Correlations between the abdominal fat-related parameters and severity of coronary artery disease assessed by computed tomography

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Background: Obesity is considered a challenging public problem, which has been proven to be closely associated with coronary artery disease (CAD). Each risk factor of CAD has been separately studied many times in the past, but very few have comprehensively and quantitatively evaluated the relationship between the abdominal fat-related parameters and severity of CAD. The aim of this study was to analyze whether the abdominal fat-related parameters were associated with severity of CAD using abdominal non-enhanced computed tomography (NECT).

Methods: Patients who went through both abdominal NECT and invasive coronary angiography (ICA) were included and retrospectively analyzed. The abdominal fat-related parameters [the ratio of visceral adipose tissue to subcutaneous adipose tissue (VAT/SAT ratio)] and traditional cardiovascular risk factors were evaluated in the participants with or without obstructive CAD. The correlations between the abdominal fat-related parameters and severity of CAD were assessed, and the multivariable logistic regression analysis was performed to investigate the parameters that could be used to predict the severity of CAD.

Results: A total of 223 consecutive subjects (obstructive CAD group, n=117; non-obstructive CAD group, n=106) were analyzed. The VAT/SAT ratio was significantly higher (0.95±0.33 *vs.* 0.70±0.25, P<0.001) in obstructive CAD (O-CAD) patients than that in non-obstructive CAD (NO-CAD) patients. There was a trend to having nonalcoholic fatty liver disease (NAFLD) in the O-CAD patients than that of NO-CAD (P=0.002); the abdominal aortic calcification (AAC) score in O-CAD patients were higher than that in NO-CAD patients (P<0.001). The multivariable logistic regression analysis demonstrated that VAT/SAT ratio, NAFLD, and AAC score were independent predictors of O-CAD after adjusting the traditional cardiovascular risk factors. The area under the curve (AUC) of the combination of the above risk factors is 0.85, which leads to an increase in AUC than each risk factor alone in differentiating patients with or without O-CAD.

Conclusions: VAT/SAT ratio, NAFLD, and AAC score are correlated with the severity of CAD, indicating their characteristics of being independent risk factors for O-CAD, irrespective of the traditional cardiovascular risk factors. Those CT-derived parameters may make positive contributions to the differentiation of the patients with increased risk of O-CAD.

Keywords: Coronary artery disease (CAD); risk factors; invasive coronary angiography; non-enhanced computed tomography (NECT)

Introduction

With the development of preventive medicine, the morbidity of coronary artery disease (CAD) is under control to a certain extent; however, the mortality of CAD remains a major problem worldwide (1-4). Besides, obesity is considered a challenging public problem (5), which has been proven to be closely associated with CAD (6-10). Numerous anthropometric adiposity measurements have been commonly used to evaluate obesity, including waist circumference (WC), body mass index (BMI), waist to height ratio (WHtR), and waist to hip ratio (WHR). However, these exhibited a weaker association between these values and risk factors for CAD unless people present with abundant visceral fat (11-13). Current researchers have reported the importance of fat distribution in cardiac metabolism (14).

Ectopic fat deposit refers to excessive adipose tissue located in an unusual position which involves visceral and subcutaneous region, muscle, and the abdominal organs (14,15). Visceral adipose tissue (VAT), being an endocrine organ, can secrete adipokines including cytokines and chemokines (14). It can also lead to insulin resistance and vascular inflammation, playing a role in obesity-mediated CAD (11,16-19). VAT is associated with cardiovascular disease and can be used as a cardiometabolic risk marker (20), while subcutaneous adipose tissue (SAT) shows the beneficial metabolic impact on the contrary (11,13,16,20-22). The VAT/SAT ratio is a unique parameter, which is relevant to vascular inflammation or cardiac events (13,16,20). Other abdominal parameters such as attenuation of other abdominal parenchymatous organs and abdominal aortic calcification (AAC) represent the abdominal fat distribution (23-34). Therefore, the combination of the above-mentioned risk factors may provide a better understanding of the association between the abdominal fat-related parameters and severity of CAD.

