ORIGINAL ARTICLE

Cardiometabolic predictive value of anthropometric parameters, vascular ultrasound indexes, and fat depots in patients at high cardiovascular risk: an 8-year prospective cohort study

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KEY WORDS

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ABSTRACT

INTRODUCTION Adiposity has a few phenotypes associated with various levels of risk for diabetes mellitus (DM), but their exact predictive value is not well understood.

OBJECTIVES We aimed to assess the predictive value of anthropometric parameters, vascular ultrasound indexes, and fat depots for long-term cardiometabolic risk.

PATIENTS AND METHODS A total of 150 patients with chronic coronary syndrome (CCS) scheduled for elective coronary angiography were enrolled and a comprehensive clinical and ultrasound assessment of adiposity was performed (2012–2013). Of them, 143 individuals were followed for 8 years for insulin resistance (IR) and/or DM development.

RESULTS At baseline, DM and prediabetes were found in 22% and 8% of the patients, respectively. It was established that 11.7% of the participants died during the follow-up. The rate of DM increased to 46% with a decrease in the prediabetes rate (3.5%). Significant correlations with the Homeostatic Model Assessment of Insulin Resistance and glycated hemoglobin were observed for major anthropometric and ultrasound variables. In the multivariable analysis, independent predictors of IR were preperitoneal fat thickness (PreFT) (per 10 mm increase: odds ratio [OR], 1.63; 95% CI, 1.22–2.33; $P = 0.003$) and body surface area (per 0.1 m^2 increase: OR, 1.59; 95% CI, 1.11–2.39; $P = 0.02$). DM was independently predicted by the high-density lipoprotein cholesterol concentration (OR, 0.93; 95% CI, 0.87–0.97; $P = 0.005$) and body fat mass (OR, 1.09; 95% CI, 1.03–1.17; $P = 0.003$).

CONCLUSIONS A complex assessment of the adipose tissue in patients with CCS is a valuable method for improving metabolic risk stratification. Some anthropometric and ultrasound parameters, such as PreFT or body surface area, were associated with IR and DM development.

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INTRODUCTION Overweight and obesity are major public health problems, also among the Polish population.[1] As shown in subsequent WOBASZ and WOBASZ II population studies,[2] overweight is currently diagnosed in 43.2% of men and 30.5% of women, while obesity in 24.4% and 25.0%, respectively. Moreover, the upward trend has been constantly observed, particularly in men.[2] The gravity of the problem is emphasized by the close relationship of overweight/obesity

WHAT'S NEW?

The adipose tissue quantity, distribution, location, and bioactive function in the body are associated with the risk of new-onset diabetes and total cardiovascular risk. Abdominal obesity is a well-known risk factor for diabetes, but its predictive value is not entirely understood. We showed one of the most complex assessments of fat distribution in patients with chronic coronary syndromes. Moreover, for the first time, we analyzed the predictive role of ultrasound indexes, such as extra-media thickness, in diagnosing insulin resistance or diabetes. Some anthropometric and ultrasound measures can be helpful in the prediction of insulin resistance and diabetes development. A complex assessment of the adipose tissue in patients with chronic coronary syndromes represents a valuable predictive method for improving cardiovascular risk stratification.

with cardiometabolic diseases, including diabetes mellitus (DM), and their impact on long-term prognosis.[1]

Despite similar cardiovascular risk factors, obese patients may have a considerably different cardiovascular risk profile and clinical prognosis.[1,3] A recent large body of evidence suggested that the adipose tissue quantity, distribution, and location, as well as the bioactive function of adipocytes in the whole body and specific fat depots are strongly associated with the risk of a new-onset DM and total cardiovascular risk.[1,4-6] Obesity and genetic predisposition are among the significant risk factors of DM but their predictive value is not well understood.[7,8]

A few major ultrasound indexes representing various tissue components of the arterial wall or fat depots associated with cardiovascular risk were previously described.[5,9] However, their prognostic ability with respect to the risk of DM is unknown. Thus, we aimed to assess the predictive value of anthropometric parameters, vascular ultrasound indexes, and fat depots to determine the cardiometabolic risk in a high-risk population.

