Hyperuricemia and Metabolic Syndrome: Lessons from a Large Cohort from Israel

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ABSTRACT: **Background:** There is a striking increase in the number of people with metabolic syndrome (MetS) as a result of the global epidemic of obesity and diabetes. Increasing evidence suggests that uric acid may play a role in MetS.
Objectives: To assess the prevalence of MetS in a large cohort from Israel and its association with hyperuricemia using the latest three definitions of MetS.
Methods: We conducted a retrospective analysis of the database from a screening center in Israel, using the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the International Diabetes Federation (IDF) and the Harmonizing definitions of MetS, to assess 12,036 subjects with an age range of 20–80 years.
Results: The mean age of the study sample was 46.1 ± 10.2 years and 69.8% were male. The prevalence of MetS was 10.6%, 18.2% and 20.2% in the revised NCEP ATP III, the IDF and the Harmonizing definitions respectively. The prevalence of hyperuricemia in subjects with MetS, for all three MetS definitions, was similar: 20.0%, 19.9% and 19.1% respectively. There was a graded increase in the prevalence of MetS among subjects with increasing levels of uric acid. The increasing trend persisted after stratifying for age and gender and after multivariate analysis (P for trend < 0.001).
Conclusions: This large cohort shows a high prevalence of MetS in Israel, but is still lower than the prevalence in western countries. Hyperuricemia is common in those subjects and might be considered a potential clinical parameter in the definition of MetS.

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KEY WORDS: metabolic syndrome (MetS), hyperuricemia, cohort, insulin resistance, gender

Metabolic syndrome, previously named syndrome X, describes a group of risk factors occurring in the same individual and a common denominator of insulin resistance [1]. The syndrome was first described in 1998 by a consultation group tasked with defining diabetes for the World Health Organization [2]. Since then, the classification has changed repeatedly [3-7] and currently three definitions are being used: the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the International Diabetes Federation (IDF), and the Harmonizing definition [5-7]. It is important to diagnose this syndrome since it is closely associated with the future development of type 2 diabetes mellitus and cardiovascular complications [8]. All current definitions of MetS include five clinical parameters in different combinations, namely: obesity, hypertriglyceridemia, low levels of high density lipoprotein, hypertension, and elevated levels of fasting glucose.

Increasing evidence suggests that uric acid may play a role in MetS [9,10]. Elevated levels of uric acid have been observed in MetS and were attributed to hyperinsulinemia, as insulin reduces renal excretion of uric acid [11]. However, hyperuricemia often precedes the development of hyperinsulinemia. The strongest evidence of a role for uric acid in the development of MetS comes from studies in animal models showing that decreasing uric acid levels may prevent or even reverse features of MetS [12]. Indeed, previous studies in the United States, in both children and adults, have shown an association between elevated serum concentrations of uric acid and MetS [13,14].

The actual prevalence of MetS has never been assessed in an Israeli population. Moreover, there are no data regarding the correlation between hyperuricemia and MetS in this population. Therefore, the goals of our study were to assess the prevalence of MetS in a large cohort from Israel and to evaluate the association between MetS and uric acid levels. The latest three current definitions of MetS were used.

PATIENTS AND METHODS

We retrospectively analyzed the health database of a screening center at the Rabin Medical Center in Israel. This referral institute is mainly for employees of different companies and has assessed approximately 20,000 subjects between the years 2000 and 2010. The population attending the center for

*The first two authors contributed equally to the development of the study

MetS = metabolic syndrome

screening includes male and non-pregnant female subjects with an age range of 20–80 years. Each subject undergoes a thorough medical history evaluation and a complete physical examination, together with a broad series of blood and urine tests, chest X-ray, electrocardiogram, exercise stress test and lung function test. Subjects may return once a year for a repeat investigation. For the purpose of this study only data from the most recent visit were assessed. The study was approved by the Helsinki Ethics committee of Rabin Medical Center.

ASSESSMENT OF METS

Hyperuricemia was defined as > 7.0 mg/dl for men and > 5.6 mg/dl for women [15]. The current three definitions of MetS were used as follows. According to the revised NCEP ATP III definition, subjects with three or more of the following criteria are considered as having MetS:

- waist circumference ≥ 102 cm in men and ≥ 88 cm in women
- triglycerides ≥ 150 mg/dl or drug treatment for elevated TG levels
- high density lipoprotein < 40 mg/dl in men and < 50 mg/dl in women
- blood pressure ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic, or drug treatment for hypertension
- fasting plasma glucose ≥ 100 mg/dl, or drug treatment for diabetes mellitus.

