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REVIEW ARTICLE

Pathophysiology associated with forming urinary stones



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Risk factors

Abstract Urolithiasis has become a chronic disease that has had a major impact on both the quality of life and working situation of the patient. It has a significant impact on the health system due to its high recurrence. Different authors have identified several factors inherent to human biology and sociodemographic variables that may lead to the development of kidney stones. Thus, in this review, the main factors that influence the formation of kidney stones are presented, and that may help in a timely intervention on some of them.

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PALABRAS CLAVE

Urolitiasis;
Factores
sociodemográficos;
Factores de riesgo

Fisiopatología asociada a la formación de cálculos en la vía urinaria

Resumen La urolitiasis se ha convertido en una enfermedad crónica que ha tenido un gran impacto en la calidad de vida y en la situación laboral de quien la padece; su tasa de prevalencia y recurrencia es cada vez mayor, lo que genera un gran impacto socioeconómico en cualquier país al afectar el sistema de salud. Se han identificado numerosos factores inherentes a la biología humana y algunas variables sociodemográficas, que favorecen el desarrollo de cálculos renales; por lo cual, en esta revisión se describen los principales factores que influyen en la formación de urolitiasis, permitiendo intervenir oportunamente sobre algunos de ellos.

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Introduction

At present, calculi in the urinary tract can be considered as a chronic disease with a major impact on the quality of life.¹ In the United States, prevalence of urolithiasis is 8.8%

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for general population, being higher in men than in women (10.6 and 7.1%, respectively).²

Approximately 13 of every 1000 hospital admissions are due to renal and ureteral lithiasis; it is a frequent cause of admission in the emergency department and it can trigger various complications.³

Its prevalence is increasing and it depends on diverse factors, resulting in an economic burden on the health system. Costs increase due to frequent consultations, diagnostic tests, prolonged hospital stays, surgical procedures, broad-spectrum antibiotics or extended regimens, and secondary hospitalizations due to complications triggered by this disease. Currently in the United States, where there are available studies on the costs, urolithiasis costs more than five billion dollars annually, including diagnosis, treatment and disability caused by the disease.^{4,5}

This demonstrates the implication of this disease for the health system, given that approximately 77% of the individuals affected by urolithiasis are included in the productive groups of the population in any country.⁶ However, these numbers may vary due to different factors such as gender, age, history of urinary tract infections, disorders of metabolic origin, dietary excess and/or deficiency, among others.³ This paper aims to describe some of the theoretical concepts associated with stone formation in the urinary tract.

Methodology

A literature search was conducted through Medline via Ovid, SciELO, and Embase from 1986 to 2014; with the following Keywords: "urolithiasis and climate," "lifestyles and urolithiasis," "socio-demographic factors and urolithiasis," "gender and urolithiasis," "age and urolithiasis," "race and urolithiasis," "genetics and urolithiasis," "anatomical abnormalities and urolithiasis," "diet and urolithiasis," "stress and urolithiasis," "hormones and urolithiasis;" the different factors were also combined with "kidney stones", and the search was conducted both in Spanish and English. It is a narrative review, instead of being a systematic review/meta-analysis.

Epidemiology

It is the third most common urological disease after urinary tract infection and prostate disease. Its prevalence varies between 2 and 20% worldwide and it appears to relate to the geographical and socioeconomic characteristics of different populations.⁷ Its incidence has considerably increased in recent decades in all industrialized countries, due to profound modifications in dietary habits and lifestyle, characterized by a high calorie intake, combined with reduced physical activity, among other risk factors.⁶

Urolithiasis has a high recurrence rate after the first episode (50%)⁸; 14% have recurrence within a year, 35% at 5 years, and 52% in 10 years.³ This risk appears to be greater in the western hemisphere, with reported prevalences of 9.5% in Europe, 12% in Canada, 13–15% in the USA, and 5.1% in the eastern hemisphere. However, the highest risk has occurred in some countries like Saudi Arabia (20.1%).⁹

The most prevalent stones are calcium (60–65%), including calcium oxalate, calcium phosphate, and others, followed by struvite (5–15%) and uric acid (5–10%); cystine stones are uncommon and they account for 1–3% of all calculi types.^{10,11}

Pathophysiology

The sequence of events in the formation of any urinary calculus includes: urinary saturation, supersaturation, nucleation, crystal growth, aggregation of crystals, crystal retention, and, finally, calculus formation. Normally, these crystals pass through the urinary tract without problem; however, occasionally, if they become very large, they may cause the obstruction of the kidney drainage system resulting in severe pain, bleeding, infection or kidney failure, sending the patient to an emergency room.¹²

There are different theories about the process of stone formation. One proposes that the stone is formed when a normally soluble salt (e.g. calcium oxalate) supersaturates the urine, and crystals begin to form; if they are sufficiently large, they can get fixed to the urothelium (usually in the terminal portion of the collecting ducts), to then grow slowly. Another theory assumes stone formation begins in the medullary interstitium, then Randall plates form in the papilla, on which oxalate or calcium phosphate crystals start to deposit.^{7,13}

During the passing of urine by the kidney, such large particles can be formed that they can be retained; these serve as a nucleus for the formation of future stones.⁷

