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A RISK FACTOR MODEL OF STONE-FORMATION

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1. ABSTRACT

A simple method for assessing the biochemical risk of forming uric acid and/or calcium-containing stones would be extremely useful for screening patients with urinary stone disease before and during their clinical management and follow-up. This paper describes a simplified procedure for calculating the overall biochemical risk of forming stones consisting of uric acid, calcium oxalate, calcium phosphate or various combinations of these common stone constituents making use of seven analyses normally carried out on 24-h urine samples in most Stone Clinics. The contribution of each risk factor towards the overall biochemical risk of forming stones (P_{SF}) is calculated from a set of "risk curves" derived from frequency distributions of the seven risk factors measured in the 24-h urine samples from a large number of idiopathic stone-formers and their controls. P_{SF} discriminates well between stone-formers and normal subjects and predicts the likely severity of the disorder in a given individual as defined by the number of stone episodes per year experienced by the patient concerned.

2. INTRODUCTION

It is generally accepted that urolithiasis is a multifactorial problem that requires a multifaceted approach to the assessment and management of patients with the disorder. In this connection, several methods for achieving this have been proposed within the past 35 years, but most have suffered from the problem that they require too many measurements to be made in each urine sample to be useful as a routine procedure. These include programs for calculating the supersaturation of urine with respect to stone-forming salts (SUPERSAT (1-3), EQUIL (4), and activity product ratio (APR) (5)), empirical measures of the point of crystallisation of calcium salts in urine (eg formation product ratio (FPR) (6)), saturation-inhibitor index (7), various quotients that combine two or more urinary risk factors for stone-formation (Tiselius Indices (8, 9)) and procedures that combine the measurement of some urinary risk factors with an empirical determination of the point of crystallisation of calcium salts in urine (Bonn Risk Index) (10). These measures of the risk of forming stones either require a large number of analyses or there is a relatively large degree of overlap between stone-formers and normal subjects with respect to the indices calculated. None provides an index that discriminates effectively between patients with stones and normal controls.

In 1978, Robertson and his colleagues (11) first described an alternative method for assessing the propensity of a given individual to form stones. This was based on a risk factor analysis model for combining the various urinary risk factors at that time thought to be important for calcium stone-formation. This technique has now been refined in the light of larger numbers of data to include seven urinary risk factors found to be significantly different between stone-formers and normals and therefore considered to be of importance in the generation of stones consisting of uric acid (UA), calcium oxalate (CaOx), calcium phosphate (CaP) or various combinations of these stone components. The seven risk factors so far identified in 24-h urine samples include urine volume, urinary pH and the excretions of calcium, oxalate, citrate, uric acid and magnesium. Other potential urinary risk factors for idiopathic stone disease, such as phosphate, were omitted from the final analysis as they were found not to be significantly different between stone-formers and normal subjects in a preliminary study. Although the mean value

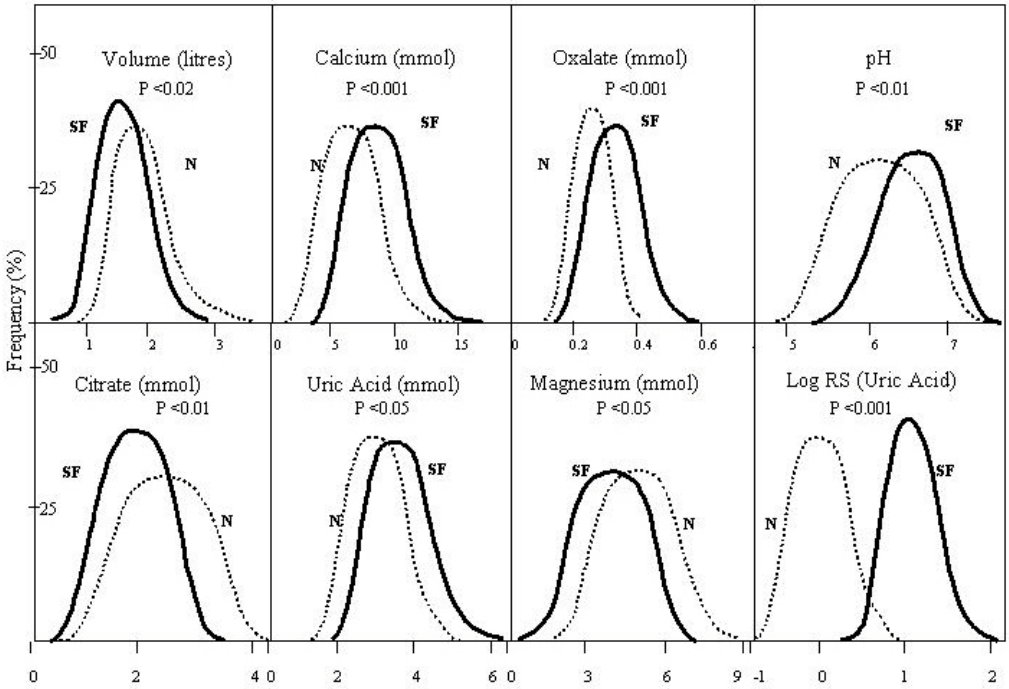

Figure 1. The smoothed frequency distributions of the urinary risk factors for calcium- and uric acid-containing stone-formation in 600 idiopathic stones-formers (SF) and 250 normal controls (N).

