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Uric acid excretion in healthy subjects: a nomogram to assess the mechanisms underlying purine metabolic disorders

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ABSTRACT

The reference range for urinary uric acid excretion has not been precisely defined. Different urinary variables have been proposed to determine the renal contribution to increased or decreased serum urate concentrations. We examined which urinary variable best indicates uric acid excretion over a wide range of serum urate concentrations. Purine metabolism was studied in 10 healthy male subjects (aged 26-58 years) both at their endogenous normal serum urate levels (normouricemic state) and after the oral administration of allopurinol (300 mg/24 h for 5 days) and ribonucleic acid (4 g/8 h for 4 days) to decrease (hypouricemic state) and increase (hyperuricemic state) serum urate concentrations, respectively. The results from patients with several conditions known to affect uric acid synthesis and/or the renal excretion of uric acid were used to validate a constructed nomogram. Over a wide range of mean serum urate levels (from 2.7 to 9.5 mg/dL) and mean 24-hour urinary uric acid excretion (171 to 1368 mg/[24 h 1.73 m^2]), the highest correlation coefficient between serum urate and uric acid excretion was obtained for the 24-hour uric acid determination ($r = 0.928$; $P < .001$). The constructed nomogram allowed the definition of the mechanism underlying hyperuricemia and hypouricemia in patients with a myriad of diseases known to affect purine metabolism. The urinary variable that best correlates with a wide range of serum urate concentrations is 24-hour urinary uric acid excretion. The constructed nomogram allows the identification of the kidney contribution to a given purine metabolic abnormality.

1. Introduction

The reference range for urinary uric acid excretion in male adults has not been precisely defined. The renal excretion of uric acid is a complex process influenced by multiple variables and mediated by several ion transporters [1]. In clinical practice, quantification of uric acid excretion is routinely determined to ascertain whether the kidneys contribute to the purine metabolic disturbance in patients with increased or diminished serum urate levels [2]. Several different variables [3-7] have been proposed to

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be in use in determining this information, although precise normal limits have not been established: uric acid excretion in urine over 24 hours, clearance of uric acid, fractional excretion of uric acid, uric acid to creatinine ratio in spot urine, and uric acid excretion per unit of glomerular filtration rate (Simkin index [4]). Most commonly, uric acid excretion in patients with gout has been reported in 24-hour urine, and the results have been compared with those obtained from control subjects with normal serum urate concentrations [1,8-10]. On the basis of this comparison, and because most patients with gout have a mean uric acid excretion rate similar to healthy subjects but at significantly increased serum urate levels, it has been concluded that hyperuricemia in gout is mainly due to inefficient uric excretion [8-10]. To our knowledge, no study has addressed the validity of the different proposed variables to assess normal urinary uric acid excretion. In addition, we are not aware of any previously published nomogram that relates serum urate concentrations to uric acid excretion in healthy subjects for different urate filtered loads. In this study, we assessed which urinary variable best indicates uric acid excretion at different urate filtered loads. We validated the constructed nomogram using data from patients diagnosed with various conditions known to affect the synthesis and/or the renal excretion of uric acid and manifested by hyperuricemia or hypouricemia.

2. Subjects and methods

All studies were conducted according to local regulations and the Declaration of Helsinki and were approved by the Institutional Research and Ethics Review Committees of La Paz University Hospital. Control subjects and patients signed a written informed consent form. Ten healthy male subjects were selected among the medical personnel (4), residents (3), and subjects referred to the vascular risk unit for evaluation of cardiovascular risk (3). All subjects proved to be healthy with no risk factors other than age (1 subject, 58 years). The medical histories of these control subjects were unremarkable, and physical examinations and routine laboratory test results were within normal limits. Control subjects were taking no medications.

