

REVIEW

Nephrolithiasis in the elderly

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Nephrolithiasis is a disease characterized by the presence of crystal concretions in the urinary tract. It is widely spread worldwide, both in the Western and non-Western countries. Several studies have pointed out a rising prevalence and incidence of kidney stone disease in the elderly population in the last several decades.

Data from large cohort studies suggest an association between the increased risk of stones formation and dietary factors such as low fluid intake, low calcium intake, high sodium intake, high animal protein intake, and high fructose intake. The kidney stones risk may also be increased by medical conditions such as obesity, diabetes, primary hyperparathyroidism, and gout. Stones may be asymptomatic or may show symptoms such as abdominal and flank pain, nausea and vomiting, urinary tract obstruction, and infections.

This review aims to outline specific features of nephrolithiasis in the elderly population, including lifestyle, eating habits, hormonal modifications and comorbidities that may affect stone formation. We also assessed the impact of age on diagnostic and therapeutic pathways. Evidence suggest that age *per se* should not preclude standard treatment but should be taken in due account during the decision-making process.

Key words: Nephrolithiasis, Elderly patients, Epidemiology, Risk factors, Treatment

Introduction

Nephrolithiasis remains one of the most challenging diseases for clinicians worldwide because of the high prevalence of subjects experiencing kidney stone formation (13 for men and 7% for women) and the elevated rate of reoccurrence after the first episode (approximately 50% within 5 years) ¹. It is common during adulthood with a higher prevalence between 40-50 years, but its incidence is increasing in patients older than 65 year old ². This is partly due to increase in life expectancy over the last decades, mainly in Western countries.

Indeed, the general demographic statistics underline that the population aged 65 years or more will rise to the 28% of the general population in 2050 (about 2 billion people), thus further increasing the prevalence of nephrolithiasis in geriatric patients ³ to 19.1% in men

and 9.4% in women. It is estimated that the elderly will represent 10-12% of all stone formers ⁴.

Elderly patients deserve specific attention in consideration of their frequent comorbidities, different dietary habits, with low fluid intake and decreased high-nutrients food consumption, physical and environmental factors and hormonal changes ⁵.

Accordingly, the management of elderly patients requires an accurate diagnostic evaluation and tailored treatment, both pharmacological and surgical, to obtain results similar to their younger counterpart. McCarthy et al. compared patients aged 80 year-old or more with a younger cohort highlighting that, although elderly had more comorbidities, later presentation with larger and more complex stones, required early ureteric stent insertion and definitive percutaneous nephrolithotomy (PCNL), there was no difference in intraoperative

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complications and as much as 39% of them could be managed on outpatient basis³.

Thus, we need to appreciate the relevance of urinary stones disease in the elderly and its association with systemic diseases like obesity, diabetes and cardiovascular disease.

EPIDEMIOLOGY

Kidney stones are a common disease in industrialized nations, with an incidence of 1/1000 persons and a risk of 13% in men and 5% in women⁶. In these countries, the prevalence of renal stones has increased to 8.8% in the 2000s, in association with the rising incidence of insulin resistance, type 2 diabetes mellitus, obesity, and cardiovascular disease⁷.

These are the consequences of sedentary lifestyle and high-protein diets leading to a higher urinary excretion of lithogenic factors (calcium, phosphates and uric acid) and to an increased urinary acidity⁸.

In the general population it is possible to recognize different kinds of stones, depending on their chemical composition: calcium oxalate, calcium phosphate, uric acid, magnesium ammonium phosphate (struvite) and cystine. Each type presents a different prevalence, with the majority of stones formed by calcium oxalate (26.3%), followed by calcium phosphate and uric acid stones (7.4 and 4.5% respectively)⁶.

Stoller et al.⁹ suggested higher incidence of uric acid stones in older patients, whereas other studies report the most common stone type in patients over 65 years being calcium oxalate^{9,10}. Furthermore, stone composition changes worldwide: in the Mediterranean area, stones are more likely to be composed by uric acid (75%), whereas in USA, calcium phosphate and calcium oxalate stones are the most widespread (70%)¹¹. Even the stone forming trend varies with geographic distribution, growing from North to South, due to higher temperatures and sunlight exposure that increase vitamin D production, with subsequent greater hypercalciuria, as well as insensible losses of water, leading to higher urine concentration¹². An higher urinary calcium concentration in a smaller urinary volume promotes the downfall of crystals, leading to stone formation.