of each of the above seven variables was found to be significantly different between stone-formers and normals, in each case there was a large degree of overlap between the data from the two populations. The risk factor model makes use of these overlapping distributions to define a set of "risk curves" which are then combined to produce an overall measure of the risk of forming stones. The principle behind the risk factor model and the method for calculating the overall measure of the risk of forming various types of calcium and/or uric acid-containing stones from these risk factors are described below.

3. MATERIALS and METHODS

Two 24-h urine samples were collected on consecutive days from 600 male, recurrent idiopathic stone-formers, aged 20-60, who had formed sterile stones consisting of calcium oxalate, calcium phosphate, uric acid or various mixtures of these stone constituents. The first 24-h sample was collected in a container to which 50 ml of 2.2M hydrochloric acid had been added as a preservative; the second 24-h collection had no preservative added to the container. Similar 24-h urine samples were collected from 250 men, aged 20-62, who had no history of renal disease or of urinary stone-formation and had no major metabolic disorder. All subjects were studied on their free, home diets. The urine samples were brought in for analysis on the morning of the day of completion of the collection.

In a second study, 24-h urines were collected in the same way from normal subjects (divided into children, adult females and adult males) and from various groups of idiopathic and secondary calcium and/or uric acid stone-formers assessed before they were prescribed any prophylactic measures to prevent them from forming further stones. The idiopathic calcium stone-formers were divided into those who had already had at least one stone recurrence (RSF) and those who so far had had only a single stone episode (SSF). The secondary calcium stone-formers consisted of patients with primary hyperparathyroidism (HPT), distal renal tubular acidosis (dRTA), enteric hyperoxaluria (secondary to small bowel disease or small bowel resection) and primary hyperoxaluria. The secondary uric acid stone-formers consisted of patients with an ileostomy.

The acidified urine samples were analysed for volume, calcium, oxalate, magnesium and citrate and the non-acidified samples for volume, pH and uric acid. These were the only urinary factors that had been previously found to be significantly different between stone-formers and normal controls. Calcium, magnesium and uric acid were measured using standard multi-channel analyser procedures. Oxalate was measured enzymatically (12) and citrate using a citrate lyase kit (Boehringer, Mannheim). The relative supersaturation of urine with respect to uric acid (RS UA) was calculated in each urine sample from a combination of urinary pH and the corresponding concentration of uric acid using a simplified version of the SUPERSAT program (3).

4. RESULTS

The data for each variable were plotted as smoothed percentage frequency distributions in both the stone-formers and the controls as shown in Figure 1. This clearly shows that although the mean values for each of the variables were significantly different between stone-

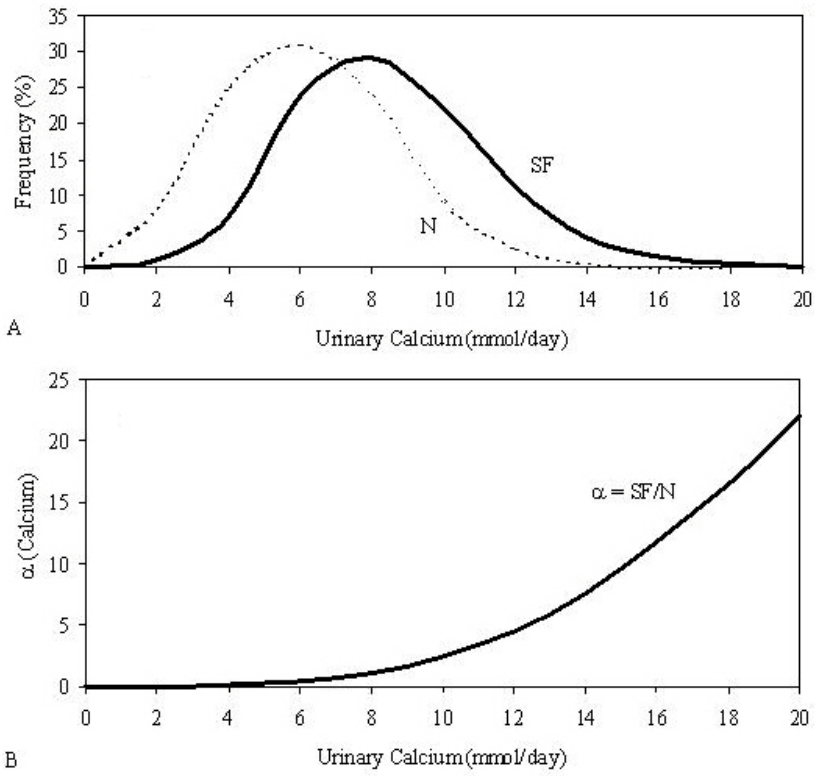

Figure 2. A: The frequency distributions of urinary calcium excretion in stone-formers (SF) and normal subjects (N) taken from Figure 1. B: The derivation of the "risk curve" for calcium (aCa) calculated from the ratio of SF/N at each level of urinary calcium.

