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VISCERAL ADIPOSITY INDEX AS HYPERURICEMIA PREDICTOR IN TYPE 2 DIABETES MELLITUS PATIENTS

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The article examines the relationship between the visceral adiposity index and hyperuricemia in type 2 diabetes mellitus patients. Hyperuricemia was found in 38.1 % of type 2 diabetes mellitus patients. Their visceral adiposity index correlated with decreased tissue sensitivity to insulin-mediated glucose absorption, impaired absorption of postprandial glucose, increased insulin resistance and increased plasma atherogenic potential. Obesity was shown to be an important risk factor for hyperuricemia, and an increased visceral adiposity index is positively associated with its risk in type 2 diabetes mellitus patients. Compared to other indices, visceral adiposity index was more discriminant in determining the hyperuricemia risk than the body mass index, waist circumference, and waist-to-height ratio index.

Key words: hyperuricemia, type 2 diabetes mellitus, visceral adiposity index

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ІНДЕКС ВІСЦЕРАЛЬНОГО ОЖИРІННЯ ЯК ПРЕДИКТОР ГІПЕРУРИКЕМІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

Вивчено взаємозв'язок індексу вісцерального ожиріння та гіперурикемії у хворих на цукровий діабет 2 типу. Гіперурикемію виявлено у 38,1 % хворих на цукровий діабет 2 типу. Індекс вісцерального ожиріння у хворих на цукровий діабет 2 типу корелює із зниженою чутливістю тканин до інсулін-опосередкованої абсорбції глюкози, погіршенням всмоктування постпрандіальної глюкози, підвищенням резистентності до інсуліну та збільшенням атерогенного потенціалу плазми. Встановлено, що ожиріння є важливим фактором ризику розвитку гіперурикемії, а значення індексу вісцерального ожиріння позитивно корелює з ризиком гіперурикемії у хворих на цукровий діабет 2 типу. У порівнянні з іншими індексами, індекс вісцерального ожиріння має більше прогностичне значення для оцінки ризику гіперурикемії, ніж індекс маси тіла, обвід талії та індекс співвідношення обвіду талії до зросту.

Ключові слова: гіперурикемія, цукровий діабет 2 типу, індекс вісцерального ожиріння

The article is based on the material of the research project: "Improve the diagnosis of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus, taking into account the etiopathogenetic", state registration No. 0119U102446.

Hyperuricemia (HU) has emerged as a great health care issue due to its increasing prevalence and significant impact on various clinical disorders. Recent epidemiological investigations have estimated the HU prevalence as 8.4–25.0 % in the general population. At that, 21 % of the US general population was revealed to develop HU. HU has been shown to be an important independent factor increasing the risks of morbidity and mortality associated with many diseases, including hypertension, diabetes mellitus (DM), dyslipidemia, chronic kidney disease, cardiovascular events, and heart failure [9, 11, 13]. This condition also contributes to the development of gout that can impair patients' quality of life. Accordingly, early diagnosing the HU high-risk individuals and preventive intervention is of especial importance in medical practice.

Although growing evidence has shown obesity or excess body fat mass as a HU risk factor [5], the role of body fat distribution in uric acid metabolism is still unclear. Previous studies showed that changes of commonly used adiposity-based indices, such as body mass index (BMI), waist circumference (WC), neck circumference relate to the serum uric acid (SUA) alterations [8, 15], demonstrating the general obesity or central obesity significant influence on SUA metabolism. However, BMI which is widely used as an index of general obesity is unable to distinguish between central and peripheral fat, subcutaneous and visceral fat, lean mass, and fat mass [3]. WC is used as a measure of central obesity, but it cannot consider differences in height.

In the population, the risk of cardiovascular and metabolic complications was shown to be determined by the distribution of fatty tissue in the human body rather than by its mass [2]. It was shown that visceral adipose tissue performs auto-, para- and endocrine functions, producing several biologically active substances that regulate metabolic processes and immune reactions involved in inflammation, insulin resistance development and progression, the pathogenesis of cardiovascular disease, and non-alcoholic fatty liver disease.

