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Renal Stones – An Update with Particular Reference to their Cause and Treatment in the Arabian Peninsula

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Introduction

Urolithiasis is a disorder that is recognised throughout the world, although its form and prevalence vary widely from one country to another[1-4]. The pattern of the disorder has altered considerably over the centuries, a process which is continuing even to this day, but the underlying trend has been for the prevalence (especially of upper urinary tract stones in adults) to increase[1-4]. At the same time, the prevalence of lower urinary tract stones in children, particularly boys, has tended to decrease and even to disappear altogether in some countries[1,2,4]. Both these trends have closely followed a general increase in the level of affluence in the populations concerned and appear to be largely related to the changes which take place in the dietary habits of individuals as their relative "standard of living" increases[1-8]. These changes include a movement away from a diet that is high in fibre and low in dairy produce and energy-rich nutrients, such as protein and refined carbohydrate, to one which is completely the reverse[1-8]. The former diet, which used to be the norm for many parts of Northern and Western Europe in the last century and early part of this century, is still common in some developing countries in the Middle and Far East today, in a belt extending from Turkey to Indonesia[1,2,9]. This type of diet, which is poor in certain nutrients, leads to a high risk of bladder stones in children. The prevalence of this form of the disorder is gradually decreasing as nutritional standards improve in the countries concerned and, by the turn of the century, may disappear altogether.

Upper urinary tract stones in adults, on the other hand, is generally associated with populations at the other end of the nutritional scale who ingest a diet that is low in fibre and high in dairy produce, animal protein and refined carbohydrate[4,6-8]. This form of the disorder has been increasing in most industrialised countries over the past 40 years[4,6,7] and is becoming particularly prevalent in countries where the in-

take of animal protein is highest[8,10].

Whatever the overall prevalence of urolithiasis in a given population, idiopathic calcium stone-formation is generally the most common form of the disorder[4]. It is mainly this aspect of the overall problem which will be discussed in this update. Details of the causes of other forms of the disorder may be found in various reviews[4,11].

Theories of Stone-Formation

Examination of the relative solubilities of the various constituents of urinary calculi suggests that stone-formation is essentially due to the precipitation of those minerals and organic acids which are sparingly soluble in urine. If so, most of the process of stone-formation should be explicable in terms of the chemical laws governing the nucleation, growth and agglomeration of crystals of these relatively insoluble compounds. In recent years, however, it has been suggested that some additional factors may be involved, such as anatomical abnormalities in the urinary collecting system[12] or damage to the urinary epithelium[13].

Many theories have been proposed over the years to account for the formation of stones, but, so far, none completely explains why some individuals form stones while others do not. Indeed, in the vast majority of patients, the disorder appears to be multifactorial rather than being due to a *unique* 'factor X' which distinguishes indisputably betweeen stone-formers and normal subjects, although, based on this philosophy, many workers are still striving to define a single diagnostic abnormality of this type. 'Factor X' has been variously described as (i) a particular normal constituent of urine that is present in abnormally high (or low) concentrations in stone-formers, or (ii) an abnormal constituent of urine that causes the nucleation, growth and agglomeration of crystals of one of the stone-forming minerals or acids, or (iii) a single anatomical, biochemical or physiological abnormality which leads to the concentration of a stone-forming mineral or acid at a particular site in the urinary tract.

The theories broadly fall in two groups – the so-called 'free-particle' and 'fixed-particle' models of stone-formation[14]. Both groups of theories share a common dependency on the concept that stone-formation is essentially a physical chemical phenomenon explicable in terms of the various processes involved in the crystallization of the relatively insoluble components of stones. The point at which the two diverge concerns the site and mechanism of the initial events involved in stone-formation. Proponents of the 'free-particle' model contend that the entire process of crystal nucleation, growth, agglomeration and entrapment takes place in an extracellular environment within the lumen of the renal tubule and, in theory, could occur in any individual who produces the requisite abnormal urinary environment[4,15]. Advocates of the 'fixed-particle' model, on the other hand, hold that the initiation step involves either some pathophysiological process or physical damage at some intracellular, interstitial, or cell-surface site which either initiates crystal nucleation and growth at that site or causes preformed crystals, present within the tubular fluid, to adhere to the tubular epithelium, thereby creating a focus for stone-formation[13,14]. This controversy constitutes the main debate within the stone field at the present time and deserves a more detailed analysis.

