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Significance of the Visceral Adiposity Index and Other Indicators in Identifying Metabolic Subtypes

ABSTRACT

Objective: Metabolic phenotypes associated with high cardiovascular risk have been described. The visceral adiposity index (VAI) is a simple indicator of increased visceral adipose tissue using anthropometric and lipid parameters. The role of the VAI score was analyzed to identify metabolic phenotypes.

Methods: The clinical and biochemical parameters and anthropometric measurements of 200 sex-matched patients were retrospectively reviewed. The study population was grouped into 4 groups according to their body mass index and metabolic syndrome criteria: metabolically healthy obese (MHO), metabolically unhealthy obese (MUHO), metabolically unhealthy nonobese (MUHNO), and metabolically healthy nonobese (MHNO). The patient's VAI scores were calculated.

Results: The VAI scores of the MUHNO group were greater than those of the MUHO and MHNO groups in males. The VAI scores of the MHO group were lower than the MUHO and MHNO groups in females. Waist circumference predicted the MUHNO group from the healthy group in men and the MHNO group from the unhealthy group in females. A VAI score higher than 5.69 and WC higher than 93 cm were described as the cutoff points to identify the MUHNO patients among the study population in males. A VAI score lower than 4.89 and WC lower than 90 cm as the cutoff point to identify the MHO patients from the unhealthy group were described in females.

Conclusion: The VAI score is a simple technique for defining individuals with high cardiovascular risk, although it may not describe all unhealthy patients. Waist circumference is still an important factor for predicting an unhealthy cardiovascular profile.

Keywords: Visceral adiposity index, metabolically unhealthy normal weight, metabolically healthy obese, metabolically unhealthy obese

Introduction

Obesity is a growing pandemic with health concerns, including various cardiovascular diseases.[1] The link between obesity and a cluster of metabolic problems such as insulin resistance, prediabetes, atherogenic dyslipidemia [high triglyceride (TG) levels and low high-density lipoprotein cholesterol levels], nonalcoholic fatty liver disease, and metabolic syndrome (MetS), is known. However, not all obese people have the same cardiometabolic risk. Furthermore, it is debatable whether individuals with a normal weight are truly healthy. Obesity and normal weight are described according to body mass index (BMI), which does not account for fat tissue distribution, especially excess visceral fat deposition, which is a key factor in cardiovascular disease (CVD).[2] In recent years, various metabolic phenotypes, such as metabolically healthy obese (MHO), metabolically unhealthy obese (MUHO), metabolically healthy nonobese (MHNO), and metabolically unhealthy nonobese (MUHNO), have been described, which include not only BMI but also accompanying metabolic diseases.[3] The primary goal of this diverse grouping is to identify metabolically unhealthy individuals with increased CVD risk.

The primary risk factors for CVD are central obesity and increased visceral adipose tissue (VAT).[2] Increased VAT is more likely to be associated with chronic inflammation or cardiometabolic syndrome.[4] Visceral obesity can be assessed using magnetic resonance imaging or computed tomography scans, which are not feasible in daily practice.[5] Body mass index and waist circumference (WC) are free of charge and can be calculated easily. The visceral adiposity index (VAI) has been shown to indirectly predict VAT using anthropometric measurements (WC and BMI) and primarily central obesity-related lipemic parameters.[6] Since the definition of VAI, studies have been conducted to determine whether it can predict the risk of cardiometabolic disease or diabetes in healthy/general populations or specific patient groups.[7-10]

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The identifying role of the different metabolic phenotypes of the VAI score has not yet been examined. The roles of VAI and other factors in identifying the four distinct metabolic phenotypes were analyzed in the current study.