Despite the introduced up-to-date methods of quantifying the mass of visceral adipose tissue in the human body (computer and magnetic resonance imaging), the anthropometric technique is still of scientific and practical value. The anthropometric method is based on the determination of surrogate indexes of visceral

adiposity BMI, Waist-to-Hip Ratio (WHR) and Waist-to-Height Ratio (WHtR) and Visceral Adiposity Index (VAI). VAI is a marker of visceral adipose tissue dysfunction that correlates independently with all components of metabolic syndrome (MetS), the risk of cardiovascular and cerebrovascular complications in the population, and thus is more informative for predicting DM than those individual MetS components.

Two kinds of central obesity are classified as subcutaneous and visceral fat mass, and WC alone is not useful to distinguish them. VAI, which was recently introduced by M. C. Amato et al., involves WC, BMI, triglycerides (TG), and high-density lipoprotein cholesterol (HDL–C), was used as a marker of visceral fat dysfunction, and it was proposed to be used as MetS indicator [12].

However, we found almost no available research concerning the VAI/HU correlation in type 2 DM patients.

The purpose of the study was to establish the visceral adiposity index/hyperuricemia correlation in patients with type 2 diabetes mellitus to assess the risk of hyperuricemia.

Materials and methods. 228 patients were assessed for type 2 DM. Among those examined, 134 women and 94 men were enrolled. The mean median (Me) age was calculated as Me 60 (58.98±9.89) years (ranged from 27 to 81). Those enrolled in the study were distributed into 2 groups: group 1 included 127 type 2 DM patients who received oral hypoglycemic therapy, and group 2 involved 101 type 2 DM patients who received insulin therapy. In group 1, the patients' median age was Me 60 (58.72±9.73) (ranged 30–81); in group 2, Me 61 (60.9±9.4) (ranged 41–81), respectively.

WC was measured with an inelastic tape to the nearest 0.1 cm at a midpoint between the bottom of the rib cage and the top of the iliac crest, following exhalation. Hip circumference was measured over thin clothing at the point of the maximum circumference of the buttocks. BMI was calculated as weight (kg) divided by height (m) squared. WHtR was calculated as WC (cm) divided by height (cm). Body adiposity index (BAI) was calculated using the formula: BAI = ((hip circumference)/((height)x(1.5))-18)). VAI was calculated using the following formulas, as proposed by M. C. Amato et al.:

VAI (men)=(WC/(39.68+(1.88×BMI)))×(TG/1.03)×(1.31/(HDL–C));

VAI (women)=(WC/(36.58+(1.89×BMI)))×(TG/0.81)×(1.52/(HDL–C)).

The VAI values <2.52 were considered normal in the age group under 30; <2.23 in the group of 31–42 years old; <1.92 in the age group of 43–52; <1.93 in the age group of 53–66; and <2.00 in those over 67 years old.

Glucose homeostasis was assessed according to the RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020 [1, 4].

Following an overnight fasting, blood was collected by venipuncture and tested immediately for glucose and glycated hemoglobin A1c (HbA1c). Serum levels of fasting plasma glucose (FPG), total cholesterol (TC), HDL–C, TG, and serum uric acid (SUA) were measured by a biochemical automated analyzer. Postprandial plasma glucose (PPG) was determined in venous blood samples taken two hours after meals. Plasma immunoreactive insulin (IRI) was determined by the ELISA Chemiluminescence Immunoassay (DRG Diagnostics, USA). Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated by the formula: HOMA-IR=fasting insulin (μmol/L)×FPG (mmol/L)/22.5. HU was defined as SUA ≥420 μmol/L in men and ≥360 μmol/L in women. Tissue sensitivity to insulin-mediated glucose assimilation was assessed according to the HOMA2_ % S, and secretory activity of beta-cells according to the HOMA2_ % B which was calculated using the HOMA Calculator v2.2 certified program. In the present study, males with SUA ≥ 420 μmol/L and females with SUA ≥ 360 μmol/L were classified as having HU.