Regarding older population and its typical comorbidities, Alexander et al.¹³ have highlighted the association between nephrolithiasis and systemic disease, such as chronic kidney disease, metabolic syndrome, cardiovascular disease and osteoporosis. Furthermore, they have observed a major risk of end stage renal disease (ESRD) when one or more kidney stone episode occurred.

Ferraro et al.¹⁴ pointed out a relevant relationship between heart disease and stone formation, as they

found, in a prospective study, that patients with a history of kidney stones presented a statistically significant increased risk of coronary artery disease.

RISK FACTORS

Risk factors for stone formation can be classified in organic (i.e. malformations of the urinary tract) and functional (metabolic imbalance)⁶. Specifically, for patients aged 65 years and older, conditions correlated with stone formation include: reduced mobility, low fluid intake, chronic infections, menopause for women as declined endogenous estrogen levels and enhances the risk of recurrent urinary tract infections¹⁵, increase of fat mass¹⁶ and bone mass reduction.

In addition, it has been discussed whether a major calcium dietary intake and pharmacological calcium supply, often prescribed in elderly in the attempt to prevent osteoporosis, may increase stones formation, because of the higher urinary calcium levels¹⁷. Indeed, Jackson et al studied a cohort of 36282 women in post-menopausal state, between 50 to 79 years, that were given 400 IU of Vitamin D and 1000 mg of oral calcium per day and found a 17% higher rate of kidney stones¹⁸.

Obesity, a disease often seen in elderly, is another important factor associated with nephrolithiasis¹⁹. As suggested by Willet et al., BMI is tightly correlated with stone formation, with an association stronger for women than for men²⁰. Other authors have further characterized BMI influence on the risk of kidney stone formation. In particular, for women, the relative risk with a BMI higher than 35 kg/m² was greater than with a BMI of 30 kg/m²¹⁹. It is possible that an increased BMI is related to a major excretion of promoters and a reduced urine concentration of inhibiting factors of stone formation^{21,22}. Ekeruo et al.²³ observed an important association between lithogenic factors (calcium, phosphate, oxalate and uric acid excretion as well as higher urinary pH) and BMI. On the other hand, they also report increased urine levels of some protective factors citrate in subjects with highr BMI²³.

Finally, obesity may lead to insulin-resistance that modifies urinary pH and uric acid levels, causing formation of uric acid stones²⁴. In addition, obese patients with insulin-resistance are exposed to a greater risk of gout, a further promoter of uric acid stone formation²².

PATHOGENESIS

The pathophysiology of stone formation is multifactorial because several physical and chemical factors may contribute.

Urine is characterized by the presence of different molecules in a status of mutual equilibrium preserved by urinary pH, urinary saturation level and calcification inhibitors²⁵. Whenever one of these factors is modified, thus altering such “equilibrium stability state”, urine becomes supersaturated of ions that may combine to create stones²⁶.

Indeed, these ions, when reaching the condition of supersaturation, might pass from a solution phase to a solid crystal phase. Interestingly, supersaturation is not affected by ions concentration, but by free ions activity, which depends on urinary pH, crystal component concentration and inhibitors of stone formation²⁷.

When ions activity enhances and the crystal component concentration increases, calcification inhibitors can reduce stone formation binding the ionic constituents of the stone in soluble complexes. Thus, the presence of inhibitors in urine increases the level of supersaturation required to form the calculi solid phase and delays the expansion of the crystals already shaped. When a specific ion activity prevails in the solution, ions join together in a stable solid phase, in the nucleation process, which might be a homogeneous nucleation or, more commonly, a heterogeneous nucleation²⁸. In the former, the nucleus of the stones is composed by the same ion crystals whereas in the heterogeneous process, the nucleus is represented by other substances, including cell debris or a mucoprotein matrix. For example, calcium oxalate crystals and uric acid crystals may aggregate into bigger stones, transfer to the urine, producing crystalluria²⁵.

