URINARY TRACT STONE DISEASE

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Introduction

Patients suffering from urinary stone are traditionally referred to a surgeon. Most are investigated only as far as establishing the site of the stone and its effect on renal function. Although a number of patients may require surgery, the majority pass the stone spontaneously and are discharged within a few days. If the patient has a recurrence, as most eventually have, it is not routine practice to establish the type of stone, screen for underlying disease, identify the urinary abnormalities or to institute preventive medical treatment. Although it was considered that surgery itself had something to offer in reducing the recurrence rate this is no longer generally held except in infected stone disease. Nevertheless it is still uncommon to involve a physician, and in particular a nephrologist, in the investigation and management of urinary stone-formers. Urinary stone disease still remains, to a large extent, outside the field of nephrology.

Incidence and Morbidity

The incidence of urinary tract stone disease is unknown. Estimates indicate that it is about 7/10,000 of the population/year. The prevalence rate is more reliable although there is wide local and national variation. An average value is about 300 per 10,000 of the population [1]. Urinary stone disease is not only common but it is also recurrent. The recurrence rate varies greatly within and between patients, and is about one episode every 8 years [2].

The high prevalence and recurrence rate of urinary tract stone is associated with a considerable amount of suffering to the patient and cost to the nation. The majority of stones occur in males and are passed spontaneously with only a few days discomfort. About a third of stone episodes, however, require surgery which may leave some patients with permanently impaired renal function. Estimates of the amount of disability (Table I), including certified days lost from work [3], consultations by family doctors [4], hospital admissions [5] and
entry to the EDTA Registry indicate that urinary stone accounts for an appreciable proportion of the disability caused by all renal disease, especially in males. Chronic renal failure due to stone disease from the EDTA Registry figures are similar to those which have been reported from the UK [6,7].

<table>
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<th>Morbidity</th>
<th>Period</th>
<th>Urinary Tract Stone</th>
<th>Renal Disease</th>
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<td>1977</td>
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Types of Stone Disease

Quantitative analysis of 1135 urinary stones collected between 1971 and 1978 in Leeds shows that there are four main stone types (Figure 1). The most common is calcium stone accounting for 79% of all stones. In 64% the calcium is combined

Figure 1. The age and sex distribution in the four stone types as defined by quantitative analysis of 1138 urinary stones collected from 1971–1978
with significant amounts of oxalate and phosphate. In the remainder calcium is combined with oxalate (33%) or phosphate (3%) alone. The second most common is infected stone (17%) which is composed of magnesium ammonium phosphate with variable amounts of calcium phosphate. Uric acid (3%) and cystine stones (1%) are uncommon. This distribution of stone types is similar to that reported from other parts of Europe [8].

The age and sex distribution of the four stone types are different (Figure 1). Cystine stone presents in children and affects males and females equally. Uric acid stone occurs predominantly in males over the age of 40. Infected stone affects all age groups but is particularly common in females during the child-bearing age. Calcium stone occurs predominantly in males between the ages of 20 and 60.

The majority of stones originate in the upper urinary tract. Only 16% are from the lower urinary tract and should be distinguished from 'endemic' bladder stones which are now uncommon in Europe.

Pathogenesis

The most acceptable theory accounting for all four stone types, assumes that crystal formation with the sparingly soluble urinary stone-forming salts and acids is the initial abnormality. If crystalluria is persistent or severe, crystal aggregates form, lodge in the urinary tract and grow to stones. The formation of crystals is dependent on 2 main factors; the level of urinary saturation with respect to the stone-forming salts and the level of urinary inhibitors of crystal formation and aggregation [9,10]. The conditions leading to crystalluria and aggregation act at two levels, in the urine itself (urinary risk factors) and in the tissues and external environment (pre-urinary risk factors) and are responsible for the urinary changes.

Cystine Stone

There is only one main urinary risk factor for cystine stone-formation [11]. If the urinary cystine concentration is persistently higher than 1250μmol/1, the solubility level of cystine in urine, cystine stones will form. The concentration is only achieved in patients who are homozygous for an uncommon recessive disease characterised by a defect in the tubular reabsorption of cystine, arginine, ornithine and lysine.

