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ETIOPATHOGENIC FACTORS OF UROLITHIASIS

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Summary.- *INTRODUCTION: Kidney stone disease affects 1 in 10 persons at least once per life-time worldwide, in 2% the disease is recurrent. For the individual stone disease can be painful and lead even to chronic kidney disease, while the costs for the health system and economy can be very high. Thus, factors causing stone disease need to be identified in order to prevent or reduce the incidence of disease.*

AIM: This review will discuss major risk factors contributing to stone disease with special emphasis on genetic and dietary risk factors.

RESULTS: Stone disease is multifactorial with a strong genetic component, gender-specific risks and prevalence, and a modifiable contribution of nutrition. The different factors contributing to the risk for developing stones are discussed.

DISCUSSION: Urolithiasis is a frequent disorder affecting almost 10% of the population with a high risk of recurrence. Treatment and prevention have to be tailored to the individual causes of disease and require an assessment of underlying predispositions and interacting modifiable environmental factors.

Keywords: *Monogenic disease. Tubulopathy. Nutrition. Gender. Age. Microbiome.*

Resumen.- *INTRODUCCIÓN: La enfermedad litiásica renal afecta a 1 de cada 10 personas al menos una vez en la vida de forma global, en un 2% la enfermedad es recurrente. Para el individuo la enfermedad litiásica puede ser dolorosa y llevar incluso a la enfermedad renal crónica, mientras que los costes para el sistema de salud y la economía pueden ser muy altos. Así, es necesario identificar los factores que causan la enfermedad litiásica con el fin de prevenir o reducir la incidencia de la enfermedad.*

OBJETIVO: Esta revisión discutirá los factores de riesgo más importantes que contribuyen a la enfermedad litiásica, con especial énfasis en los genéticos y los dietéticos.

RESULTADOS: La enfermedad litiásica es multifactorial, con un fuerte componente genético, riesgos y prevalencia específicos del género y una contribución modificable de la nutrición. Se discuten los diferentes factores que contribuyen al riesgo de desarrollar cálculos.

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DISCUSIÓN: La urolitiasis es un trastorno frecuente que afecta a casi el 10% de la población y con un gran riesgo de recurrencia. El tratamiento y la prevención tienen que ajustarse a los casos individuales de la enfermedad y requieren un estudio de los factores predisponentes y los derivados del entorno que son modificables.

Palabras clave: *Enfermedad monogénica. Tubulopatía. Nutrición. Género. Edad. Microbioma.*

INTRODUCTION

Kidney stone disease is a global health burden with an increasing estimated prevalence between 5-15% in various regions (1-3). It represents a major burden for the health system with more than 2 billion US Dollars costs for the US health system (4). The prevalence and incidence are increasing in many countries over the last 4 decades with 2 to 4-fold increases with regional differences. These differences in reported prevalence and incidence may reflect to some extent different definitions and detection methods of stone disease. However, the increase observed globally is paralleled by an increase in risk factors for stone disease. These include, as discussed below, an increase in obesity and diabetes mellitus, consumption of diets rich in salt, animal protein, sucrose, sugar-sweetened beverages, and global warming (1).

The lifetime risk to develop at least one stone episode is about 12% for men and 6% for women. About 2-5% of the population is suffering from symptomatic recurrent kidney stone disease (1,5,6).

Kidney stone formation is promoted when there is an imbalance in urine between lithogenic substances and inhibitors of crystal formation (3). Major factors promoting stone formation are calcium, oxalate, phosphate, bacterial products, cystine, low urine volume, uric acid, acidic urine pH (though not for all types of stones) while citrate, magnesium, and diluting urine reduce the risk of crystallization. Ultimately, diseases, conditions, or behavior impacting on this balance will favor stone formation or protect from disease.

In several cohort and population studies, patients with recurrent symptomatic stones have a greater risk for end stage renal disease and death (7-9). Also, patients with asymptomatic recurrent stone disease had higher risk for all-cause mortality (7). While the risk for ESRD may be explained by episodes of renal injury, the increased risk for all-cause mortality may be linked to a more complex pathology. Recurrent stone formers have been reported to develop also more pronounced vascular calcifications, an important risk factor for cardiovascular mortality (10). Prevention of recurrent stones disease is among the main strategies to prevent chronic kidney disease in developed countries (8). Analysis of the NHANES cohort suggested that only five risk factors associate with nearly 50% of the total risk for stone disease, namely BMI, fluid intake, DASH like diet, dietary calcium intake and sugar containing beverages (11). All of which are potentially modifiable.