All procedures of statistical analysis were performed using STATISTICA software version 10.0, and $p<0.05$ was considered statistically significant. We presented continuous variables as mean ± standard deviation (SD) and medians (Me) (interquartile range), while categorical variables as numbers (proportions). The estimates were compared using one-way analysis of variance (ANOVA) tests for continuous variables, and chi-square tests for categorical variables.

Results of the study and their discussion. HU was found in 38.1 % (n=72) of the examined individuals. In group 1, HU was diagnosed significantly more frequently than in group 2 (50 and 22 patients, respectively) (χ^2=4.05; p=0.04).

Table 1 presents the clinical and laboratory findings of type 2 DM patients according to SAU.

It has been established that in type 2 DM with hyperuricemia VAI, HOMA-IR is significantly higher than in type 2 DM patients with normal SAU; there is a tendency to IRI increase.

SUA levels have been found to correlate in type 2 DM patients with VAI (r=0.17, p=0.02), BMI (r=0.19, p=0.006), WC (r=0.16, p=0.003), HbA1c (r=-0.17, p=0.02), TG (r=-0.21, p=0.004), IRI (r=0.33, p=0.005), HOMA_S % (r=0.32, p=0.006), HOMA-IR (r=0.32, p=0.006).

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Assessment of the type 2 DM patients according to SAU status, (Means±SDs)

Parameter	Type 2 DM patients, normal SAU (n=114)	Type 2 DM patients, high SAU (n=75)	p
Age, years	58.77±9.72	60.39±10.21	0.28
BMI, kg/m^2	32.18±5.79	33.72±6.15	0.10
WC, cm	105.77±16.26	105.4±15.66	0.89
WHR	0.99±0.12	0.99±0.10	0.97
WHtR	62.31±10.04	62.53±10.19	0.88
VAI	3.66±2.41	4.95±5.65	**0.026**
BAI	48.01±7.06	48.54±8.86	0.99
FPG, mmol/L	8.88±2.91	9.17±2.87	0.54
PPG, mmol/L	9.76±3.01	9.67±3.21	0.86
HbA1c, %	7.66±1.74	7.73±1.95	0.79
IRI, μU/ml	18.09±11.27	24.00±14.19	**0.055**
HOMA2_B, %	85.75±56.95	92.93±68.40	0.86
HOMA2_S, %	57.45±45.38	44.26±35.64	0.40
HOMA-IR	2.51±1.45	3.38±1.83	**0.028**
TG, mmol/L	2.22±1.31	2.79±2.19	**0.028**
HDL–C, mmol/L	1.15±0.27	1.15±0.29	0.66
TC, mmol/L	5.49±1.55	5.47±1.42	0.86
SUA, μmol/mL	300.91±61.93	480.85±71.79	0.0001

Notes: BMI, body mass index; WC, waist circumference; WHR, Waist-to-Hip Ratio; WHtR, waist-to-height ratio; VAI, visceral adiposity index; BAI, body adiposity index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycohemoglobin A1c; IRI, plasma immunoreactive insulin; HOMA2_B, %, homeostasis model assessment for beta-cell function; HOMA2_S, %, homeostasis model assessment for insulin sensitivity; HOMA–IR, homeostasis model assessment for insulin resistance; TG, triglycerides; HDL–C, high – density lipoprotein cholesterol; TC, total cholesterol; SUA, serum uric acid.

Further, a comparative analysis of the clinical and laboratory findings of type 2 DM patients was carried out taking into account their VAI status (fig. 1–3).

