Association of Epicardial Adipose Tissue With Progression of Coronary Artery Calcification Is More Pronounced in the Early Phase of Atherosclerosis

Results From the Heinz Nixdorf Recall Study

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ABSTRACT

OBJECTIVES This study sought to determine whether epicardial adipose tissue (EAT) volume predicts the progression of coronary artery calcification (CAC) score in the general population.

BACKGROUND EAT predicts coronary events and is suggested to influence the development of atherosclerosis.

METHODS We included 3,367 subjects (mean age 59 ± 8 years; 47% male) from the population-based Heinz Nixdorf Recall study without known coronary artery disease at baseline. CAC was quantified from noncontrast cardiac electron beam computed tomography at baseline and after 5 years. EAT was defined as fat volume inside the pericardial sac and was quantified from axial computed tomography images. Association of EAT volume with CAC progression (log[CAC(follow-up) + 1] – log[CAC(baseline) + 1]) was depicted as percent progression of CAC + 1 per SD of EAT.

RESULTS Subjects with progression of CAC above the median had higher EAT volume than subjects with less CAC change (101.1 ± 47.1 ml vs. 84.4 ± 43.4 ml; p < 0.0001). In regression analysis, 6.3% (95% confidence interval [CI]: 2.3% to 10.4%; p = 0.0019) of progression of CAC + 1 was attributable to 1 SD of EAT, which persisted after adjustment for risk factors (6.1% [95% CI: 1.2% to 11.2%]; p = 0.014). For subjects with a CAC score of >0 to ≤100, progression of CAC + 1 by 20% (95% CI: 11% to 31%; p < 0.0001) was attributable to 1 SD of EAT. Effect sizes decreased with CAC at baseline, with no relevant link for subjects with a CAC score >400 (0.2% [95% CI: –3.5% to 4.2%]; p = 0.9). Likewise, subjects age <55 years at baseline showed the strongest association of EAT with CAC progression (20.6% [95% CI: 9.7% to 32.5%]; p < 0.0001). Interestingly, the effect of EAT on CAC progression was more pronounced in subjects with low body mass index (BMI), and decreased with degree of adiposity (BMI ≤25 kg/m²: 19.8% [95% CI: 9.2% to 31.4%]; p = 0.0001, BMI >40 kg/m²: 0.8% [95% CI: –26.7% to 38.9%]; p = 0.96).

CONCLUSIONS EAT is associated with the progression of CAC, especially in young subjects and subjects with low CAC score, suggesting that EAT may promote early atherosclerosis development. (J Am Coll Cardiol Img 2014;7:909-16) © 2014 by the American College of Cardiology Foundation.
Epicardial adipose tissue (EAT) is associated with cardiovascular risk factors, coronary artery plaque burden, and prevalent cardiovascular disease (1-3). Moreover, it is associated with future cardiovascular events independent of traditional cardiovascular risk factors, suggesting that EAT may influence atherosclerosis development, potentially via its inflammatory modulating effect (4-7).

Besides a controversial association with calcific plaque burden (1,6), a strong association of EAT with noncalcified plaque components was reported (2,8). Together with a more pronounced association of EAT with future coronary events in subjects with no or low coronary artery calcification (CAC) (6), these results support the hypothesis of a mechanistic role of EAT in the early phase of atherosclerosis. First studies suggested that EAT may promote CAC progression in selected cohorts (9-11). However, to date, data from an asymptomatic general population cohort to confirm these results is lacking. Therefore, the aim of the current analysis was to determine whether EAT predicts progression of CAC in a European population-based cohort over a period of 5 years.