The purpose of this study is to comprehensively and quantitatively analyze whether the abdominal fat-related parameters are associated with severity of CAD using abdominal non-enhanced computed tomography (NECT).

Methods

Study design and study population

A study flowchart is shown in *Figure 1*. In-patients who went through both abdominal non-enhanced CT (NECT) and invasive coronary angiography (ICA) from August 2016 to October 2017 were retrospectively analyzed, and the examination of ICA should be of the first time. Informed consents were obtained from all participants. Traditional cardiovascular risk factors such as current smoking, diabetes mellitus, hypertension, high-density lipoprotein-cholesterol (HDL-C), and other baseline characteristics were collected. Patients with incomplete information and those with a history of alcohol abuse, severe abdominal organs disease, or abdominal surgery were excluded.

Evaluating the severity of coronary artery stenosis with ICA

ICA was examined with a standard technique, in which the diameter stenosis (DS) of each major epicardial coronary artery was assessed using quantitative coronary angiography (QCA) by two of 10-year-experienced cardiologists who were blinded to patients' characteristics. In case of disagreement, a consensus was reached after consultation. All of the main coronary arteries, including left anterior descending artery (LAD), left circumflex (LX), and right coronary artery (RCA), were evaluated. Obstructive CAD (O-CAD) was defined as DS ≥50% in at least one of the main coronary arteries.

Measurements of the abdominal fat-related parameters

The abdominal fat-related parameters were acquired with abdominal NECT scan (Sensation 64, Siemens, Forchheim, Germany; Discovery CT750 HD and GE revolution, GE Healthcare, Milwaukee, WI, USA) using 120 kVp, 65 mAs, and 5-mm slide thickness. The images were captured in the supine position.

