (GE Healthcare, Waukesha, WI) was used to discern fat from the remainder of the heart with a threshold of -190 to -30 Hounsfield units (Figure 1). The volume was the sum of all voxels containing pericardial fat. The measurement of pericardial fat with the new protocol took only 10 minutes, thus reducing analysis time by approximately 50% compared with the “gold standard” method, which measures the entire pericardial fat volume encasing the heart.

The validity of the new measure was assessed in a random subset of 10 individuals from 80 DHS participants who had pericardial fat measures. The pericardial fat volume was measured using the new protocol in these 10 individuals and then compared with the measure using the previous method. The two measures were highly correlated (Pearson correlation coefficient: 0.93; $p < 0.0001$). We also examined the reproducibility of the new measure in MESA. A random sample of 10 of 159 MESA participants was selected and reread by both CT analysts. The intra-class correlation coefficients for intra-reader and inter-reader reliability were 0.999 and 0.997, respectively.

Anthropometry

Weight was measured with a Detecto Platform Balance Scale to the nearest 0.5 kg. Height was measured with a stadiometer (Accu-Hite Measure Device with level bubble) to the

nearest 0.1 cm. Waist circumference (at the umbilicus) was measured to the nearest 0.1 cm using a steel measuring tape with standard 4 oz. tension (Gulick II 150 cm anthropometric tape). Body mass index was defined as weight in kilograms divided by square of height in meters.

Other covariates

Standard questionnaires were used to collect information on demographics, alcohol use, smoking status, medical history, and medication use. Both alcohol use and cigarette smoking status were classified as never, former and current. Blood pressure was measured in the right arm of the participant after five minutes in a sitting position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). The second and third of three readings were averaged to obtain the blood pressure levels. Total and HDL cholesterol were measured in EDTA-treated plasma on a Roche COBAS FARA centrifugal analyzer (Roche Diagnostics, Indianapolis, IN). C-reactive protein was measured using the BNII nephelometer (Dade Behring Inc., Deerfield, IL). Glucose levels were measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics Inc., Rochester, NY). Diabetes was defined as fasting glucose ≥ 6.99 mmol/L (126 mg/dL) or use of hypoglycemic medication, and impaired fasting glucose was defined as fasting glucose 5.55 to 6.94 mmol/L (100 to 125 mg/dL) (13).

Statistical analysis

Cardiovascular characteristics were compared between those with and without calcified coronary plaque using analysis of variance (ANOVA) for continuous variables and chi square test for categorical variables. Pearson correlation coefficients between pericardial fat and other fat measures were calculated. Because more than half of participants had an Agatston score of zero, we used logistic regression analysis to examine the probability of the presence of calcified coronary plaque and used linear regression analysis to examine the actual score given calcified coronary plaque was present. Logistic regression analysis was used to assess the association of pericardial fat, waist circumference, and body mass index with the presence of calcified coronary plaque. The analyses for pericardial fat and waist circumference were adjusted for body size (height). In order to compare the strength of the associations with calcified coronary plaque across various fat measures, one population standard deviation was used as the unit increment for each fat measure. The interaction terms for gender and ethnicity with pericardial fat were also examined. Among those with calcified coronary plaques, linear regression analysis was used to investigate the associations of the fat measures with the amount of calcified coronary plaque. Then, each quartile of pericardial fat was compared with the lowest quartile of pericardial fat with regard to the odds of calcified coronary plaque presence. Finally, the association of pericardial fat with the presence of calcified coronary plaque was assessed after adjustment for additional cardiovascular factors. In this paper, the term “model” refers to a statistical model.

Results

Among the 159 MESA participants, 91 had plaque calcification. The mean (standard deviation) Agatston score for those with a calcified coronary plaque was 353 (695) with a range of 1 to 4994. Individuals with a calcified coronary plaque were slightly older and were more likely to be male and white compared to those without the presence of calcified coronary plaque; in addition, they also had greater height and lower levels of C-reactive protein, and were more likely to be lipids-lowering medication users and statin users (Table 1). There were no marked differences in smoking status, alcohol use, use of anti-hypertensive medications, prevalence of diabetes, systolic blood pressure, and total and HDL cholesterol levels between those with and without calcified coronary plaque. The volume of pericardial fat was greater in those with a calcified coronary plaque, but no differences in the presence of calcification were found according to either body mass index or waist circumference. Pericardial fat was positively correlated with both body mass index ($r: 0.35, p < 0.0001$) and waist circumference ($r: 0.48, p < 0.0001$).

