Intermittent elevation of serum urate and 24-hour urinary uric acid excretion

K.-H. Yu, S.-F. Luo, W.-P. Tsai and Y.-Y. Huang

Objectives. Serum urate concentrations fluctuate throughout the day, and may be subject to variation with time. However, monthly variation of urinary uric acid excretion has not been investigated. This prompted us to investigate serum urate and 24-h urinary uric acid excretion in healthy men.

Methods. Serum urate and creatinine and 24-h urinary uric acid and creatinine were measured at monthly intervals throughout a 12-month period in 12 healthy men (aged 23–61 yr) from July 2002 to June 2003.

Results. The mean age of the 12 healthy men was 35.3 ± 10.5 yr (median 33, range 23–61), and they had mean serum urate concentration 7.1 ± 1.1 mg/dl (range 4.6–10.4), mean serum creatinine 1.0 ± 0.1 mg/dl (range 0.8–1.3) and mean 24-h urinary uric acid excretion 651 ± 189 mg/day/1.73 m² (median 623, range 389–1565). Approximately 20.1 and 20.7% of the measurements displayed above normal serum urate level and daily urinary uric acid excretion of more than 800 mg, respectively.

Conclusions. The data presented here demonstrate individual variations in serum urate levels and 24-h urinary uric acid excretions in healthy men with serial measurement. Transient hyperuricaemia and hyperuricosuria are more common than expected, and both transitory and monthly variations are important factors to consider when evaluating the influence of other factors upon serum urate levels and urinary uric acid excretion. Further studies are needed to confirm these results using larger populations.

Key words: Gout, Hyperuricaemia, Urine, Uric acid, Overproducer.

Gout is a disorder of purine metabolism or the renal excretion of uric acid. It is considered to have four phases, characterized by asymptomatic hyperuricaemia, recurrent attacks of acute arthritis, intercritical gout and chronic tophaceous gout. Traditionally, hyperuricaemia and gout are classified as either primary or secondary. A more physiological classification is based on 24-h urinary uric acid excretion [1, 2]. Daily uric acid excretion of more than 600 mg, which represents uric acid excretion more than two standard deviations above the mean value for a normal male population, after 5–7 days of dietary purine restriction is considered overproduction [3]. However, it is impracticable to have patients on a purine-free diet for 5–7 days before collecting the 24-h urine sample, and in any case a purine-free diet is unlikely to represent the typical lifestyle of the patient. Thus, it is replaced by self-selected diet, under which the recommended reference value of an overproducer ranges between 700 and 1000 mg/day [1, 2, 4–12]. Twenty-four-hour urinary uric acid excretion is important in selecting urate-lowering agents and differentiating the cause of hyperuricaemia in the initial evaluation of gout and hyperuricaemia. Spot urine uric acid testing is not an accurate indicator of uric acid overproduction and is more subject to circadian rhythm variation [11, 13–15]. Furthermore, the content of the diet may have changed during the past 40 yr and might influence serum urate level and daily urinary uric acid excretion. The above factors prompted this preliminary study of monthly serum urate levels and daily urinary uric acid excretion in healthy men.

Materials and methods

Serum urate and 24-h urinary uric acid were measured at monthly intervals throughout a 12-month period in 12 healthy men (aged 23–61 yr) from July 2002 to June 2003. All subjects gave their informed consent. Twenty-four-hour urine was collected while the subjects were on self-selected diets. Dietary intake was not regulated, except for total abstinence from alcoholic beverages 1 week before urine collection. None of the subjects took medication or other substances known to influence uric acid metabolism. Moreover, no subject had a known history of lead exposure, and none had a family history of gout. Samples of venous blood were taken following overnight fasting on the morning of completing urine collection. Twenty-four-hour urinary uric acid and creatinine were measured concurrently on the day of blood sampling. The 24-h urine creatinine content then was calculated. For men, if the 24-h urine creatinine was below 20 mg/kg body weight, the collection was considered incomplete and was excluded from further analysis. Three consecutive monthly 24-h urine samples nitrogen were measured to assess daily protein intake [16]. The protein intake was calculated from the formula 6.25 × (N_u + 2), where N_u is 24-h urinary nitrogen output in grams.

