ORIGINAL ARTICLE

Obesity, Echocardiographic Changes and Framingham Risk Score in the Spectrum of Gout: A Cross-Sectional Study

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ABSTRACT

Objectives: This study aims to establish cardiovascular risk in obese and non-obese patients in stages of gout by using Framingham risk score (FRS) and transthoracic echocardiography.

Patients and methods: This single-center cross-sectional study encompassed 201 patients (160 males, 41 females; mean age 56.9±13 years; range 20 to 89 years) including 52 asymptomatic hyperuricemia, 86 gouty arthritis without tophi, and 63 gouty tophi patients. body mass index (BMI) and FRS were calculated. Left atrium (LA), interventricular septum, posterior wall (PW) of the left ventricle, fractional shortening (FS), mitral annular systolic velocity (S'), mitral annular early diastolic velocity (E') and transmitral to mitral annular early diastolic velocity ratio (E/E') were measured. Data were analyzed by Kolmogorov-Smirnov test, Shapiro-Wilk test, t-test, Mann-Whitney U test, analysis of variance test and multiple linear regression models.

Results: There was no significant difference in FRS, FS, S', E' and E/E' between obese and non-obese patients with asymptomatic hyperuricemia, gouty arthritis without tophi or gouty tophi. Obese patients in the three disease gradations had larger LA (p=0.007, p=0.004, p=0.039) and thicker PW (p=0.002, p=0.037, p=0.007). Increased BMI independently predicted the thickening of the PW in asymptomatic hyperuricemia (R^2=0.319), gouty arthritis without tophi (R^2=0.093) and gouty tophi (R^2=0.068).

Conclusion: Despite the lack of difference in FRS and functional systolic and diastolic parameters between obese and non-obese patients in the spectrum of gout, morphological heart changes were more pronounced in obese patients. In gouty tophi, it is possible that higher urate load together with chronic inflammation contribute for the alterations, as obesity worsens them.

Keywords: Cardiovascular risk, gout stages, obesity.

The rates of obesity are increasing worldwide.[1] Its prevalence has increased dramatically not only in adults, but also in children and adolescents in developed and developing countries. It has turned out to be a major health concern.[2] Given that, obesity is associated with increased morbidity and mortality rates.[3] Increased adiposity is linked to hyperuricemia.[4] Higher body mass index (BMI) and weight gain contribute for gout in males.[5] It is considered that the increased prevalence of gout is partly due to the epidemic of obesity.[6] Studies have proven a strong connection between obesity, hyperuricemia and higher risk of gout.[4,7,8] Even more, it has been suggested that obesity may be a factor linking hyperuricemia, hypertension, dyslipidemia and atherosclerosis.[5]

Obesity is a well-recognized risk factor for cardiovascular complications.[3] In the last decade, a great number of studies have made evident

the importance of hyperuricemia and gout in cardiovascular pathology. Some authors even demonstrated that chronic tophaceous gout is a qualitatively new disease characterized by high cardiovascular risk.[9-11] However, obesity and gout are frequently combined, which hinders the assessment of the risk. This gave us reason to determine the contribution of obesity to cardiovascular risk and development of heart impairments in the individual stages of gout by using the classic and one of the most commonly applied scoring system in everyday clinical practice, namely the Framingham risk score (FRS) and transthoracic echocardiography. Morphological and functional parameters of systole and diastole of the heart were measured with the latter imaging modality. We took into consideration the earlier findings indicating that left atrium (LA) size reflects the severity of left ventricular diastolic dysfunction for a prolonged period of time.[10,12] Mitral annular early diastolic velocity (E`) is a sensitive indicator of diastolic dysfunction. Unlike the left atrium size, the measurement of E′ cannot judge the duration of diastolic dysfunction.[13,14] Interventricular septum (IVS) thickness and thickness of the posterior wall (PW) of the left ventricle give a notion for the presence of left ventricular hypertrophy,[15] resulting in diastolic dysfunction. Transmitral to mitral annular early diastolic velocity ratio (E/E`) has been shown to be useful to assess left ventricular filling pressure at a fixed point of time.[13,16] Fractional shortening (FS) and mitral annular systolic velocity (S`) are common parameters of systolic function of the left ventricle.[17,18] We conducted our study bearing in mind that obesity leads to hemodynamic overload with subsequent expanded intravascular remodeling.[19] Therefore, in this study, we aimed to establish cardiovascular risk in obese and non-obese patients in stages of gout by using FRS and transthoracic echocardiography.