Free-Particle Theory

The simplest model of stone-formation defines the disorder as being due to the increased excretion of sparingly soluble minerals and organic acids in urine, leading to excessive supersaturation and precipitation of these substances within the lumen of the urinary tract. The process involves (i) the nucleation of crystal embryos within excessively supersaturated tubular fluid (or urine), (ii) the growth and aggregation of the embryos to form larger particles, (iii) the retention of one of these secondary particles which has enlarged sufficiently to become trapped at some narrow segment of the urinary tract, and (iv) the growth of this trapped particle to form a stone.

This hypothesis is supported to the extent that, in most forms of the disorder, stone-formers excrete higher amounts of one or more of the constituent ions of the salt or acid of which their stones are composed. Because of the relative insolubility in urine, any increase in the supersaturation of urine with respect to these substances exacerbates the risk of crystalluria. If crystalluria becomes persistent, the probability of an abnormally large particle forming and becoming trapped increases. Alternatively, blockage may occur by a "log-jam" mechanism in a urinary stream overcrowded with crystals. In support of this hypothesis, it has been shown that, compared with non-stone formers, (i) stone-formers pass more crystals of the mineral or organic acid which constitutes their particular type of stone[16,17], (ii) their crystals tend to be larger and more aggregated[16-18], and (iii) these abnormal crystals and aggregates exist in calyceal urine and are likely to have started forming in the collecting ducts[17]. It has also been shown that the severity of stone disease (as defined by the stone episode rate of the patient) is proportional to the percentage of large crystals and aggregates generally present in his/her urine[4].

Fixed-Particle Theory

Based on some theoretical calculations involving urine flow rates, crystallization rates and the dimensions of various parts of the urinary tract, Finlayson deduced that the 'free-particle' mechanism of stone-formation was impossible[14] and that there had to be some other abnormality present which would cause crystals to form or become "attached" to a particular fixed site either within the renal parenchyma or on the surface of the renal epithelium. He grouped this set of possible mechanisms under the term 'fixed-particle' model of stone-formation[18].

In order that crystals should adhere to cell walls and/or to each other, various biological "glues', mainly mucous substances, have been proposed. These include 'matrix substance A'[19], the polymerised form of Tamm-Horsfall muco-protein (sometimes referred to as 'uromucoid')[20,21] and a urinary protein termed PC-30[22].

Other workers believe, however, that it is not the presence of excess "glue" which is important in the causation of stones but the absence of an "anti-gluing factor" or inhibitor of crystallization. This category of protective substances includes small polyanions such as pyrophosphate[23,24] and citrate[25,26] and macromolecular polyanions such as the non-polymerised form of Tamm-Horsfall mucoprotein[27] a specific

γ-carboxyglutamic acid-containing glycoprotein called "nephrocalcin"[28-30], certain glycosaminoglycans[24,31], RNA[24,32] and more recently an aspartic acid-rich protein called "uropontin"[33] and another protein referred to as "crystal matrix protein"[34]. At the moment most interest centres around citrate, nephrocalcin, uropontin, Tamm-Horsfall mucoprotein (polymerised and non-polymerised) and crystal matrix protein.

However, whether or not any one of these turns out to be the unique 'factor X', referred to above, is a matter of conjecture. Already, there is considerable evidence that hypocitraturia may not be as potent a risk factor for calcium stone-disease as first thought[24,35]. Similarly, doubts are being cast on the roles of nephrocalcin[36] and of Tamm-Horsfall mucoprotein[4].

The "anti-gluing" property of these substances is attributed to their high negative charge density which assists their binding to calcium ions on the surface of crystals of calcium salts and at the same time causes the crystals coated in this way to repel each other rather than agglomerate. As well as inhibiting agglomeration, some of these substances, particularly the small polyanions, may retard the rate of crystal growth of either or both calcium oxalate and calcium phosphate[23-25]. It should be emphasised, however, that very few of the above list of substances inhibit both agglomeration and crystal growth of both salts[4].