The IDF and the Harmonizing definition criteria are similar to the revised NCEP ATP III definition but differ for waist circumference, which is ethnic specific. According to the IDF definition increased waist circumference must be one of the criteria, while according to the Harmonizing definition waist circumference is part of the potential five criteria. Increased waist circumference in Mediterranean populations is defined as ≥ 94 cm in men and ≥ 80 cm in women [6].

STATISTICAL ANALYSIS

We assessed the prevalence of MetS (using all three definitions) in six categories of serum uric acid levels: < 6.0 mg/dl, 6.0–6.9 mg/dl, 7.0–7.9 mg/dl, 8.0–8.9 mg/dl, 9.0–9.9 mg/dl, and ≥ 10.0 mg/dl. Logistic regression analysis was used to assess the odds ratio of MetS in the different strata of serum uric acid. Model 1 presents the crude association, model 2 is adjusted for age and gender, and in model 3 adjustment is made for age, gender, smoking status, alcohol consumption, body mass index (five categories: < 18.5, 18.5–25, 25–30, 30–35, > 35 kg/m^2) and physical activity (three categories: < 100, 100–200, > 200 minutes per week). The reference group in all comparisons was the lowest uric acid category (< 6.0 mg/dl). All analyses were conducted in Stata version 11.2 (Stata Corp LP, College Station, TX USA).

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III
TG = triglycerides
IDF = International Diabetes Federation

RESULTS

Of the 20,754 people who attended the health center between 2000 and 2010, a total of 12,036 (58%) had data on all components of MetS and comprised our study sample. The mean age of the study sample was 46.1 years (SD 10.2) and 69.8% were males.

The prevalence of MetS according to the three different definitions was 10.6%, 18.2% and 20.2% in the revised NCEP ATP III, the IDF and the Harmonizing definition groups respectively. The prevalence of the syndrome according to the two latter definitions was significantly higher than the prevalence using the revised NCEP ATP III definition ($P < 0.001$). Males were shown to have a higher prevalence of MetS than females, 11.9% vs. 7.5%, 20.5% vs. 13.1%, and 23.1% vs. 13.6% for the three definitions respectively (all P values < 0.001) [Figure 1].

The overall prevalence of hyperuricemia in subjects with MetS for all three MetS definitions was similar: 20.0%, 19.9% and 19.1% respectively. In subjects with MetS hyperuricemia was found to be more common in males than in females: 21.7% vs. 13.6%%, 22.0% vs. 12.0% and 21.0% vs. 11.6% for the three definitions respectively (all P values < 0.004). In males with MetS compared to males without MetS the prevalence of hyperuricemia was at least twice as high: 21.7% vs. 9.5%, 22.0 % vs. 8.1%, and 21.0% vs.7.9% in the three definitions respectively (all P values < 0.001). In females with MetS compared to females without MetS the prevalence of hyperuricemia was at least six

Figure 1. Prevalence of the metabolic syndrome according to three definitions: IDF (International Diabetes Federation), NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) and Harmonizing

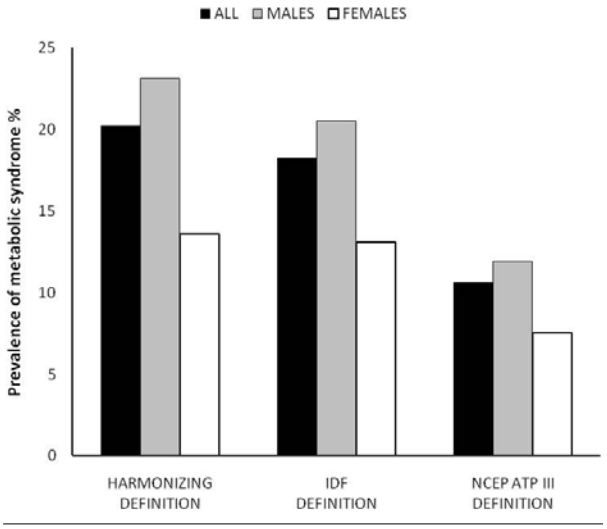
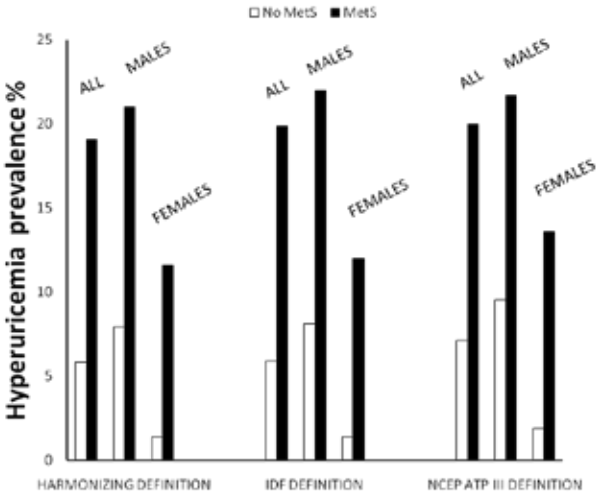


