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The relationship between metabolic syndrome severity and the risk of mortality in gout patients: a population-based study

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ABSTRACT

Objective. *To examine Metabolic Syndrome (MetS) severity using a recently validated Metabolic Syndrome Severity Score (MetSSS) in order to explore the overall associations between MetSSS and the risk of mortality related to all-causes, heart disease, diabetes mellitus, and hypertension amongst American adults with gout.*

Methods. *Mortality-linked data for 12,101 adults aged 18 to 90 years who participated in the National Health and Nutrition Examination Survey III by gout status was analysed. All 5 metabolic features were used to calculate gender-race/ethnicity-specific MetSSS Z-scores in gout patients. The calculated Z-scores are a continuous representation of all MetS conditions while accounting for gender-race/ethnicity disparities.*

Results. *A total of 3,381 deaths were observed, of which 215 had gout. The prevalence amongst adults was 2.59%. Moderate to high MetS severity was significantly prevalent amongst gout patients (47.33% vs. 21.16 % no gout; p-value <0.0001). The mean MetSSS Z-score for gout patients was significantly higher than those without gout (0.71 vs. -0.04 no gout; p-value <0.0001). A one-unit increase in MetSSS score was associated with significant increases in the risk of all-cause mortality, heart disease, diabetes- and hypertension-related mortalities.*

Conclusion. *Moderate to high MetSSS is significantly prevalent amongst gout patients. A one-unit increase in MetSSS score was associated with significant increases in the risk of all-cause mortality, heart disease, diabetes- and hypertension-related mortalities. MetS is a clinically accessible tool for predicting mortality risks in gout patients with MetS.*

Intoduction

Gout is an autoinflammatory metabolic disease. It often presents with severe joint pain during flares and chronically with severely damaged joints related to monosodium urate crystal deposition. Gout is associated with a higher prevalence of metabolic syndrome (MetS) compared with the general population (1). Increased serum urate (SU) levels and hyperuricaemia are often observed in patients with MetS (2). Hyperuricaemia, the main risk factor for gout, may play a role in promoting MetS in patients with gout (2).

MetS is a major and increasing public-health problem in around 35% of Americans. MetS leads to a 5-fold increase in type 2 diabetes mellitus (DM) risk and a 2-fold increase in heart disease risk (3). MetS has been defined by he National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), the most widely used criteria of MetS, as the presence of three or more of the following criteria: elevated waist circumference, elevated triglycerides or receiving treatment for elevated triglycerides and Low HDL-cholesterol or receiving treatment for low HDL-cholesterol, elevated blood pressure or drug treatment for hypertension, and elevated fasting blood glucose or receiving treatment for DM (4). Counting these conditions purely incorporates their presence or absence but does not account for their severity. Metabolic Syndrome Severity Score (MetSSS) is a recently validated summary score that accounts for the combined effects of all 5 metabolic features in the context of cardiometabolic risk (5).

Objective

To examine the MetS severity using a recently validated Metabolic Syndrome Severity Score (MetSSS) in order to explore the overall associations between MetSSS and the risk of mortality related to all-causes, heart disease, DM, and hypertension amongst American adults with gout.

Methods

Mortality-linked data for 12,101 adults aged 18 to 90 years who participated in the National Health and Nutrition Examination Survey (NHANES) III by gout status was analysed. Data from NHANES III were linked to national mortality records for all participants up to the time of death or end of study (*i.e.* 23 years following initial recruitment, starting in 1988). The five traditional MetS components were used to calculate gender-race/ethnicity-specific

MetSSS Z-scores in gout patients. The calculated Z-scores are a continuous representation of all MetS components while accounting for gender-race/ethnicity disparities.

Cox proportional hazard models adjusting for age, marital status, gender, income, education, race, smoking, BMI, insurance, physical activity, alcohol intake, and diet, were used to test the associations between MetS severity and risk of mortality in gout patients. Complex survey methods with sampling weights, clusters, and strata were applied to yield nationally representative prevalence and inference estimates.

