Dietary treatment of nephrolithiasis

Antonio Nouvenne
Tiziana Meschi
Angela Guerra
Franca Allegri
Beatrice Prati
Loris Borghi

Department of Clinical Sciences, University of Parma, Parma, Italy

Address for correspondence:
Loris Borghi, M.D., Ph.D.
Department of Clinical Sciences, University of Parma
Via A. Gramsci 14, 43100 Parma
Ph. +39 0521 703374
Fax +39 0521 985468
E-mail: loris.borghi@unipr.it

Summary

The prevalence of idiopathic nephrolithiasis is increasing in rich countries. Dietary manipulation could contribute to the prevention of both its first appearance and the recurrence of the disease. The target of dietary treatment is to decrease the "urinary lithogenic risk factors" such as low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hyperphosphaturia, hypocitraturia, hypomagnesuria and excessively alkaline or acid urinary pH. Due to the lack of randomized controlled trials focused on this problem, there is not ample evidence to confidently recommend dietary changes. Despite this, numerous recent and past experiences support modification of diet as having a primary role in the prevention of nephrolithiasis. In particular, it is recommended to limit animal protein and salt intake, to consume milk and derivatives in amounts corresponding to calcium intake of about 1200 mg/day and to assume fiber (40 g/day), vegetables and fruit daily avoiding foods with high oxalate content. Furthermore, vitamin C intake not exceeding 1500 mg/day plays a protective role as well as avoiding vitamin B6 deficiency and abstaining, if possible, from vitamin D supplements. Lastly, it is recommended to drink enough water to bring the urinary volume up to at least 2 L/day and, as much as possible, to use fresh or frozen products rather than prepacked or precooked foods which are often too rich in sodium chloride.

KEY WORDS: nephrolithiasis, diet, prevention.

Introduction

Like other "well-being diseases" such as obesity, hypertension, atherosclerosis, myocardial infarction and type 2 diabetes, nephrolithiasis is progressively on the increase in rich countries (1, 2), being now a very common condition affecting in the USA 10% of the population (3) with an economic burden of about 2 billion dollars per annum (4).
Only in extremely rare cases it is a result of hereditary or well-defined acquired diseases such as cystinuria, congenital hyperoxaluria, primary hyperparathyroidism, renal tubular acidosis, infections or anatomical alterations of the urinary tract (secondary nephrolithiasis), all conditions in which diet plays a marginal role. In the majority of cases stone disease strikes otherwise healthy people (idiopathic nephrolithiasis) and appears to be closely correlated to life style and diet (5).
Although only few well conducted randomized-control trials have been performed so far, large cohort studies, such as the Nurses' Health Study (6, 7) and the Health Professionals Follow-up Study (8, 9), have provided, together with various experimental studies, evidence which is consistent enough to state that appropriate dietary manipulations can successfully prevent both the first appearance and the recurrences of idiopathic nephrolithiasis. Hence, it is extremely important that not just the specialist, but the general practitioner also should be fully aware of the primary role of diet in the management of this condition.
In 90% of cases of idiopathic nephrolithiasis, the stones are made of calcium oxalate, often associated with variable traces of calcium phosphate and, occasionally, uric acid; in 10% they are made of pure uric acid (10). Nutrition has a direct impact on the mechanisms involved in the genesis of urinary calculi (11).
The first step in the genesis of a kidney stone is the formation of crystal nuclei. This event occurs when the concentration of a salt exceed the solubility limit (*supersaturation)*. Sometimes this is also accompanied by a deficit in the protective substances known as crystallization inhibitors, e.g. citrate and magnesium. By the term "urinary stone risk factors" (12), we refer to a series of conditions which, all together, either promote or prevent the crystallization of a salt.
For calcium oxalate stones, the most widely recognized urinary stone risk factors are low urine volume (< 2 L/day), hypercalciuria (> 250 mg/day [6.25 mmol]), hyperoxaluria (> 45 mg/day [0.5 mmol]), hyperuricosuria (> 700 mg/day [0.24 mmol]), hypocitraturia (< 320 mg/day [1.7 mmol]), and hypomagnesuria (< 60 mg/day [2.5 mmol])
For calcium phosphate stones, important factors are hyperphosphaturia (> 1100 mg/day [35.6 mmol]) and an excessively alkaline urine pH (> 7.0) along with low urine volume, hypercalciuria and hypocitraturia.
For uric acid stones, favoring factors are low urine volume, hyperuricosuria and an excessively acid urine pH (< 5.5).
The existence of a genetic substratum in idiopathic stone disease cannot be overlooked (13), but diet undoubtedly has a direct effect on all of the above urinary stone risk factors as well as on the subsequent pathogenic steps.

The role of water and other fluids

The urine volume plays a huge role on the saturation of lithogenic salts. We used the computer program Equil (14) to simulate the changes of the relative saturation for calcium oxalate, calcium phosphate and uric acid when the urine volume increases from 0.5 to 3.0 L/day, while keeping constant all the other urinary parameters involved in the calculation of saturation point. By this way, we saw that with diuresis below 1 L/day,

even the urine of a normal subject reaches extremely high supersaturation levels, certainly high enough to promote spontaneous crystallization of the lithogenic salts. If, on the other hand, the volume is maintained over 2.5 L/day, the urine becomes undersaturated for calcium phosphate and uric acid and only slightly supersaturated for calcium oxalate, making spontaneous crystallization impossible. Given that, in the context of these physiological variations in diuresis, ion excretion is largely independent of urine volume, this example simulates very closely what actually happens when water intake is high.