Patients with different conditions associated with hyperuricemia and hypouricemia were classified into 1 of these 4 categories: (*a*) increased synthesis of uric acid, manifested by hyperuricemia and increased uric acid excretion (eg, patients with phosphoribosylpyrophosphate synthetase [PRPPs] overactivity [Online Mendelian Inheritance in Man {OMIM}, 300661] [11,12] and Lesch-Nyhan disease [OMIM, 300322] or its variants [OMIM, 300323] due to complete and partial hypoxanthine phosphoribosyltransferase [HPRT] deficiency, respectively [13-15]); (*b*) diminished uric acid synthesis, manifested by hypouricemia and reduced uric acid excretion (eg, patients with hereditary xanthinuria [OMIM, 278300] [16]); (*c*) increased uric acid excretion, manifested by hypouricemia and enhanced urinary uric acid output (eg, patients with renal hypouricemia [17] or medullary thyroid carcinoma [18]); or (*d*) diminished uric acid excretion, manifested by hyperuricemia with decreased uric acid excretion (eg, men and women with primary gout [19,20]) or uromodulin-associated kidney disease [OMIM, 162000] [21,22]). Patients and families with genetic and acquired diseases of purine metabolism have been referred to the Metabolic and Vascular Unit at La Paz University Hospital for diagnosis or genetic counseling since 1985 [13].

2.1. Procedures

To assess the normal excretion of uric acid, healthy subjects were studied under 3 conditions: (*a*) at their baseline serum urate levels; (*b*) at diminished serum urate concentrations following the administration of allopurinol (300 mg/24 h, for 5 days); and (*c*) at increased serum urate levels after the intake of ribonucleic acid (RNA) monosodium salt (Sigma-Aldrich, St Louis, MO, USA) at a dose of 4 g/8 h for 4 days [23,24]. This protocol provided 3 different urate filtered loads, allowing us to examine the renal excretion of uric acid under 3 conditions: normouricemia, hypouricemia, and hyperuricemia. We previously reported the normal tubular components involved in the renal excretion of uric acid for different urate filtered loads in these control subjects [25]. All subjects received careful instructions from a specialized nurse to follow a weight-maintenance, isocaloric, purine-restricted diet (<75 mg/24 h of purines, with a protein content of 10%-15% [26]) for 5 days before and during the collection of two 24-hour urine samples separated by 1 week. Five days is the time length required for urinary uric acid excretion to reach a nadir [27]. Thus, two 24-hour urine samples were collected while the subjects had normal, reduced, and increased serum urate levels. The variability in the levels of 24-hour urinary creatinine with this protocol has been shown to be 9% [19]. Among the 3 different serum urate states, a period of 7 days on a self-selected diet was allowed. Twenty-four–hour urine samples were collected into a 2-L container with 3 mL of toluene as a preservative. Urine samples were kept at room temperature until they were brought to the hospital. Following overnight fast and rest, venous blood was obtained between 7:00 AM and 10:00 AM at the end of both the first and second 24-hour urine collection. Because the study was performed on an ambulatory basis, the following 3 procedures were performed to ascertain that subjects would strictly follow the protocol: (*a*) baseline weight was measured to determine if subjects would lose more than 1 kg during the 5-day periods on the purine-free diet; (*b*) careful oral and written instructions were given, including a menu to follow strictly each day during the purine-free diet; and (*c*) careful oral and written instructions were given for 24-hour urine collection, during which each subject performed his usual activities but avoided strenuous physical exertion. On the day of the study, subjects were questioned about the way they collected 24-hour urine: "How did you collect your urine from yesterday to today?" Subjects who did not collect urine appropriately were scheduled for a second visit on the next day and instructed to continue following the same purine-free diet. None of the subjects had lost more than 1 kg at the end of the purine-free diet period.

2.2. Assays and calculations

Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. All laboratory analyses were done in a "blinded" manner. Uric acid and creatinine in serum and urine were determined in a multichannel autoanalyzer (Hitachi 737; Hitachi, Tokyo, Japan) by

means of the enzyme uricase and the Jaffe method, respectively. Standard formulas were used to calculate the clearance of creatinine (Ccr) and uric acid (Cur). Uric acid excretion in 24 hours was determined by multiplying urinary uric acid concentration (milligrams per deciliter) by the urine volume (deciliters) obtained in 24 hours. The laboratory technician was instructed to homogenize the 24-hour urine samples to not miss crystalline uric acid that may have precipitated at the bottom of the jug [2]. The urate filtered load was determined by multiplying serum urate by the creatinine clearance. The fractional excretion of uric acid was calculated by dividing Cur by Ccr and expressing the result as a percentage. The Simkin index [4] was calculated as the product of urinary uric acid and serum creatinine concentrations divided by the urinary creatinine concentration. This yields the excretion of uric acid per unit of glomerular filtration rate. All urinary uric acid excretion variables were standardized for body surface area.