A solution favoring the development of urolithiasis is considered saturated regarding a substance when it contains in dissolution the highest possible concentration, that is, if an additional amount of this substance is added to this solution, it precipitates and forms crystals; the concentration at which this saturation is reached and crystallization begins is called thermodynamic solubility product (Ksp).^{9,12}

In clinical practice, supersaturation can be the result of any increase in urinary excretion of solvents (for example, calcium, oxalates, and cystine) or reduction in urine volume due to a decrease in fluid intake or extrarenal fluid loss.¹⁰

Other mechanisms by which crystals remain in the kidney:

Calcium oxalate monohydrate crystals (COM) connect rapidly with the surface of renal epithelial cells because the surface of these crystals behaves as if positively charged, while the luminal surface of epithelial cells of the tubules behaves as if negatively charged; thus this adherence is due to reactions of electrical charge, which make the crystal behave as if positively charge, and link to electrically negative molecules that emerge from the apical surface of the tubular cell; in a study, Lieske et al. concluded that immediately after adhesion, anchored crystals can serve as a preferential site for biding additional crystals; later, the crystal is endocytosed by the tubular cell, where after internalization the plasma membrane domain covering the crystal appears to exhibit increased adhesiveness for crystals because the attachment of added crystal was higher for at least 24 h after the first crystal bound; therefore, the presence of any attached or internalized COM crystal results in an increased number and/or affinity of crystal adhesion sites on the cell surface.^{12,14,15}

Anionic molecules have been found on the surface of epithelial cells and they act as COM crystal receptors; however, in the tubules there exist anions in dissolution, adhered to the surface of crystals, preventing them from connecting with epithelial cells. Changes in the quantity and the structure of specialized anionic molecules that are expressed on the surface of the epithelial cells of the tubules or those found in dissolution in the urine influence the adherence of crystals to cells, therefore, therefore participating in urolithiasis.¹²

There are also other soluble anions in the urine of renal tubules, which decrease the adherence capacity of calcium oxalate crystals to the surface of epithelial cells.¹²

Polyanionic citrate prevents the adherence of oxalate crystals, when they are found in concentrations approximately equal to those physiologically found in urine¹²; for this reason, oral potassium citrate is generally used as therapy for the prevention of stone recurrence; its therapeutic effect on the genesis of calculi is due to an increase in urinary citrates and to its alkalizing action, by intervening the combination of three different aspects: first, the formation of complexes with calcium, reducing thus calcium ion concentration; this decreases the urinary saturation of calcium salts. The second inhibits the crystallization of calcium phosphates and oxalates, by inhibiting the nucleation, growth, and aggregation of COM crystals. Finally, the third effect of citrate is raising urine pH secondary to its cellular metabolism.^{12,16,17}

Pentosan sulfate, a synthetic anion that exerts a potent inhibitory action on the increase in crystal size and is excreted in urine after oral administration, also prevents crystal adhesion.¹⁰ These facts could perhaps lead to a new generation of drugs for the treatment of renal calculi.

Numerous glycoproteins found in urine have also been examined; they appear to play a role in nephrolithiasis and include nephrocalcin, uropontine (a potent inhibitor of the increase in size of oxalate crystals), and the Tamm-Horsfal protein (a potent inhibitor of the aggregation of COM crystals) which prevents the incorporation of these crystals.¹² Nephrocalcin and uropontine, in concentrations similar to those found in human urine, show a potent inhibiting action toward the adherence of oxalate crystals. These anions suspend the adherence of crystals, by covering their surface. It has also been shown that the nephrocalcin inhibitor is abnormal in those individuals who form COM stones, because nephrocalcin molecules lack γ -carboxyglutamic acid, and normally do not inhibit COM crystallization.^{12,18}

There are factors that exacerbate kidney stone formation, and they include: having persistently concentrated urine, high urinary acidity, or lack of inhibitory substances in urine such as citrate.⁷

Associated factors

Various risk factors are recognized to predispose to urolithiasis, such as⁶:

Gender

In industrialized nations, the frequency of urolithiasis is higher in men than in women,¹⁹ with lifetime recurrence rates of up to 50%.³

According to a study by NHANES, in the United States men are more susceptible than women with a ratio of 3:1, prevalence was 7.1% in women and 10.6% in men²; in other western countries it is 4.3% in women and 6.9% in men.¹⁰

In Latin America the incidence seems higher, the risk of a kidney stone can be about 20% in men and 5–10% in women³; it appears that women have lower urinary calcium, oxalate and uric acid concentrations, and higher concentrations of citrate than men, which makes kidney stone formation less frequent in them³; however, over the years this rate has increased for females, which could be due to risk factors associated with lifestyle such as obesity.²⁰

Age

Although little is known about the effect of age on urolithiasis, it is known to affect all age groups; however, it has been shown that the age of onset of a lithiasic disease basically depends on the composition of calculi. For example, cystine stones begin to form in the first and second decades of life, followed by calcium stones between the third and fifth decades, while uric acid stones usually start in later years, over 50 years old.²¹

Children and adolescents show a low incidence in the formation of stones of all compositions.²²