The abdominal perimeter was measured at the level of the umbilicus. The abdominal adipose tissue area VAT, total adipose tissue (TAT), and SAT were quantified utilizing a semi-automated tool of ImageJ 1.52e (National Institute of Health, Bethesda, MD, USA) at the level of the umbilicus (29). VAT was calculated by manually tracing the intra-abdominal wall muscular layer with the attenuation threshold ranging from –190 to –30 HU. TAT was also measured at the level of the umbilicus with the same density threshold, and SAT was quantified by deducting VAT from TAT (21,30,35). With these two parameters, the VAT/SAT ratio was then calculated (*Figure 2*). Nonalcoholic fatty liver disease (NAFLD) was defined as the ratio of liver-to-spleen attenuation<1 (L/S ratio). Regions of interest (ROIs) with an area of over 2 cm^2 were placed at different axial levels of the liver and the spleen in the same axial image correspondingly, large vessels or biliary structures in the
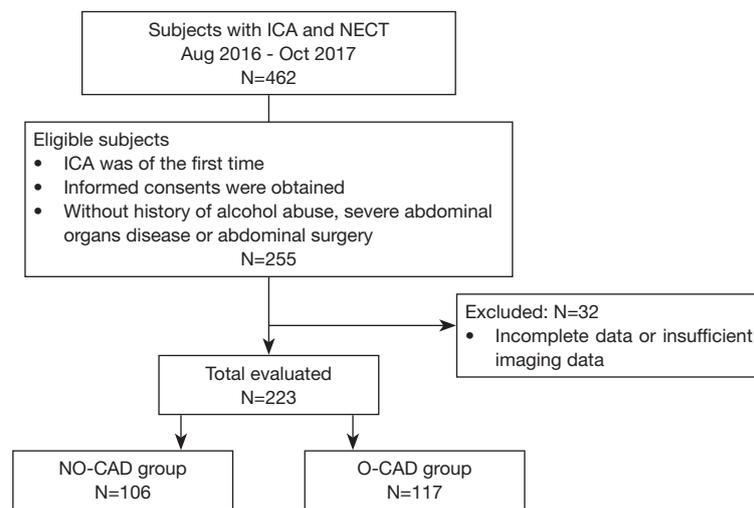
Figure 1 Study flowchart. ICA, invasive coronary angiography; NECT, non-enhanced computed tomography; CAD, coronary artery disease.
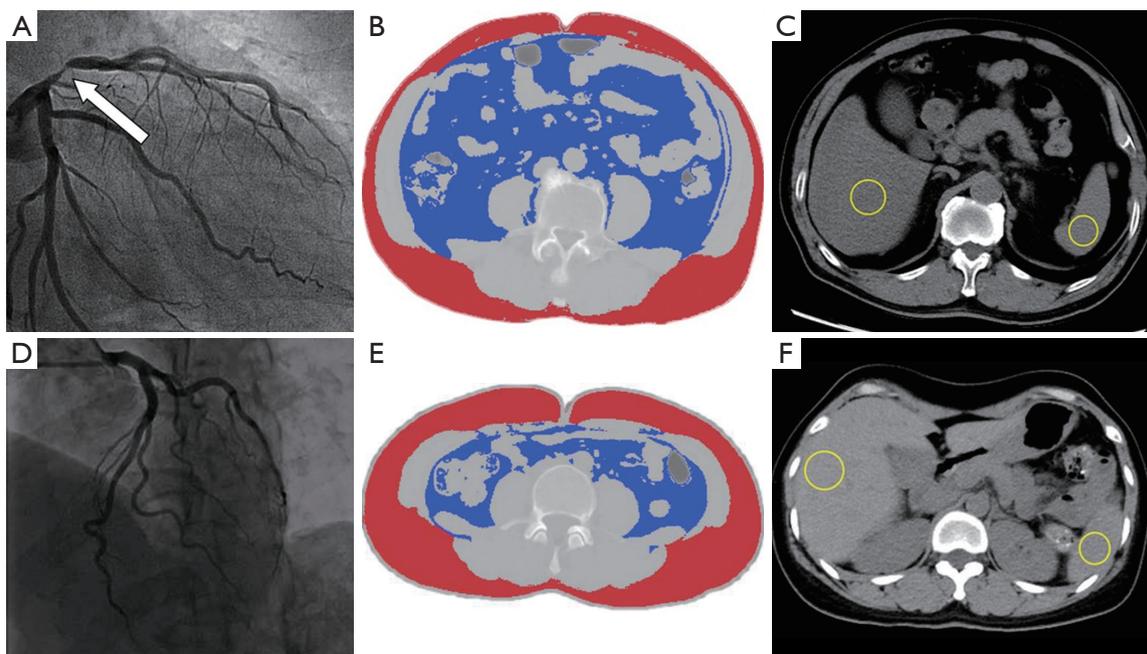
Figure 2 A 75-year-old male with O-CAD; the AAC score is 4. (A) ICA confirms the stenosis of the proximal segment of the LAD is 90% (more than 50%) (arrow); (B) the image shows the measurements of TAT, VAT, and SAT at the level of the umbilicus, and the segmentation of VAT (blue) and SAT (red) are calculated using a semi-automated tool of ImageJ software. The measurements of VAT (192.2 cm^2), TAT (318.6 cm^2), and SAT (126.3 cm^2) produce a VAT/SAT ratio of 152.2%. The measurement of abdominal perimeter is 94.4 cm; (C) the CT image demonstrates attenuation measurements of the liver and spleen, showing a diffuse fat accumulation in the liver with a mean attenuation of the liver of 40.4 HU and that of the spleen of 52.1 HU. Conversely, a 41-year-old female with NO-CAD; the AAC score is 0; (D) ICA confirms the three main vessels of the coronary artery are normal; (E) the measurements of TAT, VAT, and SAT at the level of the umbilicus are 201.4, 51.5, and 149.9 cm^2, respectively, and the VAT/SAT ratio is 34.3%. The abdominal perimeter is 80.5 cm; (F) the participant without NAFLD has a mean attenuation of the liver of 62.1 HU and that of the spleen of 51.0 HU. ICA, invasive coronary angiography; LAD, left anterior descending artery; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VAT/SAT ratio, the ratio of visceral adipose tissue to subcutaneous adipose tissue; NAFLD, nonalcoholic fatty liver disease; AAC, abdominal aortic calcification.