It could be argued that the increase in urine volume would dilute the crystallization inhibitors, and thus offset its positive effects on lithogenic salts. However, observations made on both normal subjects and idiopathic calcium stone formers dispel this argument because (a) the level of supersaturation required to cause spontaneous calcium oxalate nucleation in diluted urine is greater than that required in the non diluted urine of the same subjects (15); (b) the oxalate amount one has to add to the diluted urine to produce calcium oxalate crystallization *in vitro* is higher than that required in non diluted urine (16), and (c) the inhibitory power of the macromolecules extracted from non diluted urine is not quantitatively different from that of the macromolecules extracted from non diluted urine (16). Finally, studies in progress in our laboratory in both normal subjects and calcium stone formers show that the number and quantity of calcium oxalate crystals and crystalline aggregates produced with an oxalate load *in vitro* are markedly lower in diluted urine than in non diluted urine.

Increased urine volume might exert its antilithogenic effect also by reducing the transit time of renal intratubular fluids, thereby favoring the expulsion of the crystals (17) and inhibiting the formation of Randall's plaques (18).

By converse, low urine volume is a lithogenic risk factor (19), as shown by cohort studies in which subjects consuming less than 1.5 liters of fluid per day had about a 50% increase in incidence of kidney stone as compared to those consuming over 2.5 L of fluid per day (6-9).

Two trials are to be quoted about the beneficial effects of water. The first (20) showed that the incidence of kidney stones in a community living in warm climate and that had been educated to drink more water was ten times lower than that detected in a matched community that had not been educated to do so; the second (21), a randomized-controlled study, showed that the calcium stone formers who increased their water intake in order to increase their urine volume, from approx. 1 to approx. 2 liters per day, during 5 years had a recurrence rate of 12 % as compared to 27% who had not changed their water intake.

Whilst there is no doubt that the quantity of water consumed is important for both the primary and secondary prevention (recurrences) of stone formation, it is still controversial whether hard waters, i.e. rich in calcium and other minerals, are as effective as light waters (22).

As to the fluids other than water, some reports (23-31) suggest that coffee, tea, beer, wine, orange juice, lemon juice and blackcurrant juice can reduce the risk of stone formation, while grapefruit juice, apple juice, soda and cola drinks increase it.

In conclusion, the evidence currently available shows that a water intake sufficient to increase urine volume to at least 2 liters/day exerts an antilithogenic effect. Some fluid such as orange juice or lemon juice might elicit some additional benefits.

The role of proteins

As regards the effect of animal proteins, the findings from cohort studies are conflicting. The male subjects from the Health Professionals Follow-up Study, whose intake of animal proteins exceeded 75 g/day (upper quintile) had the highest risk of forming stones (8,9) a response not shared by the females of the Nurses' Health Study (6). Indeed, in younger women, animal proteins exerted, if anything, a moderately protective action (7). However, in a nation-wide survey in the UK (32), vegetarians showed a prevalence of urinary stone formation about half that found in a sample taken from the general population matched for age, sex and social class.

As to the urinary stone risk factors, most studies found that animal proteins (meat, fish and poultry) have an unfavorable effect because they increase calciuria, uricuria, and phosphaturia, while reducing citrate and urine pH (33). It has been estimated that in normal subjects for every 25 g increase in dietary animal protein, urinary calcium rises 32 mg (34). When overweight subjects (35) increased their habitual protein intake, from about 90 g/day to approximately 170 g/day of largely animal proteins (Atkins diet) for 6 weeks, their calciuria rose by about 90 mg/day (2.25 mmol), uricuria by about 130 mg/day (1.3 mmol), phosphaturia by about 620 mg/day (20.2 mmol), while their citraturia decreased by about 180 mg/day (0.9 mmol) and the urine pH from 6.09 to 5.67. Some studies have reported that animal proteins also produce an increase in oxaluria (36). With urine volumes kept unchanged, the final outcome of a high animal protein intake is an increase in supersaturation for both calcium oxalate and uric acid. Even more relevant is the fact that, at parity of animal protein load, these urinary effects seem more marked in stone formers, as though these subjects had a sort of genetic hypersensitivity towards such foods (37).

The mechanisms by which animal proteins produce these effects are only partially understood. The increases in uricuria and phosphaturia are directly related to the high purine and phosphorus content of animal proteins. The increase in calciuria and the reduction in citraturia and urine pH are mainly attributed to the high content of sulphurated amino acids (methionine and cysteine) which, by producing high quantities of hidrogenions, cause a metabolic shift towards a state of subclinical acidosis (38). The mechanism of the increased oxaluria is less clear. According to a widely quoted view, the oxalate precursors present in animal proteins, such as the amino acids tyrosine, tryptophan, phenylalanine and hydroxyproline, cause an increase in endogenous oxalate production (39).

It is important to point out that the vegetable proteins produce urinary effects different from those of the animal proteins. An experiment was carried out on normal subjects in which 75 g/day of exclusively animal proteins were first replaced by an equal quantity of mixed ovo-vegetable proteins, then by exclusively vegetable proteins (40). The data show that with an exclusively vegetarian intake the urine contains less calcium, less phosphorus, more oxalate, more citrate and fewer acids. These differences may be explained by the different content of purines, oxalates, sulfates and fibers. On the whole, these data clearly indicate that vegetable proteins have a much lower lithogenic potential, particularly with regard to uric acid stone disease.

Only two randomized-controlled trials have been carried out to evaluate the hypothesis that a reduction in animal proteins could prevent recurrences in idiopathic calcium stone disease. One showed that after a period of over 4 years the group treated with low animal protein and high fiber diet had a higher recurrence rate (12/50 = 24%) than the control group (2/49 = 4%) treated with high fluid and a usual calcium intake (41). It should be, however, pointed out that this trial had several major limitations: a) the water intake in the control group was higher; b) compliance with the low protein diet was actually very poor; c) there may have been differences between the two groups as regards the intake of dietary calcium and fiber, both of which influence stone formation.

