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NEPHROLITHIASIS: RISK FACTORS, PHARMACOLOGICAL TREATMENT AND PROPHYLAXIS

ARTIGO DE REVISÃO

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Abstract

***Context*:** Although literature available on renal lithiasis is extensive, very few reviews include risk factors, pharmacological treatment, metabolic study and prophylaxis.

***Purpose*:** The aims of this review are to synthesize the evidence regarding the main risk factors of nephrolithiasis and to identify current treatments for medical expulsive therapy and the most effective prophylactic options based on the metabolic study.

***Methods*:** Between august 2013 and january 2014, a different search for each subject was made using relevant search terms. The selection of articles was made according to its relevance to the aims of the review and the availability of full-text.

***Results*:** The main risk factors for nephrolithiasis are hypercalciuria, hyperoxaluria, hypocitraturia, the low urinary pH, low fluids intake and low urinary volume, past history of renal stone, the presence of metabolic syndrome, as well as obesity, hypertension and hypertriglyceridemia alone. Tamsulosin and nifedipine are the most effective and safe drugs used in medical expulsive therapy. Dietary and fluid intake recommendations based on the metabolic study may be enough for prevention of future episodes, and can be combined with alkalinizing drugs, thiazidic diuretics, allopurinol, thiol derivates and acetohydroxamic acid depending on the metabolic characteristics of stone disease.

***Conclusion*:** Several metabolic, environmental and biological factors have been identified to increase the risk of stone formation. A number of different classes of drugs have been studied for their potential use in medical expulsive treatment. The metabolic study is important to identify patients at high risk for stone recurrence in order to define the most effective prophylactic approach.

Key words: Nephrolithiasis. Kidney calculi. Risk factors. Pharmacological treatment. Prevention. Prophylaxis. Metabolic evaluation.

Resumo

***Contexto*:** Apesar da literatura sobre litíase renal ser vasta, existem poucas revisões que incluam os factores de risco, o tratamento farmacológico, o estudo metabólico e a profilaxia.

***Objectivos*:** Esta revisão tem como objectivos reunir a evidência sobre os principais factores de risco para a litíase renal e identificar os fármacos utilizados na terapia médica expulsiva (TME), bem como as melhores opções profilácticas, tendo por base o estudo metabólico.

***Métodos*:** Entre agosto de 2013 e janeiro de 2014, foram efectuadas pesquisas diferentes para cada tema, utilizando termos relevantes. A selecção dos artigos foi feita com base na sua relevância quanto aos nossos objectivos e de acordo com a disponibilidade do texto integral.

***Resultados*:** Os principais factores de risco para a litíase urinária são a hipercalciúria, hiperoxalúria, hypocitratúria, baixo pH urinário, baixo consumo de líquidos e baixo volume urinário, antecedentes de litíase, presença de síndrome metabólico, bem como a presença isolada de obesidade, hipertensão arterial e hipertrigliceridémia. A tansulosina e nifedipina são os fármacos mais eficazes e seguros na TME. O simples fornecimento de recomendações sobre a dieta e ingestão de líquidos baseadas no estudo metabólico pode ser suficiente para prevenir a recidiva de cálculos urinários, podendo também ser associada a fármacos alcalinizadores, diuréticos tiazídicos, alopurinol, derivados tióis e ácido acetohidroxâmico dependendo das características metabólicas da doença.

***Conclusão*:** Vários factores metabólicos, ambientais e biológicos aumentam o risco de litíase. Diferentes classes de fármacos podem ser utilizadas na TME. O estudo metabólico é importante para identificar doentes com alto risco de recidiva da litíase, possibilitando a prescrição mais eficaz de medidas profilácticas.

Palavras-chave: Litíase urinária. Cálculos urinários. Factores de risco. Tratamento farmacológico. Prevenção. Profilaxia. Estudo metabólico.

Introduction

Urinary calculi have been found in the tombs of Egyptian mummies and references to stone formation were made by Hippocrates.[1] Although this disease is thought to be as old as humanity, its pathogenesis and its incidence have changed over time.[2] In fact, it tends to increase with industrialization [3,4] and its prevalence varies from 1% to over 10% of the global population according to recent studies.[1,5,6] Lifetime risk to develop nephrolithiasis is 5% to 15% in western countries.[2,7–9] Several studies have shown that nephrolithiasis is more frequent among men (10,6%) than women (7,1%),[10] yet this difference tends to be reduced with increasing prevalence in women.[4,7] In Portugal it is estimated that 7% of the population will have at least one renal colic in their lifetime, with a similar distribution between men and women.[11] The prevalence is also increasing in the pediatric population.[4,7] After an initial stone, there is a 10% to 60% chance of passing a second stone within 1 to 10 years.[1,8,12–14]

Regarding the composition of calculi, calcium is the principal component of urinary calculi forming about 75% to 90% of all stones.[2,8] Calcium oxalate stones are by far the most frequent, followed by calcium phosphate (brushite and apatite), uric acid, magnesium ammonium phosphate (struvite) and cystine.[2,8,15] Rare stones are associated with xanthine, 2,8-dihydroxyadenine and drugs and will not be discussed in this review.

Nephrolithiasis has become increasingly recognized as a systemic and multifactorial disorder [15] that may lead to chronic kidney disease.[7] Its pathophysiological mechanisms are complex and diverse and include metabolic changes related to nutrition, low urine volume, hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, and abnormalities in urine.[15,16]

The economic burden of nephrolithiasis is immense and it remains a major source of morbidity in humans, partly because its pathophysiology is still unclear and its prevalence and

rate of recurrence are high. Metabolic evaluation of patients and prevention of recurrence have an important role in the medical management of this disease.[4]

Studies have shown spontaneous passage rates of 50% to 85% for distal ureteral stones.[17–19] Predictors of stone passage include stone location, size, number and structure, spasm in the ureteral smooth muscles, mucosal oedema or inflammation and ureteral anatomy.[9,17] Minimally invasive therapies, although effective, are not risk-free and may increase pain and costs.[18,19] So nowadays, a conservative non-surgical approach is recommended, except if renal pelvic decompression is needed like when pain relief can't be achieved, there are signs of infection or in case of solitary kidney. In view of this, investigators have tried to find ways of assisting the process of expulsion with the use of drugs, thereby reducing possible complications of stone passage like renal colic attacks, urinary infection, uretero-hydronephrosis and acute pyelonephritis, and reducing the need of surgery. It is called medical expulsive therapy (MET).

The literature available on renal lithiasis is extensive, and a good understanding of risk factors, methods of prophylaxis of recurrence and new therapies is warranted.

The aims of this review are to synthesize the evidence regarding the main risk factors of nephrolithiasis, and to identify the current treatments for medical expulsive therapy and the most effective prophylactic options based on the metabolic study.

The management of acute symptomatic stone passage and the use of minimally invasive techniques are beyond the scope of this review.