ormers and normals, there was a large degree of overlap between the two populations for each variable concerned. By themselves, none provided a good discriminant between those individuals with a history of stones and those without stones. This is unlike the situation in patients whose stones are due to some genetic disorder such as cystinuria, xanthinuria, 2,8-dihydroxyadeninuria or primary hyperoxaluria where the abnormal excretion of the metabolite concerned is at least one order higher in the stone-formers than it is in the normal population. These overlapping distributions were then used to define a set of "risk curves" for stone-formation as shown below.

Figure 2 contains an example of how the "risk curves" for the various risk factors were calculated. Figure 2A shows the overlapping distributions of urinary calcium excretion in stone-formers and normals taken from the data in Figure 1. The "risk curve" (aCa) for urinary calcium (UCa) was then calculated using the ratio of [UCa]SF/[UCa]N, where [UCa]SF and [UCa]N are the percentages of stone-formers and normal controls respectively at each level of urinary calcium. The "risk curve" for urinary calcium generated in this way is shown in Figure 2B. This curve represents the mathematical odds of being a stone-former rather than a normal at each level of urinary calcium. The "risk curves" for volume, pH, calcium, magnesium, oxalate, citrate and uric acid were all generated in the same way and the equations for each of these curves calculated using a quadfit analysis program. The resulting equations are detailed below. The "risk curves" for each of the urinary risk factors are shown in Figure 3. These are plotted such that 0 represents the mean value for the normal controls and the scale is defined in standard deviation (SD) units for each risk factor above and below the mean normal value for each individual factor. This shows that, by themselves, the two most important risk factors for Ca-containing stones are a low urine volume and mild hyperoxaluria. By itself, hypercalciuria is not the most important risk factor for stones. The risk factors in decreasing order of importance are: ↓ volume >↑ oxalate > ↑ pH (for CaP stones) = ↓ pH (for UA stones) > ↑ calcium = ↓ citrate > ↑ uric acid > ↓ magnesium. Each of these factors is known to affect either the supersaturation of urine with respect to Ca-containing salts or the inhibitory (or promotive) activity of urine towards the crystallisation of these salts. In the cases of citrate and magnesium, both supersaturation and inhibitory activity are affected adversely by a reduction in the urinary excretion of these two ions.

Using Bayes' Theorem, a family of algorithms (P_{SF}) was constructed from relevant combinations of the individual "risk curves" for each of the urinary risk factors. These define the risk of forming stones consisting of either uric acid or uric acid + calcium oxalate, or calcium oxalate or calcium oxalate + calcium phosphate or calcium phosphate by itself. These are defined as follows:

Risk Model

P_{SF} (UA) = $a_{RS\ UA}/(1 + a_{RS\ UA})$

P_{SF} (UA/CaOx) = $(a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA}*a_{RS\ UA})/(1 + a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA}*a_{RS\ UA})$

P_{SF} (CaOx) = $(a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA})/(1 + a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA})$

P_{SF} (CaOx/CaP) = $(a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA}*a_{pH})/(1 + a_{Ca}*a_{Ox}*a_{Mg}*a_{Cit}*a_{UA}*a_{pH})$

P_{SF} (CaP) = $(a_{Ca}*a_{Mg}*a_{Cit}*a_{pH})/(1 + a_{Ca}*a_{Mg}*a_{Cit}*a_{pH})$

where $a_{RS\ UA}$ = contribution from risk curve of urinary RS UA

= EXP(2.30258*(-6.698+9.942001*((8.59-(-0.4343*LN(0.76*EXP(-2.30258*pH)*(UA/(1000*V))/(1+294000*EXP(-2.30258*pH)*0.76))))/0.37)-2.345*(POWER(((8.59-(-0.4343*LN(0.76*EXP(-2.30258*pH)*(UA/(1000*V))/(1+294000*EXP(-2.30258*pH)*0.76))))/0.37))))

a_{Ca} = contribution from risk curve of urinary Ca

= EXP(2.30258*(-1.774+(0.276*Ca*1.5/V)-(0.0061(Ca*1.5/V)^2)))

a_{Ox} = contribution from risk curve of urinary Ox

= EXP(2.30258*(-1.0332+(1.7117*Ox*1.5/V)+(4.0949*(Ox*1.5/V)^2)))