The other trial compared a low calcium diet (i.e., free of milk and dairy products) with a low-animal protein, low-salt and nor-

mal calcium diet (42). After 5 years, the recurrence risk in the first group was higher (23/60 = 38%) than in the other group (12/60 = 20%), but it should be pointed out that, in this experiment, it was not possible to distinguish the protective effect of the low animal protein intake from that due to the higher calcium and lower salt intake.
All in all, the aforementioned dietary studies favor the view that subjects at risk for calcium or uric acid stone disease should avoid consuming large quantities of animal proteins.

The role of carbohydrates

An increased intake of sucrose was found associated with stone risk in women (6, 7), but not in men (9).
It is well-known that an acute load of glucose causes a transient calciuria rise in normal subjects and to an even greater degree in idiopathic calcium stone formers and their relatives (43). Some investigators have conjectured that this effect is mediated by insulin reducing the tubular reabsorption of calcium (44), but others refute this theory because, after comparing a diet with a high carbohydrate content (60% carbohydrates and 25% fat) with an isocaloric high-fat diet (50% fat, 35% carbohydrates), they did not find any differences in calcium excretion, despite the higher levels of insulin in the subjects on the higher carbohydrate diet (45). However, the comparison between diets with low (220 g), medium (450 g) and high (600 g) carbohydrate content, but unvaried in the content of proteins, fats and calcium, showed the level of urinary calcium to increase in proportion to the amount of carbohydrate intake (46). Moreover, optimal metabolic control in diabetic patients through insulin therapy leads to a considerable decrease in calcium excretion (47).
Surprisingly, after these early reports there have been no further studies published on the relationship between carbohydrates and calcium stone disease. Rather, interest has shifted to the relationship between metabolic syndrome, type 2 diabetes, insulin resistance and uric acid stone disease. The association between body size and risk of kidney stones was noted for the first time in 1998, and has recently been confirmed in both males and females (48). It is believed that insulin resistance, frequently associated with excess body weight, can alter the urine acidification mechanism. It has been established for some time now that gouty patients and uric acid stone formers in general stand out from the rest of the normal population and from calcium oxalate stone formers because they have a particularly acid urine pH, lower than 5.5, which leads to a marked increase in the undissociated form of uric acid which precipitates in urine (49).
The relation between glucose intolerance and uric acid stones have been thoroughly investigated. Some authors found that uric acid stone formers have a high incidence of type 2 diabetes or glucose intolerance (50-52). These patients often show an increased urinary acidity due to a reduced capacity to eliminate the acid load in the form of ammonium (50). The final result is a higher concentration of free H+ ions (low pH), higher titrable acidity and often a decrease in citraturia. Interestingly, stone formers with type 2 diabetes prevalently form uric acid stones and show a urinary risk profile very similar to that of gouty patients (51). The authors hypothesized that insulin resistance in type 2 diabetes might impair renal ammoniogenesis resulting in a low urine pH. In a subsequent study, they further supported this hypothesis by showing that patients with recurring uric acid stone disease have severe insulin resistance (52). A further study showed, in a large population of stone formers, that urine pH is strongly inversely associated with body weight (53).
Therefore, considering the close relationship between carbohydrate consumption, insulin resistance, diabetes mellitus and obesity, the overall results of these studies enables us to conclude that excessive consumption of carbohydrates, especially simple ones, should be considered as a risk factor for renal stones, even if no prospective randomized trials exist on the real possibility of preventing stone recurrences by imposing a suitable low glucide, low calorie diet on patients with such characteristics.

The role of fats

Some observations suggest that fats are also implicated in stone formation. These observations can be briefly summarized as follows: stone formers show a high prevalence of hypercholesterolemia (54); high-fat, high-cholesterol diets can induce stone disease in laboratory animals (55); urinary lipids play a role in the formation of crystals and stones (56); fat intake is correlated with oxalate excretion (57), this relationship being more evident with regard to the dietary content of arachidonic acid (58).
Other investigators found high levels of arachidonic acid in the plasma and membranes of red blood cells of stone formers (59), probably related to hypercalciuria through an alteration in transmembrane ionic transport and overproduction of prostaglandin E2. These data concur with the demonstration that ω-3 fatty acid supplementation, in the form of eicosapentaenoic acid (EPA) or fish oil, can reduce levels of arachidonic acid in plasma and tissue and this is accompanied by a decrease in the excretion of calcium and oxalate, both in humans (60) and in laboratory animals (61).
However, a recent observational study did not confirm the existence of an association between fatty acid intake and the development of kidney stones (62). Clinical trials testing the efficacy on stone prevention of high doses of ω-3 polyunsaturated fatty acids in the form of fish oil supplements have never been performed.

The role of sodium chloride

An association between salt consumption and calcium stone formation was first reported in a large cohort study (6), but some subsequent studies failed to confirm this finding (7, 9). It should, however, be recognized that it is very difficult to make reliable estimates of dietary salt intake based on food questionnaires, as attempted in those studies.
A number of interventional studies published since 1959, reviewed in 1995 (63), support the notion that salt consumption invariably increases calcium excretion and, conversely, salt intake reduction induces a decrease in calciuria. From these studies it can be estimated that an average increase of 100 mmol of salt (approx. 6 g of sodium chloride) generates an average increase in calciuria equivalent to 1 mmol of calcium (40 mg) in normal adults and 2 mmol (80 mg) in hypercalciuric stone formers. These findings have important practical implications if we consider that in some countries the average consumption of salt is at least 10-12 g/day.
Another relevant observation is that the calciuric effect of sodium chloride is additive to that of the proteins as shown by an experiment performed in normal subjects who increased their salt intake from 8 g to 12 g and their protein intake from 1 to 2 g/kg (64): calciuria increased by about 50 mg (1.25 mmol) with each modification and by 100 mg (2.5 mmol) with both modifications.
It is important to point out that in literature the term “sodium” is very often employed as synonymous of salt. This is, however, misleading because when other types of sodium salts, such as

