IJC Metabolic & Endocrine 3 (2014) 14–19

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Increased epicardial adipose tissue volume predicts insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome

Taro Narumi [1], Tetsu Watanabe *,[1], Tadateru Iwayama [1], Shinpei Kadowaki [1], Yoichiro Otaki [1], Yuki Honda [1], Satoshi Nishiyama [1], Hiroki Takahashi [1], Takanori Arimoto [1], Tetsuro Shishido [1], Takuya Miyamoto [1], Isao Kubota [1]

The Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form 6 March 2014
Accepted 18 March 2014
Available online 27 March 2014

Keywords:
Epicardial adipose tissue
Insulin resistance
Coronary artery disease

ABSTRACT

Background/objectives: Epicardial adipose tissue (EAT) reportedly secretes various adipokines that evoke insulin resistance in patients with obesity or metabolic syndrome. However, it remains unclear whether EAT also plays a role in the development of insulin resistance in lean subjects. The purpose of this study was to investigate the impact of EAT volume on the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome.

Methods: We prospectively studied 624 consecutive patients who underwent multidetector computed tomography (MDCT) and measured EAT volume between January 2009 and June 2011. Obesity was defined as body mass index ≥ 25 kg/m^2, and metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. After we excluded 385 patients with obesity or metabolic syndrome, 239 patients were enrolled in the present study.

Results: There were 102 (42.7%) subjects with insulin resistance (homeostasis model assessment ratio [HOMA-R] >2.5) and 88 (36.8%) subjects with coronary artery disease. After adjusting for age, gender, and body mass index, increased EAT volume (≥ 35 ml mean EAT volume) was independently associated with insulin resistance (odds ratio 2.6, 95% confidence interval 1.5–4.8). Furthermore, increased EAT volume was also associated with coronary artery disease (odds ratio 1.9, 95% confidence interval 1.0–3.6) after adjustment of age, gender, body mass index, and the presence of insulin resistance.

Conclusion: Increased EAT volume may play a key role in the development of insulin resistance and coronary artery disease, even in non-obese subjects without metabolic syndrome.

1. Introduction

The prevalence rates of obesity and overabundance of visceral fat are increasing in developed countries [1]. It is obvious that obesity and increased visceral fat are associated with impaired glucose tolerance and the development of metabolic syndrome [2,3], which is a cluster of risk factors for coronary artery disease [4]. Abdominal visceral fat can produce large quantities of various adipokines that are strongly associated with coronary artery disease development [5]. Although the prevalence of obesity is still markedly lower in Japan compared to Western countries (body mass index ≥ 25 kg/m^2, 28% in male and 22% in female; ≥ 30 kg/m^2, 2.9% in male and 3.4% in female), the Japanese prevalence rates of obesity and obesity-linked diseases have recently increased [6–9].

Because epicardial adipose tissue (EAT) surrounding the heart is adjacent to major coronary arteries, EAT is thought to be a source of several inflammatory mediators involved in the development of coronary artery disease [10,11]. Increased EAT volume and high levels of inflammatory mediators are significantly related to insulin resistance and coronary artery disease in obese subjects or patients with metabolic syndrome [11,12]. We previously reported that high EAT volume was associated with coronary artery disease in both obese and non-obese patients [13]. A recent study described that insulin resistance is increasingly prevalent among Japanese subjects without obvious obesity [14]. However, little is known about the pathological role of EAT in subjects without obesity or metabolic syndrome.

* Corresponding author at: Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan. Tel.: +81 23 628 5302; fax: +81 23 628 5305.
E-mail address: tewatana@med.id.yamagata-u.ac.jp (T. Watanabe).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcme.2014.03.003

The purpose of this study was to investigate the impact of increasing EAT volume on the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome.

2. Methods

2.1. Study population

We performed multi-detector row computed tomography (MDCT) in 624 consecutive patients at the Yamagata University Hospital between September 2009 and October 2011. We excluded 82 patients who had metabolic syndrome, 189 patients with obesity, and 115 patients without fasting insulin level data. The remaining 239 patients were included in the present study (Fig. 1). All subjects provided written informed consent prior to their participation, and the protocol was approved by the institution's Human Investigation Committee. The procedures were performed in accordance with the Helsinki Declaration.

2.2. Definition of metabolic syndrome

Height and body weight were measured, and venous blood samples were collected before MDCT. We defined metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria [15]. We modified these criteria for abdominal obesity by using body mass index ≥25 kg/m^2 in place of waist circumference [16]. Metabolic syndrome requires at least three of the following five criteria: body mass index ≥25 kg/m^2, elevated triglyceride ≥150 mg/dl, reduced high-density lipoprotein cholesterol (HDLc) <40 mg/dl in men and <50 mg/dl in women, elevated fasting plasma glucose ≥110 mg/dl or previously diagnosed diabetes mellitus, elevated blood pressure (systolic blood pressure ≥130 mm Hg, and/or diastolic blood pressure ≥85 mm Hg) or antihypertensive medication.