Methods

Between august 2013 and january 2014, we searched PubMed for clinical trials, comparative studies, controlled clinical trials, multicentered studies, randomized controlled trials in English, Spanish, French and Portuguese, in humans over 19 years old. A different search was made for each subject using relevant search terms and Boolean connectors (Table 1). For metabolic study search a limit of 10 years was made in order to reduce the number of results. The articles found were then selected according to our aims after reading the title, the abstract and the full text. The articles which we could not access in full text through our University server were excluded from the review. We also excluded single-case reports, studies which tested pharmacological and concomitant minimally invasive treatments like extracorporeal lithotripsy and endourologic interventions, studies that included patients with conditions other than nephrolithiasis, including urinary tract anomalies. All studies prior to 1990 were also excluded.

Table 1. Search performed in PubMed and number of articles selected.

Subject	Terms used	Search Fields	Results	Relevant results
Risk Factors	lithiasis / stone / urolithiasis / nephrolithiasis / calculi urinary / renal / kidney risk factor	Title	76	23
Pharmacological treatment	lithiasis / stone / urolithiasis / nephrolithiasis / calculi urinary / renal / kidney medical / pharmacological treatment	Tittle / Abstract	274	15
Metabolic study	lithiasis / stone / urolithiasis / nephrolithiasis / calculi urinary / renal / kidney metabolic study / investigation / assessment / evaluation	Tittle / Abstract	153	16
Prophylaxis	lithiasis / stone / urolithiasis / nephrolithiasis / calculi urinary / renal / kidney prevention / prophylaxis	Title / Abstract	204	12

Original articles were used as a main source to attain our specific aims and review articles were integrated and guidelines used in order to give a global perspective on the subject.

Risk Factors

The incidence of renal lithiasis and its high rate of recurrence require that its management rely on inhibiting stone growth and preventing the formation of new stones. This prophylactic approach requires the identification of factors which pre-dispose patients to urinary stones.

Several epidemiological factors have been implicated in a pre-disposition to urinary stone disease and they vary according to different types of stone composition.

In this review, the main risk factors identified in the literature are gathered under the following categories: metabolic factors, environmental factors, biological factors, and other diseases.

Metabolic factors

Urine composition and pH, hypertension, obesity and the presence of metabolic syndrome are the most frequently reported factors in the literature.

Urine composition

The metabolic risk of stone formation is generally discussed on the basis of several parameters of urine composition: hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria e hypomagnesuria.[20–23]

Hypercalciuria is defined as the excretion of more than 200 - 260 mg of calcium in 24h-urine [22,24] or 4mg of calcium per kg/day.[22,25] It has been identified as the most or the second most important metabolic risk factor for formation of calcium lithiasis, being one of the most frequently detected metabolic abnormality of patients with stone.[8,22,23] It is widely accepted that hypercalciuria is a major determinant for stone formation and recurrence, but some authors have found no statistical difference in hypercalciuria levels between recurrent

and first stone formers.[5,21,26] Three main body locations have been proposed as the origin of hypercalciuria. In fact, calcium transport defect might be localized in the gastrointestinal tract (absorptive hypercalciuria), kidney (excretory or renal hypercalciuria) or bone (reabsorptive hypercalciuria).[22]

Hyperoxaluria is defined as the urinary excretion of oxalate of more than 40 - 45 mg/day [22,24,25] and it seems to be associated with the formation of monohydrate calcium oxalate stones. Some authors defend that it plays the most important risk factor for nephrolithiasis.[8,11] Mean oxalate excretion level has been found to be significantly higher in stone formers than in controls.[5] In fact, a recent study carried out in Iran confirmed that stone formers had a significantly higher urine oxalate excretion and that hyperoxaluria was the most frequent metabolic abnormality in that population.[8] Several mechanisms have been proposed as a cause of hyperoxaluria. The most frequent disorder is related to enteric malabsorption of fats, which accumulate in the intestine and bind to calcium reducing the formation of intestinal calcium-oxalate complexes and increasing the intestinal absorption of oxalates. The increase in the intake of oxalate-rich food, the excessive intake of vitamin C and dietary calcium restriction may also cause dietetic hyperoxaluria.[22] Finally, this condition can result from mutations of a variety of genes causing an anomalous and incomplete degradation of oxalates that accumulate in urine. This mechanism is, however, infrequent.[22] The formation of oxalate stones seems to be related to the colonization of the gut by *Oxalobacter formigenes*, a bacteria that metabolizes oxalate to formate and carbon dioxide. Colonization with the bacteria in controls was significantly higher than in stone formers.[5] Likewise, among recurrent stone formers who had $\geq$ 4 episodes, only 7% were colonized with the bacteria.[5] Colonization of the gut by *Oxalobacter formigenes* may therefore be considered a protective factor.

Hypocitraturia can be defined as the urinary excretion of citrate of less than 320 mg/day [22,25] or less than 600 mg.[24] The daily urinary excretion of citrate was found to be lower in stone formers than in controls,[27] suggesting that urinary excretion of citrate is an important inhibitor of calcium stone formation.[28] A study performed in India noticed hypocitraturia as the most common metabolic abnormality among stone formers.[25] Some authors assert that urinary citrate has a protective effect, for its ability to bind to calcium and prevent the formation of complexes, to alkalinize urine and have a direct inhibitory effect through avoiding the formation of the nucleus of stone.[22,29] However, Parvin and collaborators found the opposite, with the risk of stone formation increasing with the rise in urinary citrate levels. To explain this unexpected result, these authors proposed that the effect of citrate as a stone formation inhibitor may have been overcome by calcium and especially oxalate, the two main risk factors of nephrolithiasis identified in their study.[8] The most important determining factor for citraturia is the intracellular pH. Urinary citrate is reabsorbed under states of acidosis, decreasing its urinary excretion.[22,29] Citraturia was inversely associated with prevalent hypertension in older women, younger women and men. Low levels of urinary citrate may therefore contribute to the increased risk for kidney stone disease observed in some studies of hypertensive subjects.[28] There seems to be a relation between citrate and potassium excretion as the depletion of potassium causes hypocitraturia.[29]

Hyperuricosuria is defined as the urinary excretion of uric acid of more than 600 mg/day.[22,24] It increases heterogeneous nucleation with oxalate calculi, playing an influential role in formation of calcium-oxalate calculi. In general, it may result from high dietary intake of purines or from pathological conditions.[15,22] Concerning the formation of uric acid stones, a high urinary uric acid excretion is suggested to be one of the most important risk factors.[30]

Hypomagnesuria can be defined as the daily urinary excretion of magnesium of less than 30 mg. It is associated with low magnesium intake or intestinal malabsorption like in

case of inflammatory bowel disease and bariatric surgery.[15,22] It is infrequent and causes the formation of calcium oxalate stones.[22] Mean urinary values of magnesium did not differ between stone formers and nonstone formers in a study carried out in Iran.[8]

Cystinuria is a genetic autosomal recessive condition characterized by a high excretion (> 250 mg/day) [7] of cystine due to a defect in renal tubular reabsorption of cystine. The concentration of cystine in urine is highly dependent of pH as a two-fold increase of solubility can be achieved with an increase of pH from 7 to 7,5.[31] The presence of severe cystinuria (>750 - 840 mg/day) [32] may need a different management, as we will describe further in this review.