a_{Mg} = contribution from risk curve of urinary Mg

= EXP(2.30258*(0.357-(0.069*Mg*1.5/V)-(0.00001314*(Mg*1.5/V)^2)))

a_{Cit} = contribution from risk curve of urinary Cit

= EXP(2.30258*(1.2983-(0.5072*Cit*1.5/V)+(0.0333*(Cit*1.5/V)^2)))

a_{UA} = contribution from risk curve of urinary UA

= EXP(2.30258*(-0.9931+(0.2654*UA*1.5/V)-(0.014*(UA*1.5/V)^2)))

a_{pH} = contribution from risk curve of urinary pH

= EXP(2.30258*(-17.087+(4.551*pH)-(0.285*(pH)^2)))

where pH = the pH of the 24-h urine sample

V = the volume in litre/day

Ca = the urinary excretion of calcium in mmol/day

Mg = the urinary excretion of magnesium in mmol/day

Ox = the urinary excretion of oxalate in mmol/day

Cit = the urinary excretion of citrate in mmol/day

UA = the urinary excretion of uric acid in mmol/day

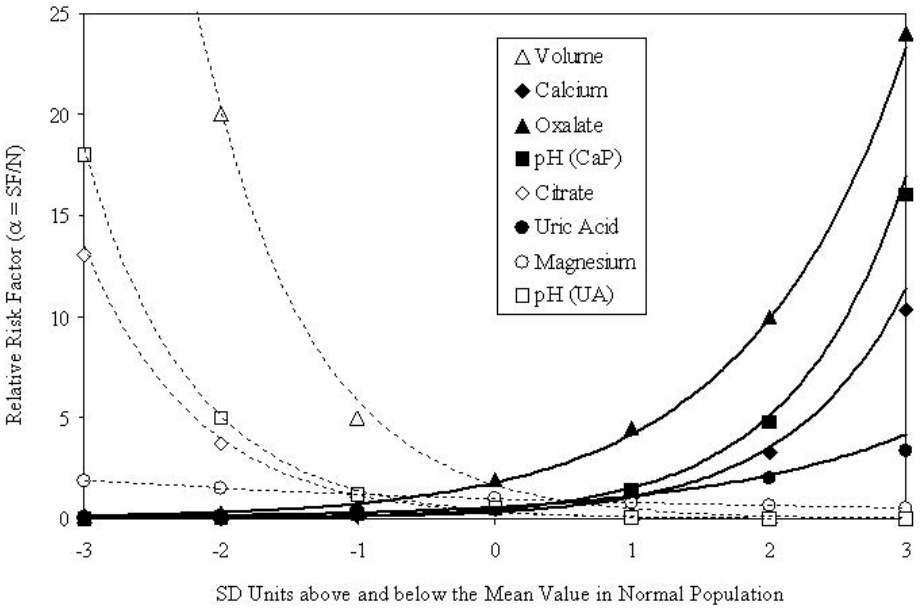

Figure 3. The "risk curves" for the various risk factors for calcium- and uric acid-containing stones calculated from the frequency distributions in Figure 1.