PATIENTS AND METHODS

Study population All consecutive patients with chronic coronary syndromes (CCSs) scheduled for elective coronary angiography at the Department of Cardiology (Medical University of Silesia in Katowice, Poland) were screened between 2012 and 2013 using the study criteria.[4] Finally, 150 patients were prospectively enrolled into the study group.

The main exclusion criteria were similar to those described previously,[4] and the most important ones included acute coronary syndrome, heart failure, chronic inflammatory diseases, neoplastic diseases, severe kidney or liver failure, secondary causes of obesity, and an unintentional weight loss of 10% in the prior 3 months or malnutrition.

Pharmacotherapy in all patients was standardized according to the appropriate European Society of Cardiology guidelines.[10-13] The baseline study visit (2012–2013) comprised a clinical assessment and measurement of anthropometric parameters, as well as evaluation of ultrasound vascular indexes and parameters of fat depots as described earlier.[4]

Afterwards, all the patients were invited for prospective follow-up visits in 2020. A total of 143 patients signed an informed consent and agreed to participate in the current study. The prospective follow-up visit included an evaluation of the medical history as well as the clinical, anthropometric, and laboratory parameters.

The study aimed to assess the predictive value of ultrasound indexes and anthropometric parameters for cardiometabolic risk in patients with a high cardiovascular risk profile in an 8-year follow-up. The primary outcome was a new diagnosis of DM and/or insulin resistance (IR). The secondary outcome was all-cause mortality.

The study protocol complied with the Declaration of Helsinki and was approved by the local Medical University of Silesia Ethics Committee (KNW/0022/KB1/127/I/13/14 and KNW/0022/KB1/77/17).

Clinical characteristics and anthropometric measurements Hypertension was defined according to blood pressure (BP) levels (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) or a history of hypertension and current antihypertensive treatment.[14] The presence of hyperlipidemia was established based on abnormal plasma lipid levels (total cholesterol [TC] >190 mg/dl, low-density lipoprotein cholesterol [LDL-C] >115 mg/dl, triglycerides [TG] >150 mg/dl, high-density lipoprotein cholesterol [HDL-C] <40 mg/dl in men and <50 mg/dl in women) or prior diagnosis and/or current treatment of hyperlipidemia.[14] The diagnoses of the analyzed cardiovascular diseases and risk factors were defined according to the European Society of Cardiology guidelines[15] and identified based on a prior diagnosis and/or current treatment of these diseases. DM was determined based on fasting plasma glucose levels greater than or equal to 126 mg/dl and/or glycated hemoglobin (HbA_{1c}) concentration greater than or equal to 6.5% or current antidiabetic treatment.[16]

Overweight and obesity were diagnosed based on the body mass index (BMI; calculated as body mass [kg]/height [m^2]) as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2), which was further divided into class I (30.0–34.9 kg/m^2), class II (35.0–39.9 kg/m^2), and class III (≥40.0 kg/m^2) obesity.

Waist circumference (WC; midpoint between the lowest rib and the iliac crest) and hip circumference were assessed using a measuring tape at the end of expiration. Increased WC was defined as per the World Health Organization (WHO; ≥102 cm in men and ≥88 cm in women) and the International Diabetes Federation (IDF; ≥94 cm in men and ≥80 cm in women) criteria. Additional measurements included: neck circumference, thigh circumference, and upper limb circumference

(evaluated together as total circumference [TCirc]). Moreover, we measured the following skinfold thicknesses: chest, abdominal, and thigh (evaluated together as total skinfold thickness) as previously described.[4]

We used the bioelectric impedance analysis method (Bodystat 1500, Bodystat, Douglas, Isle of Man) to measure the patients' body composition, including body fat percentage, similarly to the method used before.[4] All measurements were performed according to the manufacturer's manual. The intraobserver variability of measurements in the same patient was below 1%.

