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Metabolic syndrome in gout compared to autoimmune rheumatic diseases

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Abstract

Objective: To estimate the prevalence of metabolic syndrome (MetS) in gout and to compare it to the prevalence of MetS in osteoarthritis and in autoimmune rheumatic diseases with recognized risk for MetS.

Methods. The hospital's electronic database was queried for all adult patients with in-hospital admissions since its operating start (January 1st 2009) until the arbitrary date of the study (June 26th 2024). Only the first admission to the hospital within the study timeframe was retained for each unique patient. Diagnoses were defined by ICD10 coding.

Results. Patients with gout (n=996), compared to patients with rheumatoid arthritis (RA; n=4864), ankylosing spondylitis (AS; n=1403), systemic lupus erythematosus (SLE; n=304) and osteoarthritis (n=17044) had a significantly higher prevalence of MetS (12.8% compared respectively to 4.2%, 3.8%, 2.9% and 8.0%, $p < 0.001$ for all) and all of its component diagnoses, with marginal significance when compared to PsA patients (n=278; 12.8% compared to 8.6%, $p = 0.060$). Within the gout group, women were significantly older than men and they had a significantly higher prevalence of MetS (15.8% versus 10.6%, $p = 0.015$; $p < 0.001$ after weighing the data by age) and its components, excepting dyslipidemia.

Conclusion. Gout had a significantly higher prevalence of MetS and all of its component diagnoses compared to autoimmune rheumatic diseases (RA, AS, SLE) and osteoarthritis. Women with gout exhibit a significantly higher prevalence of MetS and its components (excepting dyslipidemia). The combination of gout and MetS should attract aggressive strategies for cardiovascular risk lowering.

Keywords: metabolic syndrome, gout, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus.

Introduction

Metabolic syndrome (MetS), regardless of its definition, and its components [1-7] are highly prevalent among gout patients of all races and ethnicities [2,8-21], with highly varying frequencies in the literature, averaging at approximately 50%. Intriguingly, MetS is already present at time of the first gout attack [22] and it significantly increases the risk of gout development [23,24], even in younger and thinner men. The association seems to be causal, since remittance of MetS (especially through diet [25,26]) also decreases the risk of incident gout [24], while gout and increasing levels of serum uric acid (SUA) predict the development of MetS [27,28]. Moreover, the two conditions exhibit a common proportional epidemiological tendency of increase in the last decades [29]. These observations suggest that the two conditions are driven by a common pathogenic metabolic process [6,30].

The importance of this observation lies in its association with cardiovascular comorbidity and mortality. In this sense, is has been shown that gout and MetS are associated with higher total body/trunk fat mass [31,32], higher levels of SUA [12,13], asymptomatic ischemic heart disease [8,22,33] and mortality [34] (in a proportional relationship with MetS severity [15,35]). The underlying mechanism are complex [29,36] and could involve genetic predispositions [37] (even though disputable [38], but also suggested by higher rates of MetS among gout relatives [39]), insulin resistance [13,40], disturbance of uric acid metabolism (especially uric acid over-production [4] and underexcretion [11,41]) and the presence of non-alcoholic fatty kidney disease [42].

Another possible common denominator could be chronic systemic inflammation, which would explain the relatively high prevalence of MetS in autoimmune rheumatic diseases, especially in rheumatoid arthritis (RA) [43], ankylosing spondylitis (AS) [44], psoriatic arthritis (PsA) [45] and systemic lupus erythematosus (SLE) [46]. Gout however seems to occupy a special position in the relationship with MetS since there is evidence of a significantly higher prevalence of MetS among gout patients when compared with rheumatic inflammatory diseases [5].

In this context, the main study objective was to

estimate the prevalence of MetS in gout and to compare it to the prevalence of MetS in autoimmune rheumatic diseases with a recognized risk for MetS and in patients without any inflammatory disease.