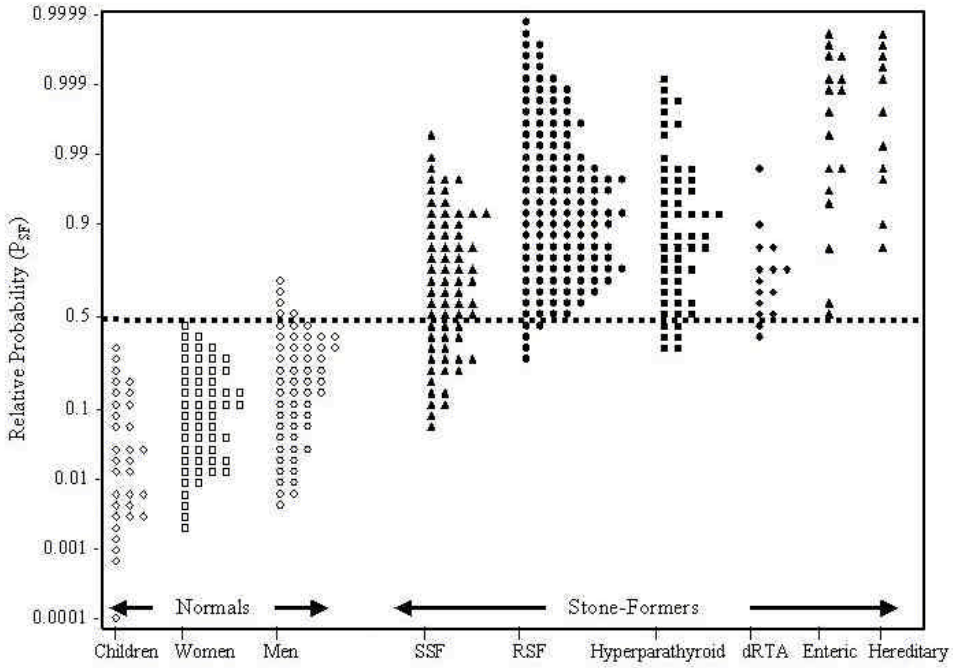

Figure 4. The overall biochemical risk of forming calcium-containing stones (PSF) in three groups of normal subjects and in various groups of primary and secondary calcium stone-formers. SSF = single episode stone-formers; RSF = recurrent idiopathic stone-formers; Hyperparathyroid = patients with primary hyperparathyroidism and stones; dRTA = patients with distal renal tubular acidosis and stones; Enteric = patients with enteric hyperoxaluria and stones; Hereditary = patients with primary hyperoxaluria and stones.

As can be seen from the above equations, an allowance is made for the effects of variation in urinary volume by adjusting all excretions to those in a urine sample with an average volume of 1.5 litre/day. This generally multiplies up the risk of stone-formation in urines with a low volume and reduces the risk in urines with a high volume although the actual outcome depends on the relationship between the factors that promote crystallisation of calcium salts in urine and those that inhibit it.

Figure 4 contains the values of P_{SF} (CaOx), P_{SF} (CaOx/CaP) or P_{SF} (CaP) [whichever was the highest in a given individual] in normal subjects and in various groups of untreated patients with a history of forming calcium-containing stones. The idiopathic calcium stone-formers were divided into two groups. The first group consisted of patients who had so far had only a single stone episode (SSF) and the second of patients with a history of recurrent stones (RSF). The secondary calcium stone-formers consist of patients with primary hyperparathyroidism (HPT), distal renal tubular acidosis (dRTA), enteric hyperoxaluria and primary hyperoxaluria. This shows that P_{SF} provides a very good discriminant at a value of around 0.5 between non-stone-formers and patients with either recurrent idiopathic calcium stones or calcium stones secondary to some metabolic disorder. The patients with a single recorded episode of stones (SSF) overlap with the non-stone-formers and the RSF. Statistically it would be expected that about 60-70% of these patients would eventually form another stone and the remainder will not form any more stones during their lifetimes.

Figure 5 contains the corresponding P_{SF} data for the risk of forming predominantly uric acid-containing stones in normal subjects and in patients with idiopathic uric acid stones and in patients with uric acid stones secondary to an ileostomy. This shows that P_{SF} (UA) provides an excellent discriminant between uric acid stone-formers and normal controls around a P_{SF} value of 0.5.

Table 1 shows an example of the power of the risk factor model to identify patients who have a significant risk of forming stones even although each of their seven urinary risk factors lies within the so-called “normal range” for each risk factor. The Table contains the urinary analysis from a patient (AGW) with a history of forming calcium-containing stones compared with the corresponding data from a normal subject (JHT) whose urinary composition is only marginally less “abnormal” with respect to each urinary risk factor than that of the stone-former. The Table shows that in the patient with calcium-containing stones, the risk of forming CaOx- and CaP-containing stones based on P_{SF} is significant (>0.5), in contrast to the P_{SF} values in the urine from the non-stone-forming individual which are all below 0.5. This emphasises the importance of combining urinary risk factors for calcium and uric acid stone-formation rather than trying to identify one (or perhaps two) “very abnormal” risk factors as the so-called “cause” of stones in a given individual.

Figure 6 shows the relationship between the severity of the disorder (as defined by the number of stone

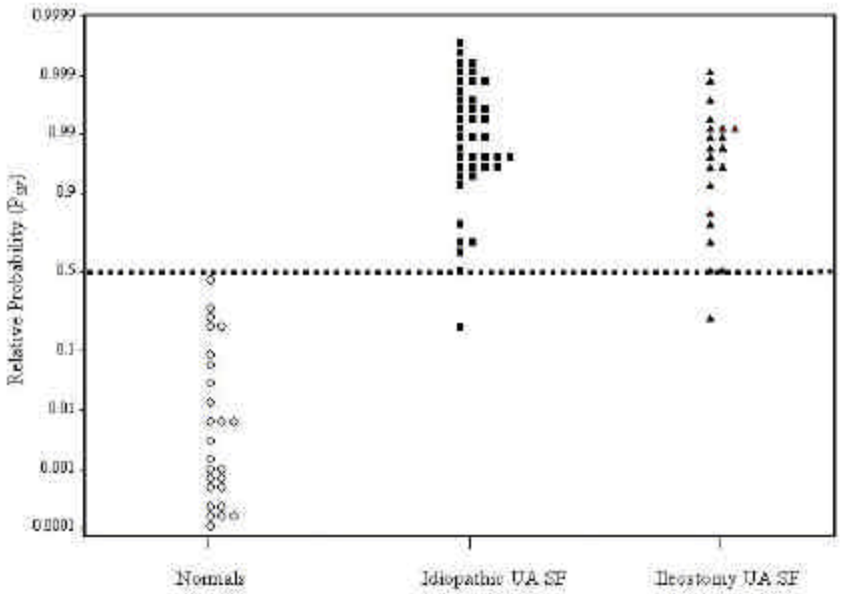

Figure 5. The overall biochemical risk of forming uric acid-containing stones in normal subjects and in patients with idiopathic uric acid stones and in patients with an ileostomy and uric acid stones.