Thus, understanding the major factors causing or contributing to kidney stone disease and its recurrence is of major importance from the point of view of the individual patient, for preserving kidney function and possibly recognizing also underlying metabolic abnormalities that may contribute to higher all-cause mortality, and for reducing health care system related costs. Urologists and nephrologists as well as general practitioners caring for patients with stone must be aware of the association of stone disease with other (metabolic) traits, the increased risk for chronic kidney disease and for the risk factors associated with stone disease to improve diagnosis and care of these patients. As discussed below, kidney stone disease is highly multifactorial and patients often have more than one risk factor.

This review will briefly discuss some of the major relevant factors and recent discoveries and will also suggest areas requiring a better understanding to improve prevention and patient care.

Genetics

Urolithiasis has a strong genetic component as evident from the highly increased risk to develop kidney stones in patients with a positive family history and from twin studies. Patients with a positive family history have a 2-3 times higher risk to develop stones (12). Likewise, studies in the Vietnam Era Twin Registry and the Washington State Twin Registry suggested a 50-60% heritability for the risk of kidney stones with a higher risk for men than women (13,14).

Several metabolic or renal traits that are relevant to the development of urolithiasis show a strong heritability. Among those parameters with clear heritability are serum calcium, magnesium and phosphate levels, urinary excretion of calcium, magnesium, citrate, urine pH and volume as well as fractional excretion of phosphate (15-17). In addition, kidney function itself shows a high heritability and at least 246 different genetic loci associate with variances in kidney function (18).

The discovery of more than 40 genes that give rise to kidney stone disease when mutated have

greatly helped to better understand normal renal function and its regulation. Their elucidation has also provided insights into processes driving stone formation and may provide future targets for better therapy and prevention.

Inheritance of disease follows both dominant as well as recessive patterns dependent on the gene affected. In some genes such as SLC34A1 the recessive form is more severe and typically is diagnosed after birth (19,20). However, also many patients have been described with only one mutated allele found (21-23). Whether this represents a truly dominant disease with later onset of symptoms or whether other mutations have been missed in these patients is currently under debate.

Genes affected by monogenic disorders typically can be grouped either into genes encoding for renal transport proteins and their direct regulators or encoding for systemic regulators of metabolic pathways and hormones impacting on intestinal or renal transport pathways, e.g. mutations affecting calcitriol levels modulating intestinal calcium absorption and renal calcium excretion. Some renal genes impair specific transport processes without primarily altering systemic metabolism, i.e. in cystinuria, while other genes cause also systemic disease such in forms of distal renal tubular acidosis with profound effects on systemic acid-base balance. In these cases the metabolic disturbance often triggers diagnosis of the genetic defect preceding the development of stone disease. These cases provide, thus, the great opportunity to prevent the development of stone disease by initiating appropriate therapies as early as diagnosis is established. Important examples are forms of renal tubular acidosis, mutations associated with hypercalcemia or hypophosphatemia where alkali therapy, phosphate supplements or avoidance of vitamin D supplements are highly beneficial. Likewise, some forms of disease are associated with neurological and/or developmental alterations and provide an early clue to monitor also renal function and development of stone disease. A list of currently known monogenic disorders is provided in recent reviews (24,25).

Monogenic stone disease often leads to the formation of stones in the first years of life and early diagnosis. Usually, monogenic causes of kidney stone disease are very rare but account for a major part of stone disease in children. However, the relevance of these mutations in adult patients remains unclear. Examination of pediatric cohorts with stone disease discovered mutations in these genes in 20-40% of patients (26,27). This relatively low detection rate may be explained either by the method of mutation detection targeting only the coding regions of the genome (using whole exome sequencing) or by the existence of other yet unknown genes causing disease when mutated. Using the same approach in adult cohorts, yielded a detection of rate of about 15% but in most cases patients were heterozygous for genes causing recessive forms of disease (28). Thus, it remains unclear whether some of these genes can act as dominant genes in adult disease and as recessive genes in pediatric disease or if other mutations in other genes or in non-coding regions participate in disease manifestation. Nevertheless, the role of mutations in genes classically considered to underlie only rare monogenic forms of urolithiasis needs further investigations in larger and further cohorts.

