Journal of the American Society of Hypertension 9(8) (2015) 600–609

Research Article

Uric acid levels within the normal range predict increased risk of hypertension: a cohort study

Adi Leiba, MD, MHA, FACP[a,b,*], Shlomo Vinker, MD[c,d], Dganit Dinour, MD[a], Eliezer J. Holtzman, MD[a], and Michal Shani, MD[c]

[a]*Nephrology and Hypertension Institute, Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel;*
[b]*Department of Medicine and Medical Education, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA, USA;*
[c]*Chief Physician's Office and Department of Family Medicine, Central District Clalit Health Services, Tel Aviv, Israel; and*
[d]*Department of Family Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

Manuscript received March 27, 2015 and accepted May 12, 2015

Abstract

There are data describing that cardiovascular risks related to serum uric acid (SUA) levels may begin below the current diagnostic level for hyperuricemia. Values from 5.2 to 6.0 mg/dL were positively associated with higher cardiovascular risk. The risk associated with lower SUA levels has not been fully assessed in healthy adults. The purpose of this study was to evaluate whether normal SUA levels, even below 5–6 mg/dL, might be related to an increased risk of hypertension, compared with low–normal SUA. This cohort study was conducted in an outpatient setting: all clinics of the largest Health Maintenance Organization in Israel, in a national distribution. A total of 118,920 healthy adults (40–70 years old), who had SUA levels screened during 2002, were eligible for the study. They were stratified according to baseline SUA, and were followed for 10 years. The study endpoint was any new diagnosis of hypertension during the study period (until December 31, 2011). During 10 years of follow–up (2002–2011), 28,436 examinees developed hypertension (23.9%). Compared with the predefined SUA reference values (2–3 mg/dL), women with SUA within the normal range had a gradual, increased risk of developing new–onset hypertension, starting at values as low as 3–4 mg/dL (adjusted odds ratio, 1.15; 95% confidence interval, 1.01–1.30). Women with SUA 5–6 mg/dL, still accepted as normouricemia, had a 66% increased risk of developing hypertension. Younger women (ages 40–50 years at baseline) in a similar SUA subgroup (5–6 mg/dL) had an even higher risk (odds ratio, 2.25; 95% confidence interval, 1.96–2.60). Similar results were seen among men. The possibility of subtle confounders exists, despite extensive adjustment. SUA within the normal range is associated with new–onset hypertension among healthy adults, compared with once very common low–normal range values. Further study is warranted to determine new cutoffs of hypo–, normo–, and hyperuricemia, which might be far lower than current scales. J Am Soc Hypertens 2015;9(8):600–609.

Keywords: Blood pressure; gout; metabolic syndrome; urate.

Introduction

Serum uric acid (SUA), a weak organic acid, is present mainly as monosodium urate at physiological pH.[1] Serum concentrations exceeding urate solubility (above 6.8 mg/dL) are pathogenic with regards to the incidence of gout, the formation of uric acid stones and urate nephropathy. Hyperuricemia is usually defined as SUA $\geq$6 mg/dl in women and $\geq$7 mg/dl in men.[2,3]

The precise role of hyperuricemia in hypertension has not been fully elucidated.[4] Some studies point toward a causative role of urate in the pathogenesis of insulin resistance, elevated blood pressure, and the metabolic syndrome.[5–7] Other studies imply that high SUA concentrations are simply a marker of the same metabolic pathways that lead both to defective renal handling of urate and hyperuricemia as well as to insulin resistance and hypertension: under–secretion of salt, renal tubulointerstitial

Conflict of interest: none.

*Corresponding author: Adi Leiba, MD, MHA, FACP, Specialist in Clinical Hypertension, ASH, Department of Medicine and Medical Education, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA 02115. Tel: 1-617-492-3500; Fax: 1-617-499-5178.