PATIENTS AND METHODS

This single-center cross-sectional study encompassed 201 age-matched patients (160 males, 41 females; mean age 56.9±13 years; range 20 to 89 years) divided into three groups: 52 asymptomatic hyperuricemia, 86 gouty arthritis without tophi and 63 gouty tophi patients

(Table 1). We analyzed consecutive patients hospitalized in University Rheumatology Clinic of "St. Ivan Rilski" Hospital in Sofia between September 2013 and May 2016. Some of the gout patients were hospitalized in view of the diagnosis, other for management of a continuous attack or choice of therapy in those with chronic tophaceous gout. Asymptomatic hyperuricemia individuals attended the outpatient clinic. They had no inflammatory arthritis or other autoimmune disease and their serum uric acid level was above the upper limit of normal with no history of gout flare. No imaging method was performed in this group for detection of silent monosodium urate crystals. Gout patients fulfilled the 2015 American College of Rheumatology and European League Against Rheumatism classification criteria,[20] as gouty tophi were described in individuals with subcutaneous tophi on physical examination. Synovial fluid analyses for detection of monosodium urate crystals and ultrasound examination for double contour sign were performed when appropriate. The study protocol was approved by the Medical University of Sofia Ethics Committee (20 May 2013, protocol No: 15). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A rheumatologist reviewed the medical documentation and performed physical examination of the subjects. Obesity was defined as BMI >30 kg/m^2.[21] The FRS was calculated by an internet calculator. FRS assesses the individual's 10-year risk for developing cardiovascular disease via seven items concerning sex, age, total cholesterol, high density lipoprotein cholesterol, smoking, the value of systolic blood pressure, and treated and untreated arterial blood pressure. According to this scoring system, individuals with low risk have 10% or less coronary heart disease risk at 10 years, those with intermediate risk have 10-20% and those with high risk have 20% or more risk.[22,23] Other clinical and laboratory assessments included current smoking status; arterial hypertension defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of antihypertensive medication; diabetes mellitus, based on physician's diagnosis and/or documented use of insulin and/or oral hypoglycemic agents;

dyslipidemia, based on elevated fasting lipid levels or low high density lipoprotein cholesterol and/or documented use of lipid-lowering agents; reduced glomerular filtration rate taken at estimated glomerular filtration rate (eGFR) <90 mL/minute calculated by the Cockroft-Gault formula, chronic kidney failure (CKF) as accepted by Kidney Disease Outcomes Quality Initiative (K/DOQI) 2002 guidelines[24] and other hematological and biochemistry parameters including the inflammatory biomarker C-reactive protein (CRP). Hyperuricemia was adopted when serum level of uric acid was higher than 6.0 mg/dL (356.9 μmol/L) for females and higher than 6.8 mg/dL (404.5 μmol/L) for males. A single measurement of the laboratory parameters was taken for the analyses. Patients were defined as having suffered a cardiovascular event if they had coronary artery disease, cerebrovascular disease and/or peripheral artery disease.[25] Exclusion criteria were a history of malignancy, exacerbated cardiac or renal failure, dilated or hypertrophic cardiomyopathy, severe valvulopathy, atrial fibrillation, arterial blood pressure >140/90 mmHg and heart rate <50 bpm or >90 bpm during the ultrasonographic measurement.

Transthoracic echocardiography was performed by an experienced certified ultrasonographer, who was unaware with the cases' clinical data. Ultrasound examinations were conducted on ALOKA-SSD-4000 (ALOKA CO LTD 6-22 I Mure Mitaka-shi, Tokyo, Japan) between June 2013 and November 2015. Measurements were performed on Philips HD11 between 20 November 2015 and May 2016. Software of both devices had comparable characteristics. Examinations were carried out according to the recommendations of the American Society of Echocardiography with 2.5 MHz transducer working with pulsed Doppler frequency of 2.5 MHz. A minimum of three cardiac cycles were recorded, analyzed and averaged. IVS thickness and thickness of the PW of the left ventricle were determined at end-diastolic phase with two-dimentionally-guided M-mode. From the parasternal long axis view, uniaxial anterior-posterior dimension of the LA was assessed. FS was estimated by the method of Teicholz. When applying pulse-Doppler for measurement of transmitral annular early diastolic