Currently, 10.6% of men and 18.4% of women form their first calculus before they turn 20 years old. These results are believed to be results of changes in lifestyle and diet among women.²¹ Recent studies have shown that geriatric patients with urolithiasis are only 10–12% of all patients who are referred to a tertiary care center for treatment of urolithiasis²³; they are also the most susceptible to complications or infection stones, especially those over 60 years of age, due to the increased frequency of urinary tract infection and concomitant urologic disease. It is estimated that in this age group the risk of urolithiasis is 20% in men and 5–10% in women.²²

Race

White race is the most affected, with a higher prevalence than in African descents and mixed-race people together, 5.2 vs. 3.8%, respectively. According to Reyes et al., there is a racial difference in electrolyte excretion related to lithogenesis such as sodium and magnesium.²⁴

Idiopathic lithiasis is more common in Caucasians compared to Blacks, regardless of the geographical area; for example, in the USA it is 5.9 vs. 1.7%, respectively. This difference is not maintained when dietary habits and environmental factors are the same. There was a significant increase in the prevalence of urolithiasis in African Americans once they had adopted Caucasian dietary habits.²⁵

Genetics

25% of patients with urolithiasis have family history; the relative risk of stone formation is more frequent in persons with a family history of calculi than in those without a family history; however, there is little information about whether the increased risk is attributable to genetic factors, environmental exposure, or some combination. A positive family history of urolithiasis has been reported in 16–37% of patients who have formed a renal calculus, compared with 4–22% of healthy people with no history.²⁶

Curhan et al. studied family history and the risk of urolithiasis in a cohort of 37,999 male participants, with a follow-up of 8 years; 4873 (12.8%) had a family history of kidney stones, 2957 of which (7.8%) reported a personal history of urolithiasis; finally, the study showed that men who have had urolithiasis are approximately three times more likely to report a family history of kidney stones.²⁷

There are also intrinsic epidemiological factors, including genetic factors, such as autosomal recessive syndromes,²⁸ with increased susceptibility to stone formation.²⁹

Hypercalciuria is the most important risk factor in calcium calculi formation. It may have genetic predisposition and it occurs in 35–65% of the cases; about half of the patients with hypercalciuria have a family history of urolithiasis, increasing the risk of urinary calcium excretion compared to those without a family history.²⁶

Hyperuricosuria may also be related to a family history; the excretion and metabolism of uric acid may be influenced by inherited factors, and men with gouty diathesis are at increased risk of urolithiasis.²⁶

Prevalence for cystinuria is 1–5% of patients with urolithiasis and lower for primary hyperoxaluria (2/million populations). Autosomal recessive inheritance was evidenced for cystinuria and primary hyperoxaluria. However, the latter has higher prevalence rates in regions with a high number of consanguineous marriages, such as in North-ern Africa or in Israeli Arabs.²⁵

Inheritance is complex and polygenic; nevertheless, familial recurrence does not necessarily imply a hereditary transmission, given that it may be influenced by environmental factors shared by family members.²⁵

Anatomical abnormalities

There are anatomical abnormalities that favor stone formation and should be part of the study protocol; they include: renal tubular ectasia or medullary sponge kidney, obstruction of the ureteropelvic junction, diverticula or cysts in the renal calyces, ureteral stricture, vesicoureteral reflux, ureterocele, and horseshoe kidney.²⁹ There also exist causal factors proper to each patient, such as vesical/urethral outlet obstruction. What all these situations have in common is that they cause urinary stasis leading to sediment condensation, and, finally, to crystallization and calculus formation.³

Hormonal factors

The incidence of kidney stones in men is associated with high levels of testosterone, mainly in the third and fourth decades of life. One of the reasons is that testosterone

increases hepatic levels of glycolic acid oxidase, which participates in urinary oxalate synthesis; an increase in testosterone can result, thus, in hyperoxaluria, which in turn may be responsible for the increased predisposition to calcium oxalate urolithiasis.³⁰

In addition, testosterone appears to promote stone formation by suppressing renal osteopontin expression and increasing urinary excretion of oxalate; on the contrary, estrogen inhibits calculus formation by increasing osteopontin expression in the kidney and decreasing urinary oxalate excretion. This would explain women's lower predisposition, mainly in their premenopausal state.^{30,31}

Specific diseases

Intestinal disease

Fluid loss due to chronic diarrhea modifies pH levels and alters the absorption of different substances, which can lead to the alteration of urine pH in a sustained manner, changing urine balance. This causes the formation of an inner nucleus to which stone-forming ions adhere. Thus, acidic urine contributes to the formation of uric acid calculi, and alkaline urine favors the appearance of calcium stones, while a pH above 7.5 is associated with struvite calculi.³

Diabetes

There are several mechanisms by which diabetes mellitus increases the incidence of urolithiasis. First, chronic hyperglycemia may cause a low-grade inflammation in gastrointestinal epithelium by altering the balance between intestinal flora and circulatory defense mechanisms; later, this inflammation leads to an increased absorption of oxalate, as seen in chronic diarrheal illnesses, where diarrheal fluid losses induced low pH and citrate levels increase urinary calcium oxalate and uric acid supersaturations.³² Secondly, chronic hyperglycemia may alter the epithelial functions of both gastrointestinal and urinary tracts for absorption and excretion of elements, thereby directly facilitating the formation of calculus.³²

