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Impact of adipose tissue composition on cardiovascular risk assessment in patients with stable coronary artery disease

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ABSTRACT

Background and aims: Visceral adipose tissue (VAT), unlike subcutaneous adipose tissue (SAT), is highly correlated with cardiovascular risk factors. This study aimed to evaluate the predictive value of adipose tissue composition, as measured by computed tomography, for cardiovascular events in patients with stable coronary artery disease.

Methods: 357 consecutive patients who underwent 64-slice computed tomography and elective percutaneous coronary intervention (PCI) were recruited. The ratio of visceral to subcutaneous adipose tissue (VAT/SAT) was calculated. Patients were divided into three groups in accordance with VAT/SAT (low VAT/SAT, <0.55 [<25th percentile]; moderate VAT/SAT, 0.55–1.03 [25th–75th percentile]; high VAT/SAT, ≥1.03 [≥75th percentile]). The investigated risk factors were hypertension, hyperglycaemia, and dyslipidaemia. We analysed the incidence of major adverse cardiovascular events (MACE), defined as the composite of cardiac death, myocardial infarction, and any revascularization.

Results: The rate of patients with two or more concomitant risk factors was significantly higher in the high VAT/SAT group ($p = 0.006$). During 1480 person-years, 109 events were documented. There was a significant association between the incidence of MACE and VAT/SAT, with the worst event-free survival rate in the high VAT/SAT group (log-rank, $p = 0.01$). In Cox analysis, the hazard ratio of high VAT/SAT for MACE was 2.72 (95% confidence interval 1.04–7.09, $p = 0.04$) compared with the low VAT/SAT after adjustment for confounding factors.

Conclusions: Increased VAT/SAT is independently associated with the incidence of MACE, indicating that adipose tissue composition is a useful predictor of cardiovascular outcome, after elective PCI.

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1. Introduction

Visceral adipose tissue (VAT) accumulation is associated with metabolic abnormalities and cardiovascular events [1–5]. Visceral adiposity has also been demonstrated to be associated with the extent of coronary atherosclerosis among patients with suspected or known coronary artery disease [6–9]. However, there are limited data regarding the effect of visceral adiposity on cardiovascular outcomes after coronary revascularization.

In contrast to VAT, subcutaneous adipose tissue (SAT) has been suggested its cardioprotective properties [10–13]. The absolute value of VAT does not exactly reflect the distribution of adipose tissue and a high VAT volume may reflect a high overall adiposity volume, as well as propensity to store adipose tissue viscerally. Previous studies have shown that the ratio of visceral to subcutaneous adipose tissue (VAT/SAT), a metric of overall adipose tissue distribution, is a correlate of cardiometabolic risks independent of body mass index (BMI) and absolute VAT values [14]. VAT/SAT has

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been also reported to be an independent predictor of cardiovascular events in patients with chronic kidney disease [15].

We hypothesized that adipose tissue composition, or the propensity to store adipose tissue viscerally relative to subcutaneously, is associated with cardiovascular risk factors and outcomes in patients with stable coronary artery disease. Therefore, the present study aimed to determine whether VAT/SAT, as measured by 64-slice computed tomography (CT), is a useful marker for detecting individuals at higher risk after elective percutaneous coronary intervention (PCI), and who might therefore benefit from intensive therapy.

2. Patients and methods

2.1. Study population

This study consisted of 357 consecutive patients who underwent 64-slice coronary CT angiography and successful elective PCI for *de novo* lesions in Chubu Rosai Hospital, Nagoya, Japan between January 2007 and December 2010. Sixty-four-slice coronary CT angiographies were performed for clinical purposes on suspicion of coronary artery disease before elective PCI (median, 22 days; interquartile range, 8–43 days). Plain abdominal CT scans were also performed while procedures of coronary CT angiographies and VAT and SAT area were measured. We excluded patients who were lost to follow-up (3 patients). All patients had angina, documented myocardial ischaemia, or both. The ethics committee of Chubu Rosai Hospital approved the study and all patients provided written informed consent. This study complies with the Declaration of Helsinki.