METHODS

STUDY PARTICIPANTS. The Heinz Nixdorf Recall study is a population-based, prospective cohort study designed to assess the predictive value of novel markers for risk stratification in addition to traditional cardiovascular risk factors. The participants (45 to 75 years of age) were randomly selected from mandatory lists of residence from the 3 adjacent cities of Bochum, Essen, and Mülheim, Germany, and were enrolled between 2000 and 2003, with a recruitment efficacy of 55.8%. Details for recruitment and study design have been previously published (12,13). For this analysis, we excluded subjects with known coronary artery disease at baseline (n = 327) or revascularization between baseline and follow-up examination (n = 154). Additionally, 159 subjects died before follow-up examination, and 407 subjects did not participate in the follow-up examination. A total of 246 subjects were excluded due to missing CAC score at baseline or follow-up examination. EAT volume or 1 or more risk factors were missing in 154 subjects, resulting in a total cohort of 3,367 subjects. All participants provided written informed consent, and the study was approved by the institutional ethics committee.

CARDIOVASCULAR RISK FACTOR ASSESSMENT. Traditional cardiovascular risk factors were measured at baseline, with details being previously published (14). Body mass index (BMI) was calculated on the basis of direct measurements as the weight divided by the square of height. Waist circumference was measured at the leanest circumference between the costal arch and the iliac crest. Blood pressure was measured using an oscillometric method (Omron, Hoofddorp, the Netherlands). The mean value of the second and third of 3 measurements taken at least 2 min apart were used. Standardized enzymatic methods were used to determine serum high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol. Diabetes was defined as a history of diabetes, being on medical treatment, or on the basis of blood glucose levels, as previously published (15). Smoking history was classified as current smokers, former smokers, and no history of smoking, assessed by computer-assisted interview (16). A positive family history of coronary heart disease was defined as premature nonfatal or fatal coronary heart disease diagnosis. An event was considered premature if it occurred before 55 years of age in men and before 65 years of age in women (17). If ancestors were unknown or died early (e.g., in the Second World War), or if information was missing, subjects were classified as not having positive family history.

CARDIAC COMPUTED TOMOGRAPHY. As part of the study, subjects underwent cardiac computed tomography (CT) for quantification of CAC. Electron beam computed tomography scans were performed utilizing a C-100 or C-150 scanner (GE Imatron, South San Francisco, California) without the use of contrast media. Imaging was prospectively triggered at 80% of the RR interval, and contiguous 3-mm-thick slices from the right pulmonary artery to the apex of the heart were obtained at an image acquisition time of 100 ms. Follow-up imaging was performed with identical scanning protocol, using an Imatron C-150 scanner. CAC was defined as a focus of at least 4 contiguous pixels with a CT density >130 Hounsfield units (HU) and quantified using the Agatston method (18). Participants and physicians remained unaware of the CAC scoring results of the baseline examination.

EPICARDIAL FAT VOLUME QUANTIFICATION. Epicardial fat volume was assessed using a dedicated workstation. The pericardium was manually traced from the right pulmonary artery to the diaphragm to determine a region of interest. Within the region of interest, fat was defined as pixels within a window...
of –195 to –45 HU and a window center of –120 HU. Overall, only pixels with HUs equivalent to fat within the pericardial sac were counted as epicardial adipose tissue. Reproducibility was tested in 100 cases and was excellent (intraclass correlation coefficient [ICC] = 0.988, p < 0.0001 for interobserver and intraclass correlation coefficient = 0.996, p < 0.0001 for intraobserver variability). Details of EAT quantification have been previously described in detail (6).