Thirdly, immunosuppression secondary to diabetes mellitus and chronic glycosuria induce urinary tract infections, which may cause urolithiasis, since some bacteria can provoke urinary supersaturation and modify the environment, thus leading to the formation of crystal deposits which may be a factor that promotes urolithiasis; in fact, 10% of urinary calculi are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme urease.³²

Finally, diabetic nephropathy induced glomerular dysfunctions can alter urinary content, which facilitates urolithiasis.³²

Daudon et al., in a study to evaluate whether the risk of uric acid calculi increases with type 2 DM, also mention key factors for an increased incidence of urolithiasis in people with diabetes; this is due to insulin resistance, characteristic of the metabolic syndrome and type 2 DM, which leads to a lower pH urinary through impaired kidney ammoniogenesis because a low urine pH is the main factor of uric acid stone formation.^{20,33}

Obesity

A body mass index greater than 30 is associated with an increased risk of kidney stone formation, since urine oxalate, uric acid, sodium, and phosphate excretion is higher in people with a similar index than those with a lower BMI.²⁰ Urolithiasis is more common in obese people than in normal-weight individuals (11.2 vs. 6.1%, respectively); that is, obese people are 1.55 times more likely to suffer from this disease.²

Dyslipidemia

Several studies^{34–37} have demonstrated the relationship with elevated triglyceride and low HDL levels, with cut off values of <45 mg/dL for men and <60 mg/dL for women that increase the risk of nephrolithiasis by 30%.³⁴ The explanation seems to be given by vascular theory which offers the connection between dyslipidemia and nephrolithiasis.³⁴ The descending vasa recta makes a close turn in the renal medulla, which generates a hostile, hypoxic, and hyperosmolar environment, causing a transition from a laminar to turbulent flow that potentiates a vascular injury. There is also buildup of plaque which could lead to calcifications and later to erode into ducts of Bellini (frequently bathed in supersaturated urine), enhancing even more the potential for calculus growth.³⁴

Kang et al., with a final analysis of 321 patients with a diagnosis of urolithiasis, whose lipid profile and 24-h urine chemistry levels were evaluated, found that 109 patients (34% of the cohort) had recurrence of urolithiasis, being this more common in the patient group with than without hypertriglyceridemia (45.9 vs. 29.7%; $p = 0.005$). There are some studies that suggest an association between hypertriglyceridemia, hypercholesterolemia, and increased recurrence of stones in the urinary tract, although there is still no solid evidence.³⁴

A benefit of statins has also been demonstrated, reducing the risk of nephrolithiasis³⁴; in case of calcium oxalate calculi, which represent 60% of nephrolithiasis cases, exposure of renal cell to oxalate or calcium oxalate crystals leads to increased production and release of reactive oxygen species and to the development of oxidative stress, followed by injury and inflammation; reactive oxygen species attack DNA, causing oxidative lesions, particularly an oxidized form of guanosine called 8-hydroxy-2-deoxyguanosine (8-OHdG).³⁶ In a study by Tsujihata et al., in which a rat model was used, levels of 8-OHdG were significantly increased in stone-former rats, but they were equally reduced in rats treated with atorvastatin, which means that atorvastatin had an inhibitory effect on oxidative DNA damage in renal tubular cells and reduced the formation of calcium oxalate deposits in kidney tissue; there was also an increase in superoxide dismutase enzyme in rats treated with atorvastatin; this enzyme is located in the vasculature and leads to the elimination of free radicals by generation of water and oxygen.³⁶

Sur et al. compared the impact of statins in nephrolithiasis in 57,326 patients with hyperlipidemia patients, members of the US Armed Forces in active duty and retired; they found that patients taking statins had a 50% lower risk of stone formation compared to patients not taking statins (3.1 vs. 3.7%, univariate OR = 0.83, 95% CI 0.76–0.91;

$p < 0.001$). Multivariate analysis indicated that statins had a protective effect against calculus formation (OR = 0.51, 95% CI 0.46–0.57; $p < 0.001$) after making adjustments for age, sex, and comorbidities. This is because statins not only maintain lower cholesterol levels, but they also reduce the expression and activity of nicotinamide adenine dinucleotide phosphate oxidase, inhibiting the production of reactive oxygen species.^{37,38}

Gout

Patients with hyperuricemia can form uric acid kidney stones and calcium oxalate calculi, pure or a mixture of both, due to urinary acidification.³⁹

In cases of primary gout, 39% of patients have urinary stones, of which 30% are asymptomatic and diagnosed only by ultrasonography.²⁰

Pregnancy

There are pathophysiological changes that make pregnant women more susceptible to urolithiasis; among them, urinary stasis caused by increased progesterone and mechanical compression, in addition to increased glomerular filtration rate, the intake of calcium supplements, and increased circulating levels of vitamin D leading to high urine pH, hypercalciuria, and hyperuricosuria; the increased glomerular filtration rate leads to an increase in tubular flow followed by decreased tubular reabsorption and increased excretion of calcium and/or uric acid. It has also been found that placental formation of 1,25-dihydroxycholecalciferol promotes intestinal reabsorption of calcium and mobilization of bone calcium.⁴⁰