sodium bicarbonate and sodium citrate, were compared with sodium chloride on an equimolar basis, they did not increase urinary calcium (65, 66), leading to the conclusion that the calciuria-producing effect of kitchen salt is due to its chloride content (67).
There is substantial agreement that the salt increases calciuria through its inhibiting effect on the tubular reabsorption of calcium (68).
Additionally, it should also be pointed out that the increase in sodium chloride in the diet is also accompanied by a significant decrease in urinary citrate (69), which on its own increases the lithogenic risk. The mechanism by which salt reduces urinary citrate is uncertain. According to a widely-shared view, it is related to the bicarbonaturic effect of the salt intake elicited by extracellular volume expansion causing a decrease in the extracellular pH.
Although there are no randomized studies testing the capacity of a low salt diet to reduce kidney stone formation on its own, there is evidence suggesting that a low salt intake may improve the beneficial effects of a low animal protein intake (42).
A balanced diet for the prevention of renal stones should contain no more than 6 g/day of sodium chloride, an amount also fulfilling the recommendations provided in the updated report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (70). To this end, it is important to inform the patient about the “hidden sources” of salt.

The role of milk and dairy products

The recommended daily intake of calcium can be satisfied by foods such as milk (approx. 120 mg per 100 ml), yogurt (approx. 120 mg per 100 g) and cheese (on average approx. 700 mg per 100 g). Abstaining from such foods leads to a very low-calcium intake (approx. 400 mg/day).
Calcium intake affects calciuria: in normal subjects an increase in calcium intake brings about an increase in calciuria equivalent to 8% of the increased amount, rising to 20% in hypercalciuric stone formers due to their peculiar ability to hyperabsorb intestinal calcium (71). This means, for example, that changing from a diet containing 400 mg of calcium to one containing 1200 mg, can increase calcium excretion in a normal subject from 120 mg/day to 180 mg/day, and in a hypercalciuric subject from 240 mg/day to 400 mg/day. This is the reason why, for many years now, physicians have been advising patients with calcium stone disease to reduce or eliminate their intake of milk and dairy products. In the light of current knowledge, this indication does not appear to be sound for three important reasons.
Firstly, the low calcium diet may not succeed in reducing calciuria in a large percentage of subjects (72), while it can cause a negative calcium balance (72) which, over prolonged periods, can lead to the onset of osteopenia/osteoporosis (73).
Secondly, reducing calcium intake increases intestinal absorption of oxalate (74,75). Oxalate is prevalently absorbed in the small intestine and colon, where, in the presence of high calcium concentration, it can form non absorbable calcium oxalate salt; conversely, if calcium level in this site is low, the oxalate will be more easily absorbed in the form of sodium or potassium oxalate. It has been estimated that oxalate excretion decreases by an average of 1.9 mg (0.02 mmol) for each 100 mg increase of calcium intake per day (76). For instance, a change in daily calcium intake from 400 mg to 1200 mg brings about a decrease in oxalate excretion from 40 mg/day to 24 mg/day. The oxalate decrease of 16 mg/day might appear trivial when compared with the concurrent increase in calciuria, which according to the example previously reported, should amount to 60 mg/day in the normocalciuric stone former, and as much as 160 mg/day in the hypercalciuric stone former with a specific hypersensitivity to calcium intake. However, viewed in terms of urine supersaturation, the implication of the changes in oxalate excretion are anything but trivial: changing from the low calcium diet to a normal calcium diet does not increase calcium oxalate supersaturation, but actually reduces it by approx. 10%.
Thirdly, when we recommend the dietary limitation of milk and dairy products, patients are likely to increase their animal protein intake in the form of meat, fish and poultry, leading to all the potential unfavorable consequences mentioned earlier.
The pathophysiological considerations reported so far agree with the results achieved in large follow-up studies (6-9). According to these studies, the risk of becoming a stone former, for men and women alike, is much lower in those who habitually consume relatively high quantities of calcium (> 1000 mg/day) than in those who consume lower quantities (< 600 mg/day). Finally, a 5-year randomized study conducted on male hypercalciuric calcium stone formers showed that a low calcium diet, achieved through the elimination of milk and dairy products, is less efficacious in the prevention of stone recurrences than a normal-calcium, low-animal protein, low-salt diet (42).
In conclusion, in the light of current knowledge, idiopathic stone formers should not be deprived of normal quantities of milk and dairy products.

The role of fruit and vegetables

Doctors are hesitant in advising stone formers to eat fruit and vegetables, because these foods are the most important dietary source of oxalate, part of which is undoubtedly absorbed to be excreted with the urine. However, their higher urinary oxalate notwithstanding (77), vegetarians show a prevalence of stone disease about half that of omnivores (32).
How can we explain this apparent paradox?
First of all, we must point out that only a few vegetables have demonstrated to significantly increase oxaluria: spinach, rhubarb, beets, nuts, chocolate, tea, wheat bran and strawberries (78).
Although a sizable proportion of urinary oxalate may derive from diet, up to 50% (79), there is great variability from person to person in intestinal absorption rate. Since about 8-10% of idiopathic stone formers show hyperoxaluria (80) and 20-30% of these show intestinal oxalate hyperabsorption (81), we can reasonably assume that the problem of oxalate hyperabsorption should affect no more than 2-3% of idiopathic stone formers.
In the great majority of cases oxalate absorption rate is rather low, about 6% with the usual dietary intake (79, 81), a proportion rising very little with the higher intakes due to the flattening of the absorption process (79, 82). Hence, important variations in intake, namely from 50 mg/day to 250 mg/day, as it may occur with a free diet, causes the oxaluria to usually increase 4-5 mg/day only (79). Perhaps this is due to the saturation of the transporters or to the supersaturation of calcium oxalate rising to such a level in the intestinal lumen as to cause the crystallization of this salt hindering its absorption.
Finally, as already mentioned previously, the absorption of dietary oxalate is strongly affected by the simultaneous dietary intake of calcium (74, 76). Some Authors have shown that even hyperoxaluria brought about by a high consumption of oxalate-rich foods can be reduced by the simultaneous consumption of milk and dairy products (83, 84).
On the other hand, fruit and vegetables display an antilithogenic effect.
In general, fruit and vegetables have a low content in protein