Urinary pH

An acidic urinary pH value (≤ 5,5) is one of the most important risk factors for uric acid stone formation.[24] It contributes to a rise in the concentration of the poorly soluble undissociated uric acid, whereas the solubility of uric acid increases strongly with increasing pH value.[30] Calcium oxalate and cystine stones also tends to form in acidic environment.[7] Contrariwise, an alkaline urine (pH ≥ 6,7) is leaning to the formation of struvite and calcium phosphate stones.[7,33]

Hypertension (HTA)

The association between kidney stone disease and hypertension has been extensively studied.[34–36] There is a high prevalence of HTA in renal stone formers and metabolic studies show that patients with primary HTA have a greater risk of renal stone formation.[36] History of high blood pressure was found to be an independent risk factor for the occurrence of kidney stones in both men and women,[35,37] although another study found this association only in women.[38]

The theories proposed for this association are the existence of a common genetic basis linking high blood pressure to kidney stone formation, which has not been clearly demonstrated, and the abnormal urinary concentrations of some lithogenic solutes: calcium, uric acid and oxalate.[36] Hypertensive stone formers have higher uricemia, increased prevalence of uric acid stones, lower urinary pH, higher sulphate excretion and higher body mass index (BMI). Losito and team suggest that a metabolic imbalance may be responsible.[36] However, urinary excretion of calcium was not different in normotensive and hypertensive subjects.[36] Citraturia was inversely associated with prevalent hypertension in older women, younger women and men with and without stone disease. Low levels of urinary citrate may contribute to the increased risk for kidney stone disease observed in some studies of hypertensive subjects.[28] Moreover, in a population of stone formers, essential hypertension is associated with lower urinary citrate and higher acid excretion which increases with the stage of hypertension.[36]

Overweight and obesity

Kidney stone patients have a much higher prevalence of both overweight and obesity.[38,39] Waist circumference was found to be an independent risk factor for kidney stones.[37] In fact, an increased body size is significantly associated with the increase of mean urinary oxalate and calcium levels as well as with a decrease of citrate excretion, when compared with normal BMI patients.[40] Women have been shown to be more prone to obesity and to have an increased excretion of these factors.[40] Likewise, when it comes to abdominal obesity it is significantly associated with nephrolithiasis in women only.[35]

In females with high BMI, an association between nephrolithiasis and increased blood pressure has been reported, although this relation is controverse.[36]

Presence of metabolic syndrome (MetS)

Metabolic syndrome may be defined as the simultaneous occurrence of hyperglycemia, hypertriglyceridemia, hypercholesterolemia, hypertension, and abdominal obesity. It is a predisposing factor for stroke, ischemic heart disease and type 2 diabetes.[37] This may explain why patients with stone disease have a higher incidence of ischemic heart disease.[34] MetS has been associated with a twofold greater occurrence of both objectively demonstrated [35] and self-reported [41] nephrolithiasis. The presence of 4 or more traits was associated with an approximate twofold increase in odds of self-reported kidney stone disease.[41] Similarly, a study in Korea involving 34,895 individuals found that the presence of ≥ 3 criteria of MetS was a strong and independent risk factor for kidney stone formation even though triglyceride concentration alone was another independent risk factor for kidney stones.[37] In subjects without history of kidney stones, the risk of calcium oxalate stone formation increases with the number of features of metabolic syndrome.[15]

A higher systolic blood pressure has been associated with overweight [40] and the combination of high blood pressure with other components of MetS significantly increases the probability of concomitant nephrolithiasis.[35]

The mechanisms explaining the relation between MetS and urinary calculi are not clear, but it has been suggested that metabolic syndrome is responsible for changes in urine composition namely for low urinary pH, decrease in citrate excretion, and increase in uric acid and calcium excretion.[15]

Environmental Factors

Diet and water ingestion, physical exercise and geography are important factors to be considered in nephrolithiasis.

Dietary patterns

Nutrition is suggested to be the major environmental risk factor in idiopathic calcium oxalate and uric acid stone disease, since diet strongly influences urine composition.[16,27,30,42] Increased ingestion of proteins, excessive calcium and potassium consumption, oxalate rich diet and low ingestion of magnesium, fruits and vegetables have been studied as potential promotors of renal lithiasis.[14] Dietary fat seems not to have a significant effect on the urinary risk factors of calcium stone disease.[14]

Protein intake. Stone formers have a significantly higher dietary intake of animal and vegetable protein and purine, which is correlated to daily urinary excretion of calcium. The link between protein content of diet and urinary calcium is confirmed.[16,27] Usual self-selected diets, which are rich in protein, sodium and fat, are related to high frequency of hypocitraturia, hyperuricosuria and urine volumes less than 2 L/day, in recurrent calcium stone formers.[16] In a balanced diet, urinary citrate excretion is significantly higher and the frequency of hypocitraturia is lower.[16] Elevated protein consumption results in excessive endogenous acid load and a subsequent increase in renal net acid excretion. An enhanced endogenous production and urinary excretion of uric acid has been reported to be mainly influenced by a high dietary purine intake. Uric acid is the end product of purine metabolism in humans and is derived from endogenous production as well as from dietary sources. Different dietary purine compounds exert different effects on purine metabolism. An ovo-lacto-vegetarian diet with moderate animal protein and purine content and a high fluid intake accounts for the lowest risk of uric acid stone formation.[30] Unlike calcium and uric acid excretion, the effect of dietary protein intake in oxalate excretion is controversial as minimal effect on oxalate excretion was found in one study [27] while a positive association between the two was found in another.[16]

Oxalate-rich food. Spinach, rhubarb, nuts and wheat bran are high in oxalate. Dietary oxalate intake is lower in stone formers then in controls, according to a study in southern north-american women.[38]

Magnesium intake has been shown to decrease the incidence of stone formation as well as prevent stone growth. This might be explained by its ability to increase the solubility of calcium oxalate. A study in a population of Trinidad and Tobago showed an advantage for a relatively high intake of magnesium in food, suggesting that it might have a protective role because a low magnesium intake was found to be highly predictive of urinary tract calculi.[34] These results seem to confirm the role of low dietary magnesium intake as an independent risk factor for the occurrence of kidney stones.[38]

Calcium and potassium intake was found to be lower in stone formers then in controls and low use of calcium supplements has been considered as an independent risk factor.[38] Most dietary potassium derives from meat, fruits and vegetables. However, meat has an acidifying effect whereas fruits and vegetables provide an alkali load that increases urinary citrate.[29] It has been shown that owing to its high content in potassium and citrate, orange and lemon juice intake induces a significant increase in urinary citrate excretion in normal males and in male stone formers with hypocitraturia.[43,44]

Fruits and vegetables consumption. A higher consumption of fruit of more than 10 times per week is associated to a lower incidence of stone development.[45] Withdrawal of fruits and vegetables in healthy subjects may increase the risk of developing renal calcium stones even in nonstone formers as it decreases the urinary excretion of potassium, magnesium, citrate and oxalate and increases that of calcium and ammonium, resulting in an increase of relative urinary saturation of calcium oxalate and calcium phosphate.[29]

Vitamin C. Ingestion of supplemental vitamin C was correlated to an increased urinary excretion oxalate in both stone formers [27,46] and nonstone formers,[46] potentially promoting the formation of calcium oxalate stones.