Sample collection and routine laboratory tests Fasting blood samples (15 ml) were obtained at baseline and after 8 years of follow-up. At both time points, the blood was drawn from an antecubital vein between 8 and 10 am after overnight fasting. The samples were processed 30 to 60 minutes after collection. Routine blood tests, including the evaluation of complete blood count and lipid profile (TC, LDL-C, HDL-C, and TG), were performed using automated laboratory techniques. HbA_{1c} levels were measured with a turbidimetric inhibition immunoassay.

Ultrasound indexes The ultrasound indexes were evaluated as described before.[4,5,17] Briefly, all the ultrasound examinations were performed by a single experienced physician using constant and standardized settings. After the enrollment, single images of an individual ultrasound index of interest were randomly analyzed by 1 observer blinded to the patients' data. Additionally, a random number of 40 scans were analyzed again by a second experienced observer to determine the intra- and interobserver variability and coefficients of variation.

Before electrocardiogram-gated ultrasound measurements of both carotid arteries, all the patients rested in a supine position for at least 5 minutes. The examination was performed using a high-resolution ultrasound device (GE Vivid 9, Milwaukee, Wisconsin, United States) with a linear transducer (9–12 MHz). The common carotid artery (CCA) intima-media thickness (IMT) was measured on a 10-mm segment starting 5 mm proximally to the carotid bulb, as stated in the Mannheim Consensus guidelines,[6] using a semiautomated GE software (intra- and interobserver coefficients of variation, 2.6% and 3.1%, respectively). The carotid IMT was measured on both sides, and average values were calculated. As defined before,[5] extra-media thickness (EMT) was the distance between the carotid media-adventitia border and the jugular wall lumen area, averaged from both CCAs. The EMT evaluation was performed after zooming the interface between the wall of the distal segment of the CCA and the neighboring jugular vein (intra- and interobserver coefficients of variation, 3.3% and 3.9%, respectively).

Epicardial and pericardial adipose tissue was quantified using transthoracic echocardiography with a 1.5–4.5 MHz transducer according to the established method (GE Vivid 9, GE Vingmed Ultrasound AS, Horten, Norway).[5,18] Epicardial fat thickness (EFT) was defined as the distance between the epicardium and the visceral layer of the pericardium. Pericardial fat thickness (PFT) was measured as the distance between the visceral and parietal pericardial layers. The maximum values were measured during the end-diastole phase in 5 consecutive heart cycles and mean values were obtained (intra- and interobserver coefficients of variation, 3.3% and 3.9% for EFT and 3.5% and 4% for PFT, respectively). As described before,[4,5] visceral adipose tissue measurements were performed using a 3.5 MHz transducer, and for subcutaneous fat (SF; to determine the maximal SF layer) assessment, using a 7.5 MHz transducer placed vertically on the skin as lightly as possible to prevent compression and to perform breath-hold assessments of fat layers. Intra-abdominal thickness was measured in a transversal projection 1 cm above the umbilicus as the interspace between the internal surface of the rectus abdominis muscle and the anterior wall of the abdominal aorta (intra- and interobserver coefficients of variation, 4.1% and 4.8%, respectively). The maximal layer of preperitoneal fat (PreFT) was assessed below the xiphoid process in a transverse view. Finally, the ultrasound fat measurements were indexed by body weight through dividing the mean values by the BMI.

Statistical analysis The distribution of variables was checked with the Kolmogorov–Smirnov test. Baseline clinical parameters and measures were compared between the groups using the *t* test for the normally distributed continuous variables and the Mann–Whitney test for the variables that did not follow normal distribution. Associations of individual parameters with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and HbA_{1c} were assessed using the Spearman correlation analysis and were shown as *R* correlation coefficients. All demographic data, baseline characteristics, anthropometric parameters, vascular ultrasound indexes, and fat depots were analyzed as potential predictors of de novo DM using univariable logistic regression models. For each variable, receiver operating characteristic analysis was performed with the area under the curve estimation and selection of the cutoff value for the best binary prediction that maximized both sensitivity and specificity. Of all these variables, the ones with clinical importance or those indicating a possible impact were included in a multivariable logistic regression model. The final model was obtained using forward/backward stepwise regression with minimization of the Bayesian Information Criterion as the target. The final model vas validated using bootstrap resampling with 1000 iterations; then, a bias-corrected *C* statistic was calculated as a measure of goodness-of-fit. A *P* value below 0.05 was considered significant.