The associations of pericardial fat, body mass index and waist circumference with the presence of calcified coronary plaque were assessed using logistic regression analysis (Table 2). An increment of one standard deviation (46.6 cm^3) in pericardial fat volume was associated with a 92% increase in the odds of the presence of calcified coronary plaque after adjusting for height ($p = 0.002$). If the Agatston score of one standard deviation above the mean, rather than zero, was used as the cutoff point for the presence of calcified coronary plaque, the odds ratio for the plaque was 2.02 for every one standard deviation increment in pericardial fat ($p = 0.0005$). We also examined the interaction terms of pericardial fat with gender and ethnicity in the analysis. The association between pericardial fat and the presence of calcified coronary plaque did not differ significantly by gender (p for interaction term = 0.14) or ethnicity (p for interaction term = 0.92). On the other hand, neither body mass index nor height-adjusted waist circumference was found to be associated with the presence of calcified coronary plaque. Then, among the 91 individuals with a calcified coronary plaque (excluding those with an Agatston score of zero), the associations of the fat measures with the amount of calcified coronary plaque were assessed using linear regression analysis. Height-adjusted pericardial fat volume, but not body mass index or height-adjusted waist circumference, was found to be significantly associated with the Agatston score. In addition, among the 159 MESA participants, the Spearman correlation coefficient between pericardial fat volumes and Agatston scores was 0.32 ($P < 0.0001$).

To investigate log-linearity of the association between pericardial fat and the presence of calcified coronary plaque, the participants were divided into quartiles according to pericardial fat volume, and odds ratios were calculated after adjusting for height (Table 3). The fourth quartile was associated with the highest odds of having calcified coronary plaque. The second and the fourth, but not the third quartiles, were consistent with a log-linear relationship. The inconsistency for the third quartile may be due to small number of participants in each quartile. The relationship between pericardial fat and the presence of calcified coronary plaque was independent of body mass index and waist circumference (Table 4, Model 1). In this model, body mass index was inversely associated with the presence of calcified coronary plaque. The independent relationship between pericardial fat

and the presence of calcified coronary plaque was also examined including cardiovascular risk factors in stepwise models using a 0.05 significance level. Only pericardial fat, age and C-reactive protein remained in the final model (Table 4, Model 2). Both pericardial fat and age were positively associated with the presence of calcified coronary plaque, but the odds ratio for the plaque was greater for every one standard deviation increment in pericardial fat than for every one year increment in age. Unexpectedly, C-reactive protein concentration was inversely associated with the presence of calcified coronary plaque. However, this association was not statistically significant without pericardial fat in the model (data not shown).

Discussion

To our knowledge, the present study is the first to investigate the association of pericardial fat and calcified coronary plaque. We found that the pericardial fat volume was positively associated with both the presence and amount of calcified coronary plaque. By contrast, neither waist circumference nor body mass index was found to be significantly related to calcified coronary plaque in the unadjusted analysis, and body mass index was inversely associated with calcified coronary plaque after adjusting for pericardial fat and waist circumference.

Our newly developed method for measuring the volume of pericardial fat appears to be valid and reproducible. Iacobellis et al measured pericardial fat thickness on the free wall of the right ventricle from both parasternal long- and short-axis views using magnetic resonance imaging or echocardiography imaging (14). However, it is not clear how this measure reflects the total volume of pericardial fat. Taguchi et al measured the volume of pericardial fat using cross-sectional CT scans 1 cm thick from the atrial appendage to the apex over the diaphragm (15), which is similar to the method used in DHS (12). However, this method is relatively time-intensive, which limits its applicability to large epidemiologic studies. In the present study, we developed a new protocol to measure the volume of pericardial fat in the region of the heart around the proximal coronary arteries on the existing cardiac CT scans. Our new measure was highly correlated with the total volume of pericardial fat. Furthermore, the new method is less time-intensive and, therefore, more efficient in large epidemiologic studies. With cardiac CT scans available in several large community-based studies, the new method allows the investigation of the role of pericardial fat in the development of coronary heart disease.

