Editorial

When, Why, and How Should We Quantify the Excretion Rate of Urinary Uric Acid?

In this issue of *The Journal*, Moriwaki, *et al* conclude that the ratio of urinary uric acid to creatinine was not an effective way to recognize uric acid overexcretors among their patients with gout[1]. Their findings mirror earlier studies from Michigan[2], Spain[3], and Seattle[4] in finding only a weak correlation between spot and 24 hour sample-based approaches to recognize individuals whose uric acid excretion is abnormally high. Thus, the verdict might appear to be in and the spot sample may seem condemned to banishment from clinical practice. To me, this judgment still seems hasty, and the evidence is worthy of a closer examination.

When 24 hour values were first commended to clinical use, subjects were maintained on a purine-free diet for at least a week, and collections were done on 3 successive days. In those early years, studies of selected populations led to the expectation that as many as 35% of gouty subjects might be overexcretors, and such restrictions appeared to be well worthwhile[5].

Over subsequent years, the expectations of significant overexcretion have drifted down to a nadir of less than 1% of gouty patients[5], and the clinical approach towards finding that 1% has become progressively more relaxed. Thus, a single 24 hour collection on a self-selected diet, as obtained by Moriwaki, *et al*, is widely presumed to provide "an accurate indicator of uric acid excretion"[1]. There is little reason to believe that this is true.

Before serving as the standard against which alternative strategies are compared, the 24 hour urine should first be shown to correlate with itself. Pak, *et al* did just that in a recent series of 225 renal stone formers who "successfully completed" a protocol including 2 separate 24 hour urine collections on self-selected diets[6]. The correlation coefficient between the replicate specimens, r = 0.68, was highly significant. When this value is squared, however, it yields a coefficient of determination of 0.46 — a finding indicating that less than half the variation observed in the entire group can be explained by differences between individuals. That variation was substantial. In the second collection, for instance, the mean 24 hour excretion of uric acid was 599 mg/day, but the 95% range (± 2 standard deviations) was 101–1097 mg/day. Thus, the study reveals large variations both within and between the participants. The intraindividual variation is such that any single 24 hour value is only a mediocre predictor of what a repeat collection might show.

The magnitude of these factors was best quantified by Ricos, *et al* who measured uric acid (among other solutes) in each of 10 weekly 24 hour collections from 53 normal volunteers[7]. All samples from each person were stored and analyzed in the same batch to minimize analytic sources of variation. Coefficients of variation were then calculated to determine within-subject (CV_i = 20.3%) and between-subject (CV_g = 22.7%) sources of biological variation. The large individual variation relative to the group variation means that the individuality index (II = CV_i/CV_g = 0.89) is low enough that "comparing a single result from a patient with the population-based reference range" is of limited diagnostic value[8]. This large and sophisticated study strongly suggests that any individual 24 hour collection provides a standard that is much closer to dross than to gold.

WHY EXCRETION RATES VARY

In considering the potential reasons for this observed discordance of replicate observations, mistimed and/or incomplete collections are the obvious first concern. "Twenty-four hour specimens" that are not 24 hour specimens may make up as much as one-third of all collection and these samples, when recognized, should be discarded[9]. The problem lies in the caveat, "when recognized." Creatinine excretion is somewhat more constant (r = 0.93 in the 225 subjects of Pak, *et al*[6]), and concurrent measurement of this solute provides some help in recognizing, and excluding, the most flagrant outlyers. Simply asking the patient about how he or she obtained the specimen is more useful, since most conscientious people will usually own up to their oversight (if they

See: Spot urine uric acid: creatinine ratio in the estimation of uric acid excretion in primary gout, *page 1306*

are asked) and will want to try again. Nevertheless, the possibility of mistiming remains a cloud that casts a shadow of suspicion over every self-timed collection.

A second, less obvious concern about home specimens is that they are often collected in calibrated plastic jugs, protected against bacterial overgrowth by an acid preservative, and stored in the family refrigerator. If the laboratory technician records the volume of the specimen and then pours a sample from the top, he or she will miss all crystalline uric acid at the bottom of the jug. Uric acid crystals are a common finding in routine analyses of acidic urine and their formation will only be enhanced by storage time, by a further lowering of pH, and by the cold[10]. This potential problem is quite obviously of greatest concern in the overexcretor whom we are trying to recognize with this test.