Fluid intake and volume of urine

Dehydration and low urinary volume are widely accepted risk factors for kidney formation [21,30] and a urine volume < 2 L/day was found to be one of the most frequent urinary abnormalities in stone formers in their normal diet.[16] An adequate fluid intake and consequently a sufficient urine volume lowers urinary uric acid concentration as well as urinary oxalate excretion.[16,30] A higher fluid load causes an extracellular osmotic dilution that decreases renal water reabsorption, thus, producing an urinary dilution and decreasing crystal precipitation.[47] Moreover, the type of fluid ingested also influences urinary composition. Alcohol was suggested to contribute to an enhanced uric acid production, thus increasing the risk of stone formation [30] and was later confirmed as one of the most important dietary risk factors.[16] An increased beer and wine intake results in higher urinary calcium, uric acid and inorganic phosphate excretion as well as in higher uricemia.[16]

Physical activity

A significantly lower number of stone formers had a daily energy consumption of more than 2000 kcal, when compared with controls, underscoring the idea that sedentary life style increases the risk of nephrolithiasis.[45]

Geography

Ambient temperature and sunlight exposure were independently associated with the prevalence of kidney stones with the tendency of stones increasing as the average annual

temperature increased. However, a slight reduction in kidney stone prevalence was found at the highest temperature.[48]

Biological factors

Past history, genetic factors, age, gender, and ethnicity have been examined in relation to nephrolithiasis.

Past history

The recurrence rate of nephrolithiasis is around 50%.[15,22,45] Current echographic evidence of nephrolithiasis is significantly related to past history of kidney disease in men but not in women.[35]

Genetics

Genetic factors seem to be involved stone disease etiology with approximately 40% of stone formers having a positive family history. Among close relatives, this factor was found to be highly predictive of urinary tract calculi,[34] as patients with nephrolithiasis have a higher presence of family history.[45] The comparison of different urinary risk factors between calcium stone forming and nonstone forming siblings revealed that stone forming sisters had significantly higher mean urinary calcium excretion and higher pH than nonstone forming sisters.[26] Stone formation was far more common in brothers than in sisters and stone forming brothers were older than those without stones. They also had higher mean daily calcium, and lower potassium excretions, as well as a higher mean age at study entry, which is logical as time is required for stone disease to develop. In what concern genetic studies it has been suggested that the ancestral haplotype in the TRPV6 gene causes hyper-activation of intestinal calcium absorption, leading to absorptive hypercalciuria.[49]

Age

Age was positive and significantly associated with the odds ratio for kidney stone development.[37] The mean age at diagnosis in a study conducted in Trinidad was 32 years, which, according to the authors, is lower than averages of 40 - 45 years reported in other studies from Ghana, Taiwan, France, and the USA.[34]

Gender

Studies reporting the role of gender in nephrolithiasis show a higher prevalence of this condition in men,[34,45] which might be explained by the thesis that in normal subjects women have a higher urinary citrate and lower urinary calcium than men.[1] However, a Portuguese study showed a similar prevalence of nephrolithiasis between men and women.[11]

Ethnicity

Differences between ethnic groups may be due to genetic or environmental factors, especially dietary patterns. Significant differences in kidney stone prevalence have been reported between white and black people.[24,50] In healthy subjects, daily urinary excretion of calcium was significantly lower and citraturia was higher in blacks compared to whites, whether they lived in Africa or in Europe.[50] Except for a higher carbohydrate intake in blacks, there were no differences in other dietary risk factors. In stone formers, there was a significantly higher prevalence of hypercalciuria and mean urinary calcium levels in white people compared with non-whites (Blacks, Asians and Hispanics) but other metabolic parameters were not different.[24] A comparison between whites and Indians living in the same geographical region found that Indian men had a lower urinary volume than white men. However, white men had an increased calcium excretion. In this region, the incidence of urinary stone disease was higher among Indians than in the other ethnic groups.[1]

Other diseases

The presence of chronic recurrent urinary tract infection is often associated with underlying anatomical abnormalities that predispose to luminal events and microbial proliferation of urease-positive microorganisms as *Proteus* sp, *Klebsiella* sp, *Pseudomonas* sp, *Staphylococcus saprophyticus* and *Ureaplasma urealyticum*. Also, urinary supersaturation of magnesium, ammonium and phosphate ions predispose to the formation of infection stones of which magnesium ammonium phosphate (struvite) is the main constituent.[2,15]

Pharmacological treatment and prophylaxis

After a first episode of nephrolithiasis, two main goals need to be achieved: first, the expulsion of the stones and second, the long-term prevention of future episodes. In view of this, several medical treatment methods have been tested. Although this review focus on pharmacological treatment, many advances have been made in non-invasive and surgical procedures in the management of nephrolithiasis. Extracorporeal shock wave lithotripsy, ureteroscopy and percutaneous nephrolithotomy are several non-pharmacological invasive and non-invasive procedures that have proved to be very useful in the management of stone disease. However, their high costs, significant rate of complications, high percentage of re-treatments and surgical and anaesthetic risks are not negligible and reinforce the need to search for effective pharmacological options.[19,51]

Medical expulsive therapy

Spontaneous passage of stones smaller than 5 mm occurs in at least half of the patients [17–19] but the mean expulsion time for a distal ureteral stone has been estimated to be greater than 10 days [19] and this process is often associated with complications like infections, pain, impaction that leads to hydronephrosis and acute pyelonephritis, sometimes needing emergency decompression.[17] Medical expulsive therapy is a strategy that has been used in order to increase the rate of spontaneous expulsion, reduce the time of expulsion, decrease possible complications and, the need for surgical intervention. It may be considered as a first-line option for stones 9 mm and smaller. The main obstacles to spontaneous expulsion are ureteral spasm and mucosal oedema or inflammation.[17]