2.3. *Data analysis*

Data were analyzed with the SPSS (Chicago IL) 11.0 statistics package. Descriptive results are expressed as the means ± SD, and appropriate 95% confidence intervals (CIs) are indicated. Comparison of quantitative variables between healthy subjects and gout patients was made by means of the Student *t* test for parametric distributions (Kolmogorov-Smirnov test). We calculated the correlation between serum urate levels and each of the 5 different variables proposed to assess uric acid excretion with the correlation coefficient of repeatability (module R 2.0.1) [28] with a bilateral approach, a precision of 95%, and a statistical power of 95%. The highest correlation coefficient indicates the uric acid excretion variable that best correlates with different serum urate concentrations.

3. Results

The mean age of the 10 control subjects was 33 years (with an SD of 10 years and a range from 26 to 58 years; median age, 34 years). Their mean weight was 65.6 kg, and their (mean ± SD) body mass index was 22.6 ± 2.3 kg/m^2 (range, 20.1-26.2 kg/m^2; median, 23.0 kg/m^2). The median urate filtered load (serum urate multiplied by the glomerular filtration rate determined by the creatinine clearance) was 6.29 mg/(min 1.73m^2) (Table 1). This was accompanied by a mean 24-hour urinary uric acid excretion of 520 mg/(24 h 1.73m^2). The administration of allopurinol markedly decreased serum urate levels to a mean of 2.7 mg/dL. The corresponding mean 24-hour urinary uric acid excretion was simultaneously reduced to 171 mg/(24 h 1.73m^2). In contrast, the administration of RNA markedly increased serum urate concentrations to a mean of 9.5 mg/dL. The urate filtered load was also increased significantly to 11.84 mg/(min 1.73m^2) with a corresponding increase in the mean 24-hour urinary uric acid excretion to 1368 mg/(24 h 1.73m^2). The uric acid to creatinine ratio and the uric acid excretion per unit of glomerular filtration rate (Simkin index [4]) were also markedly influenced by variations in serum urate concentrations (Table 1) because both uric acid excretion variables are only and directly dependent on urinary uric acid levels when the glomerular filtration rate is stable. However, in the hypouricemic state, the clearance of uric acid and the fractional excretion of uric acid were similar to those observed in the normouricemic state, although both variables markedly increased in the hyperuricemic state. The highest bilateral correlation coefficients between serum urate levels and the 5 proposed variables to assess urinary uric acid excretion were for 24-hour urinary uric acid excretion, uric acid to creatinine ratio, and uric acid excretion per unit of glomerular filtration rate ($r > 0.920$ and $P < .001$ for all 3 variables). The correlation coefficient was also highly significant for the other 2 uric acid excretion variables (clearance of urate and fractional excretion of urate). The best bilateral correlation coefficient among the 5 uric acid excretion variables was between serum urate concentrations and 24-hour urinary uric acid excretion ($r = 0.928$; $P < .001$). These data enabled us to draw a nomogram (Fig. 1) with 95% confidence limits to assess the relationship between a given serum urate and 24-hour urinary uric acid excretion.

Table 1 – Uric acid excretion in 10 healthy subjects at different serum urate levels

	Hypouricemia	Normouricemia	Hyperuricemia	*r* [a]
Serum urate (mg/dL)	2.7 ± 0.4 [*] (2.5-2.8)	5.1 ± 0.5 (4.9-5.3)	9.5 ± 1.6 [*] (8.8-10.3)	
Ccr (mL/[min 1.73 m^2])	127 ± 19 (118-135)	130 ± 24 (120-142)	126 ± 18 (118-134)	
Urate filtered load (mg/[min 1.73 m^2])	3.14 [*] (2.87-3.74)	6.29 (5.83-7.16)	11.84 [*] (10.43-12.73)	
Uric acid excretion:24-h urine (mg/[24 h 1.73m^2])	171 ± 64 [*] (142-201)	520 ± 79 (465-539)	1368 ± 479 [*] (1143-1592)	0.928 ($P < .001$)
Uric acid/creatinine ratio (mg/mg)	0.19 ± 0.06 [*] (0.16-0.21)	0.35 ± 0.10 (0.31-0.40)	1.04 ± 0.19 [*] (0.83-1.24)	0.926 ($P < .001$)
Cur (mL/[min 1.73 m^2])	8.9 ± 2.1 (7.9-9.9)	9.3 ± 2.3 (8.4-10.2)	14.4 ± 4.3 [*] (12.4-16.4)	0.504 ($P < .001$)
Fractional excretion of uric acid (%)	0.07 ± 0.02 (0.06-0.08)	0.07 ± 0.02 (0.06-0.08)	0.12 ± 0.04 [*] (0.10-0.14)	0.516 ($P < .001$)
Uric acid excretion/unit GFR (mg/[dL 1.73m^2])	0.19 ± 0.06 [*] (0.16-0.21)	0.35 ± 0.10 [*] (0.31-0.40)	1.04 ± 0.44 [*] (0.83-1.25)	0.925 ($P < .001$)

