Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

The importance of uric acid high-density lipoprotein cholesterol ratio as an indicator of visceral adiposity

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ARTICLE INFO

Keywords:
Obesity
Adiposity
Uric acid
High density lipoprotein

Received: Jul 17, 2023
Accepted: Nov 22, 2023
Available Online: 27.11.2023

DOI:
10.5455/annalsmedres.2023.07.156

Abstract

Aim: A number of anthropometric measurements are being developed to detect metabolic risks in overweight and obesity. Our purpose is to investigate the relationship of visceral adipocyte index (VAI), which is useful as a marker of adipocyte dysfunction with the ratio of uric acid to high-density lipoprotein ratio (UHR), an inflammatory marker, considering body mass index groups and accompanying metabolic syndrome (MetS).

Materials and Methods: In all, 509 female participants aged 18-60 years, admitted to the Outpatient Department of Endocrinology, Erzurum Training, and Research Hospital, were involved in this study. Our study group consisted of 409 patients (63 overweight, 202 obese, and 144 morbid obese) and 100 healthy controls. Anthropometric measurements, including height, weight, and waist circumferences, were measured, and VAI values were calculated for all participants. All subjects had been tested with biochemistry analysis for lipid profile tests and uric acid.

Results: UHR level was significantly elevated in the patient group [10.9 (3.8-30.4%)] compared with the control group [7.29 (3.44-19.3 %)]. The highest UHR level was found in the morbid obese group, 12.3 (5.8-30 %), and the lowest UHR level was in the overweight group [8.63 (3.8-17 %)]. A moderately strong positive correlation was found between VAI and UHR in both patient and control groups, and the strongest correlation was found in the overweight group ($r=0.586$, $R^2=0.319$). In addition, the UHR level was 12.2 (6-30%) in the patient group with MetS and 9.7 (3.8-23%) in the patients without MetS.

Conclusion: Since the BMI is insufficient regarding prognosis and obesity-related mortality, it should be supported with VAI, a new anthropometric cardiometabolic risk indicator. UHR might be a sensitive and accurate indicator of visceral fat excess even in the early stages of obesity and MetS.

Introduction

Obesity is a chronic global epidemic health problem with increasing prevalence in all age groups. The number of obese individuals is increasing day by day due to reasons such as rapid social and cultural changes, the aging of the population, an increase in the urbanization rate, unhealthy lifestyles, and behavioral patterns. In 2015, approximately 603.7 million adults had obesity worldwide [1]. The prevalence of obesity is predicted to increase to 50% of the global adult population by 2030 [2]. Overweight and obesity are defined by The World Health Organization (WHO) as abnormal and excessive fat accumulation that poses a health risk. It has been understood in recent years that adipose tissue acts as an active endocrine gland by secreting many bioactive peptide hormones and playing essential roles in many metabolic reactions with active mediators. Therefore, adipose tissue is now recognized as an endocrine organ. White adipose tissue, which provides the endocrine organ function of adipose tissue, is mostly in two separate groups: subcutaneous adipose tissue (abdominal, gluteal, femoral, and other subcutaneous adipose tissue) and visceral (omental) adipose tissue, which exhibits a more pathogenic profile than subcutaneous accumulation. Fat accumulation is higher in women than in men and increases with age. Measuring body mass index (BMI) is the first generally accepted approach to determine the degree of obesity. It is easy and reliable to measure but indicates excess weight rather than excess fat. In addition, the sensitivity of the BMI calculation changes in some physiological conditions. For instance, the BMI cut-off points used for females are the same as those for males, even though females have higher body fat percentages. In