and sodium chloride, a high content in potassium and magnesium, and a moderate alkalinizing potential deriving from anions such as bicarbonate and citrate. This peculiar composition may explain some favorable effects of fruit and vegetables on some of the most important urinary stone risk factors. It has been shown that high potassium intake, inherent in the large consumption of fruit and vegetables, is associated with a reduced stone risk (6-9). It has also been shown that these foods can increase citrate excretion in patients with idiopathic calcium stone disease, up to curing conditions of pronounced hypocitraturia in some cases (24, 25, 85). Moreover, they can increase the excretion of magnesium (85), another calcium crystallization inhibitor, and they can decrease calcium excretion (86). Finally, they can increase the urine pH (85, 87) with favorable effects on the solubility of uric acid.
By converse, the elimination of fruit and vegetables from the diet of normal subjects causes unfavourable changes in stone risk due to the significant increase in the supersaturation for calcium oxalate and calcium phosphate (85).
Give the above considerations, we encourage physicians to advise their patients to consume fruit and vegetables regularly, regardless if they are calcium or uric acid stone formers, provided that they exercise moderation in the consumption of foods known to elicit a marked hyperoxaluric effect.

The role of vitamins

The vitamins most implicated in stone risk are vitamin D (calcitriol), vitamin C (ascorbic acid) and vitamin B6 (pyridoxine).
A recent follow-up study did not find any association between vitamin D intake and stone risk (9). It has been known for many years, however, that some idiopathic hypercalciuric subjects have an excess of calcitriol in the blood or, in any case, an overregulation of its receptors, leading to hyperabsorption of intestinal calcium (88). Except in special cases, therefore, it is not advisable to give vitamin D supplements to stone formers, especially in association with pharmacological calcium supplements.
Vitamin C supplementation is a widespread practice due to its alleged preventive action against tumors and degenerative diseases. Being a precursor of oxalate and potentially capable of increasing oxaluria, vitamin C taken in excessive amount could be dangerous in nephrolithiasis. Truly (89-100), high intakes of ascorbic acid causes a rise in oxaluria, but of up to 1500 mg/day this effect is negligible and does not increases the risk of kidney stone (101, 102).
Pyridoxine enters the oxalic acid metabolism and a deficiency of this vitamin could lead to an increase in the endogenous production of oxalate (103). On the other hand, supplementation of pyridoxine in the diet can reduce oxaluria (104).
A high vitamin B6 intake (over 40 mg/day) was associated with a reduced risk of stones in women (102) but not in men (101).
To sum up, as regards vitamins, a diet designed to prevent stone disease should avoid excessive intake of vitamin C, supplements of vitamin D and permit the consumption of the recommended levels of vitamin B6.

Practical recommendations

In a nutshell, the recommendations we can made, in the light of current knowledge, with a view to drawing up an "antilithogenic diet" both for calcium and for uric acid stone disease, are as follows.
1. Advise patients to get their body weight down as near as possible to ideal body weight, by following a low calories diet as per the instructions below.
2. Advise patients to drink enough water to bring the urinary volume up to at least 2 liters /day. It is extremely important to instruct patients to drink the water a little at a time, and to consume a water load of approx. 500 ml before going to bed. Another essential aspect is to show patients how to measure urinary volume by themselves periodically, e.g. once a month. Other fluids may be consumed but not in substitution of water. If the patient consumes regular quantities of milk and dairy products, the water should not contain high quantities of calcium, e.g. not more than 100 mg/L, in order to avoid excessive calcium loads, especially between meals.
3. Advise patients to limit animal protein intake, by reducing above all the consumption of meat and its derivatives; the total of proteins deriving from meat, fish, chicken, eggs, milk and cheese should not exceed 50-60 g/day.
4. Advise patients to avoid excessive carbohydrates. Refined ones, in particular, should not exceed 20 g per day. It might be useful to replace sucrose with sweeteners such as saccharine or aspartame.
5. Advise patients to avoid excess of saturated fats, shifting the calorie requirement to foods rich in omega-3 fatty acids, such as olive oil, anchovies, sardines and mackerel.
6. Advise patients to limit sodium chloride consumption to no more than 6 g/day. To this end, it is extremely important for patients to be aware of the "hidden sources" of salt and to avoid the use of mixed prepacked foods which tend to be very salty.
7. Advise patients to consume milk, yogurt and cheese regularly, but not excessively and to avoid cheeses containing large quantities of sodium chloride.
8. Advise patients to consume fruit and vegetables daily, taking care to avoid foods containing very high quantities of oxalate.
9. Do not give patients vitamin D supplements; allow, if requested, vitamin C supplements of not more than 1500 mg/day; avoid vitamin B6 deficiencies.
10. Advise patients to use, as far as possible, fresh or frozen products, not prepacked or precooked foods. If this is not possible advise them to purchase products bearing a label on which the content of sodium chloride and other nutrients are listed.