liver should be avoided (30). L/S ratio was obtained using mean CT value of the liver divided by that of the spleen. The ratio of pancreas-to-spleen (P/S ratio) was defined as the mean attenuation of the head, body, and tail of the pancreas divided by that of the spleen in the same axial slice. CT attenuation of the psoas major muscle was recorded as the average value of bilateral measurements at the level of the umbilicus. According to the abdominal NECT aortic calcification marking system (32,33), a reformed method was defined. An AAC score was acquired from L1 to L4 intervertebral levels. Once a patchy calcification appeared in a vertebral segment, the system would mark down one score, whereas a single and very tiny fleck of calcification would not be counted; hence, the total scores ranged from zero to four. All the image analysis and assessment were operated by a 3-year-experienced radiologist blinded to patient information. The intra-observer reliability was determined by repeated measurements on 30 patients, and its consistency was evaluated using the intra-class correlation coefficient (ICC).

Statistical analysis

All statistical analyses were performed using SPSS 19.0. Categorical variables were shown as the frequency, and the differences between two groups were tested using Pearson's χ^2 test. Continuous variables were demonstrated as mean ± standard deviation or median with interquartile range as appropriate, and the comparison between two groups was conducted using the independent sample t-test. For further evaluating the special contributions of the abdominal fat-related parameters with CAD, the multivariate logistic regression analysis was used to screen out independent risk factors of O-CAD after considering traditional cardiovascular risk factors and other CT variables in the study. ICC was used to assess the intra-observer reliability. The receiver-operating characteristic (ROC) curve was used for evaluating the predicting ability of these independent risk factors alone and the combination of them all for discriminating O-CAD, and the MedCalc statistical analysis was used to differentiate their predicting abilities. The statistical significance for all analyses were P<0.05.

Results

A total of 223 consecutive subjects (48% males; from 34 to 90 years old; mean age 63.90±11.96 years) who were suspect of having CAD and received ICA and abdominal

NECT examinations subsequently were retrospectively analyzed. They were divided into two groups, NO-CAD group (n=106; 48%) and O-CAD group (n=117; 52%). The clinical characteristics and abdominal fat-related parameters of patients were listed in *Table 1*. A good intra-observer agreement was achieved with an ICC value of 0.91 by repeated measurements on 30 patients.

Traditional cardiovascular risk factors, including age, sex, current smoking, diabetes mellitus, hypertension, and HDL-C, were analyzed. Compared with NO-CAD subjects, patients with O-CAD were older (67.21±11.51 *vs.* 60.25±11.42 years, P<0.001), having a higher prevalence of male (P<0.001), current smoking (P<0.001), diabetes mellitus (P<0.001), and hypertension (P=0.001), and own lower HDL-C (1.07±0.27 *vs.* 1.23±0.28, P<0.001). Although BMI, triglyceride (TG), and abdominal perimeter reflected no significant differences between the two groups, the corresponding values in patients with O-CAD were higher than those with NO-CAD (25.17±3.46 *vs.* 24.92±4.08; 1.69±1.44 *vs.* 1.62±1.39; 95.23±10.27 *vs.* 95.03±16.39).

The abdominal fat-related parameters, including VAT area, SAT area, VAT/SAT ratio, L/S, P/S, and CT attenuation of the psoas major muscle as well as AAC score were calculated. VAT and VAT/SAT ratio in O-CAD patients were significantly greater than that in the NO-CAD group (161.53±61.54 *vs.* 140.01±61.20, P=0.016; 0.95±0.33 *vs.* 0.70±0.25, P<0.001). The AAC score in O-CAD patients were higher than that in NO-CAD patients (P<0.001). Moreover, patients in the O-CAD group demonstrated lower SAT, P/S, and CT attenuation of the psoas major muscle compared with the NO-CAD group (181.34±67.67 *vs.* 211.26±101.63, P=0.010; 0.74±0.21 *vs.* 0.80±0.16, P=0.021; 48.23±6.73 *vs.* 50.72±4.70, P=0.005).