Final technical concerns include the ever present possibility of simple laboratory errors either in handling of the determination itself or in recording and relaying the data. It is also important to be sure that outdated colorimetric methods are not still in use, since such techniques can lead to overestimation of uric acid excretion rates by about 20%[11]. In routine practice, such analytical inconsistencies have been shown to be a major source of error[12].

The data indicate, however, that biological rather than technical factors provide the largest source of day-to-day variations in uric acid excretion. Uncontrolled fluctuations in the intake of dietary purines are the most obvious concern. Clearly, some people routinely eat more than others do, and almost everyone varies from one day to the next in the purine content of their diet. Such changes will necessarily lead to fluctuations in urinary uric acid as those purines are metabolized and excreted[13]. Attempts have been made to allow for this factor by adjustments of the normal upper limit of 24 hour excretion from 600 mg, the level found in purine-restricted studies with replicate determinations, to 700, 800, or 1000 mg per day. These latter levels, however, are usually based more on clinical impressions than on systematic data. I believe that they regularly lead to the mislabeling as "overexcretors" of people who have entirely normal uric acid excretion when testing is repeated.

A less obvious, but perhaps more interesting, dietary consideration involves the effects of specific nutrients on the turnover of adenine nucleotides. At present, this potential source of fluctuating levels of uric acid excretion has been best recognized as a result of alcohol or fructose ingestion, but increased turnover may also occur on a dietary basis in obese individuals for reasons that remain unclear[14-16]. Non-dietary factors may also induce accelerated catabolism, with hypoxia serving, at present, as the best-studied example[17]. Overall, nucleotide breakdown appears to vary in response to a number of factors, many of which may still be unrecognized.

A final, potential source of fluctuating excretion may be found in varied rates of intestinal uricolysis. On the average, about one-third of the normal production of uric acid is metabolized further by uricase-possessing microorganisms within the gastrointestinal tract[18]. This, of course, is the large, individually undetermined variable that has always prevented us from simply equating uric acid excretion with uric acid production. It is known that the fractional intestinal uricolysis increases as uric acid is retained with renal insufficiency and that it varies considerably between individuals. It is not known, however, whether, and why, it might vary significantly from day to day in any one individual. If it does, such changes would be major determinants in the day-to-day variation in uric acid excretion rates.

WHY MEASURE EXCRETION

Having reviewed some of the known reasons for the observed fluctuation in daily excretion, it is appropriate to consider briefly why and when knowledge of excretion rates might be clinically useful. A number of justifications have been given over the years, but not all of them have been convincing to many seasoned clinicians.

One potential reason is to identify those gouty patients at risk of uric acid nephrolithiasis. The strongest evidence supporting this concern is that from the unique, longterm, pre-allopurinol experience of Dr. Ts'ai-Fan Yü in New York City[19]. She found that 22% of 2118 gouty patients gave a history of renal stones, that the prevalence of calculi increased progressively with increasing rates of uric acid excretion, and that uric acid was the chief component of 80% of the retrieved stones. Of note is that the highest risk of stone, 49%, was found in patients excreting more than 1000 mg of uric acid per day on a purine restricted diet. Thus, these relatively few, marked overexcretors carried the highest risk. In contrast, the experience from the stone clinic at the University of Chicago finds that uric acid stones are infrequent (less than 10% of all stones analyzed), that overexcretion of uric acid is extremely rare among those who do form uric acid stones, and that the most apparent etiologic factors are low urine output and a persistently acid urine — variables that are also stressed by Dr. Yü[19,20]. In considering these lines of evidence together, it seems reasonable to reserve concern about stones for those gouty individuals who markedly overexcrete uric acid and/or excrete urine that is highly concentrated and persistently acid.

A second, closely related justification for evaluating the rate of uric acid excretion is to assist in deciding between allopurinol and uricosurics for control of gouty hyperuricemia. Those physicians who invariably use allopurinol won't consider this a very helpful point[21]. Those of us, however, who are more concerned by the occasional, severe allopurinol reaction will consider a normal uric acid excretion rate along with absence of previous stones, lack of an extensive tophaceous burden, relatively normal renal function, and ability to comply with a BID dosage regimen

as factors permitting us to use our preferred uricosuric therapy.

A third reason for measuring the excretion rate is that recognition of overexcretion may provide a tipoff to a patient whose nucleotide metabolism has been accelerated by an acquired malignant disease. Although this association unquestionably happens, it is usually recognized only with leukemias, polythemia, and other aggressive conditions that are easily diagnosed. It is clearly misleading to justify urinary measurements in a gouty but otherwise healthy middle aged man on the grounds that a high excretion rate might lead to recognition of an occult solid tumor.