Materials and Methods

In this retrospective study, 609 Caucasian patients older than 18 years who visited our outpatient clinic between May 2019 and February 2021 were randomly screened. Patients with chronic renal failure, stage III–IV congestive heart failure, severe eating disorders, use of medications affecting weight gain/reduction, and malignancies were excluded. To match the numbers of the groups and sexes, we screened such a large cohort of patients for almost 2 years. Of the screened 609 individuals, 26 subjects with current infectious illnesses (12 with urinary infections, 8 with diabetic foot, and 6 with upper respiratory tract infections) or 126 subjects with incomplete data (mostly no information about WC and current medical treatment) were excluded. Obesity was defined as a BMI of 30 kg/m^2. The components of MetS were identified using the national cholesterol education program adult treatment panel [the National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP-III)] criteria.[11,12] The study groups were MHO (obesity + <3 MetS features), MUHO (obesity + ≥3 MetS features), MUHNO (no obesity + ≥3 MetS features), and MHNO (no obesity + <3 MetS features).[13] Waist circumference was measured at the midpoint between the lower rib and iliac crest. We also included the use of antidiabetic therapies, blood pressure-lowering agents, and lipid-lowering agents when defining metabolic phenotypes. Metabolically healthy obese, 84 patients; MUHO, 92 patients; MUHNO, 87 patients; and MHNO, 104 patients, were matched according to age and sex. Consequently, our final analysis included 200 people (MHO = 50 subjects, MUHO = 50 patients, MUHNO = 50 patients, and MHNO = 50 subjects).

Demographic characteristics (sex and age), anthropometric measurements (height, weight, and WC), and clinical and biochemical data (including systolic and diastolic blood pressure, comorbidities, drugs, lipid parameters, serum creatinine, serum uric acid, hs-C reactive protein, and fasting blood glucose) of the patients were retrospectively reviewed from the hospital data system during the last visit to our outpatient clinic. Body Mass Index was calculated using the following formula: weight (kg)/height (in meters) squared. Visceral adiposity index was calculated using the following formula: For males: VAI = (WC/[39.68 + (1.88 × BMI) × (TG (mmol/L)/1.03) × (1.31/HDL (mmol/L)] and for females: VAI = (WC/[36.58 + (1.89 × BMI) × (TG (mmol/L)/0.81) × (1.52/HDL (mmol/L)].[6]

MAIN POINTS

- Metabolic health extends beyond body mass index, and it is critical to identify people who are metabolically unhealthy.
- In the differentiation of metabolic subtypes, the visceral adiposity index (VAI) score can be used to distinguish between different metabolic subtypes, in addition to waist circumference, triglyceride, high-density lipoprotein cholesterol, and C-reactive protein levels.
- The VAI cutoff values should be defined on a population basis. These values were defined for metabolic subtype discrimination in this study.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethical Committee of the Ankara University approved the study (Ethical Committee Decision Number: İ05-316-22). Because this is a retrospective archive study, informed consent was not obtained. Permission was obtained from the hospital chief physician for the use of patient data: The use of patient data is appropriate after obtaining the approval of the Ankara University Ethics Committee, provided that the principles specified in the regulation on "Processing of Personal Health Data and Ensuring Privacy" (Official Gazette dated November 24, 2017, and numbered 30250) are complied with.

Statistical Analysis

The conformity of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive analyses were performed using the mean ± standard deviation for parametric data, and median (minimum and maximum), and interquartile range (IQR) for nonparametric data. Chi-square tests of independence were used for categorical variables. Comparisons of multiple median/mean values between the different groups were performed using the Kruskal–Wallis test or analysis of variance, where appropriate. Correlations between VAI and other variables were evaluated using Pearson's or Spearman's rank tests, as appropriate. The mean differences in quantitative variables in the different subgroups were analyzed using the Games–Howell multiple comparisons for post hoc analyses following the one-way analysis of variance. Differences among more than 2 groups for non-normally distributed continuous variables were evaluated by Kruskal–Wallis variance analysis. When the *P*-value from the Kruskal–Wallis test statistics was statistically significant, the Dunn test was used to determine which group differs from which others. Receiver operating characteristic (ROC) analyses were also performed to assess the discriminative ability of VAI, WC, BMI, HDL-C, and TG between groups. The Bonferroni correction was applied for all possible multiple comparisons to control the type I error rate. A *P*-value of less than .05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences Statistics statistical software (IBM corp., Armonk, NY, USA).

Results

The baseline clinical, anthropometric, and laboratory characteristics of the study groups are presented in Tables 1 and 2, respectively. There were significant differences among the study groups in terms of diabetes mellitus (DM), dyslipidemia, hypertension, and cardiovascular disease, as well as BMI, WC, systolic blood pressure, diastolic blood pressure, fasting blood glucose, lipid parameters, and high-sensitivity C-reactive protein (hs-CRP) levels (Tables 1 and 2).