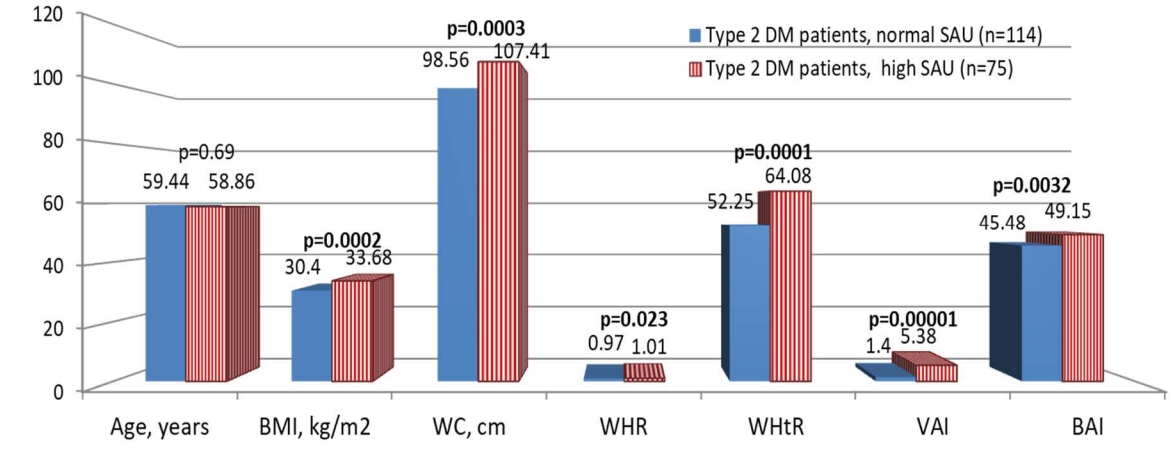

Fig. 1. Anthropometric parameters of type 2 DM patients according to their VAI status, (Means±SDs)

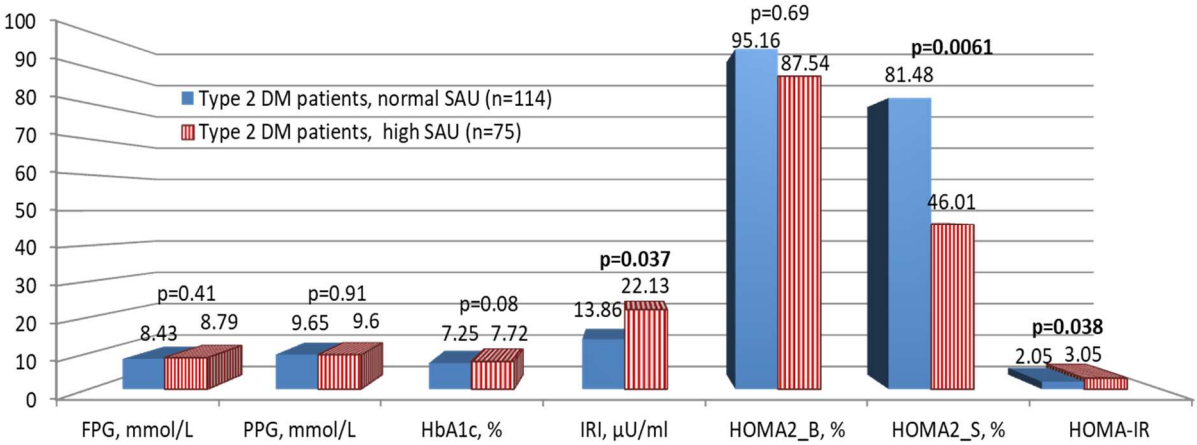

Fig. 2. Glucose homeostasis of type 2 DM patients according to their VAI status, (Means±SDs)