Composite Model of Calcium Stone-Formation

The apparent multifactorial nature of calcium stone-formation may be summarised in a general model as shown in Fig. 1. This defines the first prerequisite of stones as being a period of abnormal crystalluria which, in turn, is dependent on a set of "chemical risk factors" including the supersaturation of urine with respect to calcium oxalate and/or calcium phosphate and the balance between the various urinary inhibitors and promoters of crystallization. These chemical risk factors, which together control the thermodynamic and kinetic forces involved in the crystallization process, are controlled by a set of "urinary risk factors" which are essentially the concentrations of the ions which affect supersaturation and promotive and inhibitory activity. Beyond this array of urinary risk factors lies a multitude of environmental, genetic, metabolic, pathophysiological and demographic risk factors which between them determine the composition of urine and ultimately the risk of stones. Similar, but slightly simpler, models can be drawn up to explain the formation of cystine, uric acid, and infection stones[4].

Stone-Formation in the Arabian Peninsula

Prevalence and Stone Composition

It has become increasingly apparent in recent years that urolithiasis is particularly common among the oil-rich states of the Arabian Peninsula. Data from the United Arab Emirates[37,38], Bahrain, Kuwait and Saudi Arabia[10,39,40] indicate that the occurrence of idiopathic calcium – and/or uric acid – containing stones is particularly

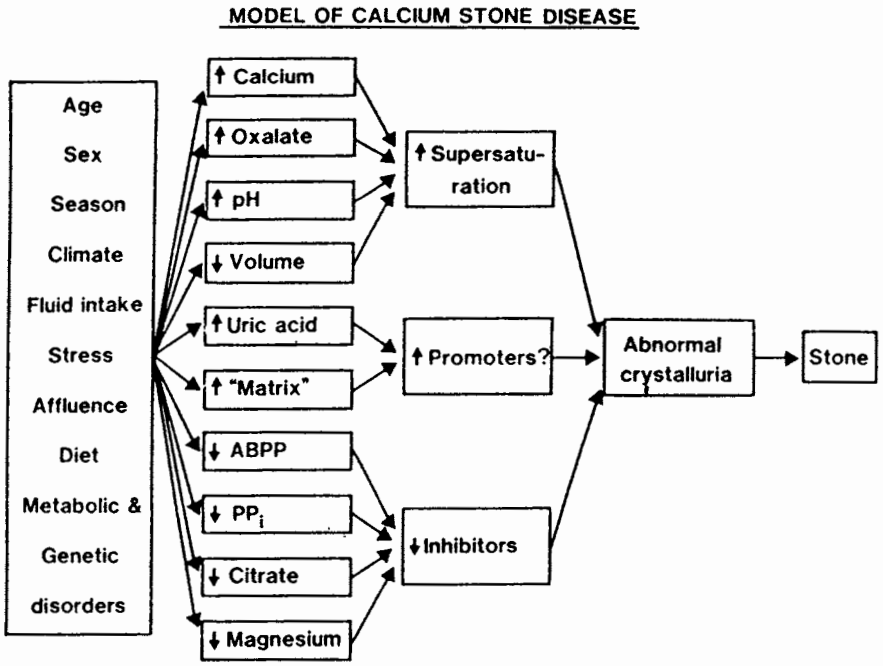

FIG. 1. A diagrammatic model of calcium stone-formation.

common and that this is essentially a problem of upper urinary tract stones affecting adults (male/female ratio about 4:1) rather than of lower tract stones in children as is still found in some countries of the north of the Arabian Gulf[4]. Table 1 shows that the age-specific expectancy of stones in men in some of the southern Gulf states ranks amongst the highest in the world, to the extent that over 20% of men in Saudi Arabia will be expected to have had at least one stone by the age of 60. This compares with values of 7.8% in the UK and 13.0% in the USA.

TABLE 1. Relationship between life-time expectancy of urolithiasis in men and urinary and dietary composition in normal men in various countries.