TABLE 1 Baseline clinical characteristics of the study group (n = 128)

Parameter	Value
Age, y	61.0 (6.3)
Male sex, n (%)	77 (60)
Weight, kg	86.3 (18.2)
BMI, kg/m^2	30.5 (5.7)
History of myocardial infarction, n (%)	43 (34)
STEMI, n (%)	23 (18)
NSTEMI, n (%)	19 (15)
Both STEMI and NSTEMI, n (%)	1 (1)
History of PCI, n (%)	52 (59)
History of CABG, n (%)	11 (9)
History of stroke, n (%)	6 (5)
Hypertension, n (%)	109 (85)
Dyslipidemia, n (%)	128 (100)
Smoking, n (%)	93 (73)
Chronic kidney disease, n (%)	8 (6)
Peripheral artery disease, n (%)	28 (22)
Type 2 diabetes, n (%)	28 (22)
Prediabetes, n (%)	10 (8)
HOMA-IR	3.02 (2.02–4.98)
HbA_{1c}, %	5.88 (5.57–6.69)
TC, mg/dl	173.5 (42.9)
LDL-C, mg/dl	99.0 (38.0)
HDL-C, mg/dl	45.5 (14.2)
Non–HDL-C, mg/dl	128.0 (40.2)
TG, mg/dl	125.5 (99–165.75)
Pharmacotherapy, n (%)	
Acetylsalicylic acid	112 (87.5)
$P2Y_{12}$ inhibitor	58 (45.3)
ACEI/ARB	118 (92.2)
β-Blocker	106 (82.8)
Statin	110 (85.9)
Fibrates	10 (7.8)
Metformin	22 (17.2)
Sulfonylureas	16 (12.5)
Insulin	6 (4.7)

Data are shown as mean (SD) or median (interquartile range) unless indicated otherwise.

SI conversion factors: to convert TC, LDL-C, HDL-C, and non-HDL-C to mmol/l, multiply by 0.0259, TG to mmol/l, by 0.0113.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides

Statistical analysis was performed using MedCalc software (version 19.1, Ostend, Belgium).

RESULTS Clinical characteristics of the study group Detailed baseline (2012–2013) clinical characteristics of the study group are presented in TABLE 1. The participants comprised a high to very-high cardiovascular risk population with a mean (SD) of 3.7 (1.0) risk factors, primarily arterial hypertension (85%), dyslipidemia (100%), and smoking (73%). Over one-third of the study group were overweight (36.7%), and almost half (48.4%) were obese (obesity class I: 28.9%; class II: 12.5%; class III: 7%, respectively). Increased WC based on both the WHO and IDF definitions was found in 74 (59%) and 100 (80%) study participants, respectively. Detailed characteristics of anthropometric and ultrasound measures are presented in TABLE 2.

On baseline evaluation (2012–2013), DM was found in 28 patients (22%), and prediabetes (preDM) in 10 individuals (8%) (TABLE 1). All medications used initially in the study population are showed in TABLE 1.

Study follow-up After 8 years of follow-up, death from any cause occurred in 15 patients (11.7%). Additionally, the number of DM cases increased to 52 (46%), and preDM was found only in 4 patients (3.5%). Moreover, 42 patients (37%) were treated with oral antidiabetic medications, and 18 (16%) used insulin.

Insulin resistance The median HOMA-IR was 3.02 (interquartile range [IQR], 2.02–4.98). There were 94 patients (73%) with a HOMA-IR greater than or equal to 2.0 and 59 patients (46%) with a HOMA-IR greater than or equal to 3.0. Among the ultrasound indexes, carotid EMT, IMT, and abdominal PreFT were found to significantly correlate with the HOMA-IR. With respect to the anthropometric measures, BMI, WC, TCirc, total skinfold thickness, and body fat mass significantly correlated with the HOMA-IR (TABLE 3). In the univariable analysis of ultrasound measures, a significant association between EMT and PreFT was found. Moreover, BMI, WC, waist-to-hip ratio (WHR), TCirc, and total skinfold thickness were also significantly linked with IR development (TABLE 4). Subsequently, in the multivariable analysis, only PreFT (per 10 mm increase; odds ratio [OR], 1.63; 95% CI, 1.22–2.33; P = 0.003) and a higher body surface area (per 0.1 m^2 increase; OR, 1.59; 95% CI, 1.11–2.39; P = 0.02) were independently associated with IR occurrence (TABLE 4). The positive (PPV) and negative (NPV) predictive values for the model were 0.71 and 0.84, respectively. The bias-corrected C statistic was 0.87.