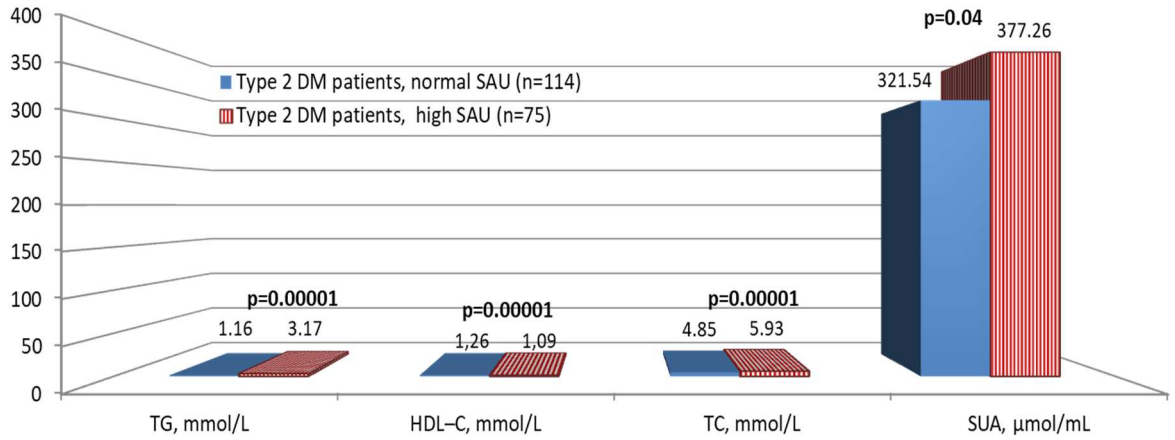

Fig. 3. Levels TG, HDL–C & SUA of type 2 DM patients according to their VAI status, (Means±SDs)

According to table 2, type 2 DM patients with high VAI have a marked decline in insulin-mediated glucose capture capacity, compensatory increased insulin resistance, and insulin secretion, worsening of postprandial glucose absorption, and increased plasma atherogenic potential.

It was found that in the overall sample of type 2 DM patients, VAI is non-linearly associated with SAU (fig. 4a), FPG (fig. 4b), PPG (fig. 4c), HbA1c (fig. 4d), HOMA_B (fig. 4e), TC (fig. 4f).