The study protocol was approved by: Rutgers-New Brunswick Health Sciences Institutional Review Board (Pro2018002906).

Results

The prevalence of gout amongst adults was 2.59% (95% CI; 2.13%–3.05%). Moderate to high MetS severity was significantly prevalent among gout patients (47.33% *vs*. 21.16 % no gout; *p*-value <0.0001). The mean MetSSS Z-score for gout patients was significantly higher than those without gout (0.71 *vs*. -0.04 no gout; *p*-value <0.0001) (Fig. 1).

A total of 3,381 deaths were recorded, of whom 215 had gout. For gout patients, a one-unit increase in MetSSS score was associated with a significant increase in the risk of all-cause mortality adjusted hazard ratio (aHR) 1.31 (95% CI; 1.13, 1.87). In a disease-specific survival model, a one-unit increase in MetSSS score was associated with an aHR 1.62 (95% CI; 1.21, 2.15) increase in heart disease-related mortality; increased risks of diabetes- and hypertension-related mortalities among gout patients aHR 2.57 (95% CI; 1.43, 4.62), aHR 1.73 (95% CI; 1.07, 2.79), respectively (Table I).

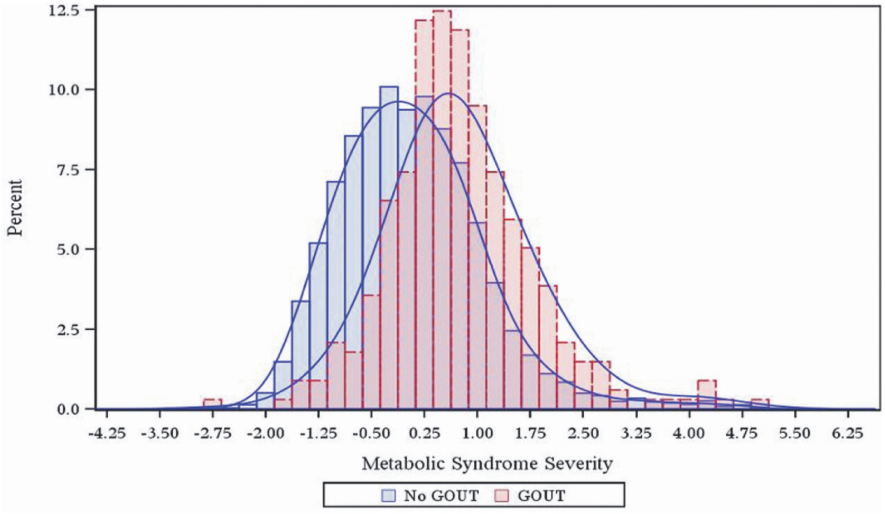

Fig. 1. The distribution of metabolic syndrome severity by gout status among adults in the United States NHANES III (n=12,101).

Table I. Association between one unit increase in Metabolic Syndrome Severity Index and the risk of mortality amongst US adults with gout, (NHANES III) 1988-1994 (n=337).

Mortality cause[a]	Unadjusted HR (95% CI)	Age and Gender Adjusted HR (95% CI)	Fully Adjusted[e] HR (95% CI)
All cause	1.29 (1.07 - 1.57)	1.21 (1.03 - 1.42)	1.31 (1.08 - 1.60)
Diseases of heart[b]	1.38 (1.09 - 1.76)	1.28 (1.04 - 1.59)	1.62 (1.21 - 2.15)
Diabetes related[c]	2.47 (2.00 - 3.04)	2.22 (1.72 - 2.88)	2.57 (1.43 - 4.62)
Hypertension related[d]	1.93 (1.55 - 2.39)	1.77 (1.44 - 2.17)	1.73 (1.07 - 2.79)

[a] Excluding mortalities related to accidents (unintentional injuries); [b] ICD-10 codes (I00-I09, I13, I20-I51); [c] ICD-10 codes (E10-E14); [d] ICD-10 codes (I10 or I12); [e] Adjusted for age, marital status, gender, income, education, race/ethnicity, poverty index, smoking, BMI, insurance, physical activity, alcohol intake and diet.
HR: Hazard ratio; US: United States; CI: confidence interval.