Table 1. Prevalence and OR (95% CI) of the metabolic syndrome according to serum uric acid levels

	Uric acid levels (mg/dl)					
	< 6	6–6.9	7–7.9	8–8.9	9–9.9	> 10
NCEP definition						
Prevalence (%) (95% CI)	6.7 (6.1–7.3)	14.1 (12.8–15.5)	21.3 (19.1–23.7)	25.4 (21.0–30.5)	33.8 (23.6–45.8)	44.4 (27.2–63.1)
Model 1	1.0	2.3 (2.0–2.6)	3.8 (3.2–4.4)	4.8 (3.6–6.2)	7.1 (4.3–11.8)	11.1 (5.2–23.9)
Model 2	1.0	2.2 (1.9–2.6)	3.8 (3.1–4.5)	5.2 (3.9–6.9)	6.8 (3.9–11.8)	11.0 (4.8–25.4)
Model 3	1.0	1.7 (1.4–2.0)	2.5 (2.0–3.0)	2.9 (2.2–4.0)	3.7 (2.1–6.6)	6.1 (2.6–14.4)
IDF definition						
Prevalence (%) (95% CI)	11.4 (10.7–12.1)	24.8 (23.2–26.5)	36.9 (34.2–39.7)	42.5 (37.3–48.0)	54.4 (42.5–65.8)	59.2 (40.3–75.8)
Model 1	1.0	2.6 (2.3–2.9)	4.5 (4.0–5.2)	5.8 (4.6–7.2)	9.3 (5.7–15.0)	11.3 (5.2–24.3)
Model 2	1.0	2.6 (2.3–3.0)	4.8 (4.1–5.6)	6.5 (5.1–8.3)	9.7 (5.8–16.1)	11.8 (5.2–26.9)
Model 3	1.0	1.9 (1.6–2.1)	3.0 (2.5–3.5)	3.2 (2.4–4.2)	4.9 (2.8–8.7)	5.6 (2.3–13.7)
Harmonizing definition						
Prevalence (%) (95% CI)	13.0 (12.3–13.8)	27.3 (25.7–29.0)	39.4 (36.7–42.2)	46.3 (40.9–51.7)	58.8 (46.8–69.8)	63.0 (43.7–78.8)
Model 1	1.0	2.5 (2.3–2.8)	4.3 (3.8–5.0)	5.7 (4.6–7.2)	9.5 (5.9–15.5)	11.3 (5.2–24.8)
Model 2	1.0	2.4 (2.1–2.7)	4.3 (3.7–5.0)	6.2 (4.8–7.9)	9.4 (5.6–15.8)	11.3 (4.9–26.2)
Model 3	1.0	1.8 (1.6–2.0)	2.8 (2.4–3.3)	3.3 (2.5–4.3)	5.2 (3.0–9.1)	5.8 (2.43–14.2)

Figure 2. Hyperuricemia prevalence in subjects with metabolic syndrome according to three definitions: IDF (International Diabetes Federation), NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) and Harmonizing. MetS = metabolic syndrome



times higher: 13.6 vs. 1.9%, 12.0 vs. 1.4%, and 11.6 vs. 1.4% in the three definitions respectively [Figure 2] (all *P* values < 0.001).

There was a graded increase in the prevalence of MetS according to all three definitions among subjects with increasing levels of uric acid. In subjects with uric acid concentrations of ≥ 10.0 mg/dl the prevalence in the three MetS criteria was 44.4%, 59.2% and 63.0% respectively. An increase in the prevalence of MetS across increasing levels of uric acid was found in all three models (*P* for trend < 0.001) [Table 1].