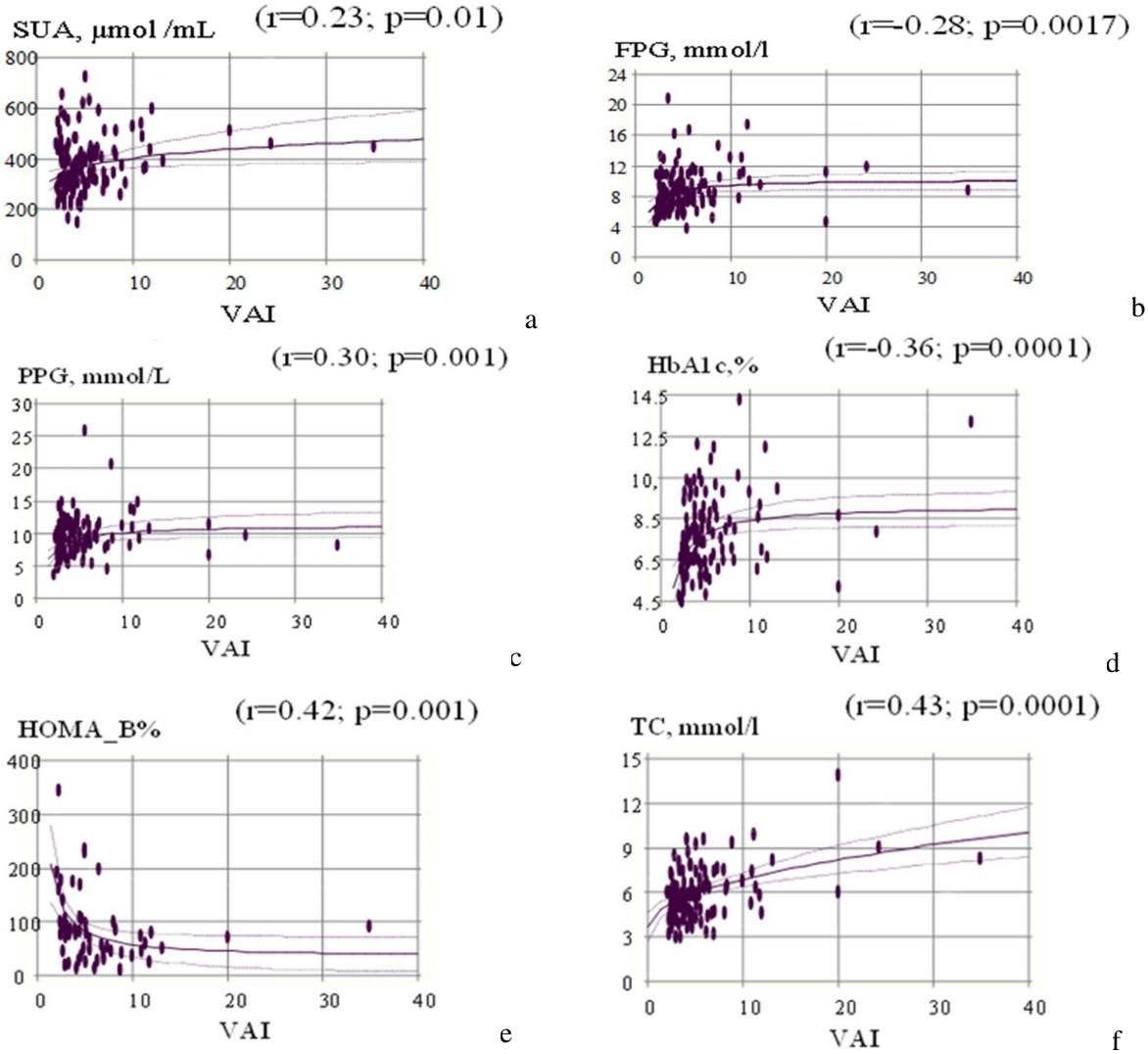

Fig. 4. Correlation of clinical and laboratory values of the examined type 2 DM patients VAI total sample. A – SAU (fig. 4a), B – FPG (fig. 4b), C – PPG (fig. 4c), D – HbA1c (fig. 4d), E – HOMA_B (fig. 4e), F – TC (fig. 4f).

The analysis of the studied clinical and laboratory parameters in the groups of type 2 DM patients, distributed by VAI values related to quartile 1–4, showed that there was a progressive decrease from first

quartile to fourth quartile in the ability to insulin-mediated glucose capture, compensatory increased insulin resistance and HbA1c level, increased plasma atherogenic potential and increased SUA concentration (table 2).

Table 2

Clinical description of the VAI quartiles in the study participants

	1st quartile (n=52)	2nd quartile (n=51)	3rd quartile (n=48)	4th quartile (n=50)	p
Age, years	58.3±10.3	60.1±11.1	58.8±8.8	59.0±9.2	0.83
BMI, kg/m^2	30.33±6.01	33.18±6.80*	32.73±5.39*	34.11±4.63*	**0.0086**
WC, cm	94.79±17.54	107.08±16.49*#	106.04±16.41*#	110.14±10.19*	**0.0001**
WHR	0.93±0.10	1.02±0.13*	1.01±0.11*	1.01±0.08*	**0.0001**
WHtR	55.14±10.37	63.86±10.37*	63.16±10.37*	65.19±6.85*	**0.0001**
VAI	1.27±0.36	2.34±0.47*#	3.91±0.62*#	7.83±3.59*	**0.0001**
BAI	45.30±8.14	49.20±8.46	48.05±9.05	49.22±5.12	0.057
FPG, mmol/L	8.48±3.07	8.01±2.43	8.83±2.81	9.33±2.81	0.14
PPG, mmol/L	9.89±3.15	8.85±2.75	9.57±2.44	10.20±3.76	0.23
HbA1c, %	7.28±1.60	7.02±1.44*#	7.63±1.57*#	8.34±2.17*	**0.003**
IRI, μU/mL	12.59±6.12	26.39±12.89*	24.43±15.35*	19.04±10.63*	**0.019**
HOMA_B, %	80.16±42.89	139.99±84.38*#	101.03±68.79*#	61.8±36.98*	**0.0014**
HOMA_S, %	89.07±68.39	36.62±21.50*#	42.39±25.86*	50.34±37.85*	**0.0066**
HOMA-IR	1.64±0.88	3.46±1.55*	3.35±1.93*	3.84±1.51*	**0.0119**
TG, mmol/L	1.11±0.34	1.67±0.42*#	2.46±0.73*#	4.25±1.49*	**0.0001**
HDL–C, mmol/L	1.31±0.33	1.19±0.20*#	1.08±0.15*	1.00±0.17*	**0.0001**
TC, mmol/L	4.76±1.31	5.48±1.68*#	5.66±1.41*#	6.42±1.69*	**0.0001**
SUA, μmol/mL	326.05±107.53	336.85±110.63	364.03±101.37*#	409.40±102.49*	**0.042**

Notes: First quartile of VAI: 0–1.68; second quartile of VAI: 1.69–2.93; third quartile of VAI: 2.94–4.91; fourth quartile of VAI: ≥4.91; * statistically significant compared to the first quartile; # statistically significant compared to the fourth quartile.