**STATISTICAL ANALYSIS.** Continuous variables are reported as mean ± SD for normally distributed data or median and quartiles (Q1; Q3) for non-normally distributed data. Discrete variables are given in frequency and percent. EAT was normally distributed, whereas logarithmic transformation of CAC score (log(CAC + 1)) was performed to normalize the CAC distribution. Correlation of EAT volume with BMI and waist circumference was calculated using the Pearson correlation coefficient. The 2-sided Mann-Whitney U test was used to assess differences in CAC comparing first versus fourth quartile of EAT. CAC progression was calculated as the difference of logarithmic CAC scores at follow-up and baseline (log(CAC + 1)[t1] - log(CAC + 1)[t0]). Using this approach, CAC progression was normally distributed. Spearman correlation coefficient revealed no relevant link among variation of time between both scans and progression of CAC (r = 0.016, p = 0.36). EAT volumes between groups of CAC progression above versus below the median were compared using the 2-sided Student t test. Linear regression analysis was performed to investigate unadjusted and multivariable-adjusted association of EAT with CAC progression using the following models: 1) unadjusted; 2) BMI-adjusted; 3) BMI, age, and sex-adjusted; 4) multivariable analysis, including model 3 + systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, lipid-lowering medication, triglycerides, diabetes, present smoking, and former smoking; and 5) including model 4 and positive family history of premature coronary heart disease. As an additional analysis, we calculated the association of EAT with CAC progression with baseline CAC score (as log(CAC + 1)) included in the model. Parameter estimates are given per sex-specific SD of EAT volume as previously described for EAT, leading to easy-to-understand effect sizes (3,6). In addition, identical regression analyses were performed using waist circumference instead of BMI in all models. Besides sex-pooled analysis, sex-specific analysis was also performed, including a test of interaction between EAT and sex. Further, regression analysis was stratified by CAC score at baseline, using the following CAC groups: 0, >0 to <100, ≥100 to <400, and ≥400. In addition to the progression of log-transformed CAC scores, we calculated regression analyses of EAT with the difference of square root of CAC at follow-up and the square root of CAC at baseline, using identical models. Also, we stratified regression analysis by age at baseline using the following age groups: <55, ≥55 to 65, and ≥65 years of age. To assess the effect in different BMI groups and rule out modeling effects of BMI and EAT due to their correlation, we further investigated the association of EAT with CAC progression stratified by BMI groups in unadjusted regression analysis (≤25, >25 to ≤30, >30 to ≤40, and >40 kg/m²). Risk factor-adjusted (model 4) regression analysis was performed in the following groups: ≤25 and >25 kg/m². To confirm the result of a positive association of EAT volume with CAC progression, we tested the association of EAT with CAC at follow-up when controlling for CAC at baseline in the model. Again, further adjustment for age, sex, and BMI as well as multivariable adjustment, ancillary to CAC at baseline was performed. Within the subset of subjects with CAC score = 0 at baseline, we determined the onset of CAC as CAC >0 at follow-up examination. The difference of EAT volume between subjects with and without onset of CAC was compared using the 2-sided Student t test. Successive logistic regression analysis was performed to determine the association of EAT with onset of CAC, using the same models as for the regression analysis of progression of CAC. Again, analysis was stratified by age groups. All analyses were performed using SAS software (version 9.2, SAS Institute Inc., Cary, North Carolina). A p value <0.05 indicated statistical significance.

**RESULTS**

Overall, 3,367 subjects (mean age 59 ± 8 years; 47% male) were included in this analysis, with detailed characteristics of the study cohort depicted in Table 1. Median CAC score at baseline was 7.0 (quartile [Q] 1: 0.0; Q3: 88.2) and 25.8 (Q1: 0.0; Q3: 190.0) after a follow-up period of 5.1 ± 0.3 years. EAT was strongly correlated with both BMI (r = 0.48; p< 0.0001) and waist circumference (r = 0.64; p < 0.0001), whereas BMI and waist circumference showed the strongest correlation (r = 0.80; p < 0.0001). Subjects with progression of CAC above the median had higher EAT volume than subjects with CAC change below the median (101.1 ± 47.1 vs. 84.4 ± 43.4; p < 0.0001).

CAC score at both baseline and follow-up examination increased with quartiles of EAT (Figure 1).
When stratifying by CAC group at baseline, we observed significantly higher CAC scores at follow-up for all CAC groups except for CAC $\leq 400$ (CAC $= 0$: n = 1,224; CAC $> 0$ to $< 100$: n = 1,335; CAC $\geq 100$ to $< 400$: n = 541; CAC $\geq 400$: n = 267).