The multivariable logistic regression analysis in *Table 2* shows that the VAT/SAT ratio [OR, 10.492; 95% confidence interval (CI), 3.130–35.170], NAFLD (OR, 2.807; 95% CI, 1.135–6.941), and AAC score (OR, 1.964; 95% CI, 1.550–2.487) are independent predictors of O-CAD after adjusting traditional cardiovascular risk factors. Diabetes mellitus (OR, 2.572; 95% CI, 1.164–5.682), a traditional cardiovascular risk factor, is still a predictor of O-CAD after the adjustment in the multivariable model.

The ROC curve analysis illustrated distinctive predicting abilities for O-CAD with independent risk factors alone and the combination of them all (*Figure 3*). The predicting abilities for independent risk factors of NAFLD, diabetes mellitus, VAT/SAT ratio, and AAC score were 0.58 (95% CI, 0.51–0.66), 0.62 (95% CI, 0.54–0.69), 0.73 (95% CI,

Table 1 Comparison between the clinical characteristics and abdominal fat-related parameters of patients with or without obstructive coronary artery disease

Variables	Obstructive CAD		P value
	No (n=106)	Yes (n=117)	
Age (y), mean ± SD	60.25±11.42	67.21±11.51	<0.001
Male, n (%)	35 (33.0)	72 (61.5)	<0.001
BMI (kg/m^2)	24.92±4.08	25.17±3.46	0.549
Current smoking, n (%)	19 (17.9)	46 (39.3)	<0.001
Diabetes mellitus, n (%)	14 (13.2)	43 (36.8)	<0.001
Hypertension, n (%)	62 (58.5)	92 (78.6)	0.001
Triglyceride (mmol/L)	1.62±1.39	1.69±1.44	0.436
HDL-C (mmol/L)	1.23±0.28	1.07±0.27	<0.001
Abdominal perimeter (cm)	95.03±16.39	95.23±10.27	0.415
TAT area (cm^2)	351.27±147.16	342.87±113.42	0.556
VAT area (cm^2)	140.01±61.20	161.53±61.54	0.016
SAT area (cm^2)	211.26±101.63	181.34±67.67	0.010
VAT/SAT ratio	0.70±0.25	0.95±0.33	<0.001
NAFLD (L/S ratio <1), n (%)	11 (10.4)	31 (26.5)	0.002
P/S ratio	0.80±0.16	0.74±0.21	0.021
CT attenuation of the psoas major muscle (HU)	50.72±4.70	48.23±6.73	0.005
AAC (score), n (%)			<0.001
0	42 (39.6)	4 (3.4)	
1	14 (13.2)	13 (11.1)	
2	20 (18.9)	16 (13.7)	
3	13 (12.3)	28 (23.9)	
4	17 (16.0)	56 (47.9)	

Continuous variables are demonstrated as mean ± standard deviation or median with interquartile range in case of skewed variables. Categorical variables are presented as numbers (a percentage). The AAC score is acquired from L1 to L4 intervertebral levels. Once a patchy calcification appears on a vertebral segment, the system will mark down one score, but a single and very tiny fleck of calcification would not be counted; hence, the total scores range from zero to four. BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VAT/SAT ratio, the ratio of VAT to SAT; NAFLD, nonalcoholic fatty liver disease; L/S ratio, liver-to-spleen attenuation ratio; P/S ratio, pancreas-to-spleen attenuation ratio; AAC, abdominal aortic calcification; SD, standard deviation.

Table 2 Multivariate logistic regression analysis for predictors of obstructive coronary artery diseases

Variables	β	Wald	P	OR	95% CI
VAT/SAT ratio	2.315	14.507	<0.001	10.492	3.130–35.170
NAFLD	1.032	4.992	0.025	2.807	1.135–6.941
AAC	0.675	31.303	<0.001	1.964	1.550–2.487
Diabetes mellitus	0.945	5.459	0.019	2.572	1.164–5.682