Uric Acid Stone

The urinary risk factors for uric acid stone-formation are low urinary pH, below 5.3, and increased uric acid concentration [11]. Uric acid stones occur in patients with a defect in renal ammonia production and/or high uric acid excretion such as occurs in primary gout, myeloproliferative disease and uricosuric drug treatment. They are not uncommon in ileostomy patients who tend to pass urine with a low pH and low volume. A low urinary volume probably also accounts
for the high incidence of uric acid stones in some hot countries.

**Infected Stones**

The main urinary risk factors responsible for formation of infected stones are high urinary ammonia and pH [11]. Both result from bacterial metabolism of urea. Stone-formation may be promoted to some extent by increased amounts of inflammatory mucoprotein and by decreased amounts of inhibitors of crystal growth, such as pyrophosphate and citrate. Urinary tract abnormalities, surgery, instrumentation, pregnancy and stone disease itself are important factors in promoting infection. Of the four types of stone disease, infected stone disease is most often associated with progressive renal damage.

**Calcium Stones**

The urinary risk factors leading to calcium stone involve the concentration not only of calcium, oxalate and pH which largely determine the urine saturation with respect to calcium oxalate and phosphate but also of glycosaminoglycans which are powerful inhibitors of calcium oxalate crystal formation [11]. High urinary uric acid concentration by virtue of its inhibitory action on glycosaminoglycans is also an important risk factor for calcium stone-formation [11].

Much of the evidence indicates that calcium oxalate rather than calcium phosphate crystalluria is the major problem. Calcium phosphate is coincidental. Its presence in the stone is largely determined by the prevailing urinary pH.

In only a minority of patients is calcium stone associated with underlying disease. Primary hyperparathyroidism, hyperoxaluria (hereditary or enteric), renal tubular acidosis and medullary sponge kidney are the most common. But Cushing's Syndrome, sarcoidosis, immobilisation, vitamin D poisoning and excessive alkali intake may sometimes be the underlying cause. In the majority of patients (over 80%), no underlying disease can be identified and these patients are classified as idiopathic calcium stone-formers.

**Idiopathic Stone-formers**

Idiopathic stone-formers as a group have abnormalities in all six urinary risk factors. In the individual, however, they may not all be present. Quantitatively, hyperoxaluria is probably most important. Historically hypercalcioria is best characterised and is now considered to be due to increased plasma 1,25(OH)_2 vitamin D [12].

At the present time there is no single pre-urinary risk factor which can account for all the urinary abnormalities in idiopathic stone disease and it must still be considered as being multifactorial in origin. However, the influence of dietary animal protein may explain many of the features of the disease [13]. Of all the dietary factors which relate to the rise in incidence of stone disease, animal protein correlates best (Figure 2). This probably explains the high occurrence of stone disease in affluent, industrialised societies since animal protein is a
Figure 2. The certified days lost from work, the hospital discharges/10,000 of the population and the animal protein intake in England and Wales between 1960 and 1977. The fall in days lost from work and animal protein intake coincides with a period of inflation and decreased spending power.

direct reflection of wealth [13]. Idiopathic stone-formers have a higher than average intake of animal protein and as we have shown experimentally this leads to significant rises in at least 3 of the 6 urinary risk factors, namely calcium, oxalate and uric acid [14].

Although all the urinary risk factors are important, it is clear that if an underlying disease is present certain urinary factors may be more affected than others. In primary hyperparathyroidism the increased excretion of calcium and high urinary pH are major abnormalities. High concentrations of urinary oxalate are important in both congenital and enteric hyperoxaluria. In the former this is due to abnormal oxalate metabolism; in the latter to hyper-absorption of oxalate. In renal tubular acidosis the failure of the kidney to acidify the urine leads to persistently high urinary pH.

Treatment

Treatment of urinary stone, as in other diseases, must be based on accurate diagnosis. It is not enough to establish the presence of stone in the urinary tract which in itself is relatively simple. The type of stone, the urinary risk factors and the underlying pre-urinary risk factors and diseases must be identified. Quantitative stone analysis, plasma and urine biochemistry, urine bacteriology and patient history are usually required. Some patients may require extensive investigations before all the important features are fully established.