However, it is generally accepted that pregnancy is not a state of increased stone formation; it has been found that pregnant women present hypercitraturia; citrate is an inhibitor of crystal growth and aggregation, therefore it can be considered a clinically significant protective factor during pregnancy, compensating the effects of hypercalciuria and hyperuricosuria.⁴⁰

The incidence of urolithiasis in pregnancy is observed in 1/200–1500 pregnancies, it is much more common in Caucasians than in African Americans, and about 75% of pregnant patients with nephrolithiasis have calcium phosphate stones.^{41,42}

Regarding complications, there is a greater risk of premature birth which may occur in up to 67% of cases,⁴³ and a higher percentage of premature rupture of membranes in pregnant women with than without nephrolithiasis (7 vs. 2.9%; $p < 0.05$),⁴² in addition to a greater need for cesarean section.⁴³

Lifestyle

Several studies associate the frequency of kidney stone formation with the lifestyle of each patient, considering that this causes a progressive increase in its incidence and prevalence; for this reason, we will focus on its most important variables:

Diet

Measures of promotion and prevention are fundamental to interfere with the progress of the disease; in addition, they constitute the first contact and a first opportunity with the patient; it is therefore important to consider some nutritional interventions associated with the disease such as the following:

- Oral liquid intake: High fluid intake produces a high daily urine volume which decreases the formation of urinary crystals and the supersaturation of stone salts, as demonstrated in the study by Pak et al., noting that urinary dilution *in vivo* and *in vitro* reduced the production rate of urinary calcium phosphate, calcium oxalate, and urate; it also increased the limit of calcium oxalate crystallization.⁴⁴
- In a systematic review, Fink et al. also coincide with this evidence, demonstrating in their study that high water consumption decreased risk of recurrent urolithiasis (RR: 0.39; CI 95%: 0.19–0.80).⁴⁵
- Therefore, urinary dilution (2 l/24 h) with an adequate water intake (2–3 l/day) becomes an effective therapeutic measure for preventing urolithiasis.^{11,46}
- Sodium intake: An increase in sodium intake may promote stone formation, including increase in urine pH, calcium and cystine excretion, and a decrease in citrate excretion. An estimated 100 mmol increase in dietary sodium causes a 25 mg rise in calcium excretion, promoting the formation of calcium-containing stones.⁴⁷
- A study by Yun et al. retrospectively evaluated natriuresis in patients with urolithiasis, and it found that there is a greater recurrence in patients with hipernatriuresis compared to normal sodium excretion (46.9 vs. 64.5%; $p=0.043$).⁴⁸ It also showed that urinary sodium is directly associated with increased levels of several urinary metabolites (uric acid, calcium oxalate, among others) with statistically significant differences ($p<0.001$).⁴⁸
- Calcium intake: Restricting dietary calcium was formerly believed to be the cornerstone in the treatment of urolithiasis; however, in recent decades different studies, like Curham et al. (RR 0.6 CI 95% 0.4–0.9) and a cohort study by Taylor (CI 95%: 0.56–0.87), have evidenced a reduced risk of urolithiasis with a higher intake of calcium.^{49,50} Similarly, in a review of a randomized study with patients with low-calcium diet or with a normal-calcium, low-animal-protein and low-salt diet (HR 0.49, CI 95%: 0.24–0.98; $p=0.04$), a decrease in oxaluria and supersaturation of calcium oxalate was found with a long-term adherence to the normal-calcium, low-animal-protein and low-salt diet, also reducing the number of recurrences of the disease.⁵¹
- Animal protein intake: An estimated addition of 75 g of protein to the diet increases in 100 mg/day urinary calcium excretion.⁵² However, studies like Taylor's found that diets with high protein content (>75 g/day) are not associated with a risk of urolithiasis; similarly, in a study by Dussol et al., which compared a low-animal-protein diet, a high-fiber-content diet, and one without intervention, with recurrence of 48, 63 and 48% respectively, the authors concluded that there is no benefit to having a low-animal-protein diet.⁵³ The analysis of previous studies shows that there is insufficient evidence on the

benefit of this diet; on the contrary, results lead to its omission from medical management, it does, however, remain a recommendation due to its indirect lithogenic effect; consequently, more studies are needed to support these results.⁴⁶

- Potassium citrate intake: Citrate, as an inhibitor of crystallization and decrease in its urinary excretion, is associated with increased risk of urolithiasis, therefore potassium citrate supplement was proposed as a management measure for the prevention of urolithiasis, as demonstrated in a study by Spivacow et al. of 215 patients with urolithiasis treated with potassium citrate, where a statistically significant increase in urinary pH and a decrease in uricosuria and calciuria were evidenced, with a remission rate of 91% with 9 recurrences.⁵⁴
- Physical activity: The effects of exercise on reducing the risk of kidney stones have been studied in very few studies and on a limited number of patients. However, there is evidence correlating immobility or bed rest with a high risk of calculi, as well as an increase in lithogenic urinary risk factors only in absence of adequate hydration during and after exercise⁵⁵; therefore, during physical activity, adequate hydration is beneficial as increased fluid intake is favorable for the prevention of renal calculi.⁴⁴

