Causes of Hypouricemia Among Outpatients

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Abstract

Background: The aim of this study was to examine the ratio and underlying causes of hypouricemia in patients visiting our outpatient clinics. The association between hypouricemia and uricosuria and other renal tubular defects was also studied.

Methods: Serum uric acid levels were determined by uricase methods in 18,330 serum samples. Hypouricemia was defined as a serum uric acid level less than 2.0 mg/dL. Fractional excretion of uric acid (FEUA) higher than 10% was considered as pathological uricosuria.

Results: The frequency of hypouricemia in our patient population was 0.51% (94/18,330). Moreover, using univariate analysis, hypouricemia was associated with age, gender, diet, drugs, and tea and coffee consumption. Multivariate analysis revealed that FEUA, drugs, and tea consumption were associated with hypouricemia.

Conclusion: Hypouricemia is a relatively uncommon finding among our outpatients and when it occurs, it is frequently caused by inappropriate uricosuria.

The serum level of uric acid (UA) depends on the balance between the breakdown rate of endogenous and exogenous purines into UA and the rate of UA excretion.[1] Hyperuricemia (UA >7 mg/dL [0.42 mmol/L] for men and UA >6 mg/dL [0.36 mmol/L] for women) leads to most of the clinical symptoms associated with increased purine metabolism. Hypouricemia, often defined as plasma or serum UA concentration <2.0 mg/dL (0.12 mmol/L), is much less common than hyperuricemia. Hypouricemia may occur secondary to a number of underlying conditions, including severe hepatocellular disease, defective renal tubular reabsorbtion of UA, overtreatment of hyperuricemia, and an inherited metabolic defect in purine metabolism.[2,3] In addition, hypouricemia can occur concomitantly with diseases such as severe liver disease, neoplasia, diabetes, acquired immunodeficiency syndrome (AIDS), and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion.[4] Moreover, hypouricemia is an abnormality often discovered incidentally in an asymptomatic patient, although hypouricemia associated with acute renal failure and nephrolithiasis has been reported.[5,6] Additionally, hypouricemia is also a sensitive indicator of decreased production or increased renal excretion of UA caused by underlying pathologies such as minimal renal tubular dysfunction.[6] Evaluation of hypouricemic patients has revealed that uricosuric drugs or toxins were the causative factor in about half of the cases. The prevalence of hypouricemia is low (0.15% to 3.38%) depending on whether it is permanent or transient in nature.[7-9]

The aim of our study was to examine the ratio and causes of hypouricemia among individuals visiting our outpatient clinical laboratory.

Materials and Methods

Fasting serum samples were obtained prospectively from 18,330 patients who visited our outpatient clinics between September 2005 and February 2008 and agreed to participate in our study. Serum UA reference values were 2.4 to 6.9 mg/dL and 3.3 to 8.6 mg/dL for women and men, respectively. All hypouricemic patients (n = 94, study group) were interviewed with respect to past medical/surgical/therapeutic drug history, tea and coffee consumption (ie, <2 cups/d, 2 to 5 cups/d, >5 cups/d), and the purine content of their diet based on a review and categorization of their dietary habits as normal, vegetarian, or red-meat restricted. In addition, post hoc we recruited separately 94 volunteers (control group; 64 females, 30 males) among individuals who were not receiving any medications, were not drinking excessive amounts (>2 cups/d) of coffee or tea, and were not vegetarians. We obtained 24 h urine collections (in containers containing boric acid as a preservative) from these 94 individuals and measured urine glucose, creatinine, potassium, phosphate, and UA levels in all samples using the methods for these analytes in the Abbott Architect c8000 Autoanalyzer (Abbott Diagnostics, Chicago). Our protocol was approved by the Local Ethics Committee, and the procedures followed were in accordance with the requirements of the Helsinki Declaration of 1975.

For the evaluation of the renal tubular defect, fractional excretion of UA (FEUA), potassium, calcium, magnesium, and phosphorus were calculated using the formula:

$$FEx = (Ux)(SCreat)/(Sx)(UCreat)$$

where x = analyte (UA, potassium [K], calcium [Ca], magnesium [Mg], or phosphorous [P]); U, urine concentration; S, serum concentration; Creat, creatinine. FEUA >10% was considered to be pathological uricosuria. Values greater than 6%, 3%, 4%, and 20% were considered to be increased for FEK, FECa, FEMg, and FEP, respectively.[11]

Continuous variables are expressed as the mean ± standard deviation (SD), while categorical variables are displayed as frequencies. Statistical analyses included bivariate correlation using Deming linear regression, univariate and multivariate linear regression, and Student *t*-test. A *P* value <0.05 was considered statistically significant.

Results

The demographic characteristics of our study population are shown in **Table 1**. Among our 18,330 patients, 55% were female and 45% were male. The mean age of patients was 35 y (range: 16 to 87 y). The mean serum UA level was 4.91 ± 1.86 mg/dL, UA values were distributed as shown in **Figure 1**, and 94 patients (study group) had UA values <2 mg/dL. The ratio of hypouricemia was 0.51% (94/18,330). Most of the hypouricemic patients were female (n = 64; 68%).

Table 1_Characteristics of Patients Enrolled in Control and Case Groups

Characteristic	Men Control Group (n = 30)	Men Case Group (n = 64)	Women Control Group (n = 30)	Women Case Group (n = 64)
Age, y	49 ± 14	49 ± 18	38 ± 16	37 ± 16
Serum (UA), mg/dL	5.26 ± 1.13	1.83 ± 0.21*	4.41 ± 1.07	1.85 ± 0.34*
FEUA, %	7.7 ± 1.91	9.93 ± 2.56*	8.75 ± 2.71	11.64 ± 4.30*

*P<0.05 versus control group subjects; UA, uric acid concentration; FEUA, fractional excretion of uric acid.