Country	Life-time stone expectancy in men (%)	Urinary oxalate (mmol/day)	Urinary calcium (mmol/day)	Dietary Ox/Ca (mmol/day)	Dietary AP (g/day)
China	1.5	–	3.5	–	21
Japan	5.4	0.31	4.1	–	39
U.K.	7.8	0.35	6.0	0.04	53
West Germany	8.0	0.36	5.8	0.06	59
Sweden	8.6	0.35	5.0	0.06	60
Canada	12.0	0.39	5.5	–	66
New Zealand	12.5	0.40	4.3	–	72
U.S.A.	13.0	0.41	5.5	0.10	76
U.A.E.	18.0	0.46	4.2	0.25	'very high'
Saudi Arabia	20.1	0.53	3.2	0.26	82

AP = animal protein: Ox = oxalate: Ca = calcium.

A more detailed study[41] indicates that the high age-specific expectancy of stones in Saudi males extends over the entire age range, including that of children. Indeed, idiopathic calcium stone-formation starts at an earlier age in Saudis and is about twice as common as in children in Western countries[41] (Table 2). Uric acid stones and rare stones (consisting of cystine, xanthine or 2,8-dihydroxyadenine) are also more common in Saudi than in Western children. On the other hand, phosphatic stones (including those due to urinary tract infection) are much less common than in the West.

TABLE 2. Composition of stones from children in various countries.

Stone type	UK (%)	Austria (%)	USA (%)	KSA (%)	Saudi/Western* frequency
Uric acid	0	3	4	15	9.0
Calcium	32	37	58	63	2.1
Infected	60	53	28	9	0.3
Rare	8	7	10	13	2.2

*Including the overall Saudi/Western prevalence ratio in children of 1.4:1, KSA = Kingdom of Saudi Arabia.

Table 3 shows that the pattern of stone-formation in Saudi adults is similar to that in children with a high predominance of calcium oxalate-containing stones and uric acid stones. Phosphatic calculi, as in Saudi children, are much less common than in most Western countries.

TABLE 3. The proportion of calculi according to predominant mineral in adult stone-formers from Saudi Arabia, the USA and the UK.

Predominant mineral	KSA (%)	USA (%)	UK (%)	KSA/UK* frequency ratio
Uric acid	14.6	10.1	4.0	5.8
Calcium oxalate	71.3	58.8	53.8	2.1
Calcium phosphate	7.6	20.3	30.9	0.4
MAP	3.7	9.3	9.6	0.6
Rare constituents	2.9	1.5	1.7	2.6

*Including the overall Saudi/UK prevalence ratio in adults of 1.6:1, KSA = Kingdom of Saudi Arabia.

Urine Composition

Studies on urine composition in Saudi Arabia have shown that, amongst both normal subjects and stone-formers, urinary volume, pH and citrate excretion tend to be low, whereas the excretions of uric acid and oxalate (particularly the latter) are considerably higher than corresponding values in the West[4] (Table 4). It should be noted that these differences are more accentuated in Saudi stone-formers than in

Saudi normals. However, hypercalciuria, which is a common finding among Western stone-formers, is rare in the Arabian Peninsula[10,38].

TABLE 4. Twenty-four urine biochemistry in male, recurrent calcium stone-formers in the UK and in Saudi Arabia.

Constituent	UK	Saudi Arabia
pH	5.92	5.68
Calcium (mmol)	8.9	4.6
Oxalate (mmol)	0.43	0.69
Citrate (mmol)	3.1	1.1
Uric acid (mmol)	3.5	4.9

It is easy to understand from these data why the pattern of stone composition in Saudi Arabia is as it is in Tables 2 and 3. The low urine pH together with the low urinary volume and hyperuricosuria markedly increase the risk of forming uric acid-containing stones; the extensive mild hyperoxaluria, low urinary volume and hypocitraturia increase the risk of forming calcium oxalate-containing stones and the low pH and low urinary calcium excretions explain the low occurrence of calcium phosphate stones in the region.

The high occurrence rate of mild hyperoxaluria (> 0.5 mmol/day) in the Saudi population is particularly noteworthy in the light of the relative importance of this abnormality in increasing the supersaturation of urine with respect to calcium oxalate, the volume of calcium oxalate crystalluria produced, the proportion of large crystals and aggregates of calcium oxalate formed in urine and the recurrence rate of stone-formation[10,42]. In these respects, mild hyperoxaluria is much more important than hypercalciuria in increasing the overall risk of forming calcium oxalate stones[10,42]. Together with the tendency to low urine volumes (as a result of mild dehydration), the high occurrence of mild hyperoxaluria is probably the main reason why the prevalence of calcium oxalate-containing stones is so high, not only in Saudi Arabia, but also throughout most of the Arabian Peninsula. The relative dominance of mild hyperoxaluria, in comparison with hypercalciuria, as a determinant of the life-time expectancy of stones in the population as seen in Table 1.