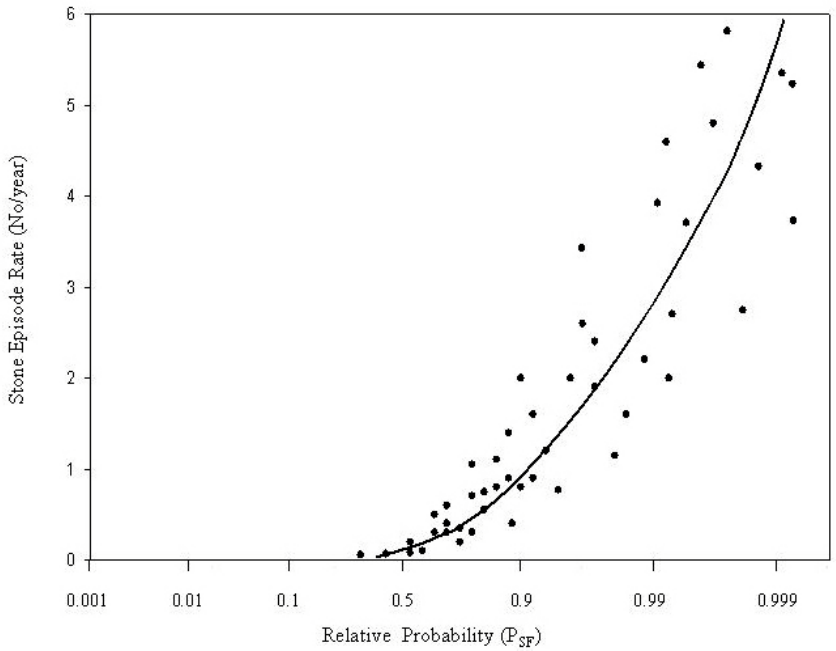

Figure 6. The severity of calcium stone-formation (as defined by the number of stone episodes per year) in a group of recurrent idiopathic calcium stones formers in relation to their biochemical risk of forming stones (P_{SF}).

episodes per year) in a group of recurrent idiopathic stone-formers plotted in relation to the maximum value of P_{SF} found in their urine. This shows that the higher the value of P_{SF}, the greater is the rate of recurrence of the disorder in the patient concerned.

Figure 7 shows how a small change in one of the urinary risk factors (in this example, calcium) in the population can greatly increase the percentage of individuals at higher risk of forming calcium-containing stones without having a major effect on the mean value of urinary calcium in the population concerned. This is an example recalculated from data obtained in a study by Robertson and Peacock (13) showing the effects on urinary calcium excretion of administering a small dose of 25-hydroxyvitamin D_3 (25 μg) to a group of normal subjects with no previous history of urinary stone disease. The distributions of 24-h urinary calcium before and during