Several genome-wide association studies have been performed to obtain further insights into the genetic architecture of common kidney stone disease. However, results provided only very few genetic loci and these were often already known from rare monogenic forms of disease. Major loci include the renal phosphate transporter SLC34A1, the calcium-sensing receptor CaSR, the calcitriol degrading enzyme CYP24A1, uromodulin UMOD, or the claudin 14 CLDN14 (29,30). It is also not surprising that there is also overlap with other GWAS examining serum phosphate, calcium or calcidiol levels as these traits impact on stone risk (31-33).

Clearly, known genetic loci associating with the risk for kidney stone disease and known monogenic and relatively rare causes of errors of metabolism or kidney function explain only a part of the heritability of kidney stone risk.

Age and Gender

Age and gender are both associated with varying risks for stone disease (2,5). While the incidence of stone disease is low in children and mostly reflects genetic conditions, the risk to develop stones increases with age with a gender specific peak between 40-50 year old men and 20-40 year old women (5,34,35). Men are commonly more affected by stone disease with a ratio around 2:1 but the prevalence of stone disease in women has been increasing over the last decades (36). As discussed above, heritability in men is higher than in women for the risk to suffer from stone disease suggesting a more important influence of environmental factors in women. A higher frequency of obesity and bariatric surgery as well dieting contributes to this rise in risk. Moreover, women who developed stone disease during pregnancy have an increased risk for recurrent stone disease. Physiologically, women have more alkaline urine pH probably due to a higher intestinal absorption of dietary organic anions and higher urinary citrate excretion.

Also renal tubular handling of calcium is different. Indeed, distinct differences in renal electrolyte handling between women and men have been described with differences in the tubular structure and relative contribution of specific segments to overall kidney function (37).

Gender differences exist not only for prevalence and risk factors but also for the types of stones typically found. Women are more prone to develop calcium phosphate and struvite containing stones than men (36).

During pregnancy due to hormonal changes aimed at improving mineral supply for the growing fetus, women have higher calciuria, elevated urine pH, and higher uric acid and oxalate urine levels bringing urine closer to supersaturation. While pregnancy itself seems not to be a risk factor for stone disease, women with pregnancies have later a higher risk for stones and the odds increase with the number of pregnancies (36). In a retrospective analysis of nearly 1.4 mio cases, the risk to develop stones during pregnancy was associated with preexisting comorbidities but also with adverse fetal outcomes and prematurity.

Nutrition

Several nutritional factors are associated with increased or decreased risks to develop kidney stones. Increased risks for kidney stone are found with diets poor in calcium, high in animal protein, salt, oxalate or sucrose, and low in magnesium or potassium (38,39).

Calcium. Calcium intake is a strong modifier of the risk to develop oxalate stones. High calcium intake is associated with a lower risk (5). Calcium complexes with oxalate not only in the urinary tract but also in the intestine. Thereby, high calcium intake reduces intestinal absorption of oxalate. Thus, patients are recommended to combine nutrients rich in calcium with nutrients that may provide an oxalate load.

Increased intestinal calcium absorption underlies some forms of hypercalcuria and stimulation of intestinal calcium absorption by calcitriol may contribute (40). Dietary calcium restriction is not part of the therapy, whereas salt restriction may be helpful stimulating renal calcium reabsorption and lowering urinary calcium excretion (40).

