Urol Res (2006) 34: 122–125
DOI 10.1007/s00240-005-0023-3

ARTICLE

Roger A. L. Sutton

The use of risk indices: do they predict recurrence?

Accepted: 2 November 2005 / Published online: 6 January 2006

Abstract A risk index which would reliably predict the likelihood of stone recurrence in the patient with renal calculi would help the clinician to select appropriate preventative therapy. However, none of the indices developed to date combines easy applicability in usual clinical settings with sufficient predictive power to be useful to the clinician in making treatment decisions.

Keywords Idiopathic calcium stones · Risk indices for recurrence · Risk factors · Calcium oxalate

My remit is to present the ''con'' position in this discussion, recognizing that it has not been my practice to use risk indices to guide the medical management of renal stone patients. This discussion applies only to so-called idiopathic calcium oxalate stones, with or without calcium phosphate as a minor component. Hereinafter, these will be referred to as ''calcium stones''.

Clinicians working in the renal stone field have, for decades, sought reliable means to predict confidently whether a patient having a first calcium stone episode will suffer from recurrent stones, and if so, how frequently. Likewise one would wish to be able to predict whether the recurrent calcium stone former (two or more stone episodes) would have many more recurrences, or perhaps none. Such information would greatly facilitate treatment decisions, for example whether to offer only general advice (on fluid intake and diet), or whether to initiate drug treatment, for example with a thiazide diuretic and/or potassium citrate. The clinical usefulness of indices that are able to distinguish the urine of normal subjects from that of stone formers is minimal. To be of practical value, the index must be shown to have predictive value with respect to the future clinical course of the stone disease.

R. A. L. Sutton
University of British Columbia, 3254 West 20th Avenue, Vancouver, BC, Canada V6L1H9
E-mail: roger.sutton@shaw.ca
Fax: +1-604-7325977

In considering this subject, it is important to remind ourselves that, for idiopathic calcium stones, very few preventative strategies have been shown to be effective in proper controlled clinical trials. These include increased urine volume, thiazide diuretics or indapamide (in unselected and in hypercalciuric patients), potassium citrate or potassium magnesium citrate (in unselected and in hypocitraturic patients), and allopurinol in hyperuricosuric patients. These drug treatments have recently been shown to also be effective in reducing stone recurrences in a clinical practice setting [1]. In addition, dietary salt and protein restriction has been shown to be superior to dietary calcium restriction in reducing stone recurrence in hypercalciuric patients [2]. No controlled studies have demonstrated the efficacy of reducing urinary oxalate excretion (for example by dietary oxalate restriction or calcium supplementation), but it seems highly probable that, in the absence of other changes in urinary risk factors, a reduction in urinary oxalate would reduce calcium oxalate stone recurrences. The reduction of urinary calcium excretion by moderating excessive salt intake has also not been demonstrated to reduce stone recurrences.

Before further considering risk indices, it may be wise to explain the use of the terms ''risk factor'' and ''risk index'' in this paper. Urinary risk factors are those urinary characteristics that are agreed to influence the likelihood of calcium stone formation or recurrence, and are routinely measured as part of the metabolic investigation of calcium stone formers. These urinary risk factors include volume, calcium, oxalate, citrate, uric acid, pH and magnesium. Urinary sodium is not a significant risk factor in its own right, but it is important because of the effect of increasing sodium excretion to cause an increase in calcium excretion. If the relative saturation of calcium oxalate in the urine sample is to be computed using the EQUIL programme [3], some additional measurements are required, including phosphate, sulphate and potassium. Because the above individual urinary risk factors do not reliably predict the subsequent course of calcium stone disease [4, 5], con-

siderable effort has been expended in trying to develop more robust indicators (risk indices).

Putative risk indices have included quotients, calculated from the above urinary risk factors, indices based on in vitro studies of crystallization in the urine, and indices based on the microscopic detection of crystalluria. Combinations of these different types of index have also been studied, in the hope of improving the ability to predict recurrences.