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addition, BMI classification in children, elderly individuals, and athletes is not very appropriate. Therefore, in addition to BMI, waist circumference (WC) measurement is also recommended in overweight or obese patients to assess abdominal obesity. WC $\geq$ 102 cm in males and $\geq$ 88 cm in females is considered high and indicative of increased cardiometabolic risk [3]. The visceral adiposity index (VAI) is a new anthropometric empirical mathematical formula based on gender-varying biochemical parameters such as triglyceride (TG), high-density lipoprotein cholesterol (HDL cholesterol) concentrations, and anthropometric measurements, including BMI and WC. It was first developed by Amato et al. in 2009 [4]. Increased VAI is associated with various diseases such as hypertension, type 2 diabetes mellitus, cardiovascular diseases, and dementia [5,6]. It has clinical importance in determining visceral obesity and predicting cardiometabolic risks in the early period. This is probably because the three variables that compose VAI (WC, TG, HDL) are included in the metabolic syndrome (MetS) criteria. Weight gain and obesity may be the main factors causing MetS. The relationship between MetS and uric acid levels has been reported in the literature [7,8]. The visceral fat percentage was significantly correlated with serum uric acid (SUA) and adiponectin concentration [9]. Local adipose hypoxia may also increase uric acid production. De novo purine synthesis occurs during fatty acid synthesis. As a result, uric acid synthesis and secretion increase. Xanthine oxidoreductase (XOR) catalyzes purines to uric acid. Adipose tissue has abundant XOR activity, similar to the other organs [10]. The ratio of uric acid to HDL (UHR) was first found to be important in 2019 in patients with type 2 DM regarding the diagnosis of MetS and being an indicator of poor diabetic control [11]. Previous studies have also shown that UHR is associated with hypertension [12], hepatosteatosis [13], and cardiovascular mortality [14]. Although the data regarding the possible link between SUA and visceral adipose tissue is insufficient, our study is the first to investigate the correlation between visceral obesity and UHR in women without a history of additional chronic diseases such as diabetes mellitus. In addition, our study is of significant importance in investigating the relationship between VAI and UHR, considering BMI groups and accompanying MetS.

Materials and Methods

Five hundred nine female participants aged 18-60 years with no comorbidities admitted to the Outpatient Clinic of Endocrinology, Erzurum Health Science University Hospital were involved in this study. Our study population consisted of 409 patients (63 overweight, 202 obese, and 144 morbid obese) with a BMI $\geq$ 25 kg/m^2 and 100 healthy women with a BMI of 18-24.9 kg/m^2. BMI was computed as weight (kg) divided by the height (m) squared, and BMI values (kg/m^2) 25.0–29.9, $\geq$ 30.0, and $\geq$ 40 were categorized as overweight, obesity, and morbid obesity, respectively. The same trained health personnel measured all participants ' anthropometric measurements, such as height, weight, and WC. WC was measured from the midpoint between the lowest costa and the anterior-superior iliac crests with a non-elastic flexible tape measure.

All subjects had been tested with routine hematology and biochemistry analysis. The venous blood samples were drawn after 12 hours of fasting. National Cholesterol Education Program Adult Treatment Panel-III guideline diagnostic criteria were used to confirm the diagnosis of MetS [15]. According to this definition, MetS was diagnosed if three or more of the following five criteria were observed: WC $\geq$ 88 cm (females), blood pressure over 130/85 mmHg, TG level $\geq$ 150 mg/dl, HDL-C level $<$ 50 mg/dl (females), and fasting glucose level $\geq$ 100 mg/dl. VAI was calculated by using the following formula.

For Females: VAI=[WC (cm) /(39.58+1.88 x BMI)]x[TG (mmol/L)/ 0,81]x[1.52/HDL-K (mmol/L)].

Patients with any chronic illness (Such as diabetes mellitus, hypertension, cardiac failure, renal or hepatic failure, neoplastic diseases, pregnancy, or breastfeeding) were excluded from the study.

Our study was approved by the Erzurum Training and Research Hospital Ethics Committee (Decision: KAEK 2023/01-12, Date: 31.05.2023). The study protocol was performed according to the Declaration of Helsinki. Our study is a prospective study and includes cases who applied to the Endocrinology and Metabolism Diseases outpatient clinic for routine examination or complaints of weight gain. All participants were informed by getting their written informed consent.