Oxalate. Only a fraction (10-30%) of the oxalate excreted by the kidneys derives from intestinal oxalate absorption with the major part stemming from hepatic metabolism of glycine, vitamin C, hydroxyproline, and glycolate (41). Some diets may also be rich in oxalate such as green tea, rhubarb, spinach, nuts, or chocolate. Nevertheless, patients forming oxalate stones may have increased intestinal net oxalate absorption. Net oxalate absorption is the result of passive mechanisms in the intestine driving oxalate absorption and active mechanisms secreting oxalate back into feces. The balance between these mechanisms determines net oxalate absorption. Mice lacking the oxalate transporters Slc26a6 (CFEX) and Slc26a1 (SAT1) develop massive oxalate stones (42,43). The Slc26a6 transporter interacts with CFTR, the gene mutated in patients with cystic fibrosis. Patients with cystic fibrosis have a higher risk to develop oxalate stones and mice lacking CFTR show a reduced ability to back-secrete oxalate into feces (44). Thus, net absorption of oxalate in the intestine is dependent on the bioavailability of oxalate in the intestinal lumen. Enteric hyperoxaluria, i.e. the increased net absorption of oxalate, is promoted by conditions when free oxalate concentrations in the intestinal lumen increase (9). These conditions include low calcium availability (to complex oxalate) due to low calcium diets, fat rich diets or fat malabsorption (which binds calcium), and changes in gut microbiome (with different bacteria able to degrade dietary oxalate, see also below). Fat malabsorption is caused by Crohn's disease, biliary and hepatic diseases, cystic fibrosis, pancreatic disorders, and short bowel syndrome. A more recent and increasing cause of malabsorption and enteric hyperoxaluria is bariatric surgery (9).

Animal protein. Animal protein is rich in phosphate and provides a substantial acid load due to its content of sulfur-containing amino acids that when converted by metabolism release sulfuric acid to be excreted by kidneys. Since low (acidic) urine pH increases the propensity to form crystals containing calcium oxalate or uric acid, diets that increase urinary acidification promote these types of stones. Consumption of animal protein rich diets (i.e. mostly white or red meat and fish) associates in many studies with higher risks for stone disease (2). In contrast, diary protein appears to associate with lower risks. Nevertheless, good studies providing evidence that a reduction in meat intake reduces stone incidence are missing.

Salt and potassium. High salt intake reduces renal reabsorption of calcium, i.e. increases urinary calcium concentration. Conversely, high potassium intake increases urinary salt excretion and reduces calcium excretion (5). Dietary potassium intake is thus associated with lower stone risks (45). Salt decreases urinary citrate excretion while potassium increases it. However, it appears that potassium must be coupled to citrate as potassium chloride is less effective in increasing urinary citrate excretion (39). However, the association of potassium with a favorable urinary risk

profile may not only reflect direct positive effects of potassium but may reflect that diets rich in potassium contain higher amounts of fruits and vegetables and thereby carry alkali equivalents, most importantly citrate (see below) (39,45).

Citrate. Urinary citrate is major inhibitor of crystal formation and hypocitraturia is a major risk factor for stone disease (46). Citrate is freely filtered in the kidney and reabsorbed by the proximal tubule through the action of the NaDC1 cotransporter. Its activity is regulated by acid-base status with increased expression during acidosis, conditions associated with high salt or low potassium intake. Thus, urinary citrate levels are low during these conditions. Consumption of diets rich in fruits or vegetables provides potassium and citrate to metabolism leading to a net alkali load downregulating NaDC-1 in kidney and increasing urinary citrate excretion.

Water. Fluid intake impacts on urinary concentration of lithogenic factors and consequently low water or fluid intake associates with unfavorable stone risk profiles and higher stone risk (2,5). It is not surprising that the use of the aquaretic tolvaptan in patients with autosomal dominant polycystic kidney disease (having also a higher risk to develop stones) improves the urinary risk profile (47). In general, it is advised that urine volume should be >2.5 l/day in stone formers providing a very effective and low cost prevention (2). The Prevention of Urinary Stones with Hydration (PUSH) trials currently tests ways to improve fluid intake in symptomatic stone formers.

Supplements. Dietary supplements are widely taken in industrialized countries and are poorly controlled and often difficult to assess. Among the widely used supplements, vitamin C and vitamin D can be associated with an increased risk for stone formation (48,49). Vitamin C as a precursor of oxalate may increase hyperoxaluria whereas vitamin D stimulates intestinal calcium absorption (and to a lesser extent phosphate absorption) thereby increasing urinary calcium concentrations (2).