Type 2 diabetes The median HbA_{1c} concentration was 5.9% (IQR, 5.6%–6.7%). Among the ultrasound indexes, a significant association between EMT or PreFT and HbA_{1c} was found. Additionally, among the anthropometric measures, BMI, TCirc, and body fat mass significantly correlated with HbA_{1c} levels (TABLE 3). In the univariable analysis, significant associations were demonstrated for EMT, IMT, PreFT, HDL-C, BMI, WC, WHR, TCirc, total skinfold thickness, and body fat mass (TABLE 5). However, in the multivariable model, the correlation was only confirmed for HDL-C

TABLE 2 Baseline anthropometric, ultrasound, and adiposity parameters of the study group (n = 128)

Parameter	Value
Waist circumference, cm	103.37 (13.8)
Waist to hip ratio	0.99 (0.11)
Total circumference, cm[a]	123.2 (11.5)
Total skinfold thickness, cm[b]	71.0 (16.5)
Body fat percentage, %	31.0 (9.3)
Body fat mass, kg	27.04 (11.23)
Intima-media thickness, μm	960 (48)
Extra-media thickness, μm	801.72 (133.6)
Epicardial fat thickness, mm	3.4 (1.4)
Pericardial fat thickness, mm	8.3 (2.7)
Maximal subcutaneous fat, cm	27.0 (10.2)
Preperitoneal fat thickness, mm	74.2 (27.9)

Data are shown as mean (SD).

a Total circumference refers to the sum of the neck, thigh, and upper limb circumferences.

b Total skinfold thickness refers to the sum of chest, abdominal, and thigh fold thicknesses.

TABLE 3 Correlation between clinical and anthropometric parameters, ultrasound indexes, and values of Homeostatic Model Assessment of Insulin Resistance and glycated hemoglobin

Parameter	HOMA-IR		HbA_{1c}	
	R[a]	*P* value	R[a]	*P* value
Clinical and anthropometric parameters				
Age	–0.170	0.07	–0.181	0.06
BMI	0.355	<0.001	0.334	0.001
Waist circumference	0.256	0.007	0.132	0.18
Total circumference[b]	0.243	0.01	0.279	0.005
Total skinfold thickness[c]	0.191	0.045	0.043	0.67
Body fat percentage (BC)	0.084	0.38	–0.073	0.47
Body fat percentage (BS)	–0.014	0.88	0.037	0.71
Body fat mass	0.200	0.04	0.244	0.01
Triglycerides	0.321	0.001	0.295	0.002
HDL-C	–0.367	<0.001	–0.451	<0.001
HbA_{1c}	0.521	<0.001	–	–
Ultrasound indexes				
Extra-media thickness	0.212	0.03	0.322	0.001
Intima-media thickness	0.196	0.04	0.142	0.16
Epicardial fat thickness	0.017	0.86	0.048	0.63
Pericardial fat thickness	0.104	0.28	0.134	0.18
Maximal subcutaneous fat	0.053	0.58	–0.148	0.14
Preperitoneal fat thickness	0.447	<0.001	0.264	0.007

Differences were considered significant at $P < 0.05$.

a Spearman correlation coefficient

b Total circumference refers to the sum of the neck, thigh, and upper limb circumferences.

c Total skinfold thicknesss refers to the sum of chest, abdominal, and thigh fold thicknesses.