In an elegant study published in 1976 [6], Robertson and colleagues described a ''saturation–inhibition index'', which utilized the calculated saturation [3] together with an in vitro measurement of inhibition of growth and aggregation of calcium oxalate crystals in a metastable solution containing 1% of urine, using the Coulter counter. The index very effectively separated normal urine from that of stone patients, and correlated significantly both with the prior stone episode rate, and with the percentage of large crystals in fresh urine. Thus this index provides a measure of severity, but was not shown prospectively to predict stone recurrence rate, and is not suitable for routine clinical use.

Pak and Galosy, in 1980 [7], developed the concept of a urinary formation product ratio minus activity product ratio (FPR−APR) discriminant score for calcium oxalate, brushite, and the combination of both salts. The FPR is determined in vitro by addition of sodium oxalate (or calcium chloride) to urine to determine the minimum level of supersaturation for spontaneous nucleation to occur. The APR is a measure of supersaturation determined in vitro by incubating urine with calcium oxalate (or brushite) crystals. The discriminant score is calculated from the measured FPR and APR, which reflect a reduction in inhibitors of crystal growth and the level of supersaturation, respectively. The discriminant scores for calcium oxalate (and brushite) very effectively separated the urine of control subjects from that of hypercalciuric stone formers; as would be expected there was more overlap between the urines of controls and normocalciuric stone formers. The FPR-APR discriminant score for calcium oxalate (but not that of brushite, nor the combined discriminant score) correlated significantly with the stone formation rate over the preceding 3 years, indicating that this index gives a measure of severity. Again, however, no prospective data were provided to show that the index reliably predicts recurrence in the individual patient, and the test is too technically demanding for routine clinical use.

In a comprehensive and critical review in 1997, Tiselius [8] summarised the urinary risk indices or formulae that had been reported up to that time to have possible value in predicting stone recurrence. These included the calcium/magnesium [9] and the calcium/citrate ratio and its derivative, the Parks-Coe Index [10], as well as other simple quotients derived from the urinary calcium, oxalate, magnesium and citrate values, and more complex indices designed to estimate the degree of saturation of the urine with calcium oxalate and calcium phosphate. In this last category, Tiselius [8] has developed activity product indices for calcium oxalate [AP (CaOx)] and calcium phosphate [AP (CaP)], with and without the employment of standardized values for urine volume and urine pH.

Tiselius [8] calculated the results of several of these quotients from data on his own patients, separated according to whether or not they had recurrent stone formation. Significant differences were observed with several indices, but there was considerable overlap in the values. He concluded [8] that ''there is, as yet, no risk factor based on findings in the urine that provides a tool for an easy prediction of whether an individual patient will continue to form stones or not''.

Having reached a similar conclusion myself from the available literature, I have continued to make treatment decisions without reference to either calculated risk quotients or in vitro crystallization or saturation tests. Treatment decisions have been based on the course of the patient's stone disease, the results of the individual urinary risk factors, and on the patient's wishes when provided with data on the available treatments. The patient with a single stone, or with infrequently recurring stones, is normally given general advice, with emphasis on measures to correct his/her abnormal risk factors, including increased fluid intake, avoidance of oxalate-rich foods, moderation of salt intake and avoidance of dietary calcium restriction. In the more frequent stone former, if general advice fails to correct abnormal risk factors, or to cause an acceptable reduction in stone formation, drug treatment has been recommended, initially directed at correcting abnormal risk factors, but recognizing that a reduction in urinary calcium or oxalate and an increase in citrate may be beneficial even if baseline values do not exceed the arbitrarily defined ''upper limits of normal'', because risk factors may be graded, as shown for volume and calcium in large epidemiological studies [5].

There are, of course, several problems with such a tailored approach to stone prevention, notably the limited formal proof of its efficacy [1], the somewhat arbitrary way in which decisions to employ drug treatment are made, and the tendency for positive risk factors to change with time in some patients.

Although no simple method for predicting stone recurrence that is applicable in a usual practice setting is yet available, there have been some interesting recent developments.