Discussion

This is the first study in the English literature utilising and assessing MetSSS in gout patients. Moderate to high MetS severity was significantly prevalent (*p*-value <0.0001) amongst gout patients. The severity of MetS is significantly associated with increased risk of heart disease-related mortality, diabetes- and hypertension-related mortality, and risk of all-cause mortality amongst American adults with gout.

MetSSS expressed by a continuous score has been demonstrated to predict future diseases, such as DM, heart disease, and chronic kidney disease (CKD). Previous studies showed that MetSSS is strongly associated with heart disease (6) and can predict heart disease better than the traditional MetS ATP-III criteria (7). In addition, MetSSS was associated with an increased risk of a progressive decline in renal function and the development of chronic kidney disease (CKD) (8). In a cohort of African-Americans, MetSSS was inversely associated with the Estimated Glomerular Filtration Rate (eGFR) at baseline, and the worsening of MetSSS was tied to a decline in eGFR, raising the potential for following MetSSS over time in surveillance for worsening GFR, which may lead to preventative lifestyle change (9).

Despite strong evidence of the association of hyperuricaemia with MetS (10), statistical association does not imply causality. Hyperuricaemia may be a surrogate marker or a confounding risk factor. If gout promotes MetS and cardiovascular risk and death, it would seem logical that treating gout would reduce the risk of cardiovascular risk and mortality. Gout is both an inflammatory and a metabolic disease. Gout involves hyperuricaemia, monosodium urate (MSU) crystallisation, inflammatory responses to MSU crystal deposition, and the metabolic effects generated by these processes.

Preventing and treating gout in patients with MetS, in order to decrease MetSSS, will likely require urate-lowering and anti-inflammatory therapy. Urate-lowering therapy in gout patients

with MetS may protect patients from cardiovascular morbidity and death.

Randomised controlled trials are needed to determine whether urate-lowering therapy in gout patients with MetS slows the development and progression of MetS and improves mortality. However, MetS is not just a metabolic disorder; it is also a pro-inflammatory state, similarly to gout, a metabolic disease that has an autoinflammatory component. There is an association between chronic low-grade inflammation, insulin resistance, and obesity-induced metabolic disease. M1 macrophages, classically activated, comprise the primary source for inflammatory cytokines in obese adipose tissue and coordinate inflammatory insulin resistance (11). Thus, there is a robust expression of pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), IL-1β, and interleukin (IL)-6 In MetS (11-13). Neutralisation of TNF-α was demonstrated to enhance the peripheral uptake of glucose in response to insulin, thus suggesting a role for TNF-α in obesity and particularly in insulin resistance (MetS) and diabetes that often accompanies obesity (13). Targeting IL-1β, a pivotal cytokine that mediates inflammation in gout and atherosclerosis, with canakinumab in combination with standard of care reduced major cardiovascular events in patients with a prior myocardial infarction (14). Thus, targeting inflammation in gout patients may help treat MetS, as well.

Conclusions

Studies published to date have not accounted for the combined severity of all five MetS features in gout patients. Moderate to high MetS severity is significantly prevalent amongst gout patients. MetS severity is significantly associated with an increased risk of mortality amongst gout patients.

We found MetSSS to be a clinically accessible tool for predicting mortality risks in gout patients with MetS. MetSSS may be suited to assess change over time (*e.g.* to detect a worsening trend or to evaluate the early impact of treatment) in aggregate severity across the cardio-metabolic risk factors that comprise the MetS in gout patients.

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