2.3. Definitions of insulin resistance and coronary artery disease

Insulin tolerance was evaluated using the homeostasis model assessment ratio (HOMA-R, HOMA-R = fasting insulin levels × fasting plasma glucose × 1 / 405), and insulin resistance was defined as HOMA-R >2.5[17]. We defined coronary artery disease as ≥50% coronary artery stenosis in each axial MDCT based on the Society of Cardiovascular CT guidelines [18].

2.4. Measurement of EAT volume

Cardiac MDCT was performed using a 64-slice MDCT scanner (Aquilion 64, Toshiba, Tokyo, Japan). Nitroglycerin was administered orally before the CT scan was performed. A total of 51–100 ml of contrast media (Iopamidol, Bayer Co. Ltd., Leverkusen, Germany) was injected at a flow rate of 3.0–4.6 ml/s depending on the patient's body weight. The region of interest was placed within the ascending and descending aorta, and scanning was commenced when the CT density reached 250 Hounsfield units at the ascending aorta or 180 Hounsfield units at the descending aorta. The scan was performed between the tracheal bifurcation and the diaphragm. Radiographic parameters were collimation width, 0.5 mm; rotation speed, 0.4 s/rotation; tube voltage, 120 kV; and effective tube current, 400–450 mA. Cardiac images were analyzed at the most motionless phase of the cardiac cycle, which was most frequently the mid-diastolic phase, with retrospective cardiac gating at 75% of the R-wave to R-wave interval.

EAT was defined as the adipose tissue between the surface of the heart and the visceral layer of the pericardium. After manually tracing a single region of interest containing the heart and EAT on cross-sectional images, an EAT image ranging from −200 to −30 Hounsfield units was extracted from the heart image. The EAT area was measured every 5 mm from the atrial appendage to the apex over the diaphragm. EAT volume was automatically calculated as the sum of the EAT areas using analysis software (ZIO station, ZIO SOFT Inc., Tokyo, Japan) [13].

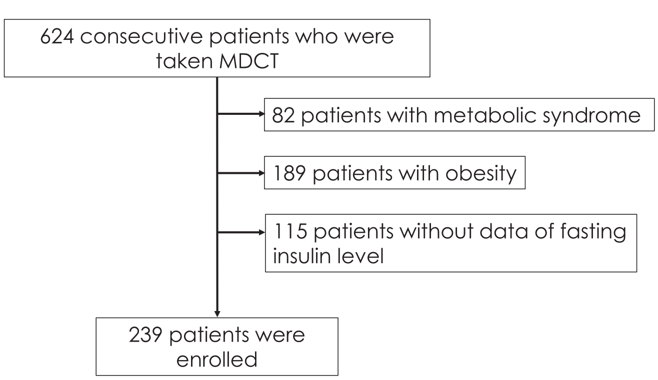

Fig. 1. Recruitment of patients who underwent MDCT at Yamagata University Hospital. MDCT, multidetector computed tomography.

2.5. Statistical analysis

Data are presented as means and standard deviations (SDs). If the data were not normally distributed, they are presented as medians and interquartile range. Unpaired Student's *t*-tests and chi-square tests were used to assess continuous and categorical variables, respectively. Mann–Whitney *U*-tests were employed for data that were not normally distributed. Univariate and multivariate analyses with logistic regression were used to determine significant predictors of insulin resistance and coronary artery disease. Multivariate analysis was adjusted by factors that were found to be significant in univariate analysis. The optimal cutoff value for EAT volume was determined as that with the largest sum of sensitivity plus specificity on the receiver operating characteristic curve. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with a standard statistical program package (JMP version 10; SAS Institute, Cary, North Carolina).

3. Results

3.1. Patient characteristics

The clinical characteristics of the 293 patients enrolled in the present study are listed in Table 1. There were 76 females (32%) and mean age was 63 (13) years old. There were 22 (9%) current smokers and 88 (37%) patients with coronary artery disease. The median EAT volume was 35 ml (interquartile range: 15–51), and the mean body mass index was 22 (2) kg/m^2. There were 102 (43%) patients with insulin resistance, and they exhibited higher serum levels of high-sensitivity C-reactive protein (hsCRP), and low-density lipoprotein cholesterol level (LDLc), as well as higher coronary artery disease prevalence compared to those without it. Furthermore, patients with insulin resistance showed higher EAT volume and were more likely to have undergone coronary artery bypass graft or percutaneous coronary intervention compared with those without insulin resistance.

3.2. Clinical features of patients with coronary artery disease

There were 88 (30%) patients with coronary artery disease in the present study. They were younger and had higher estimated glomerular filtration rate (eGFR), higher serum hsCRP levels, and lower serum HDLc levels compared to those without coronary artery disease (Table 2). Moreover, patients with coronary artery disease exhibited higher EAT volume, a greater prevalence of insulin resistance, and more plaque lesions compared to patients without coronary artery disease.