Methods

Relevant healthcare system information

In the Romanian public healthcare system, a person is uniquely identified by name and by the so-called personal numeric code (abbreviated CNP in Romanian). The hospital records CNPs and offers three types of rheumatology visits: urgent or elective in-hospital admissions (the patient occupies a department bed for at least 12 hours), day care admissions (the patient occupies a day care bed for 2-12 hours) and out-clinic consult (the patient does not occupy a bed). For each such visit and for each patient, each attending physician records diagnoses using the 10th edition of the International Classification of Diseases (ICD10). For the purpose of this analysis, in-hospital admissions were retrieved, since they require a complete ICD10 coding for financial reimbursement purposes based on specified complexity of the cases.

Patients and data

The hospital's electronic database was queried for all patients with in-hospital admissions since its operating start (January 1st 2009) until the arbitrary date of the study (June 26th 2024), comprising 15.5 years of medical records. For each patient, the software allows the retrieval of the following variables: CNP (from which sex - the first numeral from the CNP, and birthdate - the following six numerals from the CNP, were extracted), in-hospital admission date (used to calculate age at admission by subtracting birthdate), discharge date (used to calculate hospitalization time by subtracting admission date), primary diagnosis on admission, primary diagnosis on discharge and secondary diagnoses at discharge (all coded with ICD10), SUA (tested by the same laboratory using commercially available kits, with normal range of 3.5-7.2 mg/dL for men and for women 2.6-6.0 mg/dL), fasting glycaemia, serum triglycerides and serum cholesterol levels and its fractions (not reported because of high rate of missing data: > 30%). Blood pressure levels and anthropometric data such as abdominal circumference, body mass and height or body mass index (BMI), if they existed, were not subject to the possibility of automated retrieval from the electronic database.

For the purpose of the current analysis, only the first admission to the hospital within the study timeframe was retained for each unique CNP and all follow-up admissions were excluded. Also, only adult patients (i.e. aged 18 years or above) were included. As part of routine admission process, all patients give written informed consent for anonymized scientific use of personal and medical data.

ICD10 coding

Using ICD10 codes (table 1), string values of primary diagnosis on discharge and secondary diagnoses at discharge were searched for rheumatological (gout, RA, AS, PsA, SLE, osteoarthritis) and MetS-related diagnoses (obesity, primary arterial hypertension - AHT, type 2 diabetes mellitus – T2DM, dyslipidemia, asymptomatic hyperuricemia - AHU). Overleaping cases of these rheumatological diagnoses in any combination were excluded.

Table 1. Disease coding

ICD10 code	*diagnosis*
M10	gout
M05, M06	rheumatoid arthritis
M45	ankylosing spondylitis
L40.5, M07	psoriatic arthritis
M32	systemic lupus erythematosus
M15-19, M40-43, M47, M50-54	osteoarthritis
E66	obesity
I10	primary arterial hypertension
E11	type 2 diabetes mellitus
E78.0-5	dyslipidemia
E79	asymptomatic hyperuricemia

ICD - International Classification of Diseases, 10th edition.

Definition of the MetS

The International Diabetes Foundation (IDF) defined MetS as the co-occurrence of central obesity (waist circumference above normal or BMI above 30 kg/m2) and any two of the following four: elevated triglycerides (above 150 mg/dL or specific treatment), reduced HDL-cholesterol (below 40/50 mg/dL in men/women or specific treatment), elevated blood pressure (above 130/85 mmHg systolic/diastolic or antihypertensive treatment), elevated fasting plasma glucose (above 100 mg/dL or history of type 2 diabetes) [47]. The retrospective design and missing data did not allow for quantitative measurement retrieval of the IDF definition criteria. Rather, the principle of the association of obesity with any two of AHT, T2DM and dyslipidemia was retained due to existing ICD10 information. Therefore, MetS was defined for the purpose of this study with ICD10 codes as either: E66 + I10 + E11, or E66 + I10 + E78.0-5, or E66 + E11 + E78.0-5.