Statistical analysis

The sample size was calculated with the G*Power 3.1.9.4 program. According to the results of G*Power analysis, The power of the study was calculated as 95%, type 1 error: 0.04, effect size: 0.4, and allocation rate: 3, the sample size was calculated as minimum 97 for group 1 and minimum 386 for group 2. Hence, 100 participants in the control group and 409 in the patient group were enrolled in our study. SPSS 22.0 (IBM, SPSS Statistics, Version 22.0, Armonk, NY) statistical package program was used for statistical analysis of the data. The distribution of the variables in study groups was conducted by Kolmogorov–Smirnov test. Mann Whitney U and Kruskal Wallis tests were used to compare groups with non-normally distributed parameters. Dunn-Bonferroni posthoc test is used for pairwise comparison after the Kruskal-Wallis test. We used the independent t-test for comparison of normally distributed data.

All these analyses were used to explain the hypothesis of whether UHR level is a mediator of visceral adipose tissue. We used Spearman Correlation tests to detect the correlation between UHR and VAI. The Chi-square test was used for the analysis of categorical variables. Descriptive analyses were presented as median (minimum-maximum) for non-normally distributed variables. P-value $<$ 0.05 was deemed statistically significant.

Results

The current study included 509 female participants with a mean age of 35.1±11 years. The subjects were divided into four groups according to BMI level: normal BMI (n=100), overweight (n=63), obese (n=202), and morbidly obese (n=144). The demographic and

Table 1. Comparison of anthropometric and clinical characteristics of subjects.

Clinical variable	Case group (n=409) (BMI ≥ 25 kg/m^2)	Control group (n=100) (BMI < 25 kg/m^2)	Total (n=509)	p-value
Age (year)	36.2±11.1	30.7±9.6	35.1±11	<0.001
Weight (kg)	94 (57-165)	58 (43-68)	87 (43-165)	<0.001
Height (cm)	159 (145-179)	160±(148-174)	159 (145-179)	0.136
BMI (kg/m2)	36.8 (25.2-69.6)	22.5 (18-24,9)	34.2 (17.9-69.6)	<0.001
WC (cm)	104 (70-164)	66 (55-90)	100 (55-165)	<0.001
VAI	4.7 (0.80-32)	2.4 (0.80-10)	4.0 (0,8-32)	<0.001
Waist/weight	0.65±0.09	0.42±0.05	0.62 (0.35-0.96)	<0.001

Data are presented as mean± standard deviation for normally distributed parameters (age and waist/weight) and median (min-max) for nonnormal distributed parameters (Weight, height, BMI, WC, VAI). Abbreviations: BMI, Body Mass Index; WC, Waist Circumference; VAI; Visceral Adiposity Index.

Table 2. Comparison of the laboratory data in all BMI groups.

	BMI (kg/m^2)					
	<25	25-29.9	30-39.9	≥40	Total	p
	(n=100)	(n=63)	(n=202)	(n=144)	(n=509)	
Uric acid (mg/dl)	3.8 (2.1-6)	4.1(2.4-6.1)	4.8 (2.8-8.4)	5.3 (3.3-8.9)	4.6 (2.1-8.9)	<0.001
HDL (mg/dl)	50 (29-88)	49 (31-71)	46 (23-78)	44 (21-82)	47 (21-88)	<0.001
UHR (%)	7.29 (3.4-19.3)	8.63 (3.8-17)	10.6 (4.5-22.5)	12.3 (5.8-30.4)	9.8 (3.44-30.4)	<0.001
Tg (mg/dl)	73.5 (31-232)	99 (45-409)	114 (40-421)	123 (50-445)	105 (31-445)	<0.001
LDL (mg/dl)	108 (40-178)	123 (56-250)	127 (40-344)	135 (39-240)	123 (39-344)	<0.001
VAI	2.04 (0.8-10)	3.6 (1.4-17)	4.7 (0.8-32)	5.1 (1.4-23)	4 (0.8-32)	<0.001

Data are median (min-max); BMI, Body Mass Index; HDL, High-density lipoprotein cholesterol; Tg, Triglyceride; LDL, Low-density lipoprotein; cholesterol; UHR, Uric acid to HDL ratio, VAI, Visceral Adiposity Index.