Drugs that modify ureteral motility by decreasing phasic peristaltic contractions and maintaining tonic contraction, thus allowing distal migration of the stone have been tested.[19]

Since treatment alters the ureteral motility causing stasis that may lead to infection, a combination of antibiotic treatment and drugs to prevent ureteral oedema may also be used.[19]

α-blockers

Tamsulosin is a selective α1A-α1D adrenergic antagonist that has achieved good results. It seems to have an action on smooth muscles, preventing spasm and a second action blocking pain conduction to the central nervous system.[17,19] Expulsion rate of 4 mm or larger stones using tamsulosin was comparable to that of ureteroscopy and was significantly higher when compared to nifedipine and phloroglucinol (Table 2). Stone passage was achieved in a shorter time; there was a significant decrease in the number of hospitalizations and a decrease of the need for endoscopic procedures, allowing patients to do their everyday activities almost regularly.[19] Also, for stones with less than 10 mm, tamsulosin showed to increase the expulsion rate,[17,18] shorten the expulsion time and to reduce the frequency and intensity of the pain episodes.[17] This treatment also proved to be safe and it appears to have fewer adverse effects than terazosin.[18]

Alfuzosin. Although to a lower extent when compared to tamsulosin, alfuzosin increases stone expulsion rate [18,52] decreases stone expulsion time and reduces the need for analgesics.[52]

Doxazosin has been shown to increase stone expulsion rate, reduce stone expulsion time and reduce the frequency of renal colic. When compared with alfuzosin, terazosin and hyoscine B-butyl bromide (HBB) it achieved the highest expulsion rate.[52]

Terazosin achieved the lowest expulsion rate among α-blockers.[52]

Table 2. Results of trials on major drugs tested for MET

First author[ref.]	Treatment (comparisons)	Expulsion rate (%)	Mean expulsion time (days)	Analgesic requirement (%)
Dellabella[19]	Tamsulosin vs Nifedipine vs Phloroglucinol	97,1 77,1 64,3	3 5 5	0 1 2
Wang[18]	Tamsulosin vs Terazosin vs Placebo	81 78 55	6,3 6,3 10,1	-
Erturhan[17]	Tamsulosin vs Tolterodine vs Tamsulosin + Tolterodine vs Placebo	73,3 46,6 70 40	6,4 11,4 7,5 12,2	-
Gurbuz[52]	Doxazosin vs Alfuzosin vs Terazosin vs HBB	62 52,9 45,16 11	7,85 7,38 7,45 10,55	4,36 4,36 3,75 4,46
Hamidi Madani[51]	Isosorbide-SR vs Placebo	45,5 54,5	-	21,2 9,1

Calcium-channel blockers

Nifedipine is a calcium antagonist used for MET distal ureterolithiasis that has demonstrated an excellent efficacy inducing stone expulsion and relieving pain. When compared with phloroglucinol it decreased the need for hospitalization and endoscopic procedures for 4 mm or larger stones.[19] It also has been proved to achieve higher expulsion rate in distal stones smaller than 15 mm, when compared with methylprednisolone.[17]

Corticosteroids

Corticosteroids seem to decrease the inflammation caused by the impaction of large stones in the ureter, allowing its progression. However, their clinical effect has not yet been well defined.[19] The efficacy of corticosteroids has been compared with other drugs. When compared with tamsulosin, a similar expulsion rate was found between the two drugs, but expulsion time was longer with corticosteroids.[17] When compared with nifedipine, the latter achieved a better expulsion rate.[17] While stone size is generally considered as a main factor determining the possibility of spontaneous stone passage, some authors have suggested that

the use of corticosteroids in their studies may have masked that factor as they did not find any correlation between stone size and stone passage.[18,19]

Anti-cholinergic drugs

Phloroglucinol is a drug with anti-cholinergic properties that selectively acts on smooth muscles fibres in a state of spasm. Although it has proved to be superior to the watchful waiting approach, when compared with tamsulosin and nifedipine, it showed to be the least effective drug.[19]

Tolterodine is an anticholinergic agent used to reduce the resistance in the detrusor tunnel. However, it did not seem to provide additional advantages for treatment as its use alone was not effectual in increasing the expulsion rate or reducing the expulsion time.[17]

Hyoscine B-butyl bromide acts by inhibiting cholinergic transmission in the abdominal-pelvic parasympathetic ganglia, allowing a relief of spasm in the smooth muscles of the gastrointestinal, biliary and urinary tract.[52] However, it has been proved to have a negative effect on stone expulsion rate as the stone expulsion rate was reported to be lower than in a watchful waiting approach.[52]

Nitrates

It has been suggested that nitrates have potent relaxant effects on vessels and ureter smooth muscle that may reduce pain and facilitate ureteral stone passage, suggesting that it might be useful in medical expulsive therapy. However, *isosorbide-SR* has been found not to improve stone expulsion rate in patients with ureteral stones of less than 10 mm. Moreover, it increased hospitalization, side effects and analgesic requirement suggesting that it may not be a proper alternative for known α-blockers and calcium channel blockers in MET for ureteral stones.[51]

Although the advantage of a conservative approach described before, if MET proves to be unsuccessful or if complete obstruction happens, urinary tract clearing is vital and, thus, interventional treatment becomes necessary.[47,51] In a prospective study,[18] all the patients who failed to pass their stones and needed ureteroscopic manipulation had stone-induced moderate to severe mucosal inflammatory reactions with polypoid change, which lead the authors to suggest that MET might be ineffective for impacted lower ureteral stones.

Prevention of recurrence

Metabolic study

The presence of metabolic disorders in the great majority of patients with lithiasis supports the importance of metabolic evaluation protocols.[7,22,25,53] A basic metabolic evaluation in patients with urolithiasis might also estimate metabolic defects, improving the estimation of the risk of future stone formation and guiding prophylaxis programs.[6] For this reason, basic metabolic evaluation is considered as a part of the optimal management of urinary stone patients.[4,7,32] This basic evaluation includes urinary sediment and culture, blood samples with measurements of creatinine, chloride, ionised calcium, uric acid and blood cell count, as well as analysis of the calculus or fragment, to identify its exact composition.[32] Chemical analysis of the stone has become obsolete. Instead, macroscopic analysis of the structure, followed by infrared spectroscopy or X-ray diffraction is used to identify and quantify the components.[54]

The main goal of basic metabolic evaluation, in association with the assessment of other risk factors (e.g. family history of stone disease, brushite or infection stones), is to identify sub-groups of patients, high-risk and low-risk, that will benefit from different management strategies. Patients most likely to have a recurrent stone, may need pharmacological preventive therapies.[7,32]

High risk patients are those who present one or more of the following: early onset of stone disease in life, family history, brushite, uric acid and infection stones, solitary kidney, diseases associated with stone formation, genetic conditions that determine stone formation or the use of drugs associated with stone formation.[32]