In Males

The VAI scores and WC differed significantly among the men (Tables 1 and 2). Among men, the VAI scores of the MUHNO group were greater than those of the MHO, MUHO, and MHNO groups ($P < .001$, $P < .001$, and $P < .001$, respectively) (Table 3). There were no differences in the VAI scores among the other groups. The WC of men in the MUHNO group was higher than that of men in the MHO group ($P = .014$) (Table 3). There were no differences in WC among the other metabolic phenotypes. Upon the creation of ROC curves, the VAI score predicted the MUHNO group from the study population (area under the curve (AUC) = 0.836, $P < .001$), whereas WC predicted the MUHNO

Table 1. Baseline Characteristics and Anthropometrics in Different Phenotypes

	MHNO (n = 50)	MHO (n = 50)	MUHO (n = 50)	MUHNO (n = 50)	*P*
Age, year	55.78 ± 9.46	56.58 ± 9.28	58.96 ± 7.00	59.32 ± 10.18	.075*
Female, n %	24, 48	26, 52	27, 54	22, 44	.758**
Dyslipidemia	12	11	43	42	<.001**
DM	0	0	19	49	<.001**
HT	0	10	40	39	<.001**
CAD	0	0	0	26	<.001**
Smoking	11	14	10	21	.062**
ACEi	0	0	13	15	<.001**
ARB	0	0	23	21	<.001**
Beta blocker	13	15	20	21	.266**
CCB	5	5	11	12	.102**
ASA	0	0	24	31	<.001**
Statin	9	10	29	35	<.001**
BMI (kg/m^2), median (minimum−maximum), IQR	23.70 (18.8-24.9) 3.4	33.15 (31.3-43.5) 4.2	34.45 (31.1-55.6) 5.8	26.00 (18.8-29.4) 4.1	<.001*
WC (cm), F, median (minimum−maximum), IQR	87.25 (75.50-108.3), 12.0	86.05 (70.0-92.9), 6.7	100,70 (64.7-131.8), 18.9	98.00 (87.0-109.0), 9.0	<.001*
WC (cm), M	89.58 ± 9.71	88.05 ± 9.35	92.97 ± 17.43	96.96 ± 8.97	.017*
SBP (mm Hg), median (minimum−maximum), IQR	113 (100-130), 11.3	130 (100-170), 20.0	140 (100-180), 26.3	127 (94-175), 30.0	<.001*
DBP (mm Hg), median (minimum−maximum), IQR	76 (56-86), 6.6	80 (60-120), 10.0	85 (60-130), 15.0	72 (60-100), 12.0	<.001*

Values are presented as mean ± SD unless otherwise stated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic aside; BMI, body mass index; CAD, coronary artery disease; CCB, calcium canal blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; F, female; HT, hypertension; M, male; MHNO, metabolically healthy nonobesity; MHO, metabolically healthy obesity; MUHNO, metabolically unhealthy nonobesity; MUHO, metabolically unhealthy obesity; SBP, systolic blood pressure; WC, waist circumference.
*Kruskal–Wallis test.
**Chi-square test.

group from the healthy group (AUC = 0.720, *P* = .004) (Table 4). We describe a VAI score higher than 5.69 as the cutoff point to identify MUHNO patients among the study population with 78% sensitivity and 79% specificity, and the upper 93 cm of WC as the cutoff point to identify MUHNO patients among healthy subjects with 64% sensitivity and specificity in males.