Table 3. Correlation of VAI with study parameters in case and control groups.

Spearman's rho VAI	Case group	Control group	Total	p
UHR (r; R^2)	0.513; 0.252	0.572; 0.267	0.619; 0.311	<0.001
Uric Acid (r; R^2)	0.207; 0.036	0.104; 0.024	0.351; 0.084	<0.001
HDL (r, R^2)	-0.541; 0.230	-0.705; 0.337	-0.584; 0.248	<0.001

UHR, Uric acid to HDL ratio; HDL, High-density lipoprotein cholesterol; VAI, Visceral Adiposity Index.

Table 4. Correlation analysis between VAI and UHR in BMI groups.

Spearman's rho VAI		BMI (kg/m^2)			
		<25	25-29.9	30-39.9	≥40
		(n=100)	(n=63)	(n=202)	(n=144)
UHR	r	0.572	0.586	0.442	0.473
	R^2	0.267	0.319	0.205	0.298
	p	<0.001	<0.001	<0.001	<0.001

BMI, Body Mass Index; UHR, Uric acid to HDL ratio, VAI; Visceral Adiposity Index.

anthropometric characteristics of the participants are shown in Table 1. The comparison was demonstrated between the control group with the overweight, obese, and morbid obese groups in Table 2. SUA, TG, and UHR were higher, and HDL was lower in the three groups with BMI ≥ 25 kg/m^2. The median Uric acid, TG, LDL, UHR, and VAI levels according to their BMI groups were found to be increased progressively as the BMI level increased, while HDL decreased progressively. In Table 3, correlation analyses of VAI with uric acid, HDL, and UHR were performed in the case and control groups. VAI was significantly and positively correlated with UHR in both groups, slightly more strongly in the control group (r=0.619, R^2=0.311, p=0.000). In Table 4, correlation analyses were performed between VAI and UHR in all BMI groups. A stronger correlation was found between VAI and UHR in the overweight group compared to the other groups. The lowest correlation coefficient

Table 5. Frequency of metabolic syndrome in BMI groups.

MetS (-/+)	BMI (kg/m^2)			
	25-29.9	30-39.9	≥40	Total
	(n=63)	(n=197)	(n=141)	(n=401)
With MetS n, (%, total %)	21 (33.3, 13.1)	73 (37.1, 45.6)	66 (46.8, 41.3)	160
Without MetS n, (%, total %)	42 (66.7, 12.3)	124 (62.9, 36.4)	75 (53.2, 22)	241

MetS, Metabolic syndrome; BMI, Body Mass Index.

Table 6. Various parameters in participants with and without metabolic syndrome.

	Case group (BMI ≥ 25 kg/m^2)		Total	Control group (BMI < 25 kg/m^2)	p
	with MetS	without MetS		without MetS	
	n=160	n=241		n=100	
VAI	7.8 (2.8-32)	3.6 (0.8-10.9)	4.7 (0.8-32)	2.4 (0.8-10)	<0.001
UHR	12.2 (6-30)	9.7 (3.8-23)	10.9 (3.8-30.4)	7.29 (3.4-19.3)	<0.001
Uric Acid	5 (2.8-8.4)	4.8 (2.4-8.9)	4.9 (2.4-8.9)	3.8 (2.1-6)	<0.001
HDL	41.5 (21-82)	50 (23-76)	45 (21-82)	50 (29-88)	<0.001

Median (min-max), BMI, Body Mass Index; MetS, Metabolic syndrome; UHR, Uric acid to HDL ratio, VAI, Visceral Adiposity Index; HDL, High-density lipoprotein cholesterol.