In addition to the basic metabolic evaluation, specific metabolic studies include urine volume and pH profile in all patients. In calcium stone formers blood analysis should also include sodium, potassium, chloride, ionized calcium, uric acid and parathyroid hormone (PTH) in case of increased calcium levels and urinalysis should have measurements of specific weight, calcium, oxalate, phosphate, uric acid, citrate and magnesium. In case of uric acid stones, measurements of blood uric acid levels should be required, as well as urinary specific weight and uric acid levels. For cystine stones, only urinary specific weight and cystine should be added. As infection stone patients do not present any metabolic abnormalities, it is only recommended to add urine culture.[32]

To date, two 24-hours urine collection have been the gold standard for metabolic evaluation in urinary stone disease. However, it is a tedious, time-consuming and high commitment-requiring procedure, which is very often unsuitable for workers. That is the reason why a considerable rate of demotivation for collecting samples is found among stone formers, leading to low compliance, inadequate samples and consequently, to invalid results.[55] In fact, Hong and collaborators found that only half of the studied cohort provided a meaningful urine sample for metabolic evaluation. Thus, a simpler and comparable urinary metabolic evaluation method for stone formers is much needed.[55] Several studies have assessed the possibility of using spot-urine or timed urine samples for metabolic evaluation. However, it may not be possible for early morning spot urine to replace 24-hours urine collection in the evaluation of all urinary metabolic abnormalities in stone formers. This is why the European Association of Urology recommends two 24-hours consecutive urine

samples in high-risk patients.[32] Twenty-four-hours urine may be influenced by various factors including season, day-to-day variations, exercise, dietary changes and activity levels. Supersaturation values are, however, reasonably stable in most patients during months to years. Calcium oxalate saturation in either morning urine or 24-hours urine specimens appears to be the best predictor of stone risk. The creatinine-corrected calcium and citrate concentrations and the calcium oxalate saturation in early morning spot urine can be used as a substitute to measure 24-hour excretion.[20]

Long-term treatment

Diet restriction and supplementation

As we showed above, several risk factors for nephrolithiasis associated to diet have been identified, suggesting that dietary modifications play an important role in the formation of stones and therefore might be used in the management of this disease.

The main dietary modifications which have been proved to be useful in the long-term treatment of stone disease are calcium, sodium, proteins and oxalate intake.

Sodium. The consumption of dietary sodium increases the excretion of calcium.[22] The relation between the excretion of sodium and calcium has been studied and a positive correlation between the two was found,[11,56] which was stronger in hipernatriuric than in normocalciuric stone forming patients.[11] Also the risk of stone recurrence was significantly higher in stone formers with hypernatriuresis than in normonatriuresis patients, because urinary sodium alters other urinary risk factors for recurrence.[11,57] Dietary restriction of sodium seems, thus, to be essential in the long-term management of nephrolithiasis as it decreases the risk of recurrent stones.

Calcium. Several authors support that a calcium restrictive diet does not bring an advantage in the reduction of calcium nephrolithiasis.[56–58] In fact, a low calcium diet can

result in high urinary oxalate excretion and decreased bone mineral density. Moreover, patients who maintained a high or normal calcium intake were at lower risk for stones than stone formers with low calcium intake.[57] In a 5-year randomized trial to analyze different diets a lower incidence of stone recurrence was found in patients who had a normal calcium, low sodium and low animal protein diet when compared with those on a low calcium diet.[56] Secondary hyperoxaluria caused by calcium restriction can be compensated by the restriction of dietary oxalate intake.[58] However, some authors find the advantage of dietary restriction of oxalate to be questionable, as 85% to 95% of the urinary oxalate load is derived from endogenous synthesis of oxalate.[57]

Purines. Regarding the consumption of meat, rich in purines, the traditional advice to reduce the ingestion of animal protein was challenged by the results of a randomized-controlled trial (RCT) which included 99 calcium stone formers comparing a low-animal protein, high fibre, high fluid diet with a high fluid and adequate calcium intake diet. In fact, the authors concluded that a low animal protein, high fibre, high water diet has no advantage over the other.[59] These results were discussed by another group of researchers [56] who compared a group of male patients who were advised to restrict the ingestion of animal protein and sodium but had a normal-to-high intake of calcium, with a group of patients who had a low-calcium diet only. The first diet seemed to have a protective effect on the recurrence of stones, as in the normal-calcium, low-protein group, low-sodium diet had a significantly lower 5-year incidence of recurrence, when compared to low-calcium only group.[56] This line of thought is reinforced by the fact that diets with low protein intake reduce the risk of crystallization of uric acid and consequently the risk of stone forming.[30] A small sample of healthy subjects were exposed to a sequence of four different diets: a self-selected diet (SD) during 14 days, with instruction to avoid purine-rich foods as organ meats, fish, seafood and legumes; a typical affluent meat-containing Western-type diet (WD); a

balanced omnivorous diet (OD); and an ovo-lacto-vegetarian diet (VD). As the diet changed every five days from SD, WD, OD, VD, there was a decrease of urinary uric acid, ammonium, sulphate and phosphate excretion, and of the risk of uric acid crystallization as well as an increase of urinary pH value.[30] In this study, the authors concluded that for a similar level of purine intake, the risk was lower in the vegetarian diet group suggesting that it is not only the purine intake levels but also the origin of the purines that make a difference. A more recent three-arm RCT comparing low-animal-protein diet with a high-fiber diet concluded that a low-protein diet did not decrease the risk of recurrence.[12]

The reduction of urinary saturation of calcium oxalate due to dietary modifications like the restriction of dietary calcium, oxalate, sodium and meat products was the greatest in patients with moderate to severe hypercalciuria, intermediate for those with mild hypercalciuria and least for normocalciuric subjects.[58]

As for *fruits and vegetable supplementation*, it increases the urinary citrate excretion in hypocitraturic stone formers, reinforcing the idea that it might be a preventive measure in this group of patients.[29]

Fluid intake

The protective effect of a high water intake has been proved for a long time. Urine volume in patients with idiopathic calcium nephrolithiasis at the first episode has been found to be lower than in normal subjects, and adequate water intake, even when not accompanied by changes in diet, may exert an important protective effect against recurrences.[60] A high water intake results in a strong reduction of saturations of lithogenous salts which, if chronically maintained, represents the physical chemical basis for preventing recurrences.[60] An increased water intake and consequent urinary excretion ≥ 2 L significantly decreased the recurrence rate in stone formers, when compared with patients with a normal water intake.[60]

A sufficient fluid intake may be considered as the most important therapeutic measure in calcium oxalate lithiasis.[16] However, when hypercalciuria is present, it is necessary to introduce dietary or pharmacological measures to reduce the excretion of urinary calcium.[60]

Also the alkali content of drinking water may play a role in reducing calcium stone risk factors by modulating gastrointestinal alkali absorption and increasing citrate excretion.[61] Hypocitraturic patients could, therefore, benefit from a treatment with alkalizing beverages to additionally assure a sufficient fluid intake.[16]

Several different types of juices have been studied for their effect on urinary stone risk factors and an increase in citrate urinary excretion in hypocitraturic stone formers was found after an orange,[43] lemon,[44] and grapefruit juice [61] supplementation.