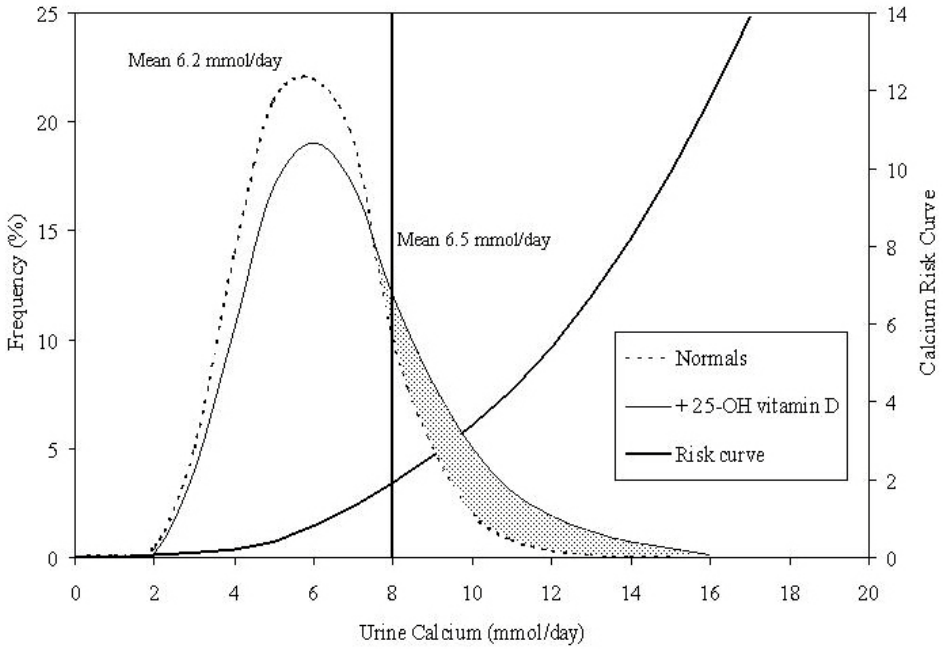

Figure 7. The effect of a small dose of 25-OH vitamin D_3 (25 μg) on the urinary calcium excretion of a group of normal male subjects showing that in spite of only a small effect on the mean value of urinary calcium excretion in the group there was a doubling in the percentage of individuals with a urinary calcium excretion of >8 mmol/day. This is shown in relation to the "risk curve" for calcium ($a_{Calcium}$).

administration of 25-hydroxyvitamin D_3 are plotted showing that there was only a small increase in the mean 24-h urinary excretion of calcium (mean basal value = 6.2 ± 0.5 mmol/day: mean treated value = 6.5 ± 0.9 mmol/day: $P > 0.05$). However, during treatment there was a marked increase (almost doubling) in the percentage of individuals located at the top end of the distribution and therefore at a greater risk of forming calcium-containing stones as defined by the "risk curve" for urinary calcium, which is shown in relation to the frequency distributions for urinary calcium excretion.

5. DISCUSSION

This paper describes a development of a procedure previously reported by us for assessing the biochemical risk of forming Ca-containing stones in the urinary tract (11). The procedure has now been extended to cover the risk of forming all types of calcium- and/or uric acid-containing stones and utilises measurements commonly made on 24-h urine samples collected from stone-formers at most Out-Patient Stone Clinics. The procedure requires only seven measurements on each urine sample, which compares well with most other published indices of the risk of stone-formation. Most other indices either require a much larger number of analyses on each urine sample (as, for example, with the measurement of supersaturation using SUPERSAT (1-3), EQUIL (4) or the Activity Product Ratio (APR) (5)) or they require a combination of urine analysis together with some empirical measurement of the initiation of crystallisation (as in the determination of the Formation Product Ratio (FPR) (6), saturation-inhibitor index (7) or the Bonn Risk Index (10)). Only the Tiselius Indices (8, 9) require fewer measurements. However, they do not discriminate as well as P_{SF} between stone-formers and non-stone-formers, presumably because they include fewer of the risk factors that appear to influence the risk of forming stones.

The risk model combines factors that are known to influence both the supersaturation of urine with respect to the main constituents of stones and the ability of urine to inhibit or promote the growth and agglomeration of calcium oxalate and calcium phosphate crystals. In this respect, it has an advantage over the SUPERSAT, EQUIL and APR procedures which are designed to measure only supersaturation. It also has an advantage over the Bonn Risk Index since that assesses the risk of crystallisation in the **supernatant** of urine **after** any crystals that may have formed naturally have been removed. Indeed, this raises a question as to the relevance of the Bonn Risk Index procedure since the urine supernatant remaining after crystallisation has taken place naturally in the urine may bear little resemblance to that before crystallisation. If there were CaOx crystals present in the original urine and they were removed, then the concentration of oxalate remaining in solution will be much less than the total concentration of oxalate present just prior to crystallisation. Similarly, if there were CaP crystals present in the original urine and they were removed, then the concentration of calcium remaining in urine will be less than the total concentration present just prior to crystallisation. These changes in the composition of the remaining supernatant of urine will greatly affect the crystallisation point determined empirically as part of the Bonn Risk Index procedure. Only if the urine sample being tested has not produced any

Table 1. High risk of stone-formation in a stone-former (AGW) with a "normal-looking" urine compared with that in a urine sample from a normal control subject (FHT)

Urinary Analyte	Patient (AGW)	Normal Control (FHT)
Volume (litre/day)	1.42	1.65
pH	6.20	6.00
Calcium (mmol/day)	5.98	5.50
Magnesium (mmol/day)	3.62	4.50
Oxalate (mmol/day)	0.40	0.35
Uric acid (mmol/day)	3.66	3.20
Citrate (mmol/day)	2.11	2.50
P_{SF} (CaOx)	0.86****	0.35
P_{SF} (CaOx/CaP)	0.90*****	0.32
P_{SF} (CaP)	0.68**	0.39

Comparison of the 24-h urine analyses and resultant biochemical risk of forming stones in (a) a patient with calcium-containing stones (AGW) and (b) a normal control subject (FHT). This shows that despite the fact that (a) the urines are very similar in composition and (b) the individual analyses of the stone-former are all in the so-called "normal ranges" for these risk factors, the resultant P_{SF} values in the stone-former are abnormally high (>0.5) whereas those of the normal control subject are all within the normal range (<0.5). (* = Risk of stone-formation shown on a scale from * to ******)

crystals naturally will the Bonn Risk Index have any meaning. By measuring the total concentrations of the various urinary risk factors for stone-formation, the P_{SF} procedure avoids this pitfall and is valid whether or not crystallisation has occurred in the urine sample concerned.