Table 7. Correlation analysis between VAI and UHR in case group with and without metabolic syndrome.

Spearman's rho VAI		with MetS	without MetS	Total	p
UHR	r	0.474	0.443	0.618	<0.001
	R^2	0.209	0.196	0.311	
Uric Acid	r	0.176	0.194	0.350	<0.001
	R^2	0.023	0.036	0.084	
HDL	r	-0.552	-0.426	-0.541	<0.001
	R^2	0.224	0.153	0.230	

MetS, Metabolic syndrome; UHR, Uric acid to HDL ratio; HDL, High-density lipoprotein cholesterol.

was found in the obese group. In addition, a moderate relationship is observed in the control group, similar to that in the overweight group (r=0.572, r=0.586, p=0.000).

In Table 5, our patient group was categorized in terms of MetS. MetS was detected in 38.6% (n=160) of the patient group. The frequency of MetS was highest in the obese group, with a rate of 45.6%. 41.3% of the patients with MetS were in the morbidly obese group. The overweight group comprised only 13.1% of patients with MetS.

The frequency of Met S was 46.8%, 37.1%, and 33.3% in the morbidly obese, obese, and overweight groups, respectively. MetS was not observed in any of the 100 patients in the control group. Plasma uric acid, UHR, and VAI levels were found to be significantly higher, and HDL levels were found to be lower in patients with MetS compared to those without MetS. No difference in HDL level was observed between the group with normal BMI and those without MetS above ≥ 25 kg/m^2 (Table 6). A moderately strong positive correlation was detected between VAI and UHR in patients with and without MetS (Table 7).

Discussion

The current study investigates VAI and UHR levels and the relationship between both parameters according to BMI level and the presence of MetS in female individuals. According to our results, VAI and UHR levels increased as the BMI level increased. Also, it was observed that VAI and UHR levels were higher in those with MetS than those without. A significant positive correlation was also shown between VAI and UHR in all BMI groups (normal, overweight, obesity, morbid obesity).

Obesity is a complex and major medical problem that increases the risk of comorbidities such as heart disease, prediabetes, type 2 diabetes mellitus, blood pressure increase, and various cancers [16]. The WHO defines overweight and obesity as abnormal and excessive fat accumulation, emphasizing the importance of adipose tissue. Although BMI is a rough ratio, it is the most commonly used parameter in the diagnosis of obesity. Since it does not take into account the amount of abdominal adiposity, it fails to differentiate body composition, fat mass, and lean body mass, subcutaneous and visceral fat deposition status. In addition, in a meta-analysis of 40

epidemiological studies, it was reported that BMI was insufficient in the assessment of mortality and cardiovascular risk [12], and it has been suggested that BMI may no longer serve as a clinical and epidemiological tool for cardiovascular risk assessment [17]. In recent years, VAI, calculated by anthropometric measurements and TG and HDL with a mathematical method, is frequently preferred in clinical practice. VAI indirectly reflects visceral adipose function and predicts cardiometabolic risks in the early period. In our study, we found that VAI increased in overweight and obese groups compared to the group with normal BMI, consistent with studies in the literature. We also found that UHR accepted as an inflammatory marker, increased in these patients. There was a strong correlation between VAI and UHR. Interestingly, this correlation was found to be strongest in the overweight group. In some other studies, in individuals with high intra-abdominal fat accumulation, It has been proven that metabolic abnormalities caused by obesity are more common than in obese individuals with peripheral fat distribution.