### TABLE 1 Baseline Characteristics (N = 3,367)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>58.9 ± 7.6</td>
</tr>
<tr>
<td>Male</td>
<td>1,572 (46.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 ± 4.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>93.0 ± 12.7</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131.7 ± 20.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.3 ± 10.6</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>1,017 (30.2)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>146.1 ± 35.6</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>59.3 ± 17.2</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>298 (9.5)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>144.9 ± 98.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>373 (11.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>745 (22.1)</td>
</tr>
<tr>
<td>Former</td>
<td>1,145 (34.0)</td>
</tr>
<tr>
<td>Never</td>
<td>1,477 (43.9)</td>
</tr>
<tr>
<td>CAC score at baseline</td>
<td>7.0 (0.0, 88.2)</td>
</tr>
<tr>
<td>CAC score at follow-up</td>
<td>25.8 (0.0, 190.0)</td>
</tr>
<tr>
<td>EAT volume</td>
<td>92.8 ± 46.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or median (quartile 1; quartile 3). BMI = body mass index; CAC = coronary artery calcification; EAT = epicardial adipose tissue; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

### EAT VOLUME AND CAC PROGRESSION.

In regression analysis, EAT showed significant association with progression of CAC as demonstrated as percent change in (CAC + 1) with 6.3% (95% confidence interval [CI]: 2.3% to 10.4%; p = 0.0019) progression attributable to 1 SD of EAT volume. This effect was even strengthened when further adjusting for BMI (14.2% [95% CI: 9.2% to 19.3%]; p < 0.0001) and remained statistically significant after additional adjustment for age and sex (9.2% [95% CI: 4.7% to 14.7%]; p < 0.0001) as well as traditional cardiovascular risk factors (6.1% [95% CI: 1.2% to 11.2%]; p = 0.014). Similar results were observed when further adjusting for baseline CAC score (detailed data not shown). Results remained unchanged when additionally adjusting for positive family history of premature coronary heart disease (6.1% [95% CI: 1.2% to 11.2%]; p = 0.014). When using waist circumference instead of BMI in the model, similar results were observed (waist circumference adjusted: 11.5% [95% CI: 6.5% to 16.8%]; percent change in CAC + 1; p < 0.0001; multivariate [MV] adjusted: 7.8% [95% CI: 2.7% to 13.2%]; p = 0.0024).

Figure 2 demonstrates the association of EAT with progression of CAC, stratified by CAC score at baseline. In age, sex, and BMI-adjusted models, 1 SD of EAT was associated with 20% (95% CI: 11% to 31%; p < 0.0001) progression of CAC + 1 in subjects with a low CAC score (0 to <100). A lower
association was found for subjects with a CAC of $\geq 100$ to $<400$ with $8\%$ (95% CI: 3% to 13%; $p = 0.003$) progression of CAC + 1 attributable to EAT. In contrast, CAC $\geq 400$ showed no relevant association of EAT with CAC progression when adjusting for age, sex, and BMI ($0.2\%$ [95% CI: $-3.5\%$ to 4.1%]; $p = 0.90$). Similar results were observed when further adjusting for established cardiovascular risk factors, with 14% (95% CI: 5% to 24%) progression of CAC + 1 attributable to 1 SD of EAT in subjects with a CAC of $>0$ to $<100$ at baseline (Figure 2). Interestingly, subjects with a CAC of 0 at baseline showed no association of EAT with CAC progression (age, sex, and BMI-adjusted: $3.3\%$ [95% CI: $-5.4\%$ to 12.9%]; $p = 0.47$; MV-adjusted: $-2.2\%$ [95% CI: $-10.9\%$ to 7.3%]; $p = 0.6$). Using the difference of the square root of CAC at follow-up and at baseline, statistical significance was observed for identical models as for the calculation of percent of change of CAC + 1 (detailed data not shown).