velocity (E), the probe volume of 2 mm was placed at the apex of the mitral valve in a four-chamber view.[18,26] S` and E` velocities were recorded with tissue Doppler imaging (TDI). During TDI, the probe volume of 2 mm was placed on the lateral wall at the level of mitral valve annulus in order to avoid the influence of the right ventricle.[27] The E/E` was obtained automatically from the computer software.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA). Means with standard deviations (SDs) and percentages were calculated to describe the clinical and echocardiographic characteristics of the patients. The distribution of data was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. Intergroup comparisons were performed by analysis of variance, Kruskal-Wallis, post hoc Tukey, t-test and Mann-Whitney U tests. Proportional differences were tested using the chi-square (χ^2), Fisher's exact tests and z-test with Bonferroni adjustment. To assess the impact of BMI on PW in the stages of gout, we performed a multiple linear regression analysis, adjusted for age, with an independent factor of BMI and dependent variable of PW of the left ventricle. Results were expressed as regression coefficients.

RESULTS

The three examined groups were age-matched (p=0.290). Subjects with acute flare were equally divided in both gout groups (p=0.110). However, gouty tophi patients had the highest values of CRP (p=0.001) in intergroup comparison. Serum concentration of uric acid was similar in both gout groups (p=0.097). Expectedly, it was higher in chronic tophaceous gout than in asymptomatic hyperuricemia subjects (p=0.006). In the three gradations of the disease process, the means of eGFR did not differ significantly (p=0.075), but the percentage of CKF patients was higher in gouty tophi compared to gouty arthritis without tophi (p=0.015). The frequency of the cases with CKF in asymptomatic hyperuricemia group was comparable to this in gouty tophi (p=0.136).

Table 1. General characteristics of patients

Index	Asymptomatic hyperuricemia (n=52)					Gouty arthritis without tophi (n=86)					Gouty tophi (n=63)					p
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	
Age (year)	52		55.23±15.94			86		56.4±12.3			63		58.89±11.03			0.290
Sex																
Male	29	55.8^{a}				71	82.6^{b}				60	95.2^{b}				<0.001
Disease duration (years)*	27			1.00^{a}	$1\text{-}5^{a}$	75			3.00	$1\text{-}33^{b}$	58			7.00	$1\text{-}45^{c}$	<0.001
Subjects with gout attack						21	24.4				23	36.5				0.110
BMI (kg/m²)	52		31.1±6.5			86		30.4±5.2			63		29.4±5.0			0.266
Hb (g/L)	52		$142.0±17.6^{ab}$			84		$145.7±14.6^{a}$			61		$136.5±17.8^{b}$			0.005
Ht (g/L)	50		$0.4±0.1^{ab}$			84		$0.4±0.1^{a}$			59		$0.4±0.1^{b}$			0.041
Uric acid (mg/dL)	52		$7.8±1.1^{a}$			85		$8.0±1.9^{ab}$			62		$8.5±1.9^{b}$			0.043
Uric acid (μmol/L)	52		$451.0±63.6^{a}$			85		$476.4±113.6^{ab}$			62		$508.0±111.8^{b}$			0.043
BUN (mmol/L)	36		$6.0±2.4^{a}$			57		$6.2±2.8^{a}$			41		$8.1±4.8^{b}$			0.013
eGFR (mL/min)	52		111.0±51.5			86		114.1±48.9			63		95.9±48.7			0.075
CRP (mg/L)*	34			4.23^{a}	$0.40\text{-}30.98^{a}$	76			5.03^{a}	$0.42\text{-}114.96^{a}$	55			9.40^{b}	$0.42\text{-}141.77^{b}$	0.001
HbA1C (%)	38		4.4±1.1			60		4.5±0.8			44		4.7±1.0			0.530
TC (mmol/L)	46		5.6±1.2			74		5.5±1.2			57		5.3±1.1			0.345
HDL (mmol/L)	44		1.2±0.3			65		1.2±0.4			48		1.1±0.3			0.247
LDL (mmol/L)	41		3.4±1.2			60		3.6±1.2			47		3.3±1.1			0.480
VLDL (mmol/L)	38		0.8±0.3			57		0.9±0.5			45		1.0±0.6			0.091
TG (mmol/L)	46		1.9±0.9			76		2.0±1.2			55		2.0±1.2			0.922
Dyslipidemia	38	86.4				63	94.0				48	96.0				0.223
BMI (>30 kg/m²)	22	42.3				41	47.7				26	41.3				0.699
Arterial hypertension	35	67.3				68	80.0				51	81.0				0.154
Patients suffered a CV event	8	15.4				8	9.3				15	23.8				0.053
Diabetes mellitus	12	23.1				9	10.5				9	14.3				0.129
eGFR (<90 mL/min)	20	38.5^{ab}				28	32.6^{a}				33	52.4^{a}				0.049
Current smoking status	8	15.4^{a}				30	35.7^{b}				23	36.5^{b}				0.021
Use of diuretics	17	41.5				13	26.0				11	28.9				0.261
FRS (%)	26		$5.7±6.0^{a}$			55		$13.6±9.5^{b}$			45		$15.8±8.2^{b}$			<0.001
LA (mm)	52		$38.3±5.7^{ab}$			86		$38.1±5.0^{a}$			62		$40.6±6.1^{b}$			0.015
IVS (mm)	52		11.8±2.0			86		12.4±1.7			62		12.6±1.9			0.065
PW (mm)	52		$11.3±2.1^{a}$			86		$12.4±1.8^{b}$			62		$12.7±2.2^{b}$			0.001
FS (%)	50		39.0±3.8			78		38.1±5.5			59		37.3±4.2			0.194
S' (m/s)*	52			0.11	0.07-0.17	84			0.11	0.07-0.90	61			0.10	0.07-0.90	0.297
E' (m/s)*	52			0.10^{a}	$0.04\text{-}0.60^{a}$	84			0.10^{a}	$0.05\text{-}0.90^{a}$	61			0.09^{b}	$0.04\text{-}0.90^{b}$	0.024
E/E' ratio	52		7.1±3.2			84		6.7±2.9			60		7.2±3.0			0.589

SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; Hb: Hemoglobin; Ht: Hematocrit; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; HbA1C%: Glycosylated hemoglobin; TC: Total cholesterol; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; VLDL: Very low-density lipoprotein cholesterol; TG: Triglycerides; CV: Cardiovascular; FRS: Framingham risk score; LA: Left atrium; IVS: Interventricular septum; PW: Posterior wall of left ventricle; FS: Fractional shortening; S: Mitral annular systolic velocity; E: Mitral annular early diastolic velocity; E/E' ratio: Transmitral to mitral annular early diastolic velocity ratio.

*Median (Min:Max). Variables presented with mean ± standard deviation were analyzed by analysis of variance and Tukey post hoc test, for variables presented by median (Min: Max) Kruskal-Wallis and Mann-Whitney U tests were applied. Proportional differences of category variables were examined by chi-square (χ^2) or Fisher's exact tests, comparisons in pairs of proportions were performed by z-test with Bonferroni adjustment.
Presence of identical superscript between different groups demonstrates lack of significant difference in mean values of examined parameter (p>0.05). Different superscripts indicate a significant difference in mean values of examined parameter (p<0.05). Absence of superscripts means no significant differences in mean values.

In the spectrum of gout BMI (p=0.266), prevalence of obesity (p=0.699), dyslipidemia (p=0.223), arterial hypertension (p=0.154), previous cardiovascular event (p=0.053), diabetes mellitus (p=0.129) and the proportion of patients treated with diuretics (p=0.261) was similar. As opposed to asymptomatic hyperuricemia, the distribution of smokers was higher in gout (p=0.021). According to the FRS, cardiovascular risk was higher in gout than in asymptomatic hyperuricemia subjects. Gouty arthritis without tophi (mean±SD; 13.62±9.48%) and gouty tophi (mean±SD; 15.79±8.24%) had an intermediate risk, while those with asymptomatic hyperuricemia were scored with a low risk (mean±SD; 5.69±6.03%). Analyzing echocardiographic changes, we did not observe any significant deviation in the thickness of the IVS (p=0.065), FS (p=0.194), S` (p=0.297) or E/E` ratio (p=0.589) in the stages of gout. LA was larger in patients with gouty tophi than in those with gouty arthritis without tophi (p=0.017), but no significant difference in its size was estimated between tophi and asymptomatic hyperuricemia patients (p=0.067). Unlike the latter, PW of the left ventricle was thicker in both gout groups (p=0.001). The mean values of E` were significantly the lowest in gouty tophi (p=0.024) (Table 1).

