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Persistent epicardial adipose tissue accumulation is associated with coronary plaque vulnerability and future acute coronary syndrome in non-obese subjects with coronary artery disease

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ABSTRACT

Objective. Epicardial adipose tissue (EAT) is recognized as a novel risk factor for coronary artery disease (CAD), and its contribution is thought to be stronger in non-obese patients than in obese patients. However, the prognostic impact of the progression of EAT accumulation after comprehensive management for atherosclerotic risk factors remains unclear. This study aimed to investigate whether an increase of the EAT volume during follow-up predicts future acute coronary syndrome (ACS) events in non-obese CAD patients. **Methods**. This study consisted of 517 non-obese CAD patients (368 men; age, 66 ± 10 years) who underwent serial multidetector computed tomography (MDCT) examinations to evaluate coronary atherosclerosis progression. The MDCT examination was used to assess the severity of stenosis, plaque characteristics, and EAT volume. All patients received comprehensive management to reduce CAD risk factors after the first MDCT examination. The MDCT examination was repeated at 6–24 months, and patients were followed-up for more than 1 year or until the occurrence of ACS events. **Results**. Of 517 patients, 159 (31%) patients were classified into increase of EAT volume during follow-up, 91 (18%) into decrease of EAT volume during follow-up, and 267 (51%) patients into constant of EAT volume during follow-up. The prevalence of obstructive plaques and MDCT-derived vulnerable features of coronary plaques were significantly elevated in patients with increase of EAT volume during follow-up. In contrast, no significant changes were observed in the other 2 groups. During the follow-up period of 4.1 ± 1.8 years (median 4.4 years) after the second MDCT examination, ACS occurred in 43 (8.3%) patients. Multivariate Cox regression analysis showed that the presence of low-attenuation plaque (hazard ratio [HR]; 1.78, $p = 0.04$) and napkin-ring sign (HR; 3.74, $p < 0.001$) at second MDCT examination, and changes of EAT volume per 10 ml (HR; 1.34, $p = 0.004$) were associated with future ACS events. **Conclusion**. Patients with increase of EAT volume during follow-up despite comprehensive management for CAD risks had an increased prevalence of obstructive plaques and plaques with high-risk features, which could be associated with unfavorable ACS outcomes in non-obese CAD patients.

1. Introduction

Growing evidence supports the physiological and metabolic importance of epicardial adipose tissue (EAT), especially in the association of cardiovascular risk profiles and the pathogenesis of coronary artery disease (CAD). EAT also represents as a novel therapeutic target for obesity-related cardiovascular diseases [1]. Significant reduction of EAT accumulation by very low calorie diet [2,3] or bariatric surgery [4,5] was observed in almost all of severe obese patients resulting in the improvement of cardiac morphology or function. However, the management for EAT accumulation and the prognostic impact of persistent EAT accumulation remain unclear in non-obese CAD patients.

Multidetector computed tomography (MDCT) has been used for the simultaneous assessment of CAD and measurement of EAT volume in the clinical setting [6–14]. Furthermore, MDCT is

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currently used to assess the serial changes in plaque morphology or EAT accumulation resulting from therapeutic intervention [15,16]. The present study aimed to investigate whether the progression of MDCT-estimated EAT volume after comprehensive management for CAD predicts long-term acute coronary syndrome (ACS) outcome in non-obese CAD patients.

2. Methods

2.1. Study population

The present study was a subanalysis of our prospective MDCT database to investigate the prognostic impact of coronary plaque characteristics on long-term cardiovascular outcomes [14,17]. From December 2005 to March 2013, a total of 550 consecutive patients who underwent serial MDCT examination for the evaluation of CAD progression were enrolled. After the MDCT examination, we excluded 33 patients with poor MDCT image quality. Finally, 517 patients (368 men; age, 66 ± 10 years) were included in the study (Fig. 1). Of the 517 patients, 138 patients (27%) had typical angina, 175 patients (34%) had atypical angina, and 84 patients (16%) had non-cardiac chest pain. The remaining asymptomatic patients (23%) were referred for evaluation of CAD in the presence of multiple CAD risk factors, peripheral arterial disease, cerebrovascular disease, abnormal findings on electrocardiogram and echocardiography. The exclusion criteria were as follows: 1) obesity defined as body mass index (BMI) $\geq$30 kg/m^2, 2) history of open heart surgery including coronary artery bypass grafting surgery, 3) chronic kidney disease, and 4) coronary revascularization within 4 weeks prior to the first MDCT examination and during 6–24 months between the first and second MDCT examination. Patients with previous coronary revascularization were included (n = 169), and segments with prior stent placement were excluded from the MDCT analysis (n = 221). The present study was approved by the Institutional Review Board of the Osaka Ekisaikai Hospital and written informed consent was obtained from all patients.