Table 2 depicts the association of EAT with progression of CAC, stratified by age at baseline examination ($<55$, $\geq 55$ to $<65$, and $\geq 65$ years of age). For subjects below 55 years of age, a strong link with progression of CAC was observed in unadjusted and fully adjusted models. In contrast, no relevant association was observed for subjects $\geq 55$ years of age (Table 2).

To further assess the interaction of BMI and EAT on CAC progression, we determined the association of EAT with CAC progression in different BMI groups. Although association of EAT with CAC progression was strongest in subjects with BMI $\leq 25$ kg/m$^2$, with approximately 20% progression of CAC + 1 per SD of EAT volume, this association decreased with increasing BMI, with no link between EAT and CAC progression in subjects with BMI $>40$ kg/m$^2$ (Table 3). These findings were confirmed in multivariable analysis, where EAT was associated with CAC progression only in subjects with BMI $\leq 25$ kg/m$^2$ (13.1% [95% CI: 1.9% to 25.6%]; $p = 0.02$), whereas no relevant link was found for overweight.

Table 2 Age-Group-Specific Linear Regression Analysis for the Association of EAT Volume With Progression of CAC

<table>
<thead>
<tr>
<th>Age Group, yrs</th>
<th>n</th>
<th>% progression in CAC + 1</th>
<th>p Value</th>
<th>% progression in CAC + 1</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>1,136</td>
<td>27.7 (16.7–40.0)</td>
<td>&lt;0.0001</td>
<td>19.8 (8.9–31.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>≥55–&lt;65</td>
<td>1,372</td>
<td>6.2 (–1.0–13.9)</td>
<td>0.09</td>
<td>2.5 (–4.8–10.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>≥65</td>
<td>859</td>
<td>0.6 (–6.6–8.5)</td>
<td>0.9</td>
<td>3.9 (–7.2–7.9)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Depicted as % progression of CAC + 1 per each SD of EAT. *Multivariate (MV) adjustment included sex, BMI, systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, lipid-lowering medication, triglycerides, diabetes, present smoking, and former smoking.

CI = confidence interval; other abbreviations as in Table 1.
and obese subjects (BMI >25 kg/m²: 5.0% [95% CI: –0.4% to 10.8%]; p = 0.07).

Sex-specific analysis showed higher CAC progression per SD of EAT in females compared with males; however, sex difference did not reach statistical significance (age and BMI-adjusted: 6.9% [95% CI: 0.4% to 13.8%]; p = 0.037 vs. 12.1% [95% CI: 5.0% to 19.7%]; p = 0.0007; for sex interaction: p = 0.12; MV adjusted: 3.8% [95% CI: –2.7% to 10.8%]; p = 0.26 vs. 7.2% [95% CI: 0.1% to 14.8%]; p = 0.046; for sex interaction: p = 0.13, for men and women, respectively). This effect was explained by different CAC distribution of both sexes at baseline (detailed data not shown).

To further confirm our results, we assessed the association of EAT with CAC score at follow-up (log [CAC(follow-up)+1]) with CAC score at baseline (log [CAC(baseline)+1]) included in the model. Per SD of EAT, CAC + 1 at follow-up increased by 7.1% (95% CI: 2.9% to 11.3%; p = 0.0007), independent of CAC score at baseline. Parameter estimates stayed stable when further adjusting for age, sex, and BMI (10.4% [95% CI: 5.5% to 15.5%]; p < 0.001), as well as in multivariable models (6.2% [95% CI: 1.4% to 11.3%]; p = 0.011).