In the group of asymptomatic hyperuricemia, 22 of the patients were obese and 30 were non-obese; in the group of gouty arthritis without tophi, 41 were obese and 45 were non-obese, while in the group with tophi, the number of obese patients was 26 and of non-obese 37. We did not estimate any significant difference in the serum concentration of uric acid, distribution of dyslipidemia, arterial hypertension, previous cardiovascular event, smoking or use of diuretics between obese and non-obese in the three examined groups. In tophaceous gout, the distribution of diabetes mellitus was higher in obese subjects than in non-obese. In the spectrum of disease, only a few of the patients with obesity had an abnormally low eGFR (Table 2).

The scores obtained by using the FRS were comparable between obese and non-obese in asymptomatic hyperuricemia, gouty arthritis without tophi and gouty tophi (7.54±7.91% vs. 4.34±3.96%, p=0.187; 12.23±8.13% vs. 15.28±10.81%, p=0.238; 15.81±8.39%

Table 2. Serum uric acid concentration, use of diuretics and distribution of conventional cardiovascular risk factors between obese and non-obese patients in three examined groups

| Index | Asymptomatic hyperuricemia (n=52) | | | | | | Gouty arthritis without tophi (n=86) | | | | | | Gouty tophi (n=63) | | | | | |
| | Obese patients (n=22) | | | Non-obese patients (n=30) | | | Obese patients (n=41) | | | Non-obese patients (n=45) | | | Obese patients (n=26) | | | Non-obese patients (n=37) | | |
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Serum uric acid (mg/dL)			8.0±0.8			7.5±1.2			7.9±1.8			8.1±2.0			8.8±2.0			8.4±1.8
Serum uric acid (µmol/L)			478.2±47.0			447.9±71.4			471.7±107.1			480.0±120.7			521.0±120.2			498.4±105.9
Dyslipidemia	17	89.5		21	84.0		31	91.2		32	97.0		20	95.2		28	96.6	
Arterial hypertension	16	72.7		19	63.3		32	80.0		36	80.0		22	84.6		29	78.4	
Patients suffered a CV event	2	9.1		6	20.0		4	9.8		4	8.9		9	34.6		6	16.2	
Diabetes mellitus	8	36.4		4	13.3		4	9.8		5	11.1		7*	26.9*		2	5.4	
eGFR (<90 mL/min)	3*	13.6*		17	56.7		7*	17.1*		21	46.7		7*	26.9*		26	70.3	
Current smoking status	3	13.6		5	16.7		13	33.3		17	37.8		9	34.6		14	37.8	
Use of diuretics	8	47.1		9	37.5		8	34.8		5	18.5		5	26.3		6	31.6	

SD: Standard deviation; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; * Points statistically significant difference between obese and non-obese patients in a group; Comparative analysis of serum uric acid was performed by using t-test. Other variables were analyzed by chi-square (χ²) or Fisher's exact test.

vs. 15.77±8.30%, p=0.990, respectively) (Figure 1a). From earlier to later stages of the disease in obese and non-obese, functional parameters of systole and diastole had similar mean values (Figure 1b-e). Obese subjects with asymptomatic hyperuricemia, gouty arthritis without tophi and chronic tophaceous gout had larger LA compared to non-obese (40.68±5.22 mm vs. 36.50±5.37 mm, p=0.007; 39.66±4.36 mm vs. 36.60±5.12 mm, p=0.004; 42.45±5.96 vs. 39.25±5.84 mm, p=0.039, respectively) (Figure 2a). Obese subjects in the group of asymptomatic hyperuricemia had thicker IVS. The latter did not demonstrate any difference between obese and non-obese patients in gouty arthritis without tophi and gouty tophi groups (Figure 2b). Regarding the PW of the left ventricle, it was thicker in obese individuals in the stages of gout

(12.41±1.66 mm vs. 10.48±2.03 mm, p=0.002; 12.71±1.67 mm vs. 12.05±1.89 mm, p=0.037; 13.50±2.46 mm vs. 12.13±1.77 mm, p=0.007, respectively) (Figure 2c).