Control subjects were studied at their baseline serum urate level (normouricemia) following the administration of allopurinol (300 mg/24 h for 5 days) to reduce serum urate concentrations (hypouricemia) and after the intake of RNA monosodium salt (4 g/8 h for 4 days) to increase serum urate levels (hyperuricemia). Data are presented as the mean ± SD and 95% CIs, with the exception of the urate filtered load that is given as the median and interquartile range. Urate filtered load is the serum urate concentration multiplied by the creatinine clearance. To convert values to SI units, multiply serum urate by 59.

[a] Correlation coefficient obtained by the repeatability formula [26].

[*] $P < .05$ compared with the normouricemic state.

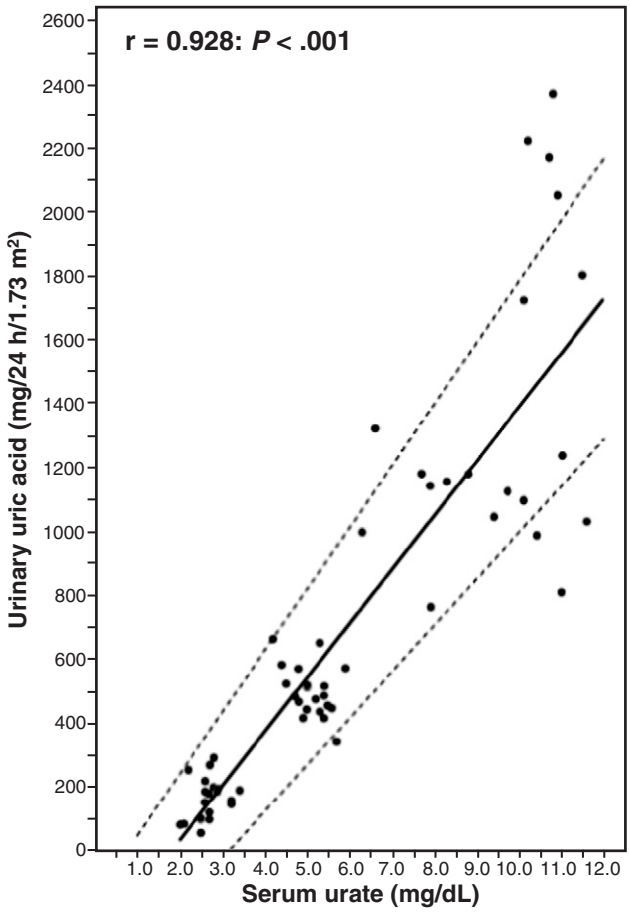

Fig. 1 – Nomogram that relates serum urate concentrations and 24-hour urinary uric acid excretion in healthy subjects at 3 serum urate levels: normouricemia, hypouricemia, and hyperuricemia. The solid line indicates the correlation equation (y = 169 × –296); and the broken lines, the 95% CIs (upper broken line, y = 193 × –468; lower broken line, y = 145 × –450).