References

1. Yoshida O, Terai A, Ohkawa T, Okada Y. National trend of the incidence of urolithiasis in Japan from 1965 to 1995. Kidney Int. 1999;56:1899-1904.
2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM Jr, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003; 63:1817-1823.
3. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H. Demographic and geographic variability of kidney stones in the United States. Kidney Int. 1994;46:893-9.
4. Clark JY, Thompson IM, Optenberg SA. Economic impact of urolithiasis in the United States. J Urol. 1995;154:2020-4.
5. Goldfarb DS. Increasing prevalence of kidney stones in the United States. Kidney Int. 2003;63:1951-2.
6. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med. 1997;126:497-504.
7. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women. Am Med Association 2004;164:885-891.
8. Curhan GC, Willet WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 1993;328:833-8.
9. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J Am Soc Nephrol. 2004;15:3225-3232.

10. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med. 1992;327:1141-1152.
11. Mandel N. Mechanism of stone formation. Sem in Nephrol. 1996; 16:364-374 .
12. Pak CYC, Skurla C, Harvey J. Graphic display of urinary risk factors for renal stone formation. J Urol. 1985;134:867-870.
13. Griffin DG. A review of the heritability of idiopathic nephrolithiasis. J Clin Pathol. 2004;57:793-6.
14. Werness PG, Brown CM, Smith LH, Finlayson B. Equil 2: a basic computer program for the calculation of urinary saturation. J Urol. 1985;134:1242-4.
15. Pak CYC, Sakhaee K, Crowther C, Brinkley L. Evidence justifying a high fluid intake in treatment of nephrolithiasis. Ann Intern Med. 1980;93:36-9.
16. Borghi L, Guerra A, Meschi T, et al. Relationship between supersaturation and calcium oxalate crystallization in normals and idiopathic calcium oxalate stone formers. Kidney Int. 1999;55:1041-1050.
17. Robertson WG. Kidney models of calcium oxalate stone formation. Nephron Physiol. 2004;98:21-30.
18. Kuo RL, Lingeman JE, Evan AP, et al. Urine calcium and volume predict coverage of renal papilla by Randall's plaque. Kidney Int. 2003;64:2150-4.
19. Borghi L, Meschi T, Schianchi T, et al. Urine volume: stone risk factor and preventive measure. Nephron. 1999;81:31-7.
20. Frank M, De Vries A, Tikva P. Prevention of urolithiasis. Arch Environ Health. 1966;13:625-630.
21. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolitiasis: a 5-year randomized prospective study. J Urol. 1996;155:839-843.
22. Schwartz BF, Schenkman NS, Bruce EJ, Leslie SW, Stoller ML. Calcium nephrolithiasis: effect of water hardness on urinary electrolytes. Adult Urology. 2002;60:23-7.
23. Shuster J, Finlayson B, Scheaffer RL, Sierakowski R, Zoltek J, Dzegede S. Primary liquid and urinary stone disease. J Chron Dis. 38:907-914.
24. Wabner CL, Pak CYC. Effetc of orange juice consumption on urinary stone risk factors. J Urol 1993;149:1405-8.
25. Seltzer MA, Low RK, McDonald M, Shami GS, Stoller ML. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol. 1996;156:907-9.
26. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. Am J Epidemiol. 1996;143:240-7.
27. Krieger JN, Kronmal RA, Coxon V, Wortley P, Thomson L, Sherrard DJ. Dietary and behavioral risk factors for urolithiasis: potential implications for prevention. Am J Kidney Dis. 1996;28:195-201.
28. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Beverage use and risk for kidney stones in women. Amm Intern Med. 1998;128: 534-540.
29. Hirvonen T, Pietinen P, Virtanen M, Albanes D, Virtamo J. Nutrient intake and use of beverages and the risk of kidney stones among male smokers. Am J Epidemiol. 1999;150:187-194.
30. Rodgers A. Effect of cola consumption on urinary biochemical and physicochemical risk factors associated with calcium oxalate urolithiasis. Urol Res. 1999;27:77-81.
31. Kebler T, Jansen B, Hesse A. Effect of blackcurrant-, cranberry-, and plum juice consumption on risk factors associated with kidney stone formation. Eur J Clin Nutr. 2002;56:1020-3.