Multivariate logistic regression analysis including traditional CAD risk factors. VAT/SAT ratio, the ratio of visceral adipose tissue to subcutaneous adipose tissue; NAFLD, nonalcoholic fatty liver disease; AAC, abdominal aortic calcification; 95% CI, 95% confidence interval.
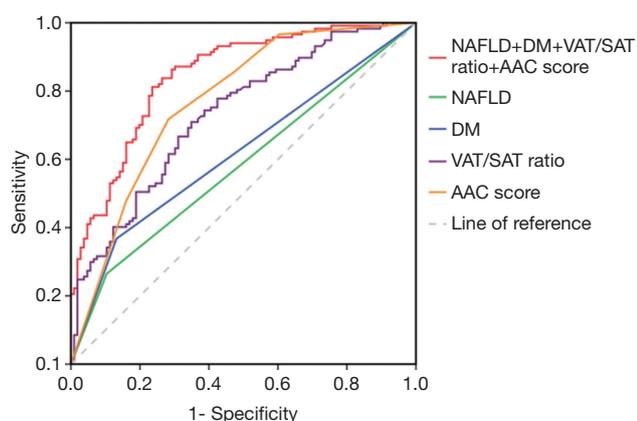
Figure 3 The ROC curve analysis of the predicting abilities of each independent risk factor alone and the combination of them all at the patient level. Green line—the area under the ROC curve of NAFLD alone for predicting O-CAD was 0.58. Blue line—the area under the ROC curve of diabetes mellitus alone for predicting O-CAD was 0.62. Purple line—the area under the ROC curve of VAT/SAT ratio alone for predicting O-CAD was 0.73. Orange line—the area under the ROC curve of AAC score alone for predicting O-CAD was 0.77. Red line—the area under the ROC curve of the combination of the four independent risk factors for predicting O-CAD was 0.85. The MedCalc statistical analysis showed lower abilities of each independent risk factor alone for predicting O-CAD than the combination of all of them (P<0.05). ROC, receiver-operating characteristic; VAT/SAT ratio, the ratio of visceral adipose tissue to subcutaneous adipose tissue; NAFLD, nonalcoholic fatty liver disease; AAC, abdominal aortic calcification.

0.67–0.80), and 0.77 (95% CI, 0.71–0.83), respectively, beyond doubt, AAC score is a better predictor of those three. The predicting ability of the combination of the above four factors is 0.85 (95% CI, 0.79–0.90). The statistical analysis demonstrated a higher ability of the combination of all risk factors than that of each single of them independently (P<0.05).

Discussion

In this study, we comprehensively assessed the correlations of the abdominal fat-related parameters and clinical characteristics between NO-CAD and O-CAD patients. Our study indicated that the factors including age, sex, current smoking, diabetes mellitus, hypertension, HDL-C, VAT, SAT, VAT/SAT ratio, NAFLD, P/S ratio, CT attenuation of the psoas major muscle, and AAC score are

correlated with the severity of CAD. The multivariable logistic regression analysis shows the VAT/SAT ratio, NAFLD, and AAC score are independent risk factors of O-CAD after adjusting traditional cardiovascular risk factors. Diabetes mellitus, a traditional cardiovascular risk factor, remains as an independent predictor in the model. The most attractive result is that a doubling in the VAT/SAT ratio is accompanied by 10.49-fold hazard of the O-CAD; thus, it is a CT-derived parameter which may contribute to the better recognition of patients with increased risk of O-CAD and to whom more attention should be paid.

At present, a few studies have separately evaluated the correlations between VAT and cardiometabolic risks, between SAT and cardiometabolic risks, between VAT/SAT ratio and vascular inflammation or cardiac events, and between NAFLD and risks of cardiovascular disease (11,13,16,18,20-29). Several studies also suggest that AAC score is correlated with CAD (30-34). However, they only focused on one of these factors at a single time which is not comprehensive enough and it might potentially cause bias (16,20,27-29,31,32). In fact, in our study, a comprehensive quantitative assessment is performed between the abdominal fat-related parameters (including TAT, VAT, SAT, VAT/SAT ratio, L/S, P/S, CT attenuation of the psoas major muscle, and AAC score) and severity of CAD. Thus, the findings of this study add valuable information to the current literature.