3.1. *Validation of the nomogram*

To determine whether the relationship between serum urate levels and 24-hour urinary uric acid excretion would be useful to assess the mechanisms underlying hyperuricemic and hypouricemic states, we plotted into the nomogram data from patients with different conditions associated with a disrupted purine metabolism. Specifically, we examined patients with different diseases that compromise the synthesis of uric acid or the renal urinary uric acid excretion (Fig. 2). All these patients have been studied at La Paz University Hospital since 1985 [13]; and all followed the same protocol as that indicated for the healthy subjects, but at their endogenous serum urate levels. Medications known to interfere with uric acid metabolism (eg, allopurinol) were withheld for at least 7 days before 24-hour urine collection. Patients with diseases known to increase uric acid synthesis, such as PRPPs overactivity (OMIM, 300661) [11,12] or Lesch-Nyhan disease (OMIM, 300322) and its variants (OMIM, 300323) due to complete and partial HPRT deficiency [13-15], respectively, had a 24-hour uric acid excretion rate within or above the reference range (Fig. 2). Since 1985, we have diagnosed 40 patients with HPRT deficiency but could only plot into the nomogram data from 4 Lesch-Nyhan patients and 1 Lesch-Nyhan variant (partial HPRT deficiency) [13] because most children were unable to provide 24-hour urine [15]. Three additional patients with Lesch-Nyhan disease aged 5, 6, and 28 years old had serum urate concentrations of 6.9, 7.3, and 15.2 mg/dL, respectively [14]. The corresponding figures for their 24-hour uric acid excretions were 2812, 2783, and 2169 mg/(24 h 1.73m^2),

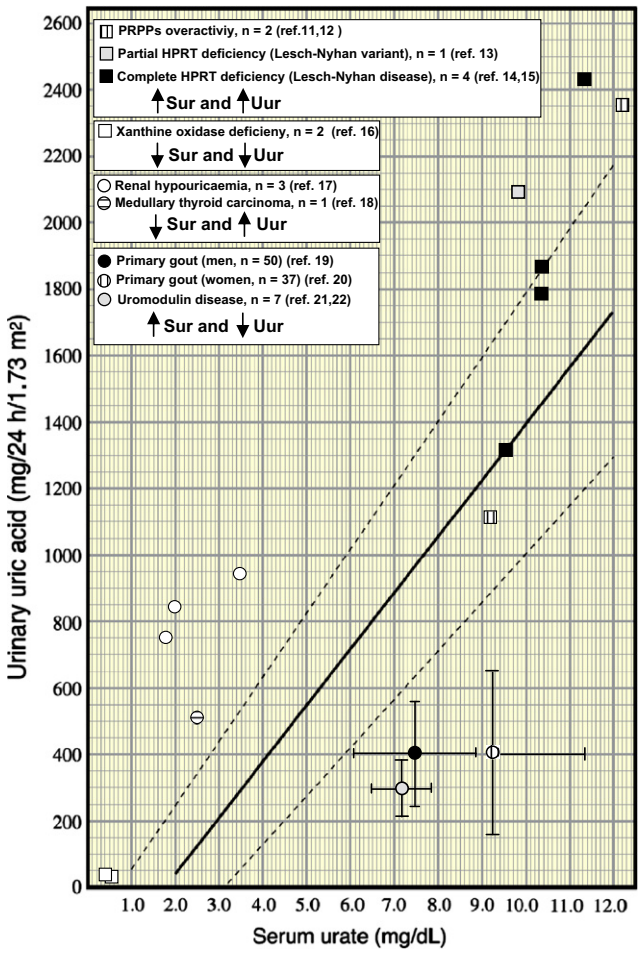

Fig. 2 – Twenty-four–hour urinary uric acid excretion as a function of serum urate concentrations in patients with different disorders of uric acid metabolism. Data were plotted into the nomogram developed for control subjects at their normal, reduced, and increased serum urate levels. Data were obtained from patients studied at La Paz University Hospital since 1985 (ref 11-22). Patients were studied while on a purine-free diet to ascertain whether their hyperuricemia or hypouricemia was due to an increased or reduced uric acid synthesis, respectively, or to a diminished or increased renal excretion of uric acid, respectively. Each symbol represents 1 patient. The bars indicate the standard deviation from the mean in patients with primary gout (men and women) and uromodulin disease. Sur indicates serum urate; Uur, urinary uric acid.

respectively [14]. These patients could not be represented in the nomogram because their urinary uric acid values were markedly higher than those obtained from healthy subjects with increased serum urate levels.

Two patients with xanthine oxidase deficiency (OMIM, 278300) [16], which is known to prevent uric acid synthesis, had a serum urate concentrations of 0.4 and 0.6 mg/dL and 24-hour uric acid excretion rates of 3 and 5 mg/(24 h 1.73m^2), respectively. The data from these patients fall at the extreme bottom left of the nomogram (Fig. 2).