Our study provides support to the notion that pericardial fat is a correlate of calcified coronary plaque. Although the accumulation of pericardial fat has long been regarded as a normal feature of the aging process (16), it may play a key role in the development of coronary heart disease (17;18). A cross-sectional study of 251 clinic-based Japanese men suggests that pericardial fat is associated with angiographically-defined coronary artery disease (15). The results from the Japanese study could, however, be biased because the study participants were limited to clinic patients referred for diagnostic coronary angiography. The present analysis, using a community-based sample, furthers our knowledge on the possible role of pericardial fat in the development of coronary heart disease. In addition, pericardial fat may be associated with components of the metabolic

syndrome, such as waist circumference, diastolic blood pressure and circulating insulin levels (19).

Our findings suggest that local fat depots rather than the total body fat are related to calcified coronary plaque. Notwithstanding the well documented role of obesity in the development of coronary heart disease (20), epidemiologic studies of the relation of body mass index and waist circumference to coronary atherosclerosis have yielded conflicting results (21). That the degree to which body mass index or waist circumference reflects the amount of fat or fat distribution varies with population characteristics may partly explain this phenomenon (21). In our data, neither body mass index nor waist circumference was associated with calcified coronary plaque in the unadjusted analysis despite their being significantly correlated with pericardial fat volume. The inverse association between body mass index and calcified coronary plaque after controlling for pericardial fat and waist circumference may reflect a possible protective role against cardiovascular disease of fat accumulation in the lower part of the body (22). C-reactive protein was also inversely associated with calcified coronary plaque after adjusting for pericardial fat, but the association was not statistically significant without pericardial fat in the model. Inconsistent results on the association of circulating levels of C-reactive protein with calcified coronary plaque from previous studies suggest that systemic inflammation is not a strong independent correlate of calcified coronary plaque (23).

Local inflammation in the coronary arteries may be the mechanisms underlying the association between pericardial fat and calcified coronary plaque. Most pericardial fat is distributed around the adventitia of the coronary arteries. In addition to the intima, media and adventitia, fat tissue around coronary arteries is also involved in inflammatory reactions (24;25). Moreover, the presence of inflammatory mediators in the tissues surrounding coronary arteries induces influx of inflammatory cells into the artery wall (26). Pericardial fat produces more inflammatory cytokines, such as monocyte chemotactic protein 1, interleukin 6, and tumor necrosis factor α , compared with subcutaneous fat (3). Therefore, inflammatory mediators released from pericardial fat may promote inflammation in local coronary arteries and lead to coronary atherosclerosis (26;27). It is worthy noting that circulating inflammatory markers do not reflect local tissue inflammation in coronary arteries (3). Pericardial fat may also take part in regulation of vasoconstriction (28) and vascular smooth muscle cell proliferation (29) in coronary arteries, which can also contribute to the pathogenesis of atherosclerosis (30). In addition, pericardial fat has a greater lipolytic activity than subcutaneous fat (31). Excess free fatty acids released from pericardial fat may promote coronary atherosclerosis through the formation of lipid cores (32) or acceleration of apoptosis (33).

The cross-sectional nature of the study limits the scope of the conclusions that can be drawn. We can not exclude the possibility that calcified coronary plaque accelerates the accumulation of pericardial fat or that a common underlying cause results in both the accumulation of pericardial fat and the calcification of coronary arteries. Also, our assessments of fat distribution were not comprehensive. Pericardial fat is closely correlated with abdominal visceral fat (12), which is a better predictor of incident coronary heart

disease events than subcutaneous fat (34), and thus it is possible that other correlated depots are more strongly related to calcification.

In summary, our data indicate that pericardial fat may be more relevant to calcified coronary plaque than either body mass index or waist circumference. Measures of pericardial fat and other regional fat depots in larger samples with longitudinal assessment of development and amount of calcium in coronary plaques are needed to confirm these findings. Given the public health importance of coronary heart disease, enhanced research in this area which may yield new therapeutic targets is imperative.