Lee et al. [11], accepting that ''single stone formers often have a pattern and severity of metabolic disorders similar to recurrent stone formers'', chose an approach based on general (non-biochemical) patient characteristics including age, sex, urine volume, smoking, wine drinking, family history, stone number and history of gouty arthritis. Only the last three correlated with the stone recurrence rate. Arbitrary scores were assigned to each characteristic, giving a maximum score of 22. Follow up periods were relatively short. Mean scores were significantly higher in recurrent than in single stone

formers; scores of >7 had 62% sensitivity and 75% specificity to predict stone recurrence. The authors acknowledge that a longer follow-up, a larger database and more variables are needed to validate the clinical use of this scoring system.

Robertson and colleagues have been interested in the mathematical analysis of risk factors for more than two decades. In a recent publication [12], this model has been developed further, with a view to improving its predictive power. The approach is based on the premise that each of the urinary risk factors (volume, calcium, oxalate, citrate, uric acid and magnesium for calcium oxalate stones, and volume, calcium, pH, citrate, uric acid and magnesium for calcium phosphate stones) contributes independently to stone risk in a continuous manner as the patient's value increasingly departs from the mean normal value. The calculations are based on the smoothed frequency distribution of each risk factor in stone formers and normal control subjects, from which a set of risk curves are derived. The contribution of each risk factor towards the relative probability (Psf) of stone formation is calculated from these risk curves. Based on this model, Robertson makes a number of important points. There is a fairly sharp dividing line at a calculated Psf of 0.5 between normals and stone formers. A curvilinear relationship is shown between Psf and the stone episode rate. However, this relationship is based on patients with very high stone recurrence rates (one third of the patients had recurrence rates of between 2 and 6 per year). Using this model, Robertson shows that small changes in risk factor values within their "normal ranges" can place the patient at a high risk for stones. There was a major overlap between the Psf values in single and (presumably severe) recurrent stone-formers, so it is not clear that this index will be clinically useful in predicting which patient, at the time of the first stone, will have recurrences. This could best be determined with a prospective study.

The "Bonn Risk Index" (BRI) will have been introduced by my co-discussant, Laube [13]. This index describes the relationship between two parameters that are measured in a fresh urine collection; the free ionised calcium concentration, determined with a calcium electrode, and the amount of ammonium oxalate that needs to be titrated into a 200 ml aliquot of urine in order to initiate crystal formation. The BRI has been reported to show a superior ability to discriminate between the urine of normal subjects and stone formers, as compared with the calcium oxalate relative saturation (computed with the EQUIL [3] program), or with the AP (CaOx) index of Tiselius [6]. The BRI combines direct measurement of the urinary free ionised calcium with an index of oxalate tolerance and calcium oxalate crystal formation. Although evidence has been presented [7, 14, 15] for abnormalities in the relationship between urinary supersaturation and the upper limit of metastability for calcium oxalate in the urine of stone formers (indicating a reduction in inhibitory activity), it is less clear what the oxalate tolerance is measuring in stone formers. Although the BRI might have predictive value for future stone formation, prospective studies are needed to test this possibility. It would be of interest to determine whether the test is best performed on timed urine collections, or perhaps on an early morning and/or postprandial urine sample. As there is still uncertainty as to whether the critical first step in stone formation involves the precipitation of calcium oxalate or calcium phosphate, inclusion of a test for the determination of the threshold for precipitation of calcium phosphate as well as calcium oxalate might improve the predictive potential of the BRI. An unusually large intake of fluid preceding the collection of the urine sample would presumably result in a lower BRI value.

Since the determination of the BRI does not involve the separate measurement of the traditional urinary risk factors (other than calcium), such as volume, oxalate and citrate, the determination of BRI per se is of very limited value as a guide to stone preventative treatment aimed at correcting obvious risk factors, using strategies that have been proved to be effective.