Table 2. Biochemical Parameters in Different Phenotypes

	MHNO (n = 50)	MHO (n = 50)	MUHO (n = 50)	MUHNO (n = 50)	*P*
FBG, mg/dL, median (minimum−maximum), (IQR)	90.25 (54-99) 13.1	88 (60-99) 13.9	105.45 (68-184) 34.9	133 (35-486) 125	<.001*
Creatinine, mg/dL	0.81 ± 0.30	0.76 ± 0.23	0.84 ± 0.26	0.85± 0.27	.610*
Total-C, mg/dL	212 ± 52	195 ± 38	218 ± 48	182 ± 57	**.001**¶
TG, mg/dL, median (minimum−maximum), (IQR)	126 (42-426), 80	132.50 (51-346), 86	162 (90-473), 86	178 (57-1066), 129	**<.001***
HDL-C, mg/dL	53 ± 14	49 ± 12	49 ± 15	42 ± 15	**.001**¶
LDL-C, mg/dL	137 ± 41	122 ± 35	140 ± 40	99 ± 44	**<.001**¶
Uric acid, mg/dL	5.37 ± 1.27	5.66 ± 1.43	5.76 ± 1.45	6.98 ± 8.10	.589*
hs-CRP (mg/L), median (minimum−maximum), (IQR)	0.55 (0.1-0.41) 0.11	0.38 (0.17-0.65) 0.15	1.43 (1.04-2.15) 0.33	3.40 (0.20-62.00) 6.60	**<.001***
VAI, F, median (minimum−maximum), (IQR)	5.48 (1.35-15.28) 4.33	3.68 (1.20-8.97) 3.74	6.46 (1.74-22.0) 7.05	8.25 (1.79-35.08), (12.51)	**.003***
VAI, M, median (minimum−maximum), (IQR)	2.92 (1.20-13.09), 2.97	3.66 (1.13-9.42) 4.53	3.46 (1.57-8.21) 2.23	7.03 (1.06-67.84) 4.27	**<.001***

Values are presented as mean ± SD unless otherwise stated. Statistically significant points were given in bold.
F, female; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; M, male; MHNO, metabolically healthy nonobesity; MHO, metabolically healthy obesity; MUHNO, metabolically unhealthy nonobesity; MUHO, metabolically unhealthy obesity; TG, triglycerides; total-C, total cholesterol; VAI, visceral adiposity ındex.
*Kruskal–Wallis.
¶One-way analysis of variance test.

Table 3. Differences of Parameters Between Groups

Parameter		(I) Metabolic Class	(J) Metabolic Class	P*
Male	VAI	MUHNO	MHO	**<.001**
			MUHO	**<.001**
			MHNO	**<.001**
	WC, cm	MUHNO	MHO	**.014**
			MHNO	.134
Female	VAI	MHO	MUHO	**.039**
			MUHNO	**.002**
	WC, cm	MHO	MUHO	**<.001**
			MUHNO	**<.001**
			MHNO	1.00
		MHNO	MUHO	**.009**
			MUHNO	**.001**
All study population	Total-C, mg/dL	MUHNO	MHNO	.210**
			MUHO	**.032****
	LDL-C, mg/dL	MUHNO	MHNO	**<.001****
			MHO	.130**
			MUHO	**<.001****
	TG, mg/dL	MUHNO	MHNO	**<.001**
			MHO	**.027**
	HDL-C, mg/dL	MUHNO	MHNO	**.003****
			MHO	.123**
	hs-CRP mg/L	MHNO	MHO	**.004**
			MUHO	**<.001**
			MUHNO	**<.001**
		MHO	MUHO	**<.001**
			MUHNO	**<.001**
		MUHO	MUHNO	1.000

Statistically significant points were given in bold.
HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MHNO, metabolically healthy nonobesity; MHO, metabolically healthy obesity; MUHNO, metabolically unhealthy nonobesity; MUHO, metabolically unhealthy obesity; TG, triglycerides; total-C, total cholesterol; VAI, visceral adiposity index.
*Kruskal–Wallis, Duncan test, adjusted *P*-values unless otherwise stated.
**One-way analysis of variance, Games–Howell, adjusted *P*-values.

In men, there was a significant association between BMI ($r = -0.22$, $P = .024$), WC ($r = 0.24$, $P = .016$), TG ($r = 0.82$, $P < .001$), and HDL-C ($r = -0.74$, $P < .001$), but no correlation between CRP ($r = 0.19$, $P = .057$) and VAI score.

In Females

In females, the VAI scores of the MHO group were lower than those of the MUHO and MUHNO groups ($P = .039$, $P = .002$, respectively).