Statistics

Nominal variables are reported as "percent of group", while continuous variables, which were found to be normally-distributed (by descriptive statistics, normality and stem-and-leaf plots, Kolmogorov-Smirnov tests), are reported as "mean (standard deviation)". Independent-samples two-tailed t tests were used to assess differences in continuous variables

diagnoses groups, while the associations of these subgroups with other categorical variables were studied using $\chi 2$ tests, weighed by age. The statistical tests were considered significant if $p < 0.05$. All the statistical analysis was performed using IBM SPSS Statistics version 25.0 for Windows (Armonk, NY, IBM Corp.).

Results

From the 59705 admissions in the selected timeframe, after excluding patients with missing data (CNP, secondary diagnoses at discharge), follow-up visits and overlapping studied diagnoses, resulted 996 gout patients, 4864 with RA, 1403 with AS, 278 with PsA, 304 with SLE and 17044 with osteoarthritis (Figure 1). All patients were Caucasian, mostly of Romanian ethnicity (99.2%) and there were no members of high MetS prevalence ethnic groups (south Asians, Hispanics, African-Americans, Native Americans).

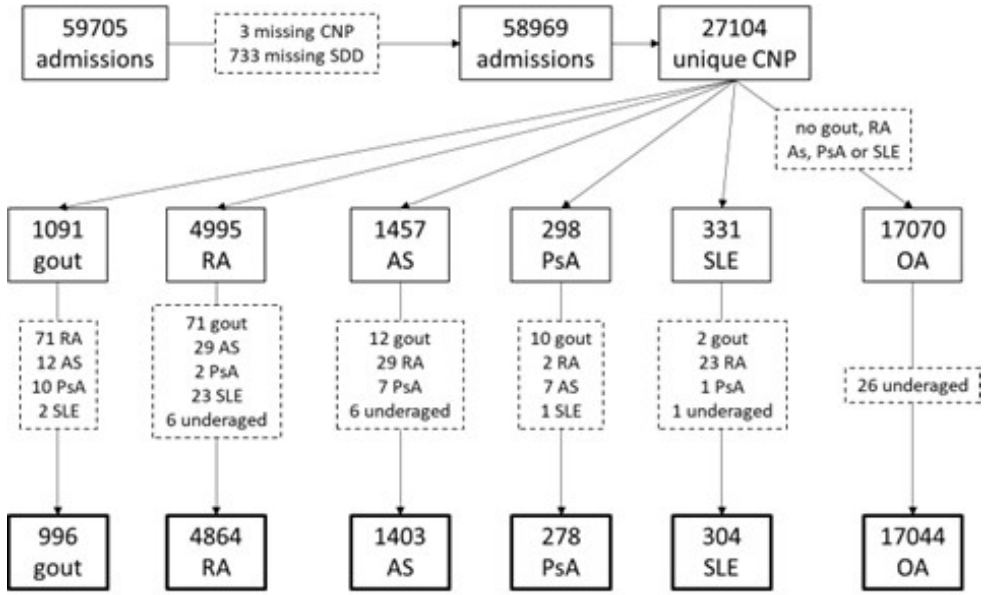

Figure 1. Patient selection flowchart of hospital admissions between 1/1/2009-6/26/2024. AS – ankylosing spondylitis; CNP – personal numeric code; OA – osteoarthritis; PsA – psoriatic arthritis; RA – rheumatoid arthritis; SDD – secondary discharge diagnoses; SLE – systemic lupus erythematosus.

The prevalence of men was significantly higher in gout compared to RA, PsA, SLE and osteoarthritis, but significantly lower compared to AS (Table 2). Gout patients were also significantly older than the rest of the subgroups. Also, patients with gout, compared to patients with RA, AS, SLE and osteoarthritis had a significantly higher prevalence of MetS (12.8% compared respectively to 4.2%, 3.8%, 2.9% and 8.0%, $p < 0.001$ for all, Table 2) and all of its component diagnoses, although not significant when compared to PsA patients (12.8% compared to 8.6%, $p = 0.060$, Table 2). AHU was more prevalent among PsA patients (6.5%), followed by osteoarthritis, SLA, AS and RA (Table 2).