2.2. Study protocol

MDCT examinations were performed at study enrollment and at 6–24 months (mean interval; 12 ± 5 months). At the first MDCT examinations, the following factors were evaluated in each patient; hypertension (blood pressure $\geq$140/90 mmHg on repeated measurements, or treatment with antihypertensive agents), hypercholesterolemia (total serum total cholesterol level $\geq$200 mg/dl, or statin treatment), diabetes mellitus (fasting plasma glucose level >126 mg/dl, or treatment with hypoglycemic drugs or insulin, or a combination of both), and current smoking status. After the first MDCT examination, all patients received individualized, comprehensive management including medications and life-style changes to manage the above-mentioned risk factors for CAD according to the AHA/ACC guidelines [18]. All patients were advised to maintain an appropriate balance of physical activity (walking for $\geq$30 min/day) and optimum caloric intake [19]. Patients were followed up in the hospital or at a clinic visit every month, and they were encouraged to adhere to the recommended changes in life-style and diet. After the second MDCT examination, patients were divided into the following 3 groups; 1) increase of EAT volume during follow-up (>10 ml); 2) decrease of EAT volume during follow-up (<10 ml) and 3) constant of EAT volume during follow-up. These patients were then followed-up for more than 1 year or until the occurrence of ACS events. The following biophysical and laboratory parameters were also assessed at the time of the MDCT examinations; BMI, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C (L/H) ratio, glucose, and C-reactive protein (CRP).

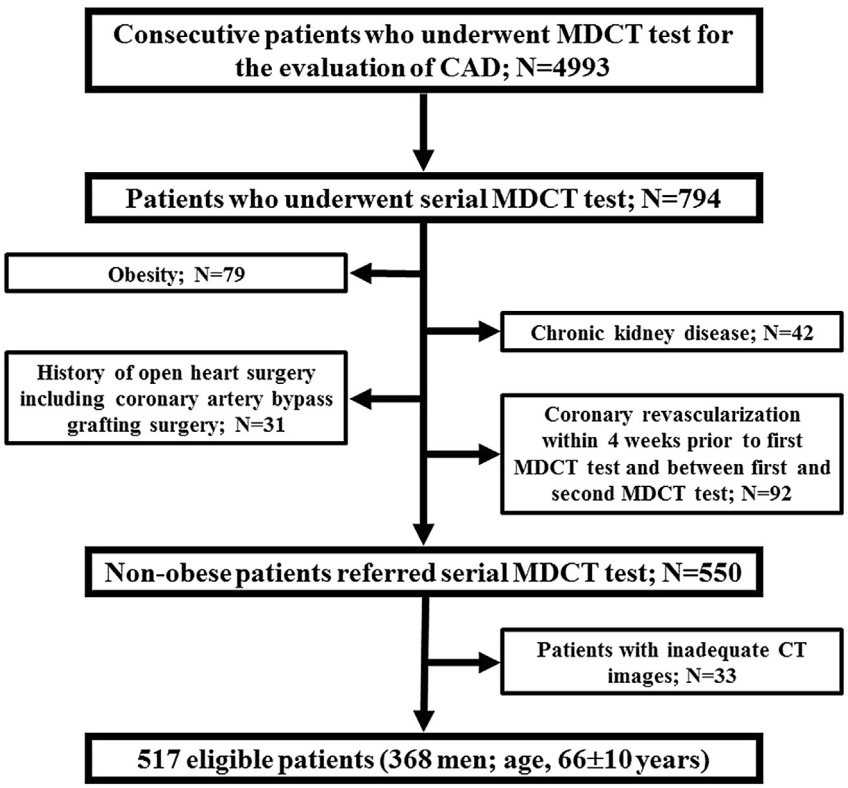

Fig. 1. Flow chart illustrating the study population. CAD = coronary artery disease, and MDCT = multi-detector computed tomography.