In general, the above mentioned pathological changes in clinical and biochemical levels indicate a higher risk of development and progression of type 2 DM chronic complications in patients with VAI referred to the fourth quartile.

Some anthropometric indices of obesity were studied to examine their correlation with HU. BMI, WC and WHtR were significantly associated with HU [6]. BMI increase and hypertriglyceridemia may potentiate the SUA effect on gout development [14]. All these studies were included in MetS, and it was still controversial which anthropometric index was the superior one. VAI either increased with SUA (r=0.21; p=0.02), or significantly increased with FPG (r=0.15; p=0.046).

Some studies also found that VAI was associated with DM. However, the underlying mechanism is not clear. SUA was characterized by both pro-oxidant and antioxidant properties, depending on the context, and it can impair endothelial function, resulting in atherosclerotic risk [10, 15]. New findings demonstrate that visceral fat, not subcutaneous depot, exhibited greater expression of pro-inflammatory, oxidative stress-related, hypoxia-induced, and proangiogenic genes; increased activated macrophage populations; and had a higher capacity for cytokine production ex vivo; thus, providing clinical evidence of the key role of visceral microenvironment in atherosclerotic vascular disease. Excessive visceral adiposity induces alterations in mitochondrial function and energy metabolism in tumor and correlates with the expression of genes related to inflammation and oxidative stress in peripheral blood cells. Visceral fat adiposity was associated with subclinical inflammation and increased oxidative stress. Therefore, the VAI mechanism intermediating HU remained to be revealed. As it is known, dyslipidemia is basic for VAI increase.

The present study demonstrated that obesity is an important risk factor of HU among type 2 DM patients. It was revealed that the visceral adiposity increase was positively associated with HU risk. Compared to other obesity indices, VAI showed better discriminatory ability for identifying the HU risk than BMI, WC and WHtR.

Recently, many studies have reported a significant correlation between obesity and HU, but very few have focused on the association of visceral adiposity and HU.

A cross-sectional study of 221 elderly individuals found that the VAI had the strongest correlation with FPG, TG, TC, HDL–C and blood pressure, and more importantly, the VAI was a good predictor of hypertriglyceridemia and reduced HDL–C [7]. Similarly, a cross-sectional study involved 1518 adults

revealed a significant association of VAI with all the components of MetS, especially hypertriglyceridemia and low HDL–C in both genders. J. Schuster et al. demonstrated in a cross-sectional study that VAI strongly correlated to FPG, HDL–C, and TG. A positive association between VAI and risk of hypertriglyceridemia and low HDL–C was demonstrated as well, adding more evidence that VAI could serve as a marker of dyslipidemia.

Yang Y. et al. showed that first degree relatives of type 2 DM patients with pre-diabetes or DM have progressively higher VAI associated with progressive hyperglycemia, and it was found to correlate with HOMA-B [14].

Conclusion

HU was found in 38.1 % of the examined type 2 DM patients; VAI in type 2 DM patients correlates with decreased tissue sensitivity to insulin-mediated glucose absorption, worsening of postprandial glucose absorption, increased insulin resistance and increased plasma atherogenic potential. The analysis of the studied clinical and laboratory levels in the groups of type 2 DM patients which were formed considering quartile-related VAI showed a progressive decrease from quartile 1 to quartile 4 in the insulin-mediated glucose capture capacity, a compensatory increase of insulin resistance and HbA1c level, increased plasma atherogenic potential and increased SUA. The above mentioned pathological changes indicate a higher risk of development and progression of type 2 DM chronic complications in patients with VAI referred to quartile 4.

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