Finally, we analyzed the influence of BMI on the thickness of the left ventricular posterior wall. A multiple linear regression analysis adjusted for age was conducted, through which we established that the increase of BMI independently predicted the thickening of the PW in asymptomatic hyperuricemia (R^2=0.319), gouty arthritis without tophi (R^2=0.093) and gouty tophi (R^2=0.068) (Table 3).

DISCUSSION

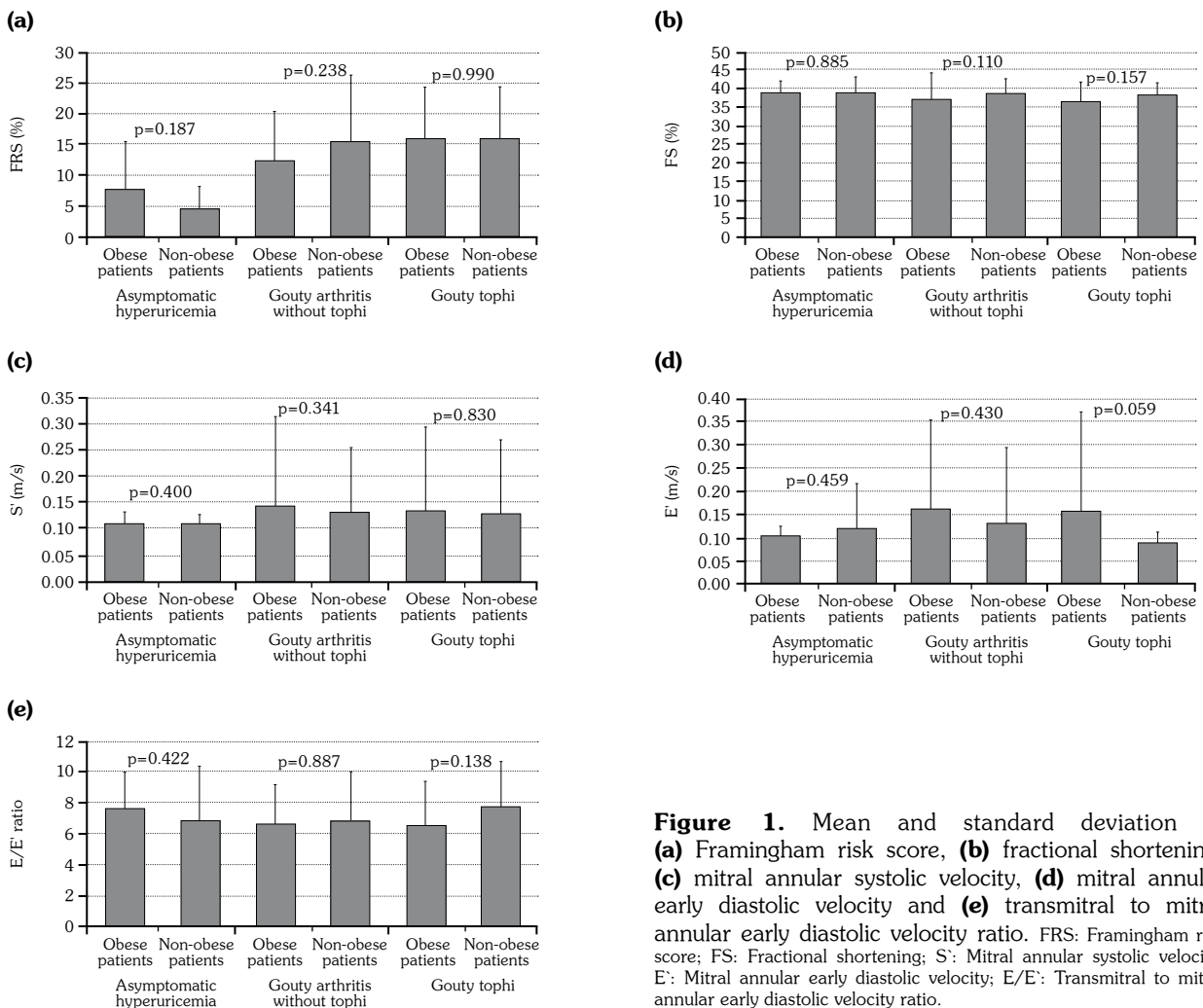The present study reveals that obese subjects in the spectrum of gout have more pronounced

