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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/m^2: 19.8% [95% CI: 9.2% to 31.4%]; $p = 0.0001$, BMI >40 kg/m^2: 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.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAC = coronary artery calcification

CI = confidence interval

CT = computed tomography

EAT = epicardial adipose tissue

HDL = high-density lipoprotein

LDL = low-density lipoprotein

MV = multivariate

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.

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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