The second phase in stone formation is the enhancing process, also divided into homogeneous or heterogeneous. The basis of this mechanism may be both organic or functional. For example, 10% or more of kidney stones is associated with malformative diseases of the urinary tract²⁹ such as medullary sponge kidney (or Cacchi-Ricci disease) and Autosomal dominant polycystic kidney disease³⁰.

Functional factors play a key role in the pathogenesis of kidney stones and can be represented by endocrine changes such as primary hyperparathyroidism, metabolic alterations such as hypercalciuria, hyperoxaluria, or other dysregulations of the uric acid, cystine and xanthine metabolisms.

Hyperparathyroidism or other bone disorders, including osteoporosis and reduced mobility, peculiar of the elderly, characterized by a greater mobilization of bone calcium might cause a reabsorption hypercalciuria²⁹. The hypercalciuria may be also due to an increased enteric reabsorption or to a deficit of the kidney tubule that does not adsorb filtered calcium. This last condition induces low blood calcium levels and secondary

hyperparathyroidism that, in turn, will maintain the hypercalciuria³¹.

The pathogenic pathway leading to other types of stones is represented by metabolic alterations. For example, uric acid is the final product of endogenous and exogenous purine metabolism through the oxidation catalyzed by xanthine oxydase, circulates in blood as urate and it is mainly disposed by kidneys. Considering that the solubility of uric acid is low, when its serum levels rise and urinary pH reduces, crystals of uric acid formation occurs, as it is possible to observe in lymphoproliferative disease and in the gout³².

CLINICAL MANIFESTATIONS

The clinical features of kidney stones are aspecific symptoms which are due to their location in the kidney, ureter or urinary bladder: pain, hematuria, urinary tract infections (UTIs) and, even, acute kidney injury (AKI), when kidney calculi cause bilateral renal obstruction or unilateral obstruction in a single functioning kidney⁶. The pain, known as ureteral or renal colic, arises abruptly, might be severe and appears when the stones partially or totally occlude the urinary tract. Usually, the pain is localized in the kidney area, migrates anteriorly to the abdomen wall and may be subsequently referred to the external genitals. This change occurs when stone gets through ureterovesical junction³³. In this phase, microscopic or macroscopic hematuria is constantly present^{6,33}. In addition, patients with kidney stone disease may frequently experience recurrent UTIs, because the stone represents a “sancta sanctorum” where bacteria cannot be reached by antibiotics. Sometime, on the other hand, infections, modifying physico-chemical urinary composition through urease producing bacteria, might induce stone formation.

Bauza et al. demonstrated the presence of bacterial growth in cultures of stones removed by endourological procedures³⁴. In these circumstances, it is possible to notice UTIs symptoms, as well as stranguria, pollachiuria, urinary urgency, even fever. In the worst cases, acute kidney injury (AKI) complicates the clinical picture. AKI is observed in 15% of hospitalized adult patients with kidney stones⁶.

AKI in this setting is significantly more frequent in the elderly population in consideration of a “physiological” in the renal functional reserve. Aging, indeed, produces a decline in renal mass, progressive glomerular atrophy, glomerulosclerosis, tubulointerstitial fibrosis. These pathological changes underlie the progressive fall in glomerular filtration rate (GFR) starts and renal plasma flow (RPF) observed in this patients population³³, facilitating kidney injury in case of obstruction.

DIAGNOSIS

Nephrolithiasis clinical evaluation comprises multiple steps. It is useful to examine stone history, such as number of stone formed, frequency, stone type, association with UTIs, kidney involved (unilateral or bilateral). General medical history is important, because several drugs predispose to calcium stone or potentiate uric acid stone formation¹¹. Furthermore, it is essential to evaluate fluid intake and dietary style that change in older patients. In fact, elderly patients are affected by a natural decrease in fluid intake that results in exceedingly concentrated urine that, in turn, facilitates stone formation and enlargement. Usually dietary intake in geriatric population is low in many nutrients, particularly calcium, leading to not only bone demineralization, but also to an increase in stone formation³³. Obviously, laboratory findings play a key role in the correct management of stone disease. It is essential to drive a complete metabolic analysis, including urinalysis, urine culture, stone analysis and blood chemistry (calcium, sodium, bicarbonate, phosphorus, uric acid, parathyroid hormone level)⁶.