Table 2. Comparison of gout with other rheumatological diseases.

	gout (n = 996)	RA (n = 4864)	AS (n = 1403)	PsA (n = 278)	SLE (n = 304)	OA (n = 17044)
women (%)	41.3	84.6*	32.9*	66.5*	91.1*	81.8*
men (%)	58.7	15.4*	67.1*	33.5*	8.9*	18.2*
age (years)	61.9 (11.0)	59.5 (12.5)*	46.3 (13.3)*	56.4 (12.5)*	48.2 (14)*	61.1 (12.5)g
HD (days)	5.7 (2.2)	5.9 (2.2)a	5.4 (2.5)b	5.3 (2.4)c	5.0 (2.5)*	6.4 (2.3)*
obesity (%)	40.3	17.9*	19.6*	28.1*	16.4*	29.6*
AHT (%)	59.5	39.5*	24.7*	43.9*	25.7*	48.3*
T2DM (%)	19.9	11.9*	9.4*	18.3d	5.3*	13.5*
dyslipidemia (%)	26.8	12.5*	10.8*	20.1e	14.5*	20.2*
MetS (%)	12.8	4.2*	3.8*	8.6f	2.9*	8.0*
AHU (%)	-	3.1	4.0	6.5	4.3	5.3
SUA (mg/dL)	7.3 (2.1)	4.7 (1.5)	5.0 (1.4)	5.1 (1.6)	4.9 (1.5)	5.0 (1.5)

Notes: Diagnoses are defined by ICD10 codes. P values represent the significance level of t tests (for age and HD, reported as "mean SD") or χ^2 tests (for the rest, reported as percentage of group). P values: * – $p < 0.001$; a – $p = 0.005$; b – $p = 0.034$; c – $p = 0.034$; d – $p = 0.568$; e – $p = 0.024$; f – $p = 0.060$; g – $p = 0.010$.

Abbreviations: AHT – arterial hypertension; AHU – asymptomatic hyperuricemia; AS – ankylosing spondylitis; HD – hospitalization duration; ICD – International classification of diseases; MetS – metabolic syndrome; OA – osteoarthritis; PsA – psoriatic arthritis; RA –

rheumatoid arthritis; SD – standard deviation; SLE – systemic lupus erythematosus; SUA – serum uric acid; T2DM – type 2 diabetes mellitus.

Within the gout group (n = 996), women were significantly older than men (Table 3), they had a significantly higher mean SUA and they also exhibited a higher prevalence of MetS (15.8% versus 10.6%, p = 0.015; p < 0.001 after weighing the data by age) and its components, excepting dyslipidemia.

Table 3. Sex differences among gout patient (n = 996).

	women (n = 411)	men (n = 585)	p
age (years)	64.9 (9.8)	59.9 (11.2)	< 0.001
HD (days)	5.8 (2.1)	5.6 (2.3)	0.069
obesity (%)	50.4	33.2	< 0.001
AHT (%)	64.2	56.2	0.011
T2DM (%)	24.1	16.9	0.005
dyslipidemia (%)	25.1	28.0	0.297
MetS (%)	15.8	10.6	0.015
SUA (mg/dL)	7.6 (2.1)	7.1 (2.1)	0.008

Notes: Diagnoses are defined by ICD10 codes. P values represent the significance level of t tests (for age, HD and SUA, reported as "mean SD") or χ^2 tests (for the rest, reported as percentage of group).
Abbreviations: AHT – arterial hypertension; HD – hospitalization duration; ICD – International classification of diseases; MetS – metabolic syndrome; SD – standard deviation; SUA – serum uric acid; T2DM – type 2 diabetes mellitus.