Abbreviations: BC, Body Fat Caliper; BMI, body mass index; BS, Bodystat; others, see TABLE 1

(OR, 0.93; 95% CI, 0.87–0.97; $P = 0.005$) and body fat mass (OR, 1.09; 95% CI, 1.03–1.17; $P = 0.003$) (TABLE 5). The PPV and NPV for the model were 0.9 and 0.86, respectively, whereas the bias-corrected *C* statistic was 0.80.

Multivariable regression analysis adjusted for clinical confounders Finally, in a multivariable regression analysis of both anthropometric parameters and ultrasound indexes adjusted for age, estimated glomerular filtration rate, TC, LDL-C, HDL-C, and TG, we demonstrated that WC, WHR, total skinfold thickness, body fat, and body fat mass as well as EMT and PreFT were positively associated with the HOMA-IR (TABLE 6). In turn, only WHR and body fat mass predicted an unfavorable increase in HbA_{1c} (TABLE 6).

DISCUSSION Our study evaluated the clinical significance of anthropometric parameters, vascular ultrasound indexes, and adipose tissue depots for cardiometabolic risk among patients at high cardiovascular risk in an 8-year prospective observational, single-center cohort study. To our best knowledge, we are the first to present a comprehensive assessment of the predictive role of several ultrasound parameters.

We found that carotid EMT, abdominal PreFT, and certain anthropometric parameters (BMI, WC, TCirc) were significantly associated with the HOMA-IR and/or HbA_{1c} levels. We established that the independent predictors of IR were PreFT and body surface area, whereas for DM the predictive factors were lower HDL-C values and body fat mass. Other vascular ultrasound indexes and anthropometric parameters failed to be recognized as independent predictors of IR and/or DM.

The relationship between coronary artery disease (CAD) and DM is a well-known paradigm. In brief, as established previously, DM increases the risk for CAD by 2- to 4-fold.[19] At the same time, ischemic events and other cardiovascular disorders are the leading cause of death in around two-thirds of the patients with DM.[20] The development of DM and CAD is a long process, and the 8-year analysis enabled us to trace its dynamics. Subclinical atherosclerosis seems to start to develop even a few years before the evident clinical diagnosis of CAD.[21] Furthermore, there is a high risk of preDM progressing to overt DM in the following 10 years of follow-up.[22,23]

Obesity is a common link between CAD and DM. As repeatedly shown, adipose tissue is a metabolically active structure that, apart from adipocytes, consists of numerous cells representing its stromal fraction and various classes of inflammatory cells.[24] Through autocrine, paracrine, and endocrine interactions, the adipose tissue contributes to the induction of a proinflammatory status and IR in obese patients.[25-27] Perivascular adipose tissue plays a vital role in modifying the endothelial function and vascular activity, especially in individuals with CCS.[28] By directly adhering to

TABLE 4 Regression analysis for the predictors of insulin resistance

Parameter	Univariable analysis		Multivariable model; $C = 0.87$[a]	
	OR (95% CI)[b]	*P* value	OR (95% CI)	*P* value
Clinical and anthropometric parameters				
BMI, kg/m^2	1.17 (1.08–1.28)	<0.001	–	–
BSA, 0.1 m^2	1.35 (1.07–1.69)	0.003	1.59 (1.11–2.39)	0.02
Waist circumference, cm	1.13 (1.08–1.20)	<0.001	–	–
Waist to hip ratio, 0.01	1.14 (1.06–1.23)	<0.001	–	–
Total circumference[c], cm	1.052 (1.012–1.10)	0.01	–	–
Total skinfold thickness[d], cm	1.04 (1.006–1.07)	0.02	–	–
Body fat (BC), %	1.05 (0.97–1.14)	0.22	–	–
Body fat (BS), %	1.02 (0.98–1.07)	0.33	–	–
Body fat mass, kg	1.06 (1.02–1.11)	0.004	–	–
Ultrasound indexes				
Extra-media thickness, µm	1.006 (1.002–1.009)	0.001	–	–
Intima-media thickness, µm	1.60 (0.71–4.15)	0.24	–	–
Epicardial fat thickness, mm	1.25 (0.94–1.68)	0.12	–	–
Pericardial fat thickness, mm	1.15 (0.99–1.35)	0.07	–	–
Maximal subcutaneous fat, cm	0.99 (0.95–1.04)	0.92	–	–
Preperitoneal fat thickness, 10 mm	1.92 (1.42–2.59)	<0.001	1.63 (1.22–2.33)	0.003

Differences were considered significant at $P < 0.05$.

a Bias-corrected

b Per 1 unit increase, unless stated otherwise

c Total circumference refers to the sum of the neck, thigh, and upper limb circumferences.

d Total skinfold thicnkess refers to the sum of chest, abdominal, and thigh fold thicknesses.