Diet

Diet histories taken from male Saudi stone-formers and normal subjects have shown that Saudis, in general, have a very high intake of animal protein and purine, an extremely high intake of oxalate and a relatively low intake of calcium (Table 5). This combination provides a very high oxalate/calcium ratio in the intestine (Tables 1 and 5) and a high acid load to the body. Between them these dietary "abnormalities" explain the more acid urine (from the acid-ash diet), the hyperuricosuria (from the high intake of purine), the extensive mild hyperoxaluria (from the high oxalate/calcium ratio in the diet) and the hypocitraturia (from the acid urine). Furthermore, hypercalciuria is rare because of the combination of the reported low circulating levels of vitamin D[43] and relatively low calcium intake inthe Saudi population[40]. When these urinary abnormalities are combined with a tendency to a low uri-

nary volume, it is not difficult to understand the high prevalence of calcium oxalate and/or uric acid stones and the relative low occurrence of phosphatic stones in the region (Tables 2 and 3).

TABLE 5. Diet histories in male idiopathic stone-formers in Saudi Arabia compared with stone-formers in the West.

Constituent	UK	USA	KSA
Animal protein (g/day)	61	85	87
Calcium (mmol/day)	24.5	25.0	13.0
Oxalate (mmol/day)	1.4	–	3.8
Purine (mg/day)	190	257	265

Prevention of Calcium Oxalate and Uric Acid Stone-Formation

Although extracorporeal shock-wave lithotripsy (ESWL) is widely used today to eliminate stones from the urinary tract once they have formed, this is, in one sense, an admission of failure on the part of researchers to identify an effective form of stone prevention. The very different urine biochemistry in stone-formers from the Arabian Peninsula compared with that in Western stone-formers raises a particularly interesting challenge in terms of devising a form of medical treatment that is suitable for the prevention of both calcium oxalate and uric acid stones, since most of the existing modalities which are currently in vogue in the West would not be likely to be beneficial in this environment. Altering the diet, in order to reduce the consumption of animal protein, purine and oxalate, would not be popular; a low calcium diet would only exacerbate the situation by further increasing urinary oxalate; thiazide diuretics would probably not have much beneficial effect since urinary calcium excretions are already low in most stone-formers; similarly, phosphate supplements would be unlikely to be efficacious since urinary calcium excretions are low and, in any case, if phosphate were to bind (or precipitate) calcium in the intestine then more oxalate could become available for absorption in the colon; magnesium supplements might be beneficial in those patients with hypomagnesiuria but most Saudi stone-formers appear to have normal-to-high urinary magnesium excretions; allopurinol should reduce the degree of hyperuricosuria and so decrease the risk of uric acid stone-formation but its value in the treatment of calcium oxalate urolithiasis is highly debatable. The only form of preventive therapy that might be of some value would be alkaline potassium citrate supplements. These have been claimed to be effective in reducing the recurrence rate of both uric acid – and calcium oxalate containing stones in the West[44,45]. By alkalinising urine and stimulating citrate production in the renal tubules, potassium citrate would be expected to solubilise uric acid (in spite of the existing hyperuricosuria) and, at the same time, eliminate the hypocitraturia which is common in the Arabian Peninsula. The only major abnormality that would not be affected by this modality would be the mild hyperoxaluria which is present in about 80% of calcium oxalate stone-formers in Saudi Arabia and is the main cause of their stones.