### Table 4: Logistic Regression Analysis for the Association of EAT Volume With Onset of CAC in Subjects With CAC = 0 at Baseline

<table>
<thead>
<tr>
<th></th>
<th>All Subjects With CAC = 0 at Baseline</th>
<th>Subjects ≥55 Years of Age With CAC = 0 at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>p Value</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.29 (1.13–1.48)</td>
<td>1.60 (1.24–2.05)</td>
</tr>
<tr>
<td>BMI-adjusted</td>
<td>1.21 (1.03–1.43)</td>
<td>1.54 (1.16–2.03)</td>
</tr>
<tr>
<td>BMI, age,* and sex-adjusted</td>
<td>1.07 (0.90–1.27)</td>
<td>1.52 (1.15–2.01)</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>1.01 (0.84–1.21)</td>
<td>1.37 (1.01–1.85)</td>
</tr>
</tbody>
</table>

*Age not included in age-specific analysis. MV adjustment included age (not for sex-specific analysis), sex, BMI, systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, lipid-lowering medication, triglycerides, diabetes, present smoking, and former smoking.

In the present analysis, we describe a link between EAT and progression of CAC as a surrogate marker of the coronary plaque burden. Although no association was observed for subjects with heavy calcification at baseline, we found a strong link of EAT volume with CAC progression for subjects with low CAC score at baseline. Together with the finding that the observed correlation between EAT volume and CAC progression as well as CAC onset was predominantly driven by subjects in the youngest decade of the investigated study cohort (45 to 55 years of age), these findings support the hypothesis that EAT may influence the atherosclerosis process at early stages. Interestingly, CAC progression was more pronounced in lean subjects, and association of EAT with CAC progression was independent of BMI, suggesting that quantification of EAT volume renders substantially different information than measurement of overall obesity despite their distinctive correlation. The present findings describe the paracrine impact of this local visceral adipose tissue on coronary plaque progression that is different from established mechanisms of atherosclerosis development.

Over the last decade, several studies investigated a potential link of epicardial and pericardial adipose tissue with CAC progression. Overall, 1,225 subjects (mean age 56.3 ± 7.2 years, 73% female) had a CAC score of 0 at baseline. Of those, 307 subjects developed CAC >0 during follow-up. Subjects with CAC onset had higher EAT volume at baseline then those with persisting CAC = 0 (83.8 ± 39.6 ml vs. 73.5 ± 35.3 ml; p < 0.0001). In univariate logistic regression analysis, 1 SD of EAT was associated with nearly 30% higher odds of developing CAC, which persisted after adjustment for BMI (Table 4). When adjusting for age, sex, and BMI, as well as for established cardiovascular risk factors, no relevant link between EAT volume and CAC onset was observed. However, when stratifying by age at baseline (<55, 55 to <65, and ≥65 years of age), we observed a strong association of EAT with CAC onset in young subjects (<55 years of age), with 60% higher odds for the development of CAC per 1 SD of EAT. In contrast, no link was observed for subjects 55 to <65 years of age (OR: 0.96 [95% CI: 0.75 to 1.23]; p = 0.8) and for subjects age 65 and older (OR: 1.01 [95% CI: 0.75 to 1.35]; p = 0.95). For subjects <55 years of age, the strong association remained after further adjustment (Table 4). Sex-specific analysis revealed no relevant sex difference for the association of EAT with onset of CAC (detailed data not shown).

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tissues with cardiovascular risk factors, coronary artery plaque burden, and coronary artery disease. Investigators from the Framingham Heart Study described an association of EAT with CAC score in a cross-sectional analysis. However, a significant link was only found when visceral abdominal adipose tissue was included in the model besides traditional risk factors; when adjusting for traditional risk factors alone, the link between EAT and CAC score did not reach statistical significance (1). Likewise, in the Heinz Nixdorf Recall study, the link of EAT with CAC score in cross-sectional analysis was ultimately explained by a shared risk factor profile (6). Besides calcific coronary atherosclerosis, association of epicardial and pericardial fat with noncalcified plaque components was also described (2,8). Ito et al. (19) reported an association of EAT with plaque burden and presence of CAD in subjects with a CAC score of 0, and Schlett et al. (20) found a link between EAT and CT-derived features of high-risk plaques. Together with our previous finding of a more pronounced association of EAT with future coronary events in subjects with low or no CAC, these results support the hypothesis that EAT may promote atherosclerosis development at early stages, and therefore, quantification of EAT from cardiac CT may enhance its prognostic value above coronary anatomy.