Recent data show that increased physical activity and lower energy intake may be associated with a lower risk of kidney stones.⁵⁶

Ferraro et al. conducted a prospective study with 3 cohorts of patients; the first cohort was the HPFS group enrolling 51,529 male health professionals; the NHS I group enrolled 121,700 nurses and the NHS II group enrolled 116,430 nurses. The final analysis included 215,133 participants. After up to 20 years of follow-up, 5355 incident cases of kidney stones occurred. In the age-adjusted analysis with increased physical activity, they found a lower risk of incidence of kidney stones in women; with a significant trend toward risk reduction in the NHS I (95% CI: 0.69–0.95; $p=0.003$) and NHS II cohorts (95% CI: 0.71–0.92; $p=0.001$); however, this association was not statistically significant for men in the HPFS cohort (95% CI: 0.80–1.04; $p=0.26$). Nevertheless, after multivariate adjustment, there was no significant association between physical activity and kidney stone risk in any of the 3 cohorts HPFS, NHS I and II (95% CI: 0.87–1.14; $p=0.94$; 95% CI: 0.85–1.19; $p=0.88$; and 95% CI: 0.90–1.18; $p=0.64$, respectively).⁵⁶

Stress

Stress-related mechanisms and kidney stone formation involve the activation of the hypothalamic-hypophyseal axis leading to secretion of vasopressin which acts on the membrane of the collecting tubule of nephrons making it more permeable to water; thus, as a result, more water will be reabsorbed, causing the formation of hypertonic urine; secondly, there will be secretion of adrenocorticotropin which acts through a secondary hyperparathyroidism mechanism and raises serum calcium levels.⁵⁷ Because stress activates the pituitary-adrenocortical axis and sympathic-adrenal axis, a major variation in blood levels of cortisol, aldosterone, and catecholamines is induced. Cortisol can increase urinary excretion of calcium, either by competing

with aldosterone at the renal intracellular level, or by reducing intestinal calcium absorption that affects bone metabolism.⁵⁸

Drugs

Drugs and stone formation in the urinary tract are associated in two ways. First, certain medications raise excretion rates of natural components triggering stone formation. Second, real drug induced calculus formation directly occurs by the precipitation of a drug or its metabolite in the urinary tract.⁵⁹ For example, protease inhibitor drugs used in HIV treatment, including atazanavir²⁰ and indinavir, the prolonged use of the latter has been associated with a 4% incidence of urolithiasis. Topiramate (antiepileptic) shares with other sulfamate or sulfonamide derivatives the property of inhibiting carbonic anhydrase, which induces hypocitraturia and increases urinary pH, resulting in an increase in calcium phosphate supersaturation.^{25,59}

Weather

There is an increasing incidence of nephrolithiasis in the tropics, especially in the summer, where the risk of stone formation is aggravated by low urine volume due to elevated temperatures which cause increased heat-induced sweating; this leads to a state of dehydration causing reduced urine volume and increase in diuretic concentrations, which facilitates the crystallization of substances excreted in urine, thus triggering stone formation.^{20,29,60} Hypotheses supporting that dry climate increases the formation of urinary calculi mainly depend on dehydration. In addition to direct sunlight exposure at room temperature, sunshine activates vitamin D and therefore increases the concentration of serum 25-hydroxyvitamin D, elevating urinary calcium levels in summer.¹⁰

The incidence of urolithiasis is higher in countries with warm climates, probably due to low urinary output and low fluid intake. These are some of the factors contributing to the geographical pattern that has characterized North American and Afro-Asian stone belts.²⁵

Geographic area

The incidence of urolithiasis in a given population depends on the geographical area, and the racial composition and socioeconomic status of the community.²⁰ The probability of urinary stone formation varies considerably in different parts of the world. It affects 1–5% of the population in Asia, 5–10% in Europe, and 13% in North America; in Brazil, there is an estimated 5% of lithiasis patients.⁶⁰ The risk of developing urinary calculi in adults appears to be greater in the western hemisphere (9.5% in Europe, 12% in Canada, 13–15% in the USA) than in the eastern hemisphere (5.1%), although the highest risk has been reported in some Asian countries, such as Saudi Arabia (20.1%).²⁵ South Western Asia represents a high-risk environment for urolithiasis; in Kuwait, for example, the time to formation of symptomatic urinary calculi was calculated in 93 days.²⁰

Conclusions

Evidence show that many factors may influence urolithiasis, either as a protective or a risk factor. The main inherent

human biological factors, with a poor probability for change, include: testosterone, white or Caucasian race, anatomical abnormalities, and genetic diseases.

There are also modifiable factors such as diet, exercise, stress, and drugs, which enable timely interventions like in the lifestyle of a person. In concordance with the literature, for the prevention of urolithiasis we suggest: adequate calcium intake, taking more than 3 l of water a day, and reducing salt and animal protein intake, such as red meat.