Abbreviations: OR, odds ratio; others, see **TABLES 1**, **2**, and **3**

TABLE 5 Regression analysis for the predictors of type 2 diabetes

Parameter	Univariable analysis		Multivariable model; $C = 0.80$[a]	
	OR (95% CI)[b]	*P* value	OR (95% CI)[b]	*P* value
Clinical and anthropometric parameters				
BMI, kg/m^2	1.18 (1.06–1.35)	0.001	–	–
Waist circumference, cm	1.09 (1.04–1.16)	0.003	–	–
WHR, 0.01	1.09 (1.01–1.17)	0.02	–	–
Total circumference[c], cm	1.11 (1.05–1.20)	<0.001	–	–
Total skinfold thickness[d], cm	1.04 (1.0001–1.08)	0.04	–	–
Body fat (BC), %	1.06 (0.96–1.17)	0.28	–	–
Body fat (BS), %	1.03 (0.97–1.08)	0.34	–	–
Body fat mass, kg	1.06 (1.02–1.13)	0.009	1.09 (1.03–1.17)	0.003
HDL-C, mg/dl	0.95 (0.90–0.99)	0.009	0.93 (0.87–0.97)	0.005
Ultrasound indexes				
Extra-media thickness, µm	1.01 (1.00–1.01)	0.01	–	–
Intima-media thickness, 0.1 µm	1.32 (1.01–1.71)	0.007	–	–
Epicardial fat thickness, mm	1.02 (0.71–1.43)	0.91	–	–
Pericardial fat thickness, mm	1.19 (0.95–1.50)	0.14	–	–
Maximal subcutaneous fat, cm	0.99 (0.94–1.05)	0.81	–	–
Preperitoneal fat thickness, mm	1.04 (1.01–1.07)	0.005	–	–

Differences were considered significant at $P < 0.05$.

a Bias-corrected

b Per 1 unit increase, unless stated otherwise

c Total circumference refers to the sum of the neck, thigh, and upper limb circumferences.

d Total skinfold thickness refers to the sum of chest, abdominal, and thigh fold thicknesses.

Abbreviations: see **TABLES 1**, **2**, **3**, and **4**

TABLE 6 Multivariable regression analysis of anthropometric parameters and ultrasound indexes associated with Homeostatic Model Assessment of Insulin Resistance and glycated hemoglobin adjusted for age, estimated glomerular filtration rate, total, low-density, and high-density lipoprotein cholesterol, and triglyceride levels

Parameter	HOMA-IR		HbA_{1c}	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Anthropometric parameters				
Waist circumference, cm	0.09 (0.03–0.15)	0.006	0.010 (–0.008 to 0.028)	0.28
WHR, 0.01	9.55 (0.14–18.97)	0.047	3.37 (0.77–5.97)	0.01
Total circumference[a], cm	0.051 (–0.015 to 0.117)	0.12	0.011 (–0.007 to 0.030)	0.22
Total skinfold thickness[b], cm	0.050 (0.004–0.095)	0.03	–0.004 (–0.017 to 0.010)	0.59
Body fat (BC), %	0.121 (–0.018 to 0.260)	0.09	–0.013 (–0.053 to 0.026)	0.51
Body fat (BS), %	0.11 (0.03–0.19)	0.005	0.022 (–0.001 to 0.045)	0.054
Body fat mass, kg	0.102 (0.044–0.160)	0.001	0.024 (0.006–0.042)	0.01
Ultrasound indexes				
Extra-media thickness, µm	6.56 (1.17–11.95)	0.02	1.49 (–0.03 to 3.02)	0.06
Intima-media thickness, 0.1 µm	0.33 (–1.09 to 1.76)	0.64	–0.26 (–0.66 to 0.14)	0.20
Epicardial fat thickness, mm	0.39 (–0.08 to 0.86)	0.10	0.103 (–0.029 to 0.235)	0.12
Pericardial fat thickness, mm	0.22 (–0.03 to 0.47)	0.08	0.047 (–0.024 to 0.117)	0.19
Maximal subcutaneous fat, cm	0.06 (–0.01 to 0.13)	0.08	–0.001 (–0.020 to 0.019)	0.93
Preperitoneal fat thickness, mm	0.041 (0.015 to 0.068)	0.003	0.004 (–0.004 to 0.011)	0.36