Lemon juice contains nearly 5 times the concentration of citric acid compared to orange juice and causes a 2-fold increase in mean daily urinary citrate excretion. It is an inexpensive and well tolerated dietary source of citrate that may improve patient compliance.[44] In fact, it has proven not only to improve hypocitraturia but also total urine volume in calcium oxalate stones patients. However, the association of this therapy with potassium citrate proved to be more effective in increasing urinary citrate than lemon therapy alone.[62] Therefore, it may be useful as adjunctive treatment for patients with hypocitraturic calcium nephrolithiasis.[44] Because maximal changes for urinary citrate and total urine volume were achieved earlier in follow-up, Penniston and colleagues [62] defend that lemon therapy might offer a similar, simpler and potentially less costly alternative, with the added benefits of improved urine volume individualized, and that encouragement and motivation should be provided to patients at each visit for sustained prevention.

The acute administration of a soft drink containing *grapefruit juice* diluted in mineral water significantly increased the urinary volume although to a lesser extent than the administration of an equal volume of mineral water. After grapefruit juice load there was an

increase of urinary citrate and magnesium which can be explained by the citrate and magnesium content of grapefruit juice, and an increase of urinary excretion of calcium that could be explained by the mineral content of the grapefruit juice or by the sugar added to the juice that could enhance the intestinal absorption of calcium and reduce the reabsorption at the renal distal tubule.[61]

The consumption of *cranberry juice* was found to decrease the urinary pH and increase the excretion of oxalate and the relative supersaturation for uric acid, therefore, being useful in the treatment of brushite and struvite stones.[42]

Blackcurrant juice also increases the urinary pH and the excretion of citrate and oxalate, underlining its potential as support of treatment of uric acid stone disease.[42]

As for *orange juice*, it seems to decrease urinary undissociated uric acid levels and urinary ammonium and increase the activity of brushite, urinary pH, potassium, citrate and net gastrointestinal absorption of alkali. However, it increases urinary oxalate without changing calcium excretion,[43] while potassium citrate has the opposite effect, it decreases calcium but do not change calcium excretion. Although it failed to decrease oxalate excretion, orange juice was proposed as an alternative to potassium citrate in case of intolerance or poor compliance.[43]

The consumption of *Gatorade*®, a carbohydrate-electrolyte sports beverage, on urinary risk factors in both stone formers and nonstone formers was investigated and the results suggested that Gatorade® increased, although within normal limits, urinary pH and excretion of uric acid, mean urinary sodium and chloride levels but, as it did not change urinary calcium excretion, it was not considered to change urinary risk factors.[13]

Consumption of *cola* was tested in 45 healthy subjects and it was found to cause unfavourable changes in metabolic risk factors of calcium nephrolithiasis, as it increased oxalate excretion in both men and women, and decreased magnesium excretion and urinary

pH in women.[63] However, a more recent study combining healthy subjects and stone formers found that cola consumption may not increase stone risk of calcium oxalate stone formation and may be used to improve daily fluid-intake.[64]

Dissolution / urine alkalinization

Chemolysis of existing stones may be possible in uric acid and some cystine stones. However, no agent is known that can be safely used neither to decrease calcium oxalate crystallization, nor to dissolve calcium oxalate stones or crystals.[3]

Potassium citrate improves hypocitraturia [62] and effectively reduces calcium oxalate stone recurrence.[65] It may also be effective in hyperuricosuric calcium oxalate stones by rising urinary citrate and retarding urate-induced calcium oxalate crystallization. Its use in moderate cystinuria (< 500 mg/day) has proven to be effective as it increases cysteine solubility decreasing its crystallization rate.[15] However, it cannot correct uric acid levels in urine and blood.[2]

Other formulations of containing potassium citrate associated with sodium and magnesium have been assessed. Sodium-potassium citrate had a poor long-term protection from recurrent calcium stone formation when a single evening dose of only 3,7 - 5 g of sodium potassium citrate was taken. Although the rate of stone formation was slightly reduced, the fraction of patients free of recurrence was no different from that in patients without medical treatment.[66] Potassium-magnesium citrate effectively prevented recurrent calcium oxalate stones, and reduced the risk of recurrence by 85%, when given for up to 3 years.[65] Alkali loading and citraturic and magnesium effects might explain these results. In fact, an increased urinary pH, citrate and magnesium levels was found in the group treated with potassium-magnesium citrate treatment compared to placebo.[65] Although less than 20% of patients in this study had hypocitraturia, the beneficial effect of citrate on calculus recurrence was not limited to this group of patients, which underscores the idea that citrate

therapy might be useful in preventing calcium oxalate lithiasis, sparing the need of an extensive metabolic study.

The effect of *Cystone*®, an Ayurvedic herbal treatment commonly used in India for stone prevention, was evaluated by a group that found no beneficial effect on the urinary composition and that it increased average stone burden. However, in that study stone formers tended to be those who had failed standard therapy, which may have influenced the results.[3]

Allopurinol acts by reducing the production of endogenous uric acid as well as its urinary excretion.[22] In case of acute pain during more than 48 hours or partial ureteral obstruction, the efficacy reaches 62,5%.[47] It can be used in hyperuricosuric uric acid and calcium oxalate stones in order to restore normal urinary levels of uric acid.[2]

The use of *thiazide diuretics* has been extensively tested and it acts by increasing tubular reabsorption of calcium, therefore decreasing urinary calcium levels. It is considered to be the most effective hypocalciuric agent.[2,22]

Thiol derivates like D-penicillamine and α-mercaptopropionylglycine or tiopropin are drugs that can be used in case of severe cystinuria as they cleave cystine molecules producing a highly soluble disulfide compound decreasing the excretion of poorly soluble cystine.[15,31] Some authors have proven the efficacy of a stepped therapeutic approach with a basic therapy of high fluid intake and alkalinization of urine and the addition of thiol derivates only when it failed to prevent stone recurrence or growth, or to dissolve pre-existing stones.[31] However, recent recommendations indicate that the better strategy to follow is to treat cystinuria according to its severity, therefore immediately administrating thiol derivates in case of severe cystinuria.[15,32]

Acetohydroxamic acid is a lithostatic drug that irreversibly inhibits urease and attenuates the rise of urinary pH and ammonium.[7,15] It is, therefore, useful in case of infection stones.

Discussion

Studies on risk factors, medical treatment and prophylaxis of nephrolithiasis have diverse geographical origin, from North America and Europe to East Asia, showing that this is a global health problem that deserves attention. Traditionally more frequent in men than in women, its prevalence is increasing in women as well as in children.