WC was lower in the MHO group than in the MUHO and MUHNO groups ($P < .001$, $P < .001$, respectively) and was consistent with that in the MHNO group. In addition, the WC of the MHNO group was lower than that of the MUHO and MUHNO groups ($P = .009$, $P = .001$, respectively) (Table 3). Following the generation of ROC curves, the VAI score and, WC predicted the MHO group from the unhealthy group (AUC = 0.751, $P = .001$; AUC = 0.768, $P < .001$ respectively). Waist circumference also distinguished the MHNO group from the unhealthy group (AUC = 0.781, $P < .001$) (Table 4). We describe a VAI score lower than 4.89 as the cutoff point with 69% sensitivity and specificity, and a WC lower 90 cm as the cutoff point with 80% sensitivity and 81% specificity to identify MHO patients among the female unhealthy groups. In addition, the lower 92 cm of WC is the cutoff point with 75% sensitivity and 71% specificity for identifying MHNO subjects among unhealthy female patients.

In females, there was a significant association with WC ($r = 0.30$, $P = .002$), TG ($r = 0.88$, $P = .001$), HDL-C ($r = -0.74$, $P < .001$), and CRP ($r = 0.26$, $P = .008$), but no correlation with BMI ($r = -0.15$, $P = .127$) and VAI score.

Other Indicators in Identifying Metabolic Subtypes

When considering lipid metrics, the frequency of statin use was higher in the unhealthy group than in the healthy group, and total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were unreliable (Table 1). Due to the current statin medication, the MUHNO group had lower total-C and LDL values than the MHNO and MUHO groups. When TG and HDL-C levels were analyzed, which were less affected by statin therapy, the MUHNO group had higher TG levels than the MHNO and MHO groups ($P < .001$, $P = .027$, respectively). The MUHNO group had lower HDL-C levels than the MHNO group ($P = .003$) (Table 3). The TG and HDL-C levels were able to differentiate MUHNO patients from MHNO subjects, but unfortunately, not MHO subjects from MUHO patients. After generating the ROC curves, the HDL-C and TG concentrations predicted the MUHNO group from the healthy group (AUC = 0.734, $P < .001$; AUC = 0.686, $P < .001$, respectively) (Table 4). We describe HDL levels lower than 43.5 mg/dL as the cutoff point with 72% sensitivity and 71% specificity and TG levels higher than 153 mg/dL as the cutoff point with 64% sensitivity and 66% specificity to identify MUHNO patients among healthy subjects (Table 4).

C-reactive protein levels are also important in identifying metabolic phenotypes (Table 3). The CRP levels were the highest in the MUHNO group (Table 2). Following the generation of ROC curves, the CRP level predicted the healthy group from the unhealthy group (AUC = 0.986, $P < .001$) (Table 4). A CRP level of 0.57 mg/dL was determined as the cutoff point with 94% sensitivity and 95% specificity to distinguish healthy individuals from unhealthy patients.

Discussion

Obesity and normal weight are described according to BMI, which does not account for fat tissue distribution, especially excess visceral fat deposition, which is the key factor in CVD.[2] However, not all obese individuals have the same cardiometabolic risk. Furthermore, it is debatable whether individuals with a normal weight are truly healthy. MetS cannot accurately predict global CVD risk compared with its components, although it is strongly associated with insulin resistance.[14,15] The term cardiometabolic health was introduced, which identifies the overall risk of CVD by traditional risk factors as well as the involvement of systemic inflammation and BMI, and attempts to identify individuals based on cardiometabolic groups began in the literature. It has been demonstrated that the existence of increased VAT and the dysregulation of inflammatory factors (↑ tumor necrosis factor alpha, ↑ interleukin 6) and adipokines (↑ leptin, ↓ adiponectin) associated with increased VAT induce CVD and metabolic heterogeneity in obese and normal-weight patients.[4,16] Dietary and exercise habits, enhanced insulin resistance, and hereditary

Table 4. Areas Under the Receiver-Operating Characteristic Curves and Cutoff Points of the Visceral Adiposity Index and Anthropometric Indicators to Predict Metabolic Phenotypes