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References

1. Tefekli A, Cezayirli F. The history of urinary stones: in parallel with civilization. *Sci World J.* 2013;2013:1–5.
2. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *Eur Urol.* 2012;62:160–5.
3. Vega M, Gonzalez M, Abreu I. Características clínico-epidemiológicas de la litiasis renal comunidad manzanillo 2006–2007. *Rev Habanera.* 2009;8:52–64.
4. Hampton T. Kidney stones. *JAMA.* 2008;299:1533.
5. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int.* 2005;68:1808–14.
6. Guillén R, Ruiz I, Stanley J, Ramírez A, Pistilli N. Evaluación de parámetros litogénicos en pacientes con urolitiasis que concurren al Instituto de Investigaciones en Ciencias de la Salud en el año 2009. *Mem Inst Investig Cienc Salud.* 2010;8:14–21.
7. Sanchez A, Sarano D, del Valle E. Nefrolitiasis. Fisiopatología, evaluación metabólica y manejo terapéutico. *Actual Osteol.* 2011;7:195–234.
8. Wood K, Gorbachinsky I, Gutierrez J. Medical expulsive therapy. *Indian J Urol.* 2014;30:60.
9. Aggarwal KP, Narula S, Kakkar M, Tandon C. Molecular mechanism of renal stone formation and the critical role played by modulators. *Biomed Res Int.* 2013;2013:1–21.
10. Wang H-H, Lin K-J, Chu S-H, Chen H-W, Chiang Y-J, Lin P-H, et al. The impact of climate factors on the prevalence of urolithiasis in Northern Taiwan. *Biomed J.* 2014;37:24.
11. Mejia LM, García-perdomo HA, Contreras R. Manejo dietario para la prevención de urolitiasis. *Rev Urol Colomb.* 2014;23:214–8.
12. Dardamanis M. Pathomechanisms of nephrolithiasis. *Hippokratia.* 2013;100–7.
13. Dasgupta R, Glass J, Olsburgh J. Kidney stones. *Clin Evid (Online).* 2009;2009:1–4.
14. Lieske JC, Norris R, Swift H, Toback FG. Adhesion, internalization and metabolism of calcium oxalate monohydrate crystals by renal epithelial cells. *Kidney Int.* 1997;52:1291–301.
15. Tostes V, Cardoso R. Revisão: recentes avanços em litíase urinária. *J Bras Nefrol.* 2001;23:166–73.
16. De Yoreo JJ, Qiu SR, Hoyer JR. Molecular modulation of calcium oxalate crystallization. *AJP Ren Physiol.* 2006;291:F1123–32.
17. Verdejo AJ, Martín MA, Ortiz JLM, Rosino EH, Yago FP, Gómez AZ. Efecto del citrato potásico en la profilaxis de la litiasis urinaria. *Arch Esp Urol.* 2001;54:1036–46.