One possible way to correct the mild hyperoxaluria, which is essentially due to the abnormally high oxalate/calcium ratio in the diet, would be to add calcium to the diet[46]. Although this approach might not succeed in the West where a high proportion of stone-formers is known to hyperabsorb calcium from the intestine and would, therefore, exhibit a marked increase in hypercalciuria, in the Arabian Peninsula, where calcium absorption is low[47] due to the paradoxically low vitamin D levels,[43] the increase in urinary calcium would be predictably small. In this connection, a pilot study, utilising two different forms of calcium supplement, has shown that urinary oxalate can be normalized without causing much, if any, increase in urinary calcium[46]. In one arm of the study, calcium supplements were combined with potassium citrate to reduce urinary oxalate and increase both urinary pH and urinary citrate without causing any increase in urinary calcium. This regime significantly reduced the supersaturation of urine with respect to both uric acid ($P < 0.001$) and calcium oxalate ($P < 0.001$) thereby markedly decreasing the risk of crystalluria[46]. With a minor modification this type of regimen should be tested in recurrent calcium oxalate and/or uric acid stone-formers on a long-term basis to determine whether or not it reduces the actual recurrence rate of stone-formation in these patients over a period of several years.

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حصـــــوات الكلى
أحدث التطورات مع التركيز على أسبابها وطرق علاجها في شبه الجزيرة العربية

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المستخلص . يختلف مدى انتشار حصى المسالك البولية من مكان إلى آخر في جميع أرجاء العالم ، ولكن الاتجاه الغالب عليه هو زيادة انتشاره ، وخاصة في السبل البولية العليا ، مع ندرة وقوعه في المثانة في الأطفال ، وخاصة الذكور ، ويعزي تغير الانتشار في العديد من الدول النامية إلى تغير نوعية الغذاء .

تستعرض المقالة النظريات المختلفة لتفسير تكون الحصوات ، حيث أظهرت التقارير أن أقطار شبه الجزيرة العربية يسود فيها انتشار حصى السبل البولية العليا ، خاصة من نوع أوكسالات الكالسيوم وحامض اليوريك . ويتوقع تكون حصاة واحدة على الأقل لدى ٢٠٪ من الرجال في المملكة العربية السعودية ببلوغهم سن الستين ، مقابل ٧,٨٪ في المملكة المتحدة و ١٣٪ في الولايات المتحدة الأمريكية .

كما تنتشر حصيات الكلى لدى الأطفال في المملكة العربية السعودية بمعدل يبلغ ضعفه في الدول الغربية ، وفي سن أصغر ، ولكن حصوات الفوسفات أقل لدى السعوديين منها لدى رعايا الدول الغربية . وقد أظهرت التحاليل البولية بين السعوديين نقص حجم البول وكمية السترات والباهاء (PH) ، بينما يزيد إخراج كميات حامض اليوريك والأوكسالات مقارنة بالدول الغربية ، كما يندر فرط البيلة الكلسية لدى السعوديين ، مع كثرة انتشارها في الدول الغربية .

وزيادة البيلة الأوكسالية الطفيفة لدى السعوديين جديرة بالاهتمام ، لأهميتها البالغة في زيادة إشباع البول بأوكسالات الكالسيوم وزيادتها لحجم بيلة بلورات أوكسالات الكالسيوم وانتكاس تكون الحصيات . وقد أظهرت دراسة الغذاء أن الأفراد السعوديين يتناولون كميات كبيرة من البروتينات حيوانية المنشأ ومن البورين ، مع كميات فائقة من الأوكسالات ، إضافة إلى عوز نسبي في تناول الكالسيوم ، وهذا يفسر زيادة حموضة البول وفرط البيلة اليوريكة ونقص بيلة السترات .

وللوقاية من حصى المسالك البولية قد ينصح المرضى تغير نمط الغذاء ، بالإقلال من البروتينات الحيوانية والأوكسالات والبورين ، ولا يتوقع أن يلقى هذا قبولاً لدى المرضى ، كما لايتوقع الحصول على فائدة باستخدام مدرات البول (ثيازايدس) أو الفوسفات ، كما أن معظم السعوديين يفرزون في البول كمية طبيعية من المغنسيوم ، ولا يتوقع استفادتهم من

الاستطباب به ، ولعل أنسب الوسائل للوقاية من انتكاس الحصيات هو استعمال سترات المغنسيوم القلوية ، كما أن إضافة الكالسيوم إلى الغذاء يقلل بيلة الأوكسالات ، وقد أظهرت دراسة مبدئية فائدته في إعادة بيلة الأوكسالات إلى القدر الطبيعي دون زيادة تذكر في بيلة الكالسيوم .