	Parameter	AUC (95% CI)	Cutoff level	*P**	Sens, %	Spec, %
Male patients	VAI, MUHNO vs other groups	0.836 (0.744-0.928)	5.69	<.001	78	79
	WC (cm) MUHNO vs healthy group	0.720 (0.604-0.835)	93	.004	64	64
Female patients	VAI, MHO vs unhealthy groups	0.751 (0.640-0.863)	4.890	.001	69	69
	WC (cm) MHO vs unhealthy groups	0.7863 (0.777-0.949)	90	<.001	80	81
	WC (cm) MHNO vs unhealthy groups	0.781 (0.670-0.893)	92	<.001	75	71
All study population	HDL-C mg/dL, MUHNO vs healthy groups	0.734 (0.643-0.826)	43.50	<.001	72	71
	TG (mg/dL) MUHNO vs healthy groups	0.686 (0.595-0.777)	153	<.001	64	66
	hs-CRP (mg/dL) healthy vs unhealthy group	0.986 (0.968-1.000)	0.57	<.001	94	95
	hs-CRP (mg/dL) MHO vs unhealthy groups	0.979 (0.956-1.000)	0.61	<.001	94	92
	hs-CRP (mg/dL) MHNO vs other groups	0.953 (0.927-0.979)	0.33	<.001	90	87
	hs-CRP (mg/dL) MHNO vs MHO	0.876 (0.810-0.942)	0.30	<.001	78	76

AUC, area under the ROC (receiver operating characteristic) curve; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; MHNO, metabolically healthy nonobesity; MHO, metabolically healthy obesity; MUHNO, metabolically unhealthy nonobesity; MUHO, metabolically unhealthy obesity; Sens, sensitivity; Spec, specificity; TG, triglycerides; VAI, visceral adiposity index; WC, waist circumference.
*Bonferroni adjustment was applied, adjusted *P*-value.

factors also contribute.[17] It has been established for approximately 10 years that VAI is an indirect indicator of VAT and reflects cardiometabolic risk in different studies.[6,18-21] The benefit of VAI is that it is easily calculated using anthropometric parameters (WC, BMI) as well as lipid parameters (TG, HDL) that are particularly related to central obesity.

In a meta-analysis, the overall risk of type 2 DM was significantly increased in MUHNO (relative risk (RR) = 4.30, 95% CI = 3.36-5.50) compared with MHNO.[22] In addition, the MUHNO group had a higher type 2 DM risk according to MHO and MUHO (RR = 1.44, 95% CI = 1.10-1.87; and RR = 2.43, 95% CI = 1.90-3.11, respectively).[22] Moreover, the risk for type 2 DM development in the MUHNO group compared with the MHNO group was also higher than in the MUHO group compared with the MHO group (RR = 4.30, 95% CI = 3.36-5.50; and RR = 3.49, 95% CI = 2.72-4.47, respectively).[22]

Because it integrates physical (BMI and WC) and metabolic (TG and HDL) parameters, the VAI score indirectly reflects additional nonclassical risk variables, such as altered adipocytokine production, enhanced lipolytic activity, and plasma free fatty acids.[23] The main and essential issue is to identify individuals with an unhealthy metabolic phenotype and a high CVD risk who require more active/protective management, irrespective of their BMI. In our study, we analyzed the discriminative role of the VAI score and other factors among different phenotypes.

To date, the age-stratified cutoff points of VAI scores have been identified in the Caucasian Sicilian population and are associated with MetS (2.52 for age < 30 years; 2.23 for age ≥ 30 and < 42 years; 1.92 for age ≥ 42 and < 52 years; 1.93 for age ≥ 52 and < 66 years; and 2.00 for age ≥ 66 years).[5] In males, the median VAI scores in the MHNO, MUHNO, MHO, and MUHO groups were 0.85, 2.20, 1.19, and 2.51, respectively, in a Brazilian population-based study.[24] In the same study, the median VAI scores of the MHNO, MUHNO, MHO, and MUHO groups were 1.08, 2.19, 1.21, and 2.73, respectively, in females.[24] The VAI scores of the study groups in both sexes were higher in our study than in the Brazilian study. In contrast to our study, the VAI score showed the highest diagnostic precision in detecting the MUHNO phenotype in both males (AUC = 0.865) and females (AUC = 0.843) and the MUHO phenotype in females (AUC = 0.903) in the Brazilian study.[24] The VAI score and WC show racial and sex-specific characteristics. Therefore, these results should be reevaluated in different races. The utility of VAI score and WC measurements in differentiating metabolic subtypes differs according to gender. MUHNO could be discriminated from MHNO by the VAI score and from healthy subjects by the WC in males. We describe a VAI score higher than 5.69 and WC higher than 93 cm as the cutoff point to identify MUHNO patients among the study population in males. However, the VAI score and WC could not distinguish MUHO patients from MHO subjects in males. In females, the VAI score can distinguish the MHO group from unhealthy patients but cannot distinguish the MHNO group from unhealthy patients. WC measurement plays a more important role in distinguishing metabolic phenotypes among females. Unlike the male group, WC measurement could distinguish the healthy group from the unhealthy group. We describe VAI scores lower than 4.89 and WC lower than 90 cm as the cutoff points to identify MHO patients among the unhealthy individuals in females, as well as WC lower than 92 cm to identify MHNO patients among the unhealthy individuals in females. These limitations of the VAI score and WC measurement preclude their use as the sole determining factor; however, along with other parameters, they can make a helpful contribution.