The finding of a stronger link of EAT with CAC progression in lean subjects is in good agreement with the current literature. Despite a strong correlation of EAT with BMI and waist circumference, Framingham investigators also found no attenuation of effect sizes for the association of EAT with CAC and prevalent CAD when controlling for these measures of general adiposity (1,3). When investigating the association of EAT with severity of CAD in 128 subjects undergoing coronary angiography for evaluation of angina pectoris, Gorter et al. (21) found that a link between EAT and CAD severity was present only in subjects with a BMI <27 kg/m². Together with our findings, these results suggest that EAT renders information relevantly differently from measures of general adiposity, as it may locally influence progression of coronary atherosclerosis above and beyond overall body fat.

The described association between epicardial adipose tissues and coronary plaque burden as well as presence of coronary heart disease is in part explained by a strong association of EAT with cardiovascular risk factors (1,6). However, there is growing evidence that the correlation of EAT with coronary heart disease may not fully be explained by risk factors. As further potential explanation, the endocrine activity of pericardial fat as visceral adipose tissue, secreting pro- and anti-inflammatory mediators and cytokines such as adiponectin, IL-6, and TNFα, is discussed in the literature (22–25). The amount of adiponectin, a stabilizer of the inhibitor of NF-kappa B released from pericardial fat (26), decreases with an increased amount of fat (27). The decrease of adiponectin enhances the activity of NF-kappa B, which leads to an increase in TNFα and, hence, to a local increase of inflammation (26). A mismatch of pro- and anti-inflammatory mediators and cytokines secreted by EAT is suspected to have a local influence on the underlying coronary arteries. Increased CD45 messenger ribonucleic acid expression in the EAT of subjects with coronary artery disease, representing elevated macrophage infiltration, and an increase of mast cells in the adventitia of coronary lesions has been observed (22,23,28). The hypothesis of a local and specific influence of EAT in coronary atherosclerosis is supported by our findings of the association of EAT with progression of coronary calcification independent of overall adiposity, despite its relatively small size compared to visceral abdominal or subcutaneous fat.

**STUDY LIMITATIONS.** Strengths of our study include the population-based design without selection of the cohort to adiposity-related traits. Traditional cardiovascular risk factors were measured using highly standardized protocols, and EAT was quantified using a reproducible volume-based method. Likewise, the same scanner technology and identical scanning protocols were used for repetitive cardiac CT measurement at initial enrollment and after 5 years of follow-up. Moreover, a potential bias by therapy was not possible because participants and their physicians were blinded to the results of the CAC scoring from the baseline examination. As a limitation, application of contrast media was not possible due to the population-based study design. Therefore, we were unable to detect noncalcified plaque components and are not able to make any conclusion on whether EAT may lead to progression of vulnerable plaques. Baseline CAC score is a predictor of CAC progression. Therefore, analysis of EAT on CAC progression may be impacted by baseline CAC. However, we performed several additional approaches including analyses in subgroups of CAC score at baseline, which confirmed the results. As a further limitation, our study is based on a predominantly Caucasian population; hence, generalizability to other ethnic groups remains uncertain. Last, in our analysis, we excluded subjects with revascularization during follow-up due to uncertainties on the
quantification of CAC after stent implantation or bypass surgery, which may have led to a selection bias.

CONCLUSIONS

EAT volume is associated with CAC progression after 5 years, especially in young subjects and subjects with low CAC score at baseline, independent of traditional cardiovascular risk factors. These findings support the hypothesis that EAT promotes early atherosclerosis development.

REFERENCES


KEY WORDS cardiac computed tomography, coronary artery calcification, epicardial adipose tissue, epidemiology, Heinz Nixdorf Recall study

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