In clinical practice, BMI and abdominal perimeter can be used to evaluate risk stratification of CAD. In the current investigation, although the values of them in patients with O-CAD are higher than that in NO-CAD subjects, there is no significant difference in these values between the two groups, suggesting a weak correlation with CAD (12,13). Therefore, our results do not validate previous anthropometric adiposity measurements including BMI and abdominal perimeter.

Adipose tissue has been considered an effective modulator. Normally, it is an organ where fat accumulates, in which the adipocytes can maintain lipid homeostasis by increasing their number and dimensions (15,18). Previous studies showed that VAT is metabolically active which can lead to systemic inflammation and insulin resistance by secreting adipokines (14,16-18). Prospective data are in favor of VAT being an independent risk factor of CAD. As Zamboni *et al.* (15) demonstrated in their study, the effect of SAT was protective (16,18,19), and SAT, being the first "buffer system" which can offset circulating dietary fat when overeat, can also deliver a satiety message to the

hypothalamus according to secreting leptin. However, the roles of VAT and SAT concerning cardiovascular health are still controversial. In this case, a better and more accurate marker for the impact of fat distribution is needed. In our study, VAT of the O-CAD patients is higher while SAT is lower than that of the NO-CAD patients, and the statistical difference is significant, indicating that VAT is harmful while SAT is protective. Therefore, the VAT/SAT ratio serves a relatively more accurate and powerful index of distribution of abdominal fat than absolute quantification of VAT or SAT does independently. Decreased CT attenuations of liver, pancreas, and psoas major muscle represent fat deposits in the abdominal organs. NAFLD has been closely related to significant coronary stenosis detected by ICA; it is also relevant to coronary arteries and abdominal arteries calcification. The prevalence of NAFLD shows obesity-associated ectopic fat deposit which is further correlated with CAD. Previous studies and a recent meta-analysis reveal that AAC score is correlated with CAD and is also a predictor of O-CAD (30-34); thus, AAC score has been used as a marker of atherosclerosis and risk assessment of CAD. It is generally accepted that the plaque in abdominal aorta is the early-stage atherosclerosis. As the disease progresses, the plaque will calcify eventually (32). The result shows the correlations between AAC and O-CAD. In summary, our study comprehensively quantifies the correlations between severity of CAD and each of abdominal fat-related parameters, clinical characteristics, and traditional cardiovascular risk factors, respectively, to more accurately reflect their contributions.

Abdominal NECT is noninvasive and can provide accurate quantification of the abdominal CT parameters. Moreover, it is inexpensive and convenient to acquire the images with no contrast injection required. Most importantly, the radiation dose is lower than CT angiography and ICA. Therefore, it is a practice approach to predict the severity of CAD using abdominal NECT parameters.

One identified limitation of our study is the nature of being a single-center and small-sample one; therefore, a larger sample and multi-center research are needed. In addition, it owns a cross-sectional design. What is more, the time bias between ICA and abdominal NECT and whether the drug therapy was administrated are hardly controlled, and these confounding factors might influence the outcomes. Thus, prospective studies are necessary to support the roles of these indicators in clinical practice. The DS of ≥50% was used to determine significant stenosis in this study which may not be accurate as the current approach to define significant coronary stenosis is >70% DS, while the DS between 50% and 69% is regarded as intermediate stenosis. However, this study focuses on the correlation between the fat-related parameters and severity of CAD rather than coronary lumen stenosis. Thus, results are valid which allow us to draw robust conclusions.

Conclusions

The abdominal fat distribution related CT parameters of VAT/SAT ratio and NAFLD, and AAC score are correlated with severity of CAD, and they become independent risk factors for O-CAD after adjusting traditional cardiovascular risk factors. Diabetes mellitus, as a traditional cardiovascular risk factor, is still included as an independent predictor. These indicators are conducive to identifying patients with increased risk of O-CAD. Besides, the combination of all the independent risk factors increases the ability for predicting O-CAD than each factor alone.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by IEC for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2017ZDKYSB086). Written informed consent was obtained from all patients.

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