18. Miller NL, Evan AP, Lingman JE. Patogenicidad de los cálculos renales. *Urol Clin N Am.* 2007;34:295–313.
19. Estrada-jasso D, Martínez-torres J, Rivera LC. Litiasis urinaria en la atención primaria. *Rev Fac Med UNAM.* 2005;48:5–7.
20. Trinchieri A. Epidemiology of urolithiasis: an update. *Clin Cases Miner Bone Metab.* 2008;5:101–6.
21. Lancina JA, Novas S, Rodríguez J, Ruibal M, Blanco A, Fernández Enrique, et al. Edad de comienzo de la enfermedad litiásica: relación con factores clínicos y de riesgo metabólico. *Arch Esp Urol.* 2004;57:119–25.
22. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. *J Urol.* 2011;185:1304–11.
23. Krambeck AE, Lieske JC, Li X, Bergstralh EJ, Melton LJ, Rule AD. Effect of age on the clinical presentation of incident symptomatic urolithiasis in the general population. *J Urol.* 2013;189:158–64.
24. Reyes L, Almaguer M, Valdivia TCJ. Estudio clínico-epidemiológico de la urolitiasis en un área urbana caribeña. *Nefrología.* 2002;22:239–44.
25. López M, Hoppe Hoppe B. History, epidemiology and regional diversities of urolithiasis. *Pediatr Nephrol.* 2010;25:49–59.
26. Park C, Ha Y-S, Kim Y-J, Yun S-J, Lee S-C, Kim W-J. Comparison of metabolic risk factors in urolithiasis patients according to family history. *Korean J Urol.* 2010;51:50.
27. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. Family history and risk of kidney stones. *J Am Soc Nephrol.* 1997;8:1568–73.
28. Türk C, Knoll T, Petrik A, Sarica K, Seitz C, Straub M, et al. Guía clínica sobre la urolitiasis. *Eur Assoc Urol.* 2010:1–102.
29. Martínez PR, Colorado SR, Escobar L. Urolitiasis y embarazo. *Ginecol Obs Mex.* 2007;75:357–63.
30. Naghii M, Hedayati M. Determinant role of gonadal sex hormones in the pathogenesis of urolithiasis in a male subject—a document for male predominancy (case study). *Endocr Regul.* 2010;44:143–6.
31. Maalouf N, Sato A, Welch B, Howard B, Cochrane B, Sakhaee K, et al. Postmenopausal hormone use and the risk of nephrolithiasis. *Arch Intern Med.* 2010;170:1678–85.
32. Davarci M, Helvacı MR, Aydın M. What is the relationship between type 2 diabetes mellitus and urolithiasis? *Bratisl Lek List.* 2011;112:711–4.
33. Daudon M, Traxer O, Conort P, Lacour B, Jungers P. Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol.* 2006;17:2026–33.
34. Masterson JH, Woo JR, Chang DC, Chi T, L'Esperance JO, Stoller ML, et al. Dyslipidemia is associated with an increased risk of nephrolithiasis. *Urolithiasis.* 2015;43:49–53.
35. Kang HW, Seo SP, Kim WT, Kim Y-J, Yun S-J, Lee S-C, et al. Hypertriglyceridemia is associated with increased risk for stone recurrence in patients with urolithiasis. *Urology.* 2014;84:766–71.
36. Tsujihata M, Momohara C, Yoshioka I, Tsujimura A, Nonomura N, Okuyama A. Atorvastatin inhibits renal crystal retention in a rat stone forming model. *J Urol.* 2008;180:2212–7.
37. Sur RL, Masterson JH, Palazzi KL, L'Esperance JO, Auge BK, Chang DC, et al. Impact of statins on nephrolithiasis in hyperlipidemic patients: a 10-year review of an equal access health care system. *Clin Nephrol.* 2013;79:351–5.
38. Khan SR. Reactive oxygen species as the molecular modulators of calcium oxalate kidney stone formation: evidence from clinical and experimental investigations. *J Urol.* 2013;189:803–11.
39. Arregui BL. Píperidemia: importancia clínica. *Revista Aula de la Farmacia.* 2009:40–8.
40. Pais VM, Payton AL, LaGrange CA. Urolithiasis in pregnancy. *Urol Clin N Am.* 2007;34:43–52.
41. Semins M, Matlaga B. Management of urolithiasis in pregnancy. *Int J Womens Health.* 2013;5:599–604.
42. Lewis DF, Robichaux AG, Jaekle RK, Marcum NG, Stedman CM. Urolithiasis in pregnancy. Diagnosis, management and pregnancy outcome. *J Reprod Med.* 2003;48:28–32.
43. Korkes F, Rauen EC, Heilberg IP. Urolithiasis and pregnancy. *J Bras Nefrol.* 2014;36:389–95.
44. 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.
45. Fink HA, Akornor JW, Garimella PS, MacDonald R, Cutting A, Rutks IR, et al. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. *Eur Urol.* 2009;56:72–80.
46. Mejía L, García-Perdomo H, Contreras R. Manejo dietario para la prevención de urolitiasis. *Urol Colomb.* 2014;23:214–8.
47. Assimos DG, Holmes RP. Role of diet in the therapy of urolithiasis. *Urol Clin N Am.* 2000;27:255–68.
48. Yun SJ, Ha Y-S, Kim WT, Kim Y-J, Lee S-C, Kim W-J. Sodium restriction as initial conservative treatment for urinary stone disease. *J Urol.* 2010;184:1372–6.
49. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med.* 2004;164:885–91.
50. Taylor EN. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol.* 2004;15:3225–32.
51. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiora U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med.* 2002;346:77–84.
52. Agarwal MM, Singh SK, Mavuduru R, Mandal AK. Preventive fluid and dietary therapy for urolithiasis: an appraisal of strength, controversies and lacunae of current literature. *Indian J Urol.* 2011;27:310–9.
53. Dussol B, Iovanna C, Rotily M, Morange S, Leonetti F, Dupuy P, et al. A randomized trial of low-animal-protein or high-fiber diets for secondary prevention of calcium nephrolithiasis. *Nephron Clin Pract.* 2008;110:c185–94.
54. Spivackow FR, Negri AL, Polonsky A, Del Valle EE. Long-term treatment of renal lithiasis with potassium citrate. *Urology.* 2010;76:1346–9.
55. Meschi T, Nouvenne A, Borghi L. Lifestyle recommendations to reduce the risk of kidney stones. *Urol Clin N Am.* 2011;38:313–20.
56. Ferraro PM, Curhan GC, Sorensen MD, Gambaro G, Taylor EN. Physical activity, energy intake and the risk of incident kidney stones. *J Urol.* 2015;193:864–8.
57. Walters DC. Stress as a principal cause of calcium oxalate urolithiasis. *Int Urol Nephrol.* 1986;18:271–5.
58. Arzo-Fabregas M, Ibarz-Servio L, Edo-Izquierdo S, Doladé-Botías M, Fernandez-Castro J, Roca-Antonio J. Chronic stress and calcium oxalate stone disease: is it a potential recurrence risk factor? *Urolithiasis.* 2013;41:119–27.
59. Hess B. Drug-induced urolithiasis. *Curr Opin Urol.* 1998;8:331–4.
60. Fernandes S, de Francesco E, Bruno CA. Dados demográficos, clínicos e laboratoriais de pacientes com litíase urinária em Fortaleza, Ceará. *J Bras Nefrol.* 2011;33:295–9.