Differences were considered significant at $P < 0.05$.

a Total circumference refers to the sum of the neck, thigh, and upper limb circumferences.

b Total skinfold thickness refers to the sum of chest, abdominal, and thigh folds.

Abbreviations: see TABLES 2, 3, and 4

the vessel wall, it significantly regulates the vascular tone and wall remodeling, and, as mentioned above, its measurement may be particularly important in the assessment of cardiovascular risk and prognosis in patients with CAD.[28]

The relationship between obesity and CAD with respect to the impact on long-term prognosis remains controversial. The highest survival benefit was observed in the overweight and obese patients and was named the "obesity paradox."[1] Notably, observations were conducted mainly using the definitions based on a simple BMI measurement.[29] Until now, several potential underlying explanations have been proposed.[1] However, the "obesity paradox" also proves the insufficient reliability of BMI in the assessment of patients with CAD. In a systematic review by Coutinho et al,[30] a simple anthropometric parameter, representing the index of central obesity, showed an advantage over BMI and ruled out the occurrence of this paradox.[30] This suggests the possibility of using more advanced and objective anthropometric measures, including ultrasound indexes, to assess the prognosis in patients with CAD more adequately.

The current data regarding the use of individual anthropometric measurements, except for WC, in assessing the risk of IR and the prognosis of CCS patients are limited. In a prospective cohort study of patients at high cardiovascular risk, Dai et al[31] demonstrated that a greater neck circumference indicated a higher incidence of cardiovascular events and all-cause mortality. Moreover, as shown by Kamiya et al,[32] an increased arm circumference, but not calf circumference, was an independent predictor of survival in older patients with cardiovascular diseases. In contrast, as shown in our study, the risk of IR and/or DM development was strictly associated only with PreFT, body surface area, and body fat mass, which are quantitative and more accurate indicators of the body fat distribution. Notably, in our analysis, the predictive value was not observed for BMI, WHR, or WC, which are widely used in clinical practice. We assume that a more complex clinical analysis, as proposed herein, using anthropometric, ultrasound, and bioimpedance methods, could enable an objective assessment of the true metabolic risk and eliminate the abovementioned "obesity paradox."

Interestingly, lower levels of HDL-C corresponded with a higher risk of new-onset DM, as previously reported in the literature. As shown by Lee et al[33] in a population-based study, both low levels and high variability of HDL-C were independent and additive predictors of DM. Most likely, HDL-C is a useful indicator of the diabetogenic potential. However, recently, interesting hypotheses were put forward concerning a direct influence of HDL-C on insulin secretion and IR.[34]

Our study has some limitations. First, those pertaining to the technical aspects of the ultrasound index measurement as described previously.[4,5] Second, we did not evaluate the ultrasound indexes during the follow-up visit. Third, we did not assess the individual fitness level in the study

patients, which was proven to modify the risk of IR and DM.[35] Fourth, we did not perform a survival analysis due to limited data on mortality.

Conclusions A complex assessment of the adipose tissue in patients with CCS is a valuable method for improving cardiovascular risk stratification. As demonstrated, some anthropometric and ultrasound parameters can be helpful in the prediction of IR and DM development. Therefore, they could be incorporated into cardiovascular risk assessment algorithms.

ARTICLE INFORMATION

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