DISCUSSION

We assessed the prevalence of MetS, and more specifically the relation between MetS and uric acid levels, in a large cohort of 12,036 subjects attending an examination center in Israel. We used the most recent acceptable definitions of MetS and for the first time specifically assessed data from an Israeli population. The prevalence of MetS in our study population was 10.6%, 18.2% and 20.2% using the revised NCEP ATP III, IDF and Harmonizing definitions of MetS respectively. This prevalence is lower than the prevalence found in other countries. For example, in a recent survey from the USA using the Harmonizing definition, the prevalence of MetS was 34.3% [16]. A significantly higher prevalence of MetS was found using the IDF and Harmonizing definition compared to the revised NCEP ATP III definition. This is not surprising since the waist circumference threshold is higher using the revised NCEP ATP III definition. According to the revised

NCEP ATP III definition, increased waist circumference is defined as ≥ 102 cm in men and ≥ 88 cm in women, while according to the IDF and Harmonizing definitions increased waist circumference is defined as ≥ 94 cm in men and ≥ 80 cm in women for people from a Mediterranean area.

Our results show an interrelationship between high uric acid levels and MetS. On the one hand, the prevalence of hyperuricemia was found to be significantly higher in subjects with MetS compared to subjects without the syndrome. Gender differences were noted. In male subjects with MetS the rates of hyperuricemia were at least twice those in men without the syndrome, while in female subjects this ratio of comparison rose to 6 [Figure 2] On the other hand, there was a graded increase in the prevalence of MetS with increasing subgroup levels of uric acid. For example, using the Harmonizing definition of MetS, the prevalence of MetS rose from 13% to 63% for uric acid levels < 6 mg/dl and > 10 mg/dl respectively. In addition, an increasing trend of odds ratio was found for the association between increasing levels of uric acid and MetS in the unadjusted, age- and gender-adjusted and multivariate analysis [Table 1]. These results are in accordance with previous studies [13,14] and show a clear association between MetS and high uric acid levels. For example, in a study from a non-institutionalized U.S. civilian population using the revised NCET ATP III definitions of MetS [13], the prevalence of the syndrome in subjects with hyperuricemia was twice as high as that in our cohort; however, the odds ratio analysis was very similar. Possibly, the difference in prevalence can be attributed to environmental and geographic variation between North America and Israeli populations.

This study is notable for the large number of subjects assessed, i.e., more than 12,000 people with complete datasets concerning MetS. Nonetheless, we are aware that the study group is not necessarily representative of the general population since it is a selective healthier population that attends an examination center. Therefore, we assume that the prevalence of MetS in the general population in Israel might be even higher.

It is uncertain whether elevated levels of uric acid are the result or the cause of MetS. The syndrome has been attributed to insulin resistance. Indeed, several studies have shown that hyperinsulinemia (the consequence of insulin resistance) is inversely related to 24 hour urinary uric acid clearance [11]. One mechanism linking hyperinsulinemia with hyperuricemia is a decreased renal excretion of uric acid. Moreover, insulin enhances renal tubular sodium absorption, which reduces renal excretion of uric acid. On the other hand, animal models have shown that uric acid has a role in the development of MetS and that decreasing uric acid levels can prevent or reverse features of MetS [12]. Two mechanisms have been suggested to explain how hyperuricemia might induce MetS. The first mechanism is related to the fact that hyperuricemia has been shown to induce endothelial dysfunction in rats, which leads to a decreased release of nitric oxide from those cells [17]. Features of MetS were shown to develop in mice lacking endothelial nitric oxide synthesis [18]. The second mechanism concerns the inflammatory and oxidative changes induced by uric acid in adipocytes [19], essential for inducing MetS in obese mice [20]. A recent review suggests some possible explanations for the association between the traditional components of MetS and elevated uric acid levels [21]. Although hyperuricemia in obese patients is mainly the result of insulin resistance, it may also be due to elevated levels of leptin [22]. Hypertension leads to vascular disease and increased vascular resistance, resulting in decreased renal blood flow, which in turn stimulates urate absorption [23]. Increased triglyceride levels may be associated with decreased uric acid excretion [24]. Apolipoprotein E polymorphism affecting TG levels may also affect uric acid levels [25]. And lastly, elevated serum glucose levels, hypertension and obesity have all been associated with chronic kidney disease, which again leads to hyperuricemia.

In conclusion, the results of our study show a high prevalence of MetS in Israel, and that hyperuricemia is very common in those subjects. The high rate of hyperuricemia in this population suggests that hyperuricemia might be considered a potential clinical parameter in the definition of MetS.

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