Finally, overexcretion is regularly sought in the expectation that its presence will lead to recognition of an underlying enzyme defect. For practical purposes, this means the uncommon, partial defects in hypoxanthine guanine phosphoribosyl transferase (HGPRT), although the much rarer increased activity of phosphoribosyl-pyrophosphate synthetase may also be uncovered by such screening. Essential absence of HGPRT leads to the classic Lesch-Nyhan syndrome of children, with its severe neurologic manifestations and an overexcretion of uric acid so severe that it is recognized, in part, by a crystal-caused obstructive uropathy rather than gouty arthritis. It is the partial defects of this gene (usually associated with normal mental and neurologic function) that may be encountered in the practice of adult rheumatology. Because these genetic defects are sex-linked, they will not be found among gouty women. In men, they have usually been found in young adults and would be exceptionally rare in the typical older man who presents with gout of recent onset. The possibility becomes progressively less likely in the presence of each associated risk factor: truncal obesity, hypertension, therapy with urate-retaining drugs such as diuretics, cyclosporine, etc. In sum, recognition of genetic defects remains perhaps the most compelling justification for assessing the uric acid excretion rate, but it seems safe to reserve such testing primarily for the young man with precocious gouty arthritis. Rheumatologists and clinics with a special interest in urate metabolism will, and should, want to continue broader testing.

A PRACTICAL APPROACH

In assessing the uric acid excretion rate, it seems important both to recognize the true overexcretor and to avoid mislabeling as such of individuals who are well within 2 standard deviations of the normal mean. I feel it is appropriate to do this in a 2 stage process beginning with a spot, midmorning urine specimen obtained after a light, low purine, low fructose breakfast and without a preceding exercise session. The product of the urinary uric acid concentration and the plasma creatinine divided by the urinary creatinine yields the excretion rate per unit GFR[11]. The normal adult mean is 0.4 (± 0.1 SD) mg of urinary uric acid per deciliter of glomerular filtrate. Alternatively, it is also valid to think of the units as the excretion rate in mg/min at a GFR normalized to 100 ml/min. If the value is greater than 0.6 mg/dl (2 SD), the test can be repeated. If a high level is found again, then it is appropriate to ask the patient to follow a low purine diet for a week and to collect 24 hour specimens on its final 3 days. Simple appropriate screening restricts this arduous undertaking to a small minority of gouty individuals and converts it into a high yield procedure.

The choice of the simple $U_u \times P_c \div U_c$ formulation as the screening tool offers a number of theoretical and practical advantages: (1) It is physiologically sound. Unlike the uric acid to creatinine ratio, which is similarly convenient but has units with little or no inherent meaning, this test yields an excretion rate normalized to the GFR — perhaps the most fundamental variable of normal renal function. Moriwaki, *et al* dismiss this approach on the grounds that most normal serum creatinine values are close to 1.0 mg/dl and inclusion of the serum creatinine will have little effect on the normal numerical value[1]. This might seem to be true, but a serum creatinine of 0.8 mg/dl, for instance, differs markedly from one of 1.2 and results in an excretion rate that is just as markedly different. (2) This formulation corrects for differences in body size. It is unreasonable to employ "normal" values that do not take this critical aspect into consideration. The highly significant differences between 24 hour excretion values of normal men and women, for instance, are readily reconciled when they are normalized per unit body size[5]. Most tellingly, the uric acid excretion per unit GFR remains constant throughout the remarkable growth period of childhood and adolescence (whereas the uric acid to creatinine ratio does not)[22,23]. This attribute is particularly valuable in the early recognition of family members carrying partially defective HGPRT. The familial implications of this defect provide a major impetus behind our need to provide accurate diagnoses of affected adults. It is obviously far easier to obtain spot urine samples from the children at issue than it is to get meaningful 24 hour collections. (3) It is convenient, does not require storage or preservatives, and eliminates timing errors. These simple features remove most of the technical concerns inherent in evaluating excretion rates. They do not, of course, affect biologic sources of variation.