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Figure 1.
A cross-sectional CT scan of the heart with pericardial fat indicated as the gray area within the hand-drawn circle

Table 1

Characteristics of 159 MESA participants according to the presence or absence of calcified coronary plaque, 2001–2002

	Presence of calcified coronary plaque		p-value
	No (N=68)	Yes (N=91)	
Age *, year	62.4 (5)	65.8 (5)	0.0001
Male, %	35.8	60.4	0.002
Black, %	64.2	40.7	0.004
Height *, cm	167 (9)	171 (10)	0.01
Smoking status, %			0.42
Never	48.5	39.6	
Former	34.9	45.1	
Current	16.7	15.4	
Alcohol use, %			0.06
Never	32.8	16.7	
Former	28.1	36.7	
Current	39.1	46.7	
Systolic blood pressure *, mmHg	135 (21)	139 (20)	0.22
Any anti-hypertensive medication, %	40.3	46.2	0.46
Total cholesterol *, mmol/L	4.90 (0.83)	4.87 (0.88)	0.92
HDL cholesterol *, mmol/L	1.33 (0.36)	1.26 (0.36)	0.25
Any lipid-lowering medication, %	11.9	27.8	0.02
C-reactive protein †, mg/L	3.06 (1.4, 6.6)	2.04 (0.9, 5.5)	0.03
Statin use, %	11.9	26.7	0.02
Prevalence of diabetes, %			0.89
Normal	69.7	64.8	
Impaired fasting glucose	22.7	24.2	
Diabetes	7.6	11.0	
Pericardial fat *, cm ³	72.2 (34)	99.6 (51)	0.0002
Body mass index *, kg/m ²	28.9 (4)	28.5 (4)	0.58
Waist circumference *, cm	99.4 (13)	101 (12)	0.30

* Mean (standard deviation)

† Median (Interquartile range)

Table 2

Association of pericardial fat, body mass index, and waist circumference, respectively, with the presence and, in those with calcified plaque, amount (Agatston score) of calcified coronary plaque, MESA, 2001–2002

	OR (95% CI) [*] of the presence of calcified coronary plaque (N=159)	p-value	Difference in Agatston score (95% CI) (N=91)	p-value
Model 1 [†]				
Pericardial fat [‡] , 46.6 cm ³	1.92 (1.27, 2.90)	0.002	162 (32, 292)	0.015
Model 2				
Body mass index [‡] , 4.4 kg/m ²	0.91 (0.67, 1.25)	0.574	62 (–83, 208)	0.399
Model 3 [‡]				
Waist circumference [‡] , 12.5 cm	1.13 (0.81, 1.56)	0.472	–9 (–159, 141)	0.905

* Odds ratio (95% confidence interval)

[†] Adjusting for height

[‡] Per standard deviation

Table 3

Association of pericardial fat (quartiles) with presence of calcified coronary plaque, MESA, 2001–2002

	OR (95% CI) [*] of the presence of calcified coronary plaque [†] (N=159)	p-value
1 st quartile, 23.9 – 52.6 cm ³	1	
2 nd quartile, 52.6 – 78.4 cm ³	2.62 (1.03, 6.66)	0.042
3 rd quartile, 79.0 – 107.2 cm ³	1.52 (0.62, 3.76)	0.364
4 th quartile, 107.5 – 259.6 cm ³	4.65 (1.71, 12.67)	0.003

* Odds ratio (95% confidence interval)

[†] Adjusting for height

Table 4

Association of pericardial fat with presence of calcified coronary plaque, MESA, 2001–2002

	OR (95% CI) * of the presence of calcified coronary plaque (N=159)	p-value
Model 1		
Pericardial fat [†] , 46.6 cm ³	2.24 (1.38, 3.64)	0.0011
Body mass index [‡] , 4.4 kg/m ²	0.56 (0.33, 0.95)	0.033
Waist circumference [‡] , 12.5 cm	1.33 (0.76, 2.31)	0.31
Model 2 [‡]		
Pericardial fat [†] , 46.6 cm ³	2.10 (1.28, 3.45)	0.003
Age, year	1.14 (1.06, 1.23)	0.0003
C-reactive protein, mg/L	0.92 (0.86, 0.99)	0.024

* Odds ratio (95% confidence interval)

[†] Per standard deviation[‡] Including age, gender, race, height, smoking status, alcohol drinking status, systolic blood pressure, use of anti-hypertensive medications, total and HDL cholesterol, use of lipid-lowering medications, C-reactive protein, use of statins, diabetic status and pericardial fat in the model with a stepwise selection at the 0.05 significance level