In the recent report of Daudon et al. [16], serial crystalluria in early morning urine samples was shown to be highly predictive of calcium stone recurrence. Urine samples were examined with a polarizing microscope, employing a 10 cu mm (Malassez) cell. All crystals (except very small calcium phosphate grains) and aggregates were counted and measured, but for the purpose of the "Crystalluria Index" the specimen was either positive or negative for crystals. One hundred and eighty one patients, of whom 72 had recurrences and 109 did not, each had between 3 and 33 urines examined over periods of 3–20 years. The Crystalluria Index was calculated as the number of samples with crystals divided by the total number of samples examined in each patient. Twenty-four hour urines were analysed for the usual risk factors. The patients destined to have stone recurrence had, at referral, significantly higher urine calcium excretions (mean 7.9 vs 6.4 mmol per day) and lower urine volumes (mean 1.4 vs 1.6 l per day) but the presence or absence of crystalluria proved to be by far the most robust discriminator. Crystals were present in over 50% of samples (Crystalluria Index >0.5) in 87.5% of patients with recurrences, but only in 15.6% of those without recurrence ($P < 0.0001$). Stones residing in the kidneys did not appear to influence the presence of crystalluria. These investigators also commented that "recurrence of stones was consistently preceded by persistence or reappearance of crystalluria, allowing for an increase in the intensity of stone prevention measures".

It would be of interest to know whether any particular species of crystal was more predictive of recurrence than others, and also to know whether the time interval between the urine samples is important—for example would three or more daily urine samples at the time of initial investigation be similarly predictive?

Although crystalluria would appear to be a promising indicator of the future course of stone disease, unfortunately physicians in office practice are somewhat

resistant to performing careful microscopic examinations during clinics, and are not necessarily particularly expert. Most physicians do not have a technician available in the clinic. So the practicability of the test is uncertain. It would be much enhanced if it were possible, for example, to develop a simple indicator dip test for crystals, along the lines of testing for red blood cells in the urine.

In conclusion, risk indices for stone recurrence, with very different discriminatory power, do exist, but as yet none of them combines easy applicability to usual clinical practice settings with sufficient predictive power to help the physician to make confident choices among the available stone prevention strategies.

References

1. Mardis HK, Parks JH, Muller G, Ganzel K, Coe FL (2004) Outcome of metabolic evaluation and medical treatment for calcium nephrolithiasis in a private urological practice. J Urol 171:85
2. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Gianinni A (1996) Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol 155:839
3. Werness PG, Brown CM, Smith LH, Finlayson B (1985) EQUIL 2: a basic computer program for the calculation of urinary saturation. J Urol 142:1242
4. Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G (1999) A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. J Urol 162:27
5. Curhan GC, Willett WC, Speizer FE, Stampfer MJ (2001) Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 59:2290
6. Robertson WG, Peacock M, Marshall RW, Marshall DH, Nordin BE (1976) Saturation–inhibition index as a measure of the risk of calcium oxalate stone formation in the urinary tract. N Engl J Med 294:249
7. Pak CY, Galosy RA (1980) Propensity for spontaneous nucleation of calcium oxalate. Quantitative assessment by urinary FPR-APR discriminant score. Am J Med 69:681
8. Tiselius H-G (1997) Risk formulas in calcium oxalate urolithiasis. World J Urol 15:176
9. Evans RA, Forbes MA, Sutton RAL, Watson L (1967) Urinary excretion of calcium and magnesium in patients with calcium-containing stones. Lancet II:958
10. Parks JH, Coe FL (1986) A urinary calcium–citrate index for the evaluation of nephrolithiasis. Kidney Int 30:85
11. Lee Y-H, Huang W-C, Lu C-M, Tsai J-Y, Huang J-K (2003) Stone recurrence predictive score (SRPS) for patients with calcium oxalate stones. J Urol 170:404
12. Robertson WG (2003) A risk factor model of stone-formation. Front Biosci 8:1330
13. Laube N, Hergarten S, Hoppe B, Schmidt M, Hesse A (2004) Determination of the calcium oxalate crystallization risk from urine samples: the Bonn Risk Index in comparison to other risk formulas. J Urol 172:355
14. Asplin JR, Parks JH, Chen M et al (1999) Reduced crystallization inhibition by urine from men with nephrolithiasis. Kidney Int 56:1505
15. Asplin JR, Parks JH, Nakagawa Y, Coe FL (2002) Reduced crystallization inhibition by urine from women with nephrolithiasis. Kidney Int 61:1821
16. Daudon M, Hennequin C, Boujelben G, Lacour B, Jungers P (2005) Serial crystalluria determination and the risk of recurrence in calcium stone formers. Kidney Int 67:1934