Once clinical examination has been completed, imaging techniques play a key role confirming or not kidney stones diagnosis and identifying stones site, size and number. The most suitable imaging evaluation for kidney stones depends on clinical situation and the stone type. Imaging techniques able to diagnose kidney stones include ultrasound (US), abdominal radiography, intravenous pyelography (IVP), non-contrast-enhanced computed tomography (CT)^{35,36}. US represents the primary diagnostic choice, being safe for risk of radiation and reproducible. US sensitivity and specificity are high, with 90 and 65-84% rate respectively, whereas the specificity is decreased by the frequent false positive caused by the morphological variability of the urinary tract. However, US finding tightly relies on stone size (it is possible to identify calculi larger than 5 mm in the 91% of cases) and localization (63% for ureter, 90% for urinary bladder and 85-88% for other sites)³⁷.

However, in case of acute urolithiasis, non-contrast-CT has become the gold standard, being able to determine stone diameter, density, inner structure, skin-to stone distance³⁸. Indeed, non-contrast-CT is rated as a more accurate imaging technique than US in the nephrolithiasis diagnosis process, because CT improves stone size and site determination and highlights nephrological and urological complications. Consequently, non contrast-CT is currently acknowledged as the most reliable imaging technique in nephrolithiasis diagnosis, reaching a sensitivity of 94-100% and a specificity of 94-97%³⁹.

TREATMENT

Once the diagnosis has been reached, the management of these patients depends on several factors that should be carefully evaluated, particularly in the elderly. The medical treatment for renal colic, an intense cramping pain, should be non steroid anti-inflammatory drugs, paracetamol or morphine-like drugs⁴⁰.

Concomitant UTIs requires antibiotic therapy, possibly sensitivity-guided, whereas fever not subsiding by early antipyretics and antibiotics often requires immediate drainage of the collecting system by ureteral stenting or nephrostomy. In such cases, active stone treatment by extracorporeal shock wave lithotripsy (ESWL) and ureteroscopic or percutaneous removal³³ should be delayed to resolution of the infection⁴¹.

Ureteral stones may be suitable for observation, in the absence of infection and after the acute phase. As much as 90% of ureteral stones up to 4 mm may pass spontaneously⁴². Medical treatment to facilitate expulsion may be used as well, though efficacy of the current drug of choice (tamsulosin) is often questioned⁴³.

Renal stones may also be suitable for observation, providing they remain asymptomatic, cause no UTI, and do not grow rapidly. This clinical condition, i.e. the asymptomatic renal stone, can often represent a diagnostic dilemma, particularly in the elderly. While observation would appear particularly suitable for the elderly, one should bear in mind that such patients may have reduced efficiency of their immune system⁴⁴ potentially leading to serious infectious complications.

When planning active stone treatment by ESWL, ureteroscopic or percutaneous procedures, several factors should be taken into account ranging from patient general status and wish, stone size, position, presumptive composition, anatomy of the urinary tract, concomitant bacteriuria etc.⁴⁵. Given the risk of potentially lethal septic complications associated with endourological procedure⁴⁶, great attention has been paid to develop guidelines for proper antibiotic prophylaxis and management of infective complications⁴⁷. Question remains whether such procedures are associated with greater risks in the elderly population⁴⁸. Some reports pointed out no significant difference in the outcome of flexible ureteroscopy and retrograde intrarenal surgery⁴⁹ in the elderly, though case volume may play a relevant in this setting⁵⁰.

The issue of percutaneous nephrolithotripsy (PCNL) seems to be more complex, because it has been seen as a challenging procedure in this patient population⁵¹. Specific procedural issues that may impact on outcomes, particularly in the elderly, range from patient positioning to the procedure exit strategy⁵²⁻⁵⁶.

FINAL REMARKS

Elderly patients have become a wide part of the entire kidney stone population. As a