Uric acid and creatinine concentrations of both serum and 24-h urine were measured using a Hitachi 7470 autoanalyser (Hitachi, Tokyo, Japan) employing the uricase differential spectrophotometric method for uric acid [17] and the Jaffé method for creatinine [18]. The reference range of serum urate is 2.7–8.0 mg/dl, and the
reference range of serum creatinine is 0.4–1.4 mg/dl in this hospital. External quality control was provided by participation in two programmes: the National Quality Control Program conducted by the government and the international program run by the College of American Pathologists. Internal and external quality control procedures yielded consistently satisfactory results. Body mass index (BMI, body weight in kilograms divided by the square of height in metres) was recorded. The 24-h urinary uric acid excretion was corrected for body surface area (mg/day/1.73 m²). All data were expressed as mean ± s.d. and coefficient of variation of serum urate level, and 24-h urinary uric acid excretion was calculated accordingly. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 10.0 for Windows, 1997; SPSS, Chicago, IL, USA).

No ethical approval was required for this study.

Results

Of the 144 samples, four urine samples were excluded from further analysis owing to incomplete collection, demonstrated by low urinary creatinine excretion (<20 mg/kg body weight). The other 140 (97.2%) samples were used for urinary data analysis. The 12 healthy men had mean age 35.3 ± 10.5 yr (median 33, range 23–61), BMI 23.4 ± 2.3 (range 20.0–29.0), serum urate level 7.1 ± 1.1 mg/dl (range 4.6–10.4), serum creatinine level 1.0 ± 0.1 mg/dl (range 0.8–1.3), 24-h urine volume 1664 ± 578 ml (range 700–3490), urinary uric acid 45.4 ± 17.8 mg/dl (range 16–100), urinary creatinine 123.5 ± 53.3 mg/dl (range 50–265), uric acid clearance 6.8 ± 2.1 ml/min (range 3.6–16.9), creatinine clearance rate 124.2 ± 40.5 ml/min (range 78.1–349.0), 24-h urinary uric acid excretion 687 ± 231 mg/day (median 643, range 390–1900), 24-h urinary creatinine excretion 1821 ± 563 mg/day (range 1180–5025), and protein intake 83.5 ± 14.6 g/day (range 50.8–125.0) (Table 1). The 24-h urinary uric acid excretion corrected for body surface area was 651 ± 189 mg/dl/1.73 m² (median 623, range 389–1565). A statistically significant correlation was identified between 24-h urinary uric acid excretion and daily protein intake (Spearman’s correlation coefficient, rₜ = 0.807, P < 0.001). The correlation between 24-h urinary uric acid excretion and serum urate was poor (rₜ = 0.189, P = 0.807).

Table 2 lists the mean, s.d. and coefficient of variation of serum urate level and 24-h urinary uric acid excretion for each subject. The mean serum urate level was 7.1 ± 1.1 mg/dl. The coefficient of variation in urate among the study population ranged from 5 to 12%, with a mean of 9%. In contrast, the coefficient of variation of repetitive determinations of serum urate of known samples throughout the year in our laboratory was 1.8% or less. Mean 24-h urinary uric acid excretion was 687 ± 231 mg. The coefficient of variation of daily urinary uric acid excretion in the study population ranged from 13 to 35%, with a mean of 23%.

Figures 1 and 2 show the monthly levels of serum urate and 24-h urinary uric acid excretion, respectively, of all the subjects. Twenty-nine (20.1%) of the 144 serum urate determinations exceeded 8.0 mg/dl (Fig. 1). Seven of these 12 subjects (58.3%) experienced transient hyperuricaemia at some time during the study period. Twenty-nine (20.7%) of the total 140 urine determinations exceeded 800 mg/day (Fig. 2). All but one of the subjects (91.7%) had daily excretion of uric acid exceeding 800 mg at some time during the study period. Notably, subject G had nine measurements of both hyperuricaemia and daily uric acid excretion exceeding 800 mg, and eight of these measurements exceeded 1000 mg/day. This subject was probably a case of asymptomatic hyperuricaemia. The proportion in this study (1 in 12) is similar to that in the general population. However, even excluding subject G, 15.2% of serum urate and 15.5% of urinary uric acid determinations remained above the upper limit of the reference range. The study contained 29 urinary uric acid excretions exceeding 800 mg daily, with 12 blood determinations (41.4%) simultaneously displaying hyperuricaemia. Ten determinations (7.1%) exceeded 1000 mg/day, eight of which came from subject G, who had the highest BMI. Notably, the sample contained four extreme