Against these points is the fact that the test correlates weakly with 24 hour data. As already discussed, however, this point seems soft when the 24 hour findings do not correlate well with themselves. It has also been argued that spot urine screening may not detect all partial enzyme defects[2]. The same may be said of 24 hour collections, particularly those that are incomplete or mishandled. The observed variation around the mean is sufficiently great that minor defects may be missed by any current approach. But minor defects should not be of any great concern. The ultimate

goal of excretion rate screening is to identify those patients whose overproduction of urate may put them at significant renal risk, and not to identify benign variations in normal purine metabolism.

To me, the detection of significant overexcretors remains a worthy goal, but the single, uncontrolled 24 hour collection seems irretrievably flawed as our chosen way of getting there. I have offered a simple, alternative strategy based on a physiologically sound screening of midmorning spot urine samples followed by serial 24 hour collections on a controlled diet in the small minority of patients who fail the screen. True overexcretion is rare and 24 hour evaluations are cumbersome. These facts, however, do not provide adequate justification for skipping assessments of excretion rates or for doing them badly. The proposed 2 step approach should make it possible to quantify the excretion of uric acid accurately, but only in those few patients who really need to have this done.

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REFERENCES

1. Moriwaki Y, Yamamoto T, Takahashi S, et al. Spot urine uric acid to creatinine ratio used in the estimation of uric acid excretion in primary gout. J Rheumatol 2001;28:1306-10.
2. Wortmann RL, Fox IH. Limited value of uric acid to creatinine ratios in estimating uric acid excretion. Ann Intern Med 1980;93:822-5.
3. Perez-Ruiz F, Calabozo M, Alonso-Ruiz A, Ruiz-Lucea E, Herrero-Beites A. Analysis of the methods for the classification of renal handling of urate in gout [abstract]. Arthritis Rheum 1997;40 Suppl:S48.
4. Simkin PA. Test of urinary excretion of uric acid [letter]. Ann Intern Med 1979;91:926-7.
5. Löffler W, Simmonds HA, Gröbner W. Gout and uric acid nephropathy: some new aspects in diagnosis and treatment. Klin Wochenscr 1983;61:1233-9.
6. Pak CYC, Peterson R, Poindexter JR. Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. J Urol 2001;165:378-81.
7. Ricos C, Jimenez CV, Hernandez A, et al. Biological variation in urine samples used for analyte measurements. Clin Chem 1994;40:472-7.
8. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci 1989;27:409-37.
9 Wheeler LA, Sheiner LB. Clinical estimation of creatinine clearance. Am J Clin Pathol 1979;72:27-31.
10. Yamakita J, Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Hada T. Effect of urine storage on urinary uric acid concentrations. Ann Clin Biochem 2000;37:355-9.
11. Simkin PA, Hoover PL, Paxson CS, Wilson WF. Uric acid excretion: quantitative assessment from spot, midmorning serum and urine samples. Ann Intern Med 1979;91:44-7.
12. Boisson RC, Eynard JC, Crozier M, Grafmeyer DC. French experience of quality assessment of quantitative urinary analysis. Clin Chim Acta 2000;297:285-95.
13. Hesse A, Siener R, Heynck H, Jahnen A. The influence of dietary factors on the risk of urinary stone formation. Scanning Microsc 1993;7:1119-27.
14. Faller J, Fox IH. Ethanol induced alterations of uric acid metabolism. Adv Exp Med Biol 1984;165:457-62.
15. Raivio KO, Becker MA, Meyer LJ, Greene ML, Nuki G, Seegmiller JE. Stimulation of human purine synthesis de novo by fructose infusion. Metabolism 1975;24:861-9.
16. Matsuura F, Yamashita S, Nakamura T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. Metabolism 1998;47:929-33.
17. Sahebjani H. Changes in urinary uric acid excretion in obstructive sleep apnea before and after therapy with nasal continuous positive airway pressure. Chest 1998;113:1604-8.
18. Sorensen LB, Levinson DJ. Origin and extrarenal elimination of uric acid in man. Nephron 1975;14:7-20.
19. Yu TF. Nephrolithiasis in patients with gout. Postgrad Med 1978;63:164-70.
20. Asplin JR. Uric acid stones. Semin Nephrol 1996;16:412-24.
21. Wortmann RL. Effective management of gout: an analogy. Am J Med 1998;105:513-4.
22. Stapleton FB, Nash DA. A screening test for hyperuricosuria. J Pediatr 1983;102:88-90.
23. Miller LA, Noe HN, Stapleton FB. Uric acid excretion in children with urolithiasis. J Pediatr 1989;115:923-6.