E-mail: aleiba@mah.harvard.edu

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2015.05.010

inflammation, etc.[8,9] Possibilities of SUA acting as a marker, or that of reverse causality, that is hypertension, the metabolic syndrome, and diabetes causing renal impairment and increased SUA, as well as the existence of multiple subtle confounders, have not been settled despite considerable research.[10]

There are data describing a cardiovascular risk from SUA that may begin below the current diagnostic level of hyperuricemia. Values from 5.2 to 6.0 mg/dL, but not lower, were positively associated with higher cardiovascular risk or mortality.[11–15]

These studies were conducted among diabetic, elderly, or other patients at high risk for cardiovascular disease. The potential risk incurred within the normal spectrum of SUA has not been fully assessed in healthy, non–hypertensive, non–diabetic adults. Neither was it assessed in the low–normal range. Since SUA levels in the population have increased during the 20th century,[16,17] we looked at data from the original 1948–1950 Framingham study.[18] Mean serum uric acid was reported as 5.12 ± 1.11 mg/dL for men and 4.01 ± 0.94 mg/dL for women.[19] We thus determined our reference value of low–normal SUA as 1–2 standard deviations (SD) below this ''historical'' mean: 2–3 mg/dL for women and 3–4 mg/dL for men. Our assumption is that true low–normal values should be elucidated from early 20th century population's range, before the era of obesity and accompanying rise in uric acid.

We wanted to evaluate healthy adults with normal SUA values above this low–normal reference range, with regard to the incidence of new onset hypertension.

Methods

Israel has a national health system in which healthcare is delivered to all citizens and permanent residents by four health maintenance organizations (HMOs). Clalit Health Services (CHS) is the largest HMO in Israel, serving 54% of the population.[20] All parts of the country and all populations are covered by this HMO. Patient medical records in CHS have been completely computerized since 2002, and an extensive healthcare database has been created. CHS Institutional Review Board approved the study prior to data collection. The study design is shown in Figure 1.

Baseline Socio–demographic Data

The age, gender, and socio–economic status of each subject was documented at baseline. Demographic data were updated directly from the population registry of the Ministry of Interior. A patient was defined as being of ''low socio–economic status'' if he or she was exempt from making monthly payments to the National Insurance Institute (Social Security) or was eligible for a copayment discount.

Baseline Clinical Parameters

The first documented height, weight, and clinic blood pressure measurement during 2002 by a nurse or a physician was also retrieved and documented as baseline body mass index (BMI) and blood pressure. Blood pressure measurement was taken at rest in the sitting position using an automated oscillometric device.

Baseline (2002) smoking status was reported by the examinees. Both current and past smokers (ever smokers) were defined as ''smokers'' at baseline.

Laboratory Values

All laboratory tests are free of charge and sent to one central lab. The results are reported directly to the primary care physician and recorded automatically in the patient's electronic medical record. Baseline serum uric acid, low–density lipoprotein (LDL) cholesterol, fasting blood glucose, and plasma creatinine were recorded from the first blood test panel taken during 2002, the year of study entrance. Estimated glomular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.

Since SUA is part of the full chemistry panel, and, by definition, we included only subjects who had uric acid screening in 2002, we also had baseline glucose, lipid profile, and plasma creatinine for more than 90% of the cohort. SUA was universally measured with the same technique, using uric acid/uricase assay (STA-375; Cell Biolabs Inc, San Diego, CA). The assay measures uric acid in biological samples with no need for pretreatment. Detection sensitivity limit for uric acid is 0.5 μM.

SUA and eGFR were also evaluated at the end of the study. Laboratory results of samples taken during 2010–2011 were recorded.

Medication Database

All community pharmacies affiliated with CHS are computerized and report to one central repository. CHS issues medications and requires nominal copayment. This system ensures that all prescriptions are documented and continuously updated.

Clinical Diagnoses Registry

The CHS database enables an accurate registry of clinical diagnoses. Each chronic diagnosis in the registry has a special algorithm that incorporates, validates, and weighs data from all sources available, including medical diagnoses at hospital discharge or community–based visits, laboratory tests, or medications purchased. The data are continuously updated, and the algorithm results are revised monthly. This registry was used both for exclusion of examinees with baseline chronic cardiovascular diseases as