2.2. Protocol for 64-slice CT scans and adiposity measurements

Abdominal 64-multislice CT scans were performed in the supine position (Light Speed VCT; GE Healthcare, Waukesha, Wisconsin, USA) and the images were obtained during a breath-hold after normal expiration. Collimation of the detector was 64 × 0.625 mm, the gantry rotation speed was 350 ms/rotation, the tube voltage was 120 kV with a current of 350–700 mA, and the table feed was 8 mm/rotation. Abdominal adiposity measurements were performed at the umbilicus level, which is approximately the level of lumbar segments 4 and 5. Adipose tissue areas were determined and distinguished from other tissues semi-automatically using dedicated software (Advantage Workstation 4.2; GE Healthcare). SAT was defined as extraperitoneal adiposity between the skin and muscle, with attenuation ranging from −150 to −50 Hounsfield units (HU). Intraperitoneal adiposity with the same density as SAT was defined as VAT [6,7]. Two experienced analysts, who had not been informed of characteristics and clinical outcomes of the patients, measured VAT and SAT. A total of 30 randomly selected lesions were measured for evaluation of inter- and intra-observer agreement. The inter- and intra-observer variabilities of VAT and SAT were well correlated ($r = 0.99$ [$p < 0.001$] and $r = 0.99$ [$p < 0.001$], respectively). The VAT/SAT ratio was calculated. Patients were divided into three groups in accordance with VAT/SAT (low VAT/SAT, <25th percentile; moderate VAT/SAT, 25th–75th percentile; high VAT/SAT, ≥75th percentile).

2.3. Assessment of cardiovascular risk factors

Cardiovascular risks factors were defined as follows based on the definition of metabolic syndrome [16]: (1) risk TG, serum triglyceride levels ≥150 mg/dl; (2) risk HDL, high-density lipoprotein cholesterol levels <50 mg/dl in women or <40 mg/dl in men; (3) risk HT, known hypertension or blood pressure ≥130/85 mmHg; and (4) risk FBS, known diabetes or fasting glucose ≥100 mg/dl.

2.4. Coronary angiography and PCI

Baseline angiography was evaluated by independent investigators who were not involved in the procedures and were blinded to the outcomes. A computerized quantitative analysis system (QCA-CMS System, version 6.0.39.0; MEDIS, Leiden, The Netherlands) was used with a guide catheter for calibration. The operators in charge, who were blinded to the adiposity measurements, determined the method and device for PCI according to angiography and conventional intravascular ultrasound findings.

2.5. Clinical follow-up

Clinical follow-up data were obtained through admission and outpatient medical records or by telephone interview. Follow-up was concluded on January 5th, 2015. The endpoint of the study was major adverse cardiac events (MACE), defined as the composite of cardiac death, non-fatal myocardial infarction, and any revascularization, including target lesion revascularization and revascularization of new lesions. Events at the time of the index interventional procedure and during the index hospitalization were not assessed. For multiple occurrences of events, the time to the first event was used as the time when MACE was detected. Myocardial infarction was defined as the development of signs and/or symptoms of ischaemia accompanied by an elevation of creatine kinase-myocardial band or troponin T levels at least two-fold higher than normal, or new significant Q waves in two or more contiguous leads [17]. The target lesion was defined as the area covered by the stents plus 5-mm margins proximal and distal to the edge of the stent. Any revascularization was based on clinical findings, such as the presence of ischaemic symptoms, a positive functional ischaemia assessment, or an ischaemic change in an electrocardiogram. The events were assessed by investigators who were blinded to the clinical data.

2.6. Statistical analyses

All normally and non-normally distributed continuous values are expressed as the mean ± standard deviation and median (interquartile range), respectively. Categorical variables are expressed as numbers (proportion). We compared normally distributed continuous variables using analysis of variance, and non-normally distributed variables (triglycerides, brain natriuretic peptide, total adipose tissue, VAT, SAT, and VAT/SAT) using the Kruskal–Wallis test. Categorical variables were compared using Fisher's exact test or the chi-squared test. Event-free survival was analysed using Kaplan–Meier estimation with the log-rank test. The Cox proportional hazards model was used to estimate the contribution of VAT/SAT for prediction of cardiovascular events during follow-up. We considered age, male sex, body mass index, statins, and conventional coronary risk factors (current smoker, estimated glomerular filtration rate, diabetes mellitus, hypertension, and dyslipidaemia) as candidate variables for inclusion in multivariate analysis. We further adjusted for the absolute VAT area as a candidate variable in multivariate analysis. A p value < 0.05 was considered statistically significant. Calculations were performed using SPSS statistical software version 18.0 (SPSS Institute Inc., Chicago, IL, USA) and R 2.13.1 (R Development Core Team 2011, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. Low VAT/SAT,

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