There are two aims in treatment. The first is to get rid of stones already present in the urinary tract. The second is to prevent stone recurrence. Surgery is
essential in all patients where the stone blocks the ureter or outlet of the renal pelvis. However surgery has no place in the prevention of stone recurrence, except in infected stone disease.

Cystine Stones

Cystine stone formation can be prevented, and stones in situ even dissolved, if the urine can be maintained under-saturated with cystine. An inexpensive approach is to increase the fluid intake to ensure a urinary volume continuously over 4L/day. This can be usefully combined with a high alkali intake since cystine is slightly more soluble in alkaline urine. The disadvantages of this treatment are polyuria, nocturia and the large dose of alkali required. A more expensive approach, and one associated with significant side effects, is to give penicillamine, up to 4g/day. A cysteine-penicillamine complex, soluble in urine, is formed and the urinary cystine concentration lowered.

Uric Acid Stones

When the urinary pH falls below 5.4 uric acid crystalluria occurs even in the face of a normal urinary uric acid concentration. Stone formation can be prevented by keeping the urinary pH high with oral alkali. In addition, and particularly in uricosuric subjects, allopurinol can be given to decrease uric acid production. The risk of xanthine stone formation is increased, but rarely occurs.

Infected Stones

A combined medical and surgical approach is always required to treat infected stones. Dissolution of the stone is impracticable. The first step is surgical. Any anatomical obstruction to urinary flow should be corrected and the stone completely removed. If stone fragments are left they act as a nidus for infection and crystal growth, and the stone rapidly reforms. The second step is to keep the urine sterile with antibiotics. In some patients this can be a difficult problem if the urine becomes reinfected with antibiotic resistant organisms. Urease inhibitors, which have not been marketed so far, may be useful in such patients.

Calcium Stone

It is virtually impossible to under-saturate the urine and dissolve calcium oxalate stones. Medical treatment is therefore aimed at reducing the urinary risk factors and preventing new stone formation.

In primary hyperparathyroid patients, parathyroidectomy usually stops stone recurrence. High fluids and oestrogen, in post-menopausal women, can be used where parathyroidectomy is impracticable. Enteric hyperoxalurics respond to a low oxalate and high calcium diet. Treatment of hereditary hyperoxaluria is disappointing; a high fluid intake should be given but the prognosis remains poor. Some patients with renal tubular acidosis benefit from oral acid and, where there
is hypercalciuria, from thiazides. Where an underlying disease is present, such as Cushing’s Syndrome, treatment should be directed at removing it.

Many treatments have been advocated for idiopathic calcium stone. Although substantial reduction in the stone recurrence rate has been shown with a low calcium and low oxalate diet [15], orthophosphate supplements [16], thiazide diuretics [17] and allopurinol [18], none has been subjected to a controlled trial (Figure 3). Moreover, several have been studied over too short a time period to be convincing since any treatment always shows a decrease in the stone recurrence rate over the first few years. The criteria for the choice of treatment for idiopathic calcium stone remain arbitrary. It is logical, however, at the present time to prescribe treatment for the patient that reduces the urinary risk factors which are raised.

To reduce the rising incidence of stone disease in the population it is probable that only a substantial change in the diet, especially in its protein content, will be effective [19]. This may require active intervention or as shown in Figure 2, may take place naturally if affluence is curbed.

![Figure 3](image)

**Figure 3.** The effect of treatment with a low calcium and low oxalate diet [15], thiazide diuretics [17], allopurinol [18] and oral phosphate supplements [16] on the stone recurrence rate of urinary stone-formers. The axes are expressed as cumulative sums (cusum)

**Acknowledgments**

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Open Discussion

OREOPoulos (Toronto) We were concerned about the effect the prolonged low calcium diet would have on the bone mineral. In a prospective study in a small number of patients with idiopathic stones and a few hypercalciurics, we did find a decline in bone mineral density and I am wondering whether you have observed the same thing or whether you are concerned about putting a patient on a low calcium diet over long periods?

PEACOCK Most of the population one is looking at is male and many of them have hyperabsorption of calcium, so what one is really doing is reducing the amount of calcium being absorbed but even on a low calcium intake the amount of calcium is still substantial and is still normal. When we looked at the loss of bone with time on a low calcium, low oxalate diet we could find no decrease in bone mass. If you take this into the post menopausal women who are certainly at risk of losing bone naturally because of lack of oestrogens, then of course one would think very carefully about prescribing a low calcium diet for this group, and I am sure this is not the treatment for the idiopathic female stone former.
ROSENVELT (Tel Aviv) I would like to ask you, considering the multifactorial aetiology of the stones, when you start to work up your patient.