32. Robertson WG, Peacock M, Marshall DH. Prevalence of urinary stone disease in vegetarians. Eur Urol. 1982;8:334-9.
33. Goldfarb S. Dietary factors in the pathogenesis and prophylaxis of calcium nephrolithiasis. Kidney Int. 1988;34:544-555.
34. Kerstetter JE, O'Brien KO, Insogna KL. Low protein intake: the impact on calcium and bone homeostasis in humans. J. Nutr. 2003; suppl. 1:855-861.
35. Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CYC. Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming prospensity, and calcium metabolism. Am J Kidney Dis. 2002;40:265-274.
36. Robertson WG, Heyburn PJ, Peacock M, Hanes FA, Swaminathan R. The effect of high animal protein intake on the risk of calcium stone-formation in the urinary tract. Clin Sci. 1979;57:285-8.
37. Nguyen QV, Kalin A, Drouve U, Casez JP, Jaeger P. Sensitivity to meat protein intake and hyperoxaluria in idiopathic calcium stone formers. Kidney Int. 2001;59:2273-2281.
38. Alpern RJ, Sakhaee K. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis. 1997;29:291-302.
39. Jaeger Ph, Robertson WG. Role of dietary intake and intestinal absorption of oxalate in calcium stone formation. Nephron Physiol. 2004;98:64-71.
40. Breslau NA, Brinkley L, Hill KD, Pak CYC. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Met. 1988;66:140-6.
41. Hiatt RA, Ettinger B, Caan B, Quesemberry CP Jr., Duncan D, Citron JT. Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. Am J Epidemiol. 1996;144:25-33.
42. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002;346:77-84.
43. Lemann J Jr., Piering WF, Lennon E. Possible role of carbohydrate-induced calciuria in calcium oxalate kidney-stone formation. N Engl J Med. 1969;280:232-7.
44. Holl MG, Allen LH. Sucrose ingestion, insulin response and mineral metabolism in humans. Am Inst Nutrition. 1987;1229-1233.
45. Garg A, Bonanome A, Grundy SM, Unger RH, Breslau NA, Pak CYC. Effects of dietary carbohydrates on metabolism of calcium and other minerals in normal subjects and patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1990; 70:1007-1013.
46. Thom JA, Morris JE, Bishop A, Blacklock NJ. Increased availability of dietary carbohydrate: a factor in the genesis of idiopathic calcium oxalate urolithisis? In: Smith LH, Robertson WG, Finlayson B. eds. Urolithiasis Clinical and Basic Research New York and London: Plenum Press. 1981:369-372.
47. Raskin P, Stevenson MRM, Barilla DE, Pak CYC. The hypercalciuria of diabetes mellitus: its amelioration with insulin. Clin Endocrinol. 1978;9:329-335.
48. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. Am Med Association. 2005;293:455-462.
49. Asplin JR. Uric Acid Stones. Sem Nephrol. 1996;16:412-424.
50. Sakhaee K, Adams-Huet B, Moe OW, Pak CYC. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int. 2002;62:971-9.
51. Pak CYC, Sakhaee K, Moe O, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology. 2003;61:523-7.
52. Abate N, Chandalia M, Cabo-Chan AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel feature of renal manifestation of insulin resistance. Kidney Int. 2004;65:386-392.
53. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CYC. Association of urinary pH with body weight in nephrolithiasis. Kidney Int. 2004;65:1422-5.
54. Hatch M, Schepers A, Grunberger I, Godec CJ. A retrospective analysis of the metabolic status of stone formers in the New York city metropolitan areas. NY State J Med. 1991;91:196-200.
55. Schmiedl A, Schwille PO, Bonucci E, Erben RG, Grayczyk A, Sharma V. Nephrocalcinosis and hyperlipidemia in rats fed a cholesterol and fat-rich diet: association with hyperoxaluria, altered kidney and bone minerals, and renal tissue phospholipid-calcium interaction. Urol Res. 2000;28:404-415.
56. Khan SR, Glenton PA, Backov R, Talham DR. Presence of lipids in urine, crystals and stones: implications for the formation of kidney stones. Kidney Int. 2002;62:2062-2072.
57. Masai M, Ito H, Kotake T. Effect of dietary intake on urinary oxalate excretion in calcium renal stone formers. Br J Urol. 1995;76: 692-6.
58. Naya Y, Ito H, Masai M, Yamaguchi K. Association of dietary fatty