Diagnoses of patients are taken from the clinical records of our hospital. The most frequent initial diagnoses in our hypouricemic patients were osteoarthritis (n = 33; 35%), diabetes mellitus (n = 15; 16%), and hypertension (n = 14; 15%) (**Table 2**). The frequent initial diagnoses in normouricemic patients were as follows: dermatologic lesions (n = 35; 37%), preoperative control (n = 22; 21%), hypertension (n = 10, 11%), diabetes mellitus (n = 10, 11%), thyroid illness (n = 11, 10%), and other (n = 9, 8%). In addition, hypouricemia was accompanied by uricosuria, phosphaturia, kaliuria, calciuria, and magnesuria in 70 (75%), 12 (11%), 12 (11%), 5 (5%), and 4 (4%) patients, respectively. Nonsteroidal anti-inflammatory and anti-hypertensive agents were the most frequently used uricosuric drugs (**Table 3**). Some of the normouricemic patients (n = 25) were on antibiotics (n = 10, 11%), angiotensin-converting enzyme inhibitors (n = 11, 10%), or metformin (n = 4, 4%) medication. Most of the normouricemic patients (n = 69) had no drug history.

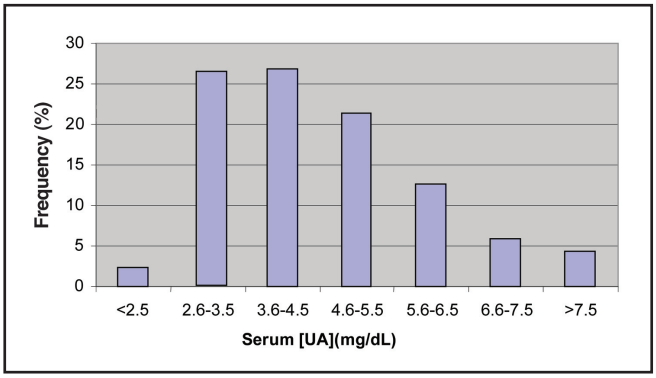

Figure 1_Distribution of serum uric acid (UA) values.

Table 2_Initial Diagnoses in Outpatients (n = 94) with Hypouricemia

Diagnosis	n (%)
Osteoarthritic pain	33 (35)
Diabetes mellitus	15 (16)
Hypertension (HTN)	14 (15)
Hyperlipidemia	7 (8)
Hyper- or hypothyroidism	5 (5)
HTN + hyperlipidemeia	6 (6)
Solid neoplasm	4 (4)
Dermatologic lesions	3 (4)
Other	7 (7)
Total	94 (100)

Table 3_Therapeutic Drugs Used by Outpatients (n = 94) With Hypouricemia

Drug(s)	n (%)
Fenopropen	19 (20)
Losartan	10 (11)
Fenofibrate	6 (7)
Losartan + fenofibrate	6 (7)
Phenylbutazone	6 (7)
Salicylates	5 (5)
Allopurinol	1 (1)
Chlorprothiexene	1 (1)
None	1 (41)
Total	55 (100)

By using univariate analysis, serum UA levels were found to be associated with age, gender, diet, tea (but not coffee) consumption, therapeutic drugs (ie, those listed in **Table 3**), and FEUA. On multivariate analysis, serum UA levels were significantly associated with tea consumption, therapeutic drugs, and FEUA.

Discussion

The ratio of hypouricemia among our outpatient population was 0.51%, and the most common cause of hypouricemia in this population was the use of uricosuric drugs. Therapeutic drugs such as acetohexamide, allopurinol, azathioprine, bishydroxicoumarin, clofibrate, contrast media, fenofibrate, fenoprofen, guaifenesin, halogenate, losartan, phenylbutazone, probenicid, salicylates, and tienilic acid interfere with the renal tubular UA transport and lower serum UA levels.[4] Hypouricemic side effect of antihypertensives should be used as uricosuric since hypertension and hyperuricemia are well-defined risk factors of coronary heart disease.[12]

The most frequently used therapeutic drugs (**Table 3**) in our hypouricemic patients were fenoprophen, losartan, and fenofibrate, consistent with the literature. Hypouricemia associated with the use of these drugs has been reported to normalize in 15 days after cessation of their use.[12] In our study, remeasurement of serum UA levels was planned, but none of the patients came back.

Hypouricemia has been regarded frequently as an insignificant clinical finding; however, hypouricemia associated with increased oxidative stress has been reported to trigger acute renal failure in patients with nephrolithiasis after heavy exercise.[12] Additionally, pathological uricosuria can lead to hypouricemia and uric acid nephrolithiasis. Therefore, it has been recommended that hypouricemic patients should be evaluated for uricosuria and uric acid nephrolithiasis.[5] Increased fluid intake and alkalization of the urine can prevent supersaturation of urine with uric acid in managing uric acid stones.[13]

The ratio difference between inpatients and outpatients should be the subject of a new study. Bairaktari and colleagues reported the ratio of hypouricemia to be 1.24% in hospitalized patients.[10] The higher ratio of hypouricemia in inpatients

versus outpatients may be due to a decrease in renal blood flow, difficulties in nutrition, or inadequate fluid intake in hospitalized patients.

In conclusion, FEUA, various therapeutic uricosuric drugs, and tea consumption were consistently associated with hypouricemia. Hypouricemia occurs relatively infrequently among outpatients; however, when it does occur, it is frequently caused by inappropriate uricosuria. New studies comparing hypouricemia in outpatients and hospitalized patients may shed light into the importance of hypouricemia. LM

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