PEACOCK Well this is obviously a difficult problem. What we tend to see in our own unit is referred patients from the urologists and they tend to refer at the second stone episode, so that is one way of doing it. I think certainly a patient who has passed two stones should be fully investigated. My own view would be that every patient who passes a stone should have full investigations. Now in the difficult patients this requires quite extensive investigations but the majority of patients can be assessed fairly simply on history, examination, x-ray analysis and diet history, urine examination and then analysis of the 24 hour urine. In addition to that, blood needs to be taken and possibly one of the most important things is to keep the stone and analyse it qualitatively because this classifies the patient very rapidly.

KANIS (Oxford) I wonder whether I could ask two questions. The first relates to your control patients because you show quite a marked effect of treatment, and I wonder whether these were studied prospectively. The reason for asking this is that if one is presented with a patient who has just had a stone and if one then uses his prehistoric data as control data, any treatment even if it is ineffective will tend to show benefit. So I wonder whether your control patients were studied prospectively or whether they were taken from the history of the patients themselves before you decided to treat them?

PEACOCK The data that I showed you on the cumulative plots with allopurinol, low calcium, low oxalate, come from various sources. In all of these, what they have done is take the patient as his own control and so estimate the recurrence rate before treatment and then a recurrence rate on treatment. That in actual fact is completely inadequate because anything you start will have a very high efficiency over the first year and will get less positive the second year, less positive the third year and so you have to go on for as long as the history of the patient lasts. In other words if the history is for twenty years before you started you should really go on for a further twenty years on treatment. These are some of the drawbacks in studying treatment in these patients; the very long recurrence rate. So the ideal method is to have a controlled study which we are now doing and to have a no treatment group. But even then there are problems because many patients going to urologists and then passing on to a clinician have already started themselves on low dietary products, high fluid intake. So even that control group has already altered itself and so it is a very difficult problem to come down and see what is a good form of treatment and really what is efficient; but what I have shown you this afternoon are the ones in the literature which are considered to have some effect.

KANIS Could you speculate about the mechanism for changes in urinary calcium excretion with changes in protein diet?

PEACOCK Well I could speculate for an hour. This is an area we are actively interested in at the moment. Published data would suggest that it is not from the gut. My own hunch is that it is from the gut, but it is not dependent on vitamin D.
FOURNIER (Amiens) I am a little confused by your statement about the treatment of renal tubular acidosis by giving the patient acid, since the diagnostic criterion of this disease is that acid load cannot decrease the pH of the urine, therefore I am asking you what are your clinical data to show that the nephrocalcinosis and nephrolithiasis will improve, which results are in contradiction with all that is written in the textbooks.

PEACOCK Yes, I am glad you raised that point, because you see the standard treatment is alkaline and the reason we give this is to reduce to some extent the urine calcium and also of course to correct the acidosis if possible. Now what this does in terms of the urinary risk factors is to increase the urine pH so there is no chance of calcium phosphate ever dissolving, so these patients will continue to pass calcium phosphate stones on alkali. The only hope one has is in the few patients who can in actual fact acidify just below 6.2. If you can bring the urine pH just below 6, then you will prevent calcium phosphate precipitation, although you must obviously be very careful that you don’t increase the systemic acidosis and so this has to be done extremely carefully.

FOURNIER But you increase the calcium excretion and you increase the hyperparathyroidism by giving them an acid load.

PEACOCK I don’t think you increase the hyperparathyroidism; there is no evidence in our laboratory to suggest that this is true and the same applies when you treat the ‘hyperparas’ with acid. Acid does not stimulate parathyroid hormone. The hypercalciuria is very variable and I do not think you can assume that a small dose of acid will necessarily produce hypercalciuria, and even so it is not the calcium concentration that is important, it is the urinary pH that is the main determinant.

FOURNIER But do you have clinical, control data showing the superiority of acid therapy versus alkali therapy in this condition?

PEACOCK We have not got enough cases.