In other words, even if the individual is not obese, increased visceral adipose tissue may cause atherogenic and metabolic abnormalities [18]. In our study, the reason why the BMI group, in which the relationship between UHR and VAI was strongest, was the overweight group may be due to the possibility that the adipose distribution of these individuals is more central (visceral) compared to obese and morbidly obese individuals. In addition, no statistical difference was found regarding VAI in patient groups with BMI $\geq$ 25. Therefore, it cannot always be said that visceral obesity increases as the BMI level increases. Because obese individuals have a heterogeneous phenotype, each phenotype is associated with a different degree of cardiovascular risk. This is considered as "obesity paradox". The explanation of this paradox has gained significant importance in recent years and guided the new classification of obesity [19]. In this context, health authorities have defined new obesity phenotypes in addition to the metabolically unhealthy obesity phenotype. The first of these phenotypes is Metabolic Healthy Obese (MHO). MHO was defined as an obesity phenotype with lower cardiovascular risk, without metabolic syndrome, compared to other obese phenotypes. Despite having a high BMI, they are metabolically healthy. They have increased insulin sensitivity, a balanced lipid profile, and plasma proinflammatory cytokine levels. Compared to the metabolically unhealthy obese, these individuals have lower visceral and liver fat accumulation. The risks of cardiovascular events and mortality are also lower. 10-30% of obese individuals in Europe are in the MSO phenotype, mostly female [20]. The metabolically abnormal obese (MAO) group, which is a different phenotype, differs significantly from the MHO subtype with accompanying central obesity, MetS, type 2 diabetes mellitus, high blood pressure, and cardiometabolic risks. Another phenotype, metabolically obese normal weight (MONW), is also known as a metabolically abnormal subtype with no obesity. Although these individuals have normal BMIs, they have the same cardiovascular risks and metabolic complications as MAO. It was reported that at least 29% of individuals with normal BMI are obese regarding fat ratio. Together with all these data, it is noticed that BMI measurement, which does not reflect body composition and fat distribution, is insufficient to define obesity [19].

The ratio of uric acid to HDL increases with inflammatory conditions. In the study of Kızılay et al., hyperuricemia and lower HDL were detected in the presence of MetS. [21]. Studies have shown that UHR is a better marker of MetS than SUA, and its correlation with WC is more significant with UHR than SUA [22].

In our study, UHR and VAI were significantly higher in patients with MetS than those without MetS. Even in patient groups, UHR and VAI levels were much higher in patients with MetS than in patients without MetS, and SUA level was slightly higher in patients with MetS than patients without MetS. In addition, our study shows that the distribution of adipose tissue is more related to inflammation and comorbidity than the amount of adipose tissue. Therefore gender gender-specific VAI calculations should be performed in addition to BMI to manage obesity.

There are some strengths and limitations of our study. One of the strengths of our study is to include individuals who do not have any chronic diseases or drug history, such as diabetes mellitus or hypertension that affect uric acid and HDL levels. As it is known, physiologically, SUA levels are higher in males than in females and increase with age due to the decrease in uricosuric estrogen in the postmenopausal period [23]. Including only female individuals with a non-elderly age range is strength of the study in terms of the accuracy and generalizability of the results and the adequacy of the number of subjects.

One of the limitations of this study is that visceral adiposity was defined solely based on waist circumference and VAI calculations without using any imaging techniques, including bioelectrical impedance analysis for the detection of visceral fat. Because of the strong association between the percentage of visceral adipose tissue detected by imaging techniques and the VAI level, which has been proven in the literature [24], was considered in the planning of this study.

Conclusion

The combination of HDL cholesterol and uric acid formulated as UHR may be a new and sensitive marker of metabolic and inflammatory disorders. UHR should take its place as a metabolic marker in the clinical approach to overweight, obesity, and metabolic syndrome. This clinical study should be supported by newer studies with more patients to investigate the clinical effects that may lead to novel treatments.

Source of finance

This research received no external grant or other form of financial support.

Conflict of interest

The authors have no conflicts of interest.

Ethical approval

This study was approved by the Erzurum Training and Research Hospital Ethics Committee (Decision: KAEK 2023/01-12, Date: 31.05.2023).

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