Increased or reduced serum urate concentrations may also be due to a disturbance in the renal handling of urate. Three patients with renal hypouricemia [17] and one with medullary carcinoma of the thyroid [18] are represented (Fig. 2). The daily urinary uric acid excretion in these 3 patients was 850, 765, and 952 mg/(24 h 1.73m^2) [17]. The patient with medullary carcinoma of the thyroid had a serum urate level of 2.5 mg/dL and a urinary uric acid excretion of 510 mg/(24 h 1.73m^2) [18] that was attributed to the uricosuric effect of her increased calcitonin secretion [18].

Extensive series of men (n = 50) [19] and women (n = 37) [20] with primary gout are also represented in the nomogram (Fig. 2). The mean relationships between serum urate and 24-hour urinary uric acid excretion in both series lie in the lower right corner of the nomogram. This indicates an increased serum urate level due to a reduction in 24-hour urinary uric acid excretion. This relationship was most pronounced in patients with uromodulin-associated kidney disease (OMIM, 162000) [21,22] (Fig. 2); a mean serum urate concentration of 7.2 mg/dL was accompanied by a mean 24-hour urinary uric acid excretion of only 294 mg/(24 h 1.73 m^2) [21].

4. Discussion

This study aimed to assess the normal limits for uric acid excretion in control subjects over a wide range of serum urate concentrations. The results show that among the 5 urinary variables proposed to determine uric acid excretion in adult healthy subjects [2-7], the best bilateral correlation coefficient over a wide range of serum urate concentrations was obtained for the 24-hour urinary uric acid excretion. The nomogram drawn, with its 95% confidence limits (Fig. 1), relating serum urate levels to 24-hour urinary uric acid excretion, proved to be very useful to differentiate the mechanisms underlying a myriad of diseases manifested by an increased or decreased serum urate concentration or 24-hour uric acid excretion (Fig. 2).

Normal urinary uric acid excretion in adults has not been precisely defined. Age [29], sex [30], circadian rhythm [19,31], dietary purine intake [32,33], urinary collection [2], and technical concerns [2,34] are among the factors that may have prevented wide acceptance of a variable indicative of normal urinary uric acid excretion. Thus, wide-ranging uric acid excretion rates (from 600 mg/24 h [8] to 1139 mg/24 h [4]) have been considered "normal." In addition, to our knowledge, no study has ascertained the reference range for uric acid excretion at increased serum urate concentrations, as those observed in gout patients, although it is well known that uric acid excretion is markedly dependent on the urate filtered load (the product of serum urate concentration and the glomerular filtration rate). In fact, no study has compared the renal excretion of uric acid in gout patients and healthy subjects at pharmacologically increased serum urate concentrations. Demonstration that patients with gout show significantly diminished urinary uric acid excretion compared with healthy subjects at similarly increased urate filtered loads would provide an additional direct evidence for a disruption in the tubular handling of uric acid in these patients. This study provides the first direct evidence to establish that male and female gout patients have an inefficient uric acid excretion rate, which may explain their increased serum urate levels (Fig. 2). This finding is consistent with the knowledge that, in more than 90% of the patients with primary gout, a diminished urinary uric acid excretion is thought to be responsible for their increased serum urate concentrations [3,8,10,14,19,20,35,36]. The constructed nomogram may be useful for any individual patient with gout in whom assessment of the mechanism underlying an increased serum urate level is considered part of the clinical workup. In addition, the constructed nomogram allowed the precise classification of a myriad of patients with a disturbance of purine metabolism. Patients with increased uric acid synthesis due to overproduction (eg, PRPPs overactivity [11,12] or Lesch-Nyhan disease [14,15] and its variants [13]) or decreased uric acid synthesis due to the lack of conversion of hypoxanthine and xanthine into uric acid (eg, xanthine oxidase deficiency [16]), as well as patients with increased uric acid excretion due to overexcretion (eg, in the case of renal hypouricemia [17] or medullary thyroid carcinoma [18]) or decreased uric acid excretion due to underexcretion (eg, in the case of primary gout [19,20] or uromodulin-associated kidney disease [21,22]), were clearly separated from the healthy subjects' limits (Fig. 2).