Several metabolic factors have been related to stone formation and recurrence. They seem to depend on a relation between environmental and biological factors that need further investigation. The reason why some individuals develop these metabolic abnormalities remains unclear. Hypercalciuria, hyperoxaluria and hypocitraturia are, to date, the best established metabolic abnormalities related to urine composition. As for hyperuricosuria and hypomagnesuria, although several studies show a relation with nephrolithiasis, not only the mechanisms are not completely clear but also these abnormalities are usually present in a minority of patients. Regarding a low urinary pH, it is established as an important risk factor for stone disease and some authors even consider it to be one of the most important risk factors of calcium stones.[30] Metabolic syndrome is settled as a risk factor for nephrolithiasis, but its components individually do not all have that same weight. Overweight, obesity, hypertriglyceridemia and hypertension have demonstrated to be independently associated with nephrolithiasis.

Environmental factors related with the risk of stone formation have also been studied: diet, fluid intake and therefore, volume of urine, physical activity of subjects and to their geographical location. In fact, the increased consumption of proteins and the low consumption of magnesium, calcium and potassium are independent risk factors well supported by evidence. As for oxalate-rich food intake, we found very few evidence of its association with the risk for developing nephrolithiasis, since most of the oxalate is produced in the body. The consumption of fruits and vegetables changes urine composition, and should

be encouraged. Low fluid intake and the consequent low urinary volume, as well as the consumption of alcohol are very well established as risk factors for nephrolithiasis. Poor physical activity and low expenditure of energy are independent risk factors for stone disease, which are certainly associated with overweight and obesity, described before.

As for biological factors, past and family history play an important role. However, there is still a lot to uncover about the genetic mechanisms that may influence this association. As far as age and gender are concerned, there is a positive association between age increase and incidence of stone disease, yet in gender the situation is different. Although most of the studies found a higher prevalence in male subjects, in Portugal males and females seem to be equally affected. Although the role of ethnicity has not yet been well defined, it appears that white and Indian people are more affected than black and Asian people.

Regarding the treatment of kidney stones, if a compound was found that could dissolve calcium stones it would certainly represent a new class of treatment for renal stones.[3] In the meantime, medical treatment is effective and safe and it can be used as a first approach to distal ureteral stones having less than 10 mm. It can also be used in case of surgical risk or previous definitive treatment. Tamsulosin is the most tested drug for MET and has proved its safety and efficacy. Other α-blockers have also been tested but show considerably lower efficacy. Nifedipine also presents good results in randomized trials. A multi-centred double-blind placebo-controlled randomized trial called SUSPEND (Spontaneous Urinary Stone Passage Enabled by Drugs) is currently ongoing in the UK comparing clinical and cost effects of tamsulosin and nifedipine in the management of ureteric stones.[67] Isosorbide-SR did not represent a proper alternative to tamsulosin or nifedipine. Also, drugs with anti-cholinergic effect like phloroglucinol and tolterodine had unsatisfactory results, and HBB proved to be nocuous. Developing new drugs remains a field to be explored.

Given the high prevalence of metabolic disorders in stone formers, there is a large consensus in the literature about the importance of a metabolic study of patients with nephrolithiasis. Basic metabolic evaluation is therefore regarded as part of the optimal management urinary stone patients as it allows practitioners to suggest preventive therapies, depending on the results of the study. A specific metabolic evaluation is recommended for patients at high risk of recurrence and will allow the introduction of specific prophylactic measures. Depending on the stone composition, different blood and urine analysis can be requested, according to the most frequent metabolic abnormalities associated to each type of stone, and to the availability of treatment. This complete metabolic evaluation may involve high costs and is time consuming. In patients with low-risk of recurrence it may not change therapeutic management as these patients will follow general prophylactic measures. Therefore, it is only recommended for patients at high risk of recurrence.

Indeed, there are some general measures that should be prescribed to all patients. The introduction of prophylactic measures oriented by the metabolic study is strongly recommended in high risk patients. All patients should be advised to have a balanced diet and to control weight. Moreover, a fluid intake of a least 2 L/day is strongly advised to all patients.

According to the results of the specific metabolic study, different prophylactic measures can be implemented. In case of hypercalciuric stone formers, evidence determines that a sodium restricted diet is recommended with a normal calcium intake. In this group of patients, also thiazidic diuretics have extensively shown their value. For hyperoxaluric patients, a sodium and oxalate-rich foods restriction is useful, as well as a magnesium potassium citrate supplementation. In hyperuricosuric patients, a reduction or elimination of alcohol intake is recommended and alkalizing drugs and allopurinol can be useful. As far as hypocitraturic patients are concerned, supplementations of citrate through the increase of

lemon juice and fruits and vegetables intake, or introduction of potassium-citrate are valuable options. In case of hypomagnesuria, patients should be encouraged to increase magnesium intake in food and, in case of concomitant hypocitraturia, they should take magnesium-potassium citrate. In acidic urinary pH a raise to neutral levels can be achieved with potassium citrate and fruit and vegetables supplementation which also favours diuresis. In case of alkaluria, cranberry juice may be useful. As for infection stones, treatment with acetohydroxamic acid is recommended.

The role of a low animal-protein diet remains controversial to reduce the risk of recurrence. Although reviews continue to recommend a low ingestion of proteins, the original studies analysed have mixed results. The three randomized-controlled trials in patients with calcium or calcium oxalate stones [12,56,59] were long term, longitudinal studies with good sample sizes, but the comparisons made were different and the characteristics of patients also differed. This may have accounted for the conflicting results. A closer look at the evidence by means of a meta-analysis should allow drawing more consistent conclusions about the advice on diet patterns.

The relation between gut colonization by *Oxalobacter formigenes* and the occurrence of oxalate stones, associated to the decrease in urine oxalate levels of healthy subjects after ingestion of *Oxalobacter formigenes*,[7] brings new possibilities to the prevention and deserves to be studied further.

This was a review on the risk factors of nephrolithiasis, its medical treatment and prophylaxis of recurrence. It provided us with a comprehensive understanding of the main issues that are currently faced by clinicians when treating a patient with kidney stones, even though its wide scope did not allow us to go deeper in each of the sections included.

Nephrolithiasis is a frequent problem, and it may be under some conditions treated with a pharmacological approach. Recognizing the risk factors of recurrence and identifying patients at high risk is crucial to determine the best prophylactic measures.

A strength of this review is that we tried to avoid bias in reporting by including studies that showed positive as well as studies showing negative results, underscoring existing controversies. Methodological quality of the studies was not an inclusion criterion, and therefore it has not been assessed but we are aware that in some cases, this might have influenced our results.

Further lines of research have been pointed out along the discussion, stressing that this is a very attractive field for collaborative research between clinical and bench researchers.

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