Figure 1. Mean and standard deviation of **(a)** Framingham risk score, **(b)** fractional shortening, **(c)** mitral annular systolic velocity, **(d)** mitral annular early diastolic velocity and **(e)** transmitral to mitral annular early diastolic velocity ratio. FRS: Framingham risk score; FS: Fractional shortening; S`: Mitral annular systolic velocity; E`: Mitral annular early diastolic velocity; E/E`: Transmitral to mitral annular early diastolic velocity ratio.
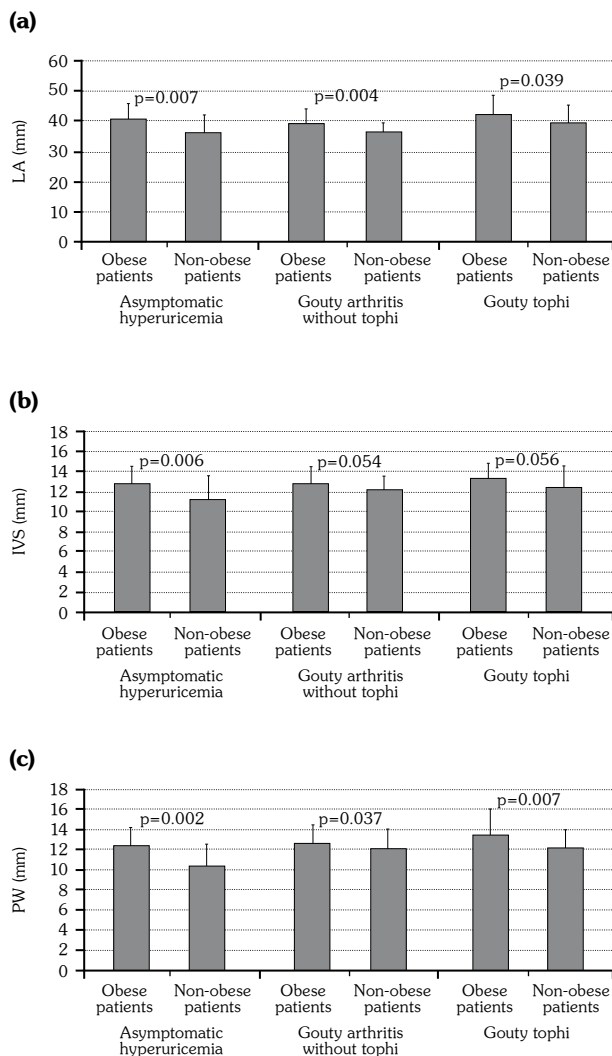
Figure 2. Mean and standard deviation of **(a)** left atrium size, **(b)** interventricular septum thickness and **(c)** thickness of posterior wall of left ventricle in obese and non-obese patients in three examined groups. LA: Left atrium; IVS: Interventricular septum; PW: Posterior wall.

morphological heart changes compared to non-obese individuals despite the similar systolic and diastolic functional parameters and the comparable results for the FRS, accountable for a cardiovascular risk.

In general, obesity is characterized with increased blood volume, hemodynamic overload and hyperdynamic circulation.[19] This in part could explain our observations of larger LA and thicker left ventricular PW in obese subjects versus non-obese in the three disease gradations. In the whole cohort, without considering the role of obesity, a lack of a clear deviation was found in the IVS in the course of the disease. PW thickness was numerically the highest in gouty tophi. We measured the largest size of LA under the most severe gout the tophaceous gout, but paradoxically, it was commensurable with those in asymptomatic hyperuricemia. In our case, we sought the explanation for this result in the equal prevalence of CKF in these patient groups. The literature supports the well-known LA enlargement in chronic kidney disease patients, including those with mild to moderate CKF.[28] In such cases, LA enlargement is mainly due to volume expansion and also to inflammation.[29] Namely, inflammation is the other non-hemodynamic marker that correlates with LA size.[30] There are now data in patients with gout, which make evident that the existence of subcutaneous tophi has a significant impact on LA enlargement. They suggest that maintenance of chronic inflammatory process and higher level of oxidative stress, in addition to hyperuricemia, are responsible for the alteration.[10] Moreover, the severe inflammation and higher total body urate load in gouty tophi stage have been shown to be associated with higher risk