Given that a significant correlation was documented between the 5 different uric acid excretion variables proposed [2-7] and a wide range of serum urate concentrations (Table 1), which variable should be chosen to assess normal uric acid excretion? The answer to this question is debatable because convenience may be one of the considered factors. The best correlation found in this study was between serum urate and 24-hour urinary uric acid excretion corrected for body surface area. This correction should always be performed because uric acid excretion correlates with body surface area in males and females [30]. Moreover, absolute uric acid excretion in children increases with age but decreases when it is normalized by 1.73 m^2 body surface area [37]. In addition to mistimed and/or incomplete collection, several arguments have been raised against 24-hour urine collection. For instance, it has been argued that 24-hour urine data do not correlate well with themselves in routine clinical practice [2]. However, when a careful protocol is pursued and subjects are motivated to strictly follow a purine-free diet, only very minor differences in 24-hour urine volume and creatinine and urate excretion rates have been found [19,30]. Given the normal variability of 26% [38] for 24-hour creatinine excretion, our finding of only 9% variability exemplifies the precision of the obtained data [19]. Other proposed methods of assessing uric acid excretion, such as the Simkin index [4,39], have the disadvantage that they do not take into account diurnal variations in uric acid excretion

[40]. This is problematic because the uric acid in a 2-hour sample collected during a usual working day has a poor correlation with uric acid excreted over a 24-hour period [5]. The significant and similar correlation found in this study between serum urate levels and 3 of 5 variables indicative of urinary uric acid excretion (24-hour uric acid [milligram per 24 hours per 1.73 m^2], the Simkin index [milligram per deciliter], and the uric acid to creatinine ratio [milligram per milligram]) may be due to the fact that the same urine sample was chosen to calculate these 3 variables and thus rendered similar results.

The proposed nomogram relating serum urate concentrations to 24-hour urinary uric acid excretion (Fig. 1) has a number of limitations. Firstly, our study was carried out in adult white men with normal renal function under precise experimental conditions and thus may not be useful for subjects belonging to other races or patients with renal insufficiency who are known to have an increased uric acid excretion rate per nephron. Secondly, validation of the nomogram included an ample variety of diseases that affect purine metabolism; but we did not plot patients with other genetic diseases such as purine nucleoside phosphorylase deficiency (OMIM, 613179); glycogenosis type II (OMIM, 232300), V (OMIM, 232600), and VII (OMIM, 232800); or conditions associated with a disruption in purine homeostasis (eg, drugs or metabolic syndrome). However, the constructed nomogram allowed the definition of the mechanism underlying the purine metabolic disorder in 9 genetic and acquired diseases. Creatinine in serum and urine was determined by the Jaffe reaction that detects noncreatinine chromogens. This analytical method was used to develop the initial Modification of Diet in Renal Disease equation [41]. Reasonably good comparisons have been obtained between carefully calibrated enzymatic and Jaffe creatinine methods [42], but both methods have limitations. Care should be taken with the Jaffe method for samples from neonates or containing unusual protein concentrations or cephalosporins. In contrast, dopamine and dobutamine interferences have been reported for enzymatic creatinine assays based on the generation of hydrogen peroxide [42]. Thus, both methods do not show complete specificity for creatinine.

In summary, 24-hour urinary uric acid excretion showed the best bilateral correlation over a wide range of serum urate concentrations and enabled us to construct a nomogram with 95% confidence limits. This nomogram proved to be very useful to define the mechanisms (increased or decreased uric acid synthesis and increased or decreased uric acid excretion) involved in a myriad of patients with diseases known to affect purine metabolism and expressed by an increased or decreased serum urate concentration and/or urinary uric acid excretion. This nomogram may be useful for the clinician willing to assess the underlying disturbance in purine metabolism in patients with primary gout [43] and other primary and secondary conditions usually reflected by an abnormal serum urate concentration [44].

Significant associations between single nucleotide polymorphism in both *URAT1* and *SCL2A9* (also known as *GLUT9*) genes, serum uric acid levels, and the diagnosis of gout have been reported [45,46]. Since then, other several loci with significant associations to serum uric acid levels have been found, namely, the genes *PDZK1*, *GGKR*, *LRRC16A*, *SLC16A9*, *SLC22A11*, *ABCG2*, and *SLC17A1-SLC17A3* [47]. Studies including patients with gout assumed that all included subjects had a uric acid tubular transport defect. In accordance to Indraratna et al [48], we believe that the statistical power of these association studies with different genetic polymorphisms would be increased if 2 well-defined populations of patients with gout are defined: normal uric acid excretors ("overproducers") and patients with impaired uric acid excretion ("underexcretors"). The results of our study may help to classify gout patients according to the presence or absence of a tubular defect, and its identification may ultimately contribute to personalized medicine [49].

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Conflict of Interest

All authors deny potential conflicts of interest.

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