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum urate (mg/dl)*</th>
<th>Range (mg/dl)</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.05 ± 0.91</td>
<td>6.6–10.4</td>
<td>0.11</td>
</tr>
<tr>
<td>B</td>
<td>7.64 ± 0.78</td>
<td>5.9–8.6</td>
<td>0.10</td>
</tr>
<tr>
<td>C</td>
<td>7.50 ± 0.57</td>
<td>6.7–8.3</td>
<td>0.08</td>
</tr>
<tr>
<td>D</td>
<td>7.06 ± 0.47</td>
<td>6.4–7.9</td>
<td>0.07</td>
</tr>
<tr>
<td>E</td>
<td>5.54 ± 0.30</td>
<td>4.8–5.9</td>
<td>0.05</td>
</tr>
<tr>
<td>F</td>
<td>6.67 ± 0.54</td>
<td>5.5–7.4</td>
<td>0.08</td>
</tr>
<tr>
<td>G</td>
<td>8.47 ± 0.76</td>
<td>7.6–10.3</td>
<td>0.09</td>
</tr>
<tr>
<td>H</td>
<td>7.42 ± 0.88</td>
<td>6.3–9.3</td>
<td>0.12</td>
</tr>
<tr>
<td>I</td>
<td>5.46 ± 0.56</td>
<td>4.6–6.4</td>
<td>0.10</td>
</tr>
<tr>
<td>J</td>
<td>5.97 ± 0.62</td>
<td>5.1–7.2</td>
<td>0.10</td>
</tr>
<tr>
<td>K</td>
<td>7.62 ± 0.84</td>
<td>6.4–9.1</td>
<td>0.11</td>
</tr>
<tr>
<td>L</td>
<td>7.64 ± 0.54</td>
<td>6.5–8.4</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Mean ± s.d.
CV, coefficient of variation.
values exceeding 1200 mg/day, of which only three had hyperuricaemia, with serum urate of 8.4, 8.4 and 8.9 mg/dl, respectively.

**Discussion**

Significant individual, diurnal and seasonal variations of serum urate have been reported [19, 20]. The coefficient of variation in serum urate among the study population ranged from 5 to 12%, with a mean of 9%. The variation of urinary excretion of uric acid was more notable than that of serum urate. Similar urinary uric acid excretion (639 ± 224 mg/day), in 84 healthy subjects, has been reported from another study in this country [21]. Ricos et al. also found considerable individual variation in urinary uric acid excretion [22]. Transient hyperuricaemia and hyperuricosuria are
more common than was expected. The transient hyperuricaemia and high urinary uric acid excretion appeared to be unrelated to any readily detectable pathological conditions. The major variations seen in the urinary uric acid excretion with time seemed principally due to variations in dietary protein consumption rather than serum urate level. More than half (58.3%) of the subjects experienced transient hyperuricaemia and all but one of the subjects (91.7%) had daily uric acid excretion exceeding 800 mg at some time during the study period. The present investigation is similar to that of Goldstein et al., in which 10 of 12 subjects experienced transient hyperuricaemia at some time during the course of 1 yr; however, Goldstein et al. reported a larger coefficient of variation in serum urate (15–22%, mean 17.5%) and a lower mean serum urate level among the study population [20]. Furthermore, in the Framingham study, a higher percentage of the male population displayed at least one elevated measurement when considering four biennial determinations than when considering just one determination [23].

The diagnosis of gout and its derangement of uric acid metabolism are usually based on the measurement of serum urate and 24-h urinary uric acid excretion. However, the distinction between gouty and non-gouty subjects in terms of serum urate levels and urinary uric acid excretion is not clear. Perez-Ruiz et al. indicated that, although filtering of glomerular uric acid was higher in patients with gout than in normal controls, 24-h uric acid excretion did not differ statistically significantly between these two groups [4]. In the study of Perez-Ruiz et al., the normal male controls had lower serum urate level (5.0 ± 0.85 mg/dl) and excreted 594 ± 143 mg/day/1.73 m², in contrast to 651 ± 189 mg/day/1.73 m² in the male subjects in the present study. In an earlier report from Puig et al. of 10 healthy Spanish male subjects, the 24-h urinary uric acid excretion was 410 ± 83 mg/day/1.73 m² and the serum urate was 5.1 ± 0.8 mg/dl [8]. In Nishida’s report of 62 healthy Japanese male subjects, the 24-h urinary uric acid excretion was 604.8 ± 218.4 mg/day, not corrected for body surface area, and the serum urate was 5.88 ± 1.51 mg/dl [24]. Simkin has demonstrated that gout sufferers excrete an average of 41% less uric acid than normal subjects for any given plasma concentration of urate, and also that the capacity of the excretory mechanism for uric acid is not reduced in cases of gout. However, gouty subjects require urate levels 2–3 mg/dl higher than normal subjects to achieve equivalent uric acid excretion rates [1, 2, 25]. It is difficult to characterize subjects as having normouricosuria or hyperuricosuria, particularly if multiple examinations are performed. It has not been possible to demonstrate the existence of two populations, one normouricaemic and one hyperuricaemic. Neither has it been possible to identify any cut-off point above which clinical complications develop and below which they do not. Consequently, any definition of hyperuricaemia or hyperuricosuria must be considered arbitrary. Despite these problems, previous population studies have clarified the association of hyperuricaemia with gout and its correlates [23, 26].