Table 3. Results from multiple linear regression, adjusted for age, with dependent variable posterior wall of left ventricle and an independent factor-body mass index

Dependent variable - PW	Factors	Coefficient	t	p	R²
	Age	0.05	3.22	0.002	
Asymptomatic hyperuricemia	Body mass index	0.16	4.07	<0.001	0.319
	Constant	3.62	2.23	0.030	
Gouty arthritis without tophi	Body mass index	0.11	2.94	0.004	0.093
	Constant	9.12	8.13	<0.001	
Gouty tophi	Body mass index	0.11	2.09	0.041	0.068
	Constant	9.39	5.84	<0.001	
PW: Posterior wall of left ventricle.					

of cardiovascular death.[11] By registering the highest serum CRP in gouty tophi, despite the equality of the subjects with flare in both gout subdivisions, we indirectly judged for the highest level of persistent inflammation. Also, in recent years, the proinflammatory activity of the adipose tissue has been demonstrated in animal models due to its lipotoxic effect connected to cardiac steatosis and lipoapoptosis.[31,32] We believe that the varying degrees of inflammation in the stages of gout along with the proinflammatory activity due to increased fat accumulation[33] potentiate the detrimental effect on the heart leading to pronounced morphological heart changes. In this study, we focused on the role of obesity on the ultrasonographic heart alterations, particularly in the context of gout. This was confirmed by the constructed regression models, which revealed that weight gain is an independent predictor of left ventricular wall changes. The increase of BMI influenced thickening of the PW of the left ventricle in the three disease stages. Nevertheless, its impact was the weakest in gouty tophi patients, in whom it should be suspected that the above mentioned factors would likely be more damaging for the heart.

Furthermore, evidence exists to suggest that obesity impacts the diastole, impairs left ventricular relaxation and alters left ventricular filling indexes.[34,35] However, in obese individuals, left ventricular filling pressures are usually normal at rest,[36] which could explain our observation for the comparable values of E/E` in obese and non-obese in the disease continuum. Across the disease spectrum, gouty tophi patients had the worst diastolic function as a whole, without registering a great variation in the functional diastolic parameters between obese and non-obese subjects. Based on these results, we assume that maintenance of inflammatory state in chronic tophaceous gout and all its consequences has a great importance in the pathogenesis of left ventricular diastolic dysfunction as the abnormal fat accumulation.

It has been shown that the extent of cardiac remodeling in obesity increases with its severity and duration.[19] In obesity, cardiac output is often higher, but myocardial contractility is reduced, even if the ejection fraction is normal.[37] Often, obese compared to normal weight subjects have reduced midwall left ventricular fractional

shortening and lower S` measured by TDI.[38,39] Nevertheless, in our cohort, FS and S` did not change significantly between obese and non-obese individuals, as we did not estimate a great variation in their mean values. In this context, it should be born in mind that in obese individuals, the presence of subclinical systolic and diastolic dysfunction can be judged by larger LA and thicker PW of the left ventricle. This led us to suggest that compensatory mechanisms aiming to preserve functioning of the heart, despite the morphological alterations, take place in patients with obesity.

Several limitations of our study deserve mention. This was a single-center cross-sectional study and laboratory parameters were measured at a fixed point of time. Also, FRS was not calculated in all subjects due to incomplete data for lipid panel. Due to poor ultrasound window in a minority of obese patients, FS and some TDI parameters were not recorded. Furthermore, in asymptomatic hyperuricemia, no additional imaging methods for detection of silent monosodium urate crystals were performed. Moreover, echocardiographic examinations were performed by one researcher. With this in mind, we are between the few who have determined cardiovascular risk in obese and non-obese in the spectrum of gout using a most widely applicable scoring system and transthoracic echocardiography.

In conclusion, given the comparable systolic and diastolic function in obese and non-obese, the scores obtained by using the FRS enabled us to procure a quick and accurate orientation on the cardiovascular risk. Following the assessment by this prediction tool, we calculated higher cardiovascular risk estimates in gout patients than in asymptomatic hyperuricemia, while a difference depending on body weight from the earlier to later disease stages was not seen. We suggest that combined application of a scoring system with a non-invasive and harmless imaging method would be an appropriate approach for the assessment of cardiovascular risk in the individual stages of gout, in which the prevalence of obesity is high.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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