The relative risk of cardiometabolic complications in the MUHNO group was higher, with values ranging from 1.41 to 3.14, when the MHNO group was used as a reference.[25] Consistent with these results, we determined that the VAI score, an indirect indicator of VAT, was higher in the MUHNO group in both men and women.

Another important finding of our study was that HDL-C and TG levels contributed to the differentiation of the MUHNO group, and hs-CRP levels contributed to the differentiation of the healthy group, independent of gender. Lear et al[26] identified that the higher risk factor levels for CVD in South Asians were predominantly due to the phenotype of having greater VAT than Europeans, even at the same BMI. They claim that this result is associated with VAT being a significant mediator in total-C, LDL-C, total-C/HDL-C in men and in HDL-C, TG, and total-C/HDL-C in women.[26] Another study discovered that in Japanese participants with mild obesity and/or poor glucose tolerance, visceral fat mass was a substantial and independent predictor

of serum hs-CRP levels.[27] However, the roles of CRP, TG, and LDL-C in differentiating metabolic phenotypes have not been defined so far.

In summary, the role of the VAI score and WC measurement is sex-dependent and should be considered race-specific. The most important result of our study is that the VAI score can distinguish MUHNO from MHNO in the male gender. However, in females, the VAI score can identify MHO from the MUHO group. WC measurement plays a better role in distinguishing metabolic phenotypes among females. The Hs-CRP, TG, and LDL-C levels can also play an important role in differentiating metabolic phenotypes. It is important to prioritize metabolic health in the clinical evaluation of patients; however, it is also important that no single factor is sufficient and that the identified factors are evaluated together.

Some limitations of this study must be considered. This study was based on a limited number of patients to form four age- and sex-matched metabolic phenotypes. Because of the retrospective design, the diet and exercise preferences of the patients were also unknown. Cutoff values of VAI were defined for metabolic subtype discrimination with a limited number of participants. Community-based studies are needed to define VAI cutoff values for metabolic subtype discrimination in the Turkish population. On the other hand, the main groups of medications are given in Table 1. These medications can affect the results and VAI calculations, since they may somehow change insulin resistance, glucose, and lipid levels.

The strength of this study is that it is one of the few studies examining the association of VAI with different metabolic subtypes with comprehensive patient data. In addition, for the first time, we calculated the cutoff values for VAI and WC measurements to identify metabolic health.

Metabolic health extends beyond BMI, and it is critical to identify people who are metabolically unhealthy. Our study highlights the usefulness of VAI in differentiating metabolic subtypes and defining cutoff values. The VAI score is a simple technique for defining individuals with high CVD risk before MetS appears, although it may not describe all unhealthy patients. Other variables, such as WC, TG, HDL-C, and CRP levels, as well as the VAI score, can be used to distinguish different metabolic subtypes.

Ethics Committee Approval: This study was approved by the Ethics committee of Ankara University (Approval No: İ05-316-22, Date: 8/2022).

Informed Consent: Because this is a retrospective archive study, informed consent was not obtained. Permission was obtained from the hospital chief physician for the use of patient data: The use of patient data is appropriate after obtaining the approval of the Ankara University Ethics Committee, provided that the principles specified in the regulation on "Processing of Personal Health Data and Ensuring Privacy" (Official Gazette dated November 24, 2017, and numbered 30250) are complied with.

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