acids with urinary oxalate excretion in calcium oxalate stone-formes in their fourth decade. BJU International 2002;89:842-6.
59. Baggio B, Budakovic A, Nassuato MA, et al. Plasma phospholipid arachidonic acid content and calcium metabolism in idiopathic calcium nephrolithiasis. Kidney Int. 2000;58:1278-1284.
60. Baggio B, Gambero G, Zambon S, et al. Anomalous phospholipid n-6 polyunsaturated fatty acid composition in idiopathic calcium nephrolithiasis. J Am Soc Nephrol. 1996;7:613-620.
61. Buck AC, Davies R, Harrison T. The protective role of eicosapentaenoic acid (EPA) in the pathogenesis of nephrolithioasis. J Urol. 1991;146:188-194.
62. Taylor EN, Stampfer MJ, Curhan GC. Fatty acid intake and incident nephrolithiasis. Am J Kidney Dis. 2005;45:267-274.
63. Massey LK, Whiting SJ. Dietary salt, urinary calcium, and kidney stone risk. Nutr Rev. 1995;53:131-4.
64. Kok DJ, Iestra JA, Doorenbos CJ, Papapoulos SE. The effects of dietary excesses in animal protein and in sodium on the composition and the crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. J Clin Endocrinol Metab. 1990;71: 861-7.
65. Kurtz TW, Al-Bander HA, Morris RC Jr. Salt-sensitive essential hypertension in men. N Engl J Med. 1987;314:1043-8.
66. Lemann J Jr., Pleuss JA, Gray RW, Hoffmann RG. Potassium administration reduces and potassium deprivation increases urinary calcium excretion in healty adults. Kidney Int. 1991;39:973-983.
67. Muldowney FP, Freaney R, Barnes E. Dietary chloride and urinary calcium in stone disease. Q J Med. 1994;87:501-9.
68. Wills MR, Gill JR, Bartter FC. The interrelationships of calcium and sodium excretions. Clin Sci. 1969;37:621-630.
69. Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CYC. The potential role of salt abuse on the risk for kidney stone formation. J Urol. 1993;160:310-2.
70. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension. JAMA. 2002;288:1882-8.
71. Lemann J Jr., Adams ND, Gray RW. Urinary calcium excretion in human beings. N Engl J Med. 1979;30:535-541.
72. Coe FL, Favus MJ, Crockett T, et al. Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1,25 (OH)2D3 levels in patients with idiopathic hypercalciuria and in normal subjects. Am J Med. 1982;72:25-32.
73. Hess B. Low calcium diet in hypercalciuric calcium nephrolithiasis: first do no harm. Scanning Microsc. 1996;10:547-556.
74. Zarembski PM, Hodgkinson A. Some factors influencing the urinary excretion of oxalic acid in man. Clin Chim Acta. 1969;25:1-10.
75. Lemann J Jr., Pleuss JA, Worcester EM, Hornick L, Schrab D, Hoffmann R. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healty adults. Kidney Int. 1996;49:200-8.
76. Lemann J Jr., Pleuss JA, Gray RW. Inceased dietary calcium intake reduces urinary oxalate excretion in healthy adults. In: Walker VR, Sutton RAL, Cameron ECB, Pak CYC, Robertson WG eds. Urolithiasis New York and London: Plenum Press. 1989:435-8.
77. Marangella M, Bianco O, Martini C, Petrarulo M, Vitale C, Linari F. Effect of animal and vegetable protein intake on oxalate excretion in idiopathic calcium stone disease. Br J Urol. 1989;63:348-351.
78. Massey LK, Roman-Smith H, Sutton RAL. Effect of dietary oxalate and calcium on urinary oxalate and risk of formation of calcium oxalate kidney stones. J Am Diet Assoc. 1993;93:901-6.
79. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. Kidney Int. 2001;59:270-6.
80. Levy FL, Adams-Huet B, Pak CYP. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med. 1995;98: 50-9.
81. Hesse A, Schneeberger W, Engfeld S, Von Unruh GE, Sauerbruch T. Intestinal hyperabsorption of oxalate in calcium oxalate stone formers: application of a new test with [13C2] oxalate. Am Soc Nephrol. 1999;10:329-333.
82. Hess B, Jost C, Zipperle L, Takkinen R, Jaeger P. High-calcium intake abolishes hyperoxaluria and reduces urinary crystallization during a 20-fold normal oxalate load in humans. Nephrol Dial Transplant. 1998;13:2241-7.
83. Massey LK, Sutton RAL. Modification of dietary oxalate and calcium reduces urinary oxalate in hyperoxaluric patients with kidney stones. J Am Diet Accoc. 1993;93:1305-7.
84. Savage GP, Charrier MJS, Vanhanem L. Bioavailability of soluble oxalate from tea and the effect of consuming milk with the tea. Eur J Clin Nutr. 2003;57:415-9.
85. Meschi T, Maggiore U, Fiaccadori E, et al. The effect of fruits and vegetables on urinary stone risk factors. Kidney Int. 2004; 66: 2402-2410.
86. Lemann J, Bushinsky DA, Hamm LL. Bone buffering of acid base in humans AJP-Renal Physiol. 2003;285:811-832.
87. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc. 1995;95:791-7.
88. Broadus AE, Insogna KL, Lang R, Ellison AF, Dreyer BE. Evidence for disordered control of 1,25-dihydroxyvitamin D production in absorptive hypercalciuria. N Engl J Med. 1984;311:73-80.
89. Tiselius HG, Almgard LE. The diurnal urinary excretion of oxalate and the effect of pyridoxine and ascorbate on oxalate excretion. Eur Urol. 1977;3:41-6.
90. Schmidt KH, Hagmaier V, Hornig DH, Vuilleumier JP, Rutishauser G. Urinary oxalate excretion after large intakes of ascorbic acid in man. Am J Clin Nutr. 1981;34:305-311.
91. Pendse AK, Purchit AK, Ghosh R, Goyal A, Singh PP. The effect of ingestion of megadoses of ascorbic acid on urinary oxalate excretion in normal subjects and stone formers. In: Schwille PO, Smith LH, Robertson WG, Vahlensieck W eds. Urolithiasis and related clinical research. New York and London: Plenum Press. 1985:225-8.
92. Chalmers AH, Cowley DM, Brown JM. A Possible etiological role for ascorbate in calculi formation. Clin Chem. 1986;32:333-6.
93. Urivetzky M, Kessaris D, Smith AD. Ascorbic acid overdosing: a risk factor for calcium oxalate nephrolithiasis. J Urol. 1992;147: 1216-8.
94. Wandzilak TR, D'Andre SD, Davis P, Williams HE. Efffect of high dose vitamin C on urinary oxalate levels. J Urol. 1994;151: 834-7.
95. Liebman M, Chai W, Harvey E, Boenisch L. Effect of supplemental ascorbate and orange juice on urinary oxalate. Nutrition. Research. 1997;17:415-425.
96. Trinchieri A, Ostini F, Nespoli R, Severa F, Zanetti G, Pisani E. Hyperoxaluria in patients with idiopathic calcium nephrolithiasis. J Nephrol. 1998;11:70-2.
97. Auer BL, Auer D, Rodgers AL. The effect of ascorbic acid ingestion on the biochemical and physico-chemical risk factors associated with calcium oxalate kidney stone formation. Clin Chem Lab Med. 1998;36:143-8.
98. Baxmann AC, De OG, Mendonca C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. Kidney Int. 2003;63:1066-1071.
99. Traxer O, Huet B, Poindexter J, Pak CYC, Pearle M. Effect of ascorbic acid consumption on urinary stone risk factors. J Urol. 2003;170:397-401.
100. Chai W, Liebmna M, Kynast-Gales S, Massey L. Oxalate absorption and endogenous oxalate synthesis from ascorbate in calcium oxalate stone formers and non-stone formers. Am J Kideny Dis. 2004;44:1060-9.
101. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol. 1996;155:1874-1851.
102. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol. 1999;10:840-5.
103. Di Tommaso L, Tolomelli B, Mezzini R, et al. Renal calcium phosphate and oxalate deposition in prolonged vitamin B6, deficiency: studies on a rat model of urolithiasis. BJU International. 2002; 89:571-5.
104. Chetyrkin SV, Kim D, Belmont JM, Scheinman JI, Hudson BG, Voziyan PA. Pyridoxamine lowers kidney crystals in experimental hyperoxaluria: a potential therapy for primary hyperoxaluria. Kidney Int. 2005;67:56-60.