Compared to gout patients without MetS (n = 869), gout patients with MetS (n = 127) were older (63.5 (8.8) years versus 61.7 (11.2) years, p = 0.076) and they had a significantly longer hospitalization duration (6.3 (2.7) days versus 5.6 (2.1) days, p < 0.001), but similar levels of SUA (7.2 (2.1) compared to 7.3 (2.1) mg/dL, p = 0.487).

Discussion

In our study, gout had a significantly higher prevalence of MetS and all of its component diagnoses compared to autoimmune rheumatic diseases (RA, AS, SLE) and osteoarthritis. As all the above cited studies observe, the significantly higher prevalence of MetS in gout compared to controls (without inflammatory/autoimmune rheumatic diseases, but possibly with osteoarthritis) is a well-established literature fact. However, there is scarce literature evidence for this comparison of gout with autoimmune rheumatic diseases in terms of MetS prevalence [5], which is concordant with our observation. Long-term exposure to nonsteroidal anti-inflammatory drugs, which carry a risk for AHT and its complications, as well as long-term and/or high-dose exposure to therapeutic glucocorticoids, which impact the metabolism more severely, are common for gout and autoimmune rheumatic diseases, but chronic inflammation is not, since gout usually and initially manifests in flares, with asymptomatic and non-inflammatory periods (normal acute phase reactants between attacks). Hyperuricemia on the other hand tends to persist in the inter-critical periods of gout and could therefore be responsible for the observed excess MetS (for example by inhibiting AMP-Activated Protein Kinase - AMPK [29]). This reasoning was tested by interventional studies which aimed to reduce cardiovascular risk through urate-lowering therapy, with positive results [48, 49]. However, although recent observational [50] and genetic evidence [51] confirm serum urate as an independent cardiovascular risk factor, they show that urate does not account for all of the excess cardiovascular comorbidity (MetS components). Therefore, it remains a mystery why gout behaves as a hub for the MetS, since both hyperuricemia and cardiovascular comorbidity seem to be the expression of another common underlying pathological mechanism, even though they both are capable of aggravating each other. Since dividing cells involve both purine and lipid metabolism for DNA and membrane synthesis, defective/inefficient purine management could explain both hyperuricemia and MetS, especially by AMPK activity and misuse of adenosine signaling.

Arguably in the context of studied populations, the stereotypical gout patient with MetS is a man. From this point of view, our observation however seems surprising: women with gout had a significantly higher mean SUA and a significantly higher prevalence of MetS and its components (excepting dyslipidemia), even after controlling for age, which was significantly higher in women. Although the literature favors man for the higher prevalence of MetS [52] (especially in unselected patients), there are consistent data on the fact that the prevalence of MetS is similar among sexes [53-55] and even higher in women [14,56-58]. Race, age, sexual development (puberty, menopause) and underlying predisposing conditions (for example sleep apnea [56] and psychiatric conditions [59,60]) seem to determine sex-differences among MetS patients. Gout seems to be associate with a higher prevalence of MetS in postmenopausal women, which target them for more aggressive lifestyle and pharmacologic intervention.

The study design and results bare limitations which must be taken into consideration when interpreting the results. The most important is the surrogate nature of the target conditions (MetS and its components) which were defined non-clinically by ICD10 codes (a process which is subject to bias by multiple user inputs), without recordable measured variables (waist circumference, insulin resistance, cholesterol and triglycerides levels. Further prospective studies should address these issues, as well as recoding information on family history, diet, physical activity, smoking status, alcohol consumption, stress exposure and concomitant relevant diagnoses (such as endocrine disorders and sleep apnea). Once external influences are controlled by study designs, the common genetic predisposition to hyperuricemia/gout and MetS warrants further inquiry, especially genetic studies of AMPK activity and adenosine signaling.

Conclusion

Gout had a significantly higher prevalence of MetS and all of its component diagnoses compared to

autoimmune rheumatic diseases (RA, AS, SLE) and osteoarthritis. Women with gout had a significantly higher mean SUA and a significantly higher prevalence of MetS and its components (excepting dyslipidemia). The combination of gout and MetS should attract aggressive strategies for cardiovascular risk lowering.

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