Figure 4 shows that P_{SF} provides a very good discriminant at a value of around 0.5 between non-stone-formers and patients with either recurrent idiopathic calcium stones or calcium stones secondary to some metabolic disorder. The patients with a single recorded episode of stones (SSF) overlap with the non-stone-formers and the RSF. Statistically it would be expected that about 60-70% of these patients would eventually form another stone and the remainder will not form any more stones during their lifetime. It would be interesting to know if the SSF patients with P_{SF} values > 0.5 are essentially those who eventually become RSF and if the SSF patients with P_{SF} values < 0.5 are those who form no further stones.

One major advantage of the risk factor model over other procedures for assessing the risk of urolithiasis is that it can identify patients who have a significant risk of forming stones even although all of their seven urinary risk factors apparently lie within the so-called "normal ranges" for these variables (Table 1). Thus, it is not necessary to have a gross abnormality in one single urinary risk factor to increase the risk of forming stones. Indeed, this route to calcium and uric acid stone-formation appears to be the exception rather than the rule. More often, it would appear that these types of stone-formation are due to a combination of small differences in individual urinary risk factors rather than to a single gross abnormality. This emphasises the importance of combining urinary risk factors for calcium and uric acid stone-formation rather than trying to identify one (or perhaps two) "very abnormal" risk factors as the so-called "cause" of stones in a given individual. The model also dispenses with the concept of "normal range" for the various urinary risk factors since it defines the risk attribuTable to each urinary risk factor in terms of an increasing continuum instead of a discrete value at which each variable suddenly becomes "abnormal". This is a new concept to many clinicians and chemical pathologists who like to define disease in terms of distinct abnormality in one or more factor associated with the disorder. According to them, the risk of the disorder commences only at values of 2 standard deviation units above or below the mean normal value. In contrast, the risk model considers that the probability of forming stones is already increased in patients who are in the top (or bottom) halves of the so-called "normal ranges" for their urinary risk factors and that this risk increases exponentially as the risk factors increase (or decrease) as the case may be.

The model also allows an assessment to be made of the likely severity of the disorder in a particular patient (Figure 6). As PSF increases above a value of about 0.5, the likelihood of the patient becoming a recurrent stone-former increases and as PSF increases beyond 0.9, the probability of the patient having multiple annual recurrences also increases.

Figure 3 emphasises the point previously made by several groups that hypercalciuria per se is not the most important risk factor for calcium stone-formation. Based on the "risk curve" concept, the two most important risk factors for calcium oxalate stone-formation are a reduction in urinary volume and an increase in urinary oxalate and the two most important risk factors for calcium phosphate stone-formation are a decrease in urinary volume and an increase in urinary pH. This confirms the findings from in vitro studies which show that it is extremely difficult to cause urine to form either calcium oxalate or calcium phosphate crystals by only increasing the concentration of calcium in the urine sample, even when the concentration of calcium reaches values only rarely found in stone-formers (14, 15). On the other hand, by simply increasing urinary oxalate or pH within the so-called "normal range" of these variables, crystallisation of calcium oxalate or calcium phosphate is observed to occur within a few minutes. Calculation of the effect of increasing or decreasing the seven urinary risk factors on the supersaturation of urine with respect to calcium oxalate and

calcium phosphate are generally consistent with the findings in Figure 3.

Another feature of the risk factor model is that it clearly shows how changes in one or more urinary risk factors in the population because of some environmental stimulus (such as a change in diet or lifestyle, a seasonal or acute increase in exposure to UV light, or living or working in a hot environment) may increase the risk of stone-formation without producing a major increase (or decrease) in the mean value of the risk factor(s) concerned in the population. An example of this is shown in Figure 7. This shows that if a small number of individuals in a given population are more "sensitive" to a given stimulus than the main section of the population, then these are the individuals who are going to be at most risk of forming stones. This "hypersensitivity" may be genetic in origin or may be acquired through diet or lifestyle. Such "hypersensitivity" may apply to individuals who, for example, hyperabsorb calcium, or who show an exaggerated metabolic response to some dietary stimulus such as an increase in the intake of sodium, animal protein or refined sugars or who have a slight abnormality in their renal buffering capacity. Anything that causes an adverse change in one or more of the seven urinary risk factors described in this paper will increase the risk of forming calcium- or uric acid-containing stones.

Finally, it should be possible to utilise the measurement of P_{SF} to screen a patient before prophylaxis and then assess the likely efficacy of the preventative treatment in that patient by measuring P_{SF} during the treatment period. This will enable physicians to follow the course of the prescribed treatment and will allow an assessment to be made of patient compliance, which is known to be a major problem in the conservative and medical management of patients with urolithiasis.

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