The mean serum urate in the present study was 7.1 ± 1.1 mg/dl, which is similar to a recent nation-wide population study in Taiwan [27] but is higher than previous data from Taiwan in the 1960s [28]. In this national multistage stratified sampling study [27], the mean serum urate in males aged 4 yr and over was 6.63 ± 1.78 mg/dl, and was 6.90 ± 1.74 for those aged between 23 and 61 yr. An epidemiological study of hyperuricaemia conducted in Taiwan in 1991 [29] found a very similar serum urate distribution curve to that reported in the study of Akizuki [30] in the 1980s and that of Mikkelsen [31] in the 1960s, but found a higher mean serum urate level for men (6.1 ± 5.8 vs 4.9 mg/dl). The mean serum urate level in this study (6.14 ± 1.43) [29] was also higher than those in the studies in Framingham (5.12 ± 1.11) [23], Tecumseh (4.90 ± 1.40) [31] and Taiwan (4.99 ± 0.91) [28] in the 1960s. According to the Normative Aging Study in America, serum urate levels increased steadily from 1961 to 1978, the mean rising from below 5.5 mg/dl in 1961–1963 to above 6.5 mg/dl in 1975–1978 [32]. However, no comparable survey has been conducted in America for more than two decades since that study. Multiple causes exist for the rising serum urate level, and may include Western diet, alcohol consumption, diuretic [33] and environmental factors [21, 34]. However, the increase in serum urate levels cannot be explained simply by a Westernized diet, since the average calorie intake and protein consumption of the population in Taiwan are less than 90% of those in America and many European countries [35]. Chou found that hyperuricaemia was associated with the consumption of organs, such as heart, kidney, liver and tripe [36]. The trend of elevated hyperuricaemia observed in Taiwan may also be occurring in other developed or developing countries, and this issue deserves further study.

Twenty-four-hour urinary uric acid excretion is important in selecting urate-lowering agents and differentiating the cause of hyperuricaemia in the initial evaluation of gout and hyperuricaemia. However, several different reference ranges have been suggested for 24-h urinary uric acid. Under a self-selected diet, the upper limit of 24-h urinary uric acid excretion was defined as over 700 [4], 750 [5], 800 [6, 7] or 1000 mg/day, 800–1000 mg/day being considered borderline [1, 2, 8–11]. Daily urinary uric acid excretion exceeding 800 mg has been the most widely adopted cut-off value in defining overproduction. This preliminary investigation suggests that 24-h urinary uric acid may fluctuate in normal healthy men, and thus a level exceeding 1000 mg appears a more appropriate cut-off value for defining overproduction, since most subjects (11 out of 12) may occasionally excrete more than 800 mg/day of uric acid. Moreover, in our previous studies [37, 38] and the study by Yu [39], between 18 and 22% of gout patients were classified as uric acid overproducers if 800 mg/day was chosen as the cut-off point, contradicting the generally held belief that fewer than 10% of gout patients are overproducers [1, 2, 6, 12]. If 1000 mg/day is used instead, 6.4–8.5% of patients are classified as overproducers. However, the sample size in this study was too small to use in establishing normal limits and further studies aimed at confirming these results in larger populations and different geographical areas are needed.

In summary, the present preliminary study shows intermittent elevations in serum urate levels and 24-h urinary uric acid excretions in healthy men and also demonstrates that transient elevations and monthly variations are important factors to consider in evaluating the influence of other factors on serum urate levels and urinary uric acid excretion.

The authors have declared no conflicts of interest.

References