Obesity. Obesity defined as a BMI greater than 30 kg/m^2 is associated with an increased risk for nephrolithiasis, particularly for calcium oxalate or uric acid stones (5,50,51). The global prevalence of obesity has risen over the last decades and in 2019 about 6-8% of children,11% of men, and 6-15% of women were considered obese (52). Obesity associates with insulin resistance and diabetes mellitus leading to decreased urinary ammonium excretion and more acidic urine pH promoting the formation of uric acid crystals and uric acid stones (53). Also, obese patients are more likely to undergo bariatric surgery.

Other factors

Systemic disorders. Nephrolithiasis is often seen as an isolated kidney disorder but often a systemic disease underlies development of stones or promotes its development. Systemic disorders that can cause stone disease are primary hyperparathyroidism, Crohn's disease, diabetes and metabolic syndrome, or gout (5).

Microbiome. In the gut microbiome, the bacterial strains *Oxalobacter*spp, *Bifidobacterium*spp, and *Lactobacillus*spp can degrade oxalate and thereby reduce oxalate bioavailability. Whether changes in the (relative) abundance or activity of these bacteria underlies forms of enteric hyperoxaluria remains to be established (9). Association studies provided evidence for positive associations between the presence of these bacteria and lower prevalence of oxalate stones (54,55). Moreover, networks between different bacterial species were found in urine and stool of healthy individuals which were not detected in stone formers (56,57). The use of antibiotics that can alter the composition of the gut microbiome has been associated with a higher risk for kidney stones (58,59). The role of the intestinal and renal microbiome will deserve further studies to clarify its role in the pathomechanisms of stone disease and its potential for prevention and treatment.

Drugs and toxins. Drugs and toxins account for a smaller fraction of stones. Drugs altering renal handling of solutes relevant for stone disease can increase the propensity to form stones. Among such drugs are the anti-migraine drug topiramate that has a strong inhibitory effect on carbonic anhydrases thereby causing renal tubular acidosis. Several antibiotics including sulphonamides, ceftriaxone or trimoxazole can induce stones either directly because of their low solubility or by causing dysbiosis and increasing hyperoxaluria (60). Among the toxins causing kidney stone disease is melamine, an urea derivative widely used by chemical industry and has found its way to patients probably as food contaminant. Melamine is nephrotoxic but also forms crystals with uric acid leading to obstructive nephropathy (61).

Climate. Climate changes due to global warming have been associated with higher prevalence and incidence of stone disease. Even though the mean temperature has increased by less than 1°C in many regions of the world, seasonal heat waves have increased and are associated with increased overall mortality (62). Heatstrokes can predispose to acute kidney injury while increased water losses during episodes of heat may predispose to increased urinary supersaturation as consequence of antidiuresis. The

impact of weather and climate on stone disease likely reflects lower urine volumes in a warmer environment. The critical role of hydration and dehydration and diluting urine has been discussed above. Climate differences may also explain geographic differences and seasonal variations of kidney stone episodes occurring more frequently in warmer regions or during summer months (2,63-66). The increase in warm episodes with global climate warming is predicted to increase also the temperature-related incidence of stones (2).

Urinary tract infections. Urinary tract infections (UTI) cause formation of stones composed of struvite (magnesium ammonium phosphate) and variable amounts of calcium-phosphate or calcium-oxalate. The mechanisms connecting UTI and stone formation are not fully understood. This type of stone is more frequent in women possibly owing to fact that UTIs are more frequent in women and associates with higher age, the presence of anatomical alterations or bladder dysfunction, indwelling catheters or diabetes mellitus, all factors favoring bacterial growth (67,68).

SUMMARY AND CONCLUSION

Urolithiasis is a complex multifactorial disease with high prevalence and recurrence rates. Diagnosis should consider both genetic components as well as environmental factors, most notably dietary patterns. A careful metabolic work-up of patients is critical for diagnosis and prevention. Assessment of nutrition is important as it opens a window for prevention of disease. Nevertheless, many recommendations are based only on a small number of well controlled studies and further interventional studies are required. Likewise carefully conducted observational studies to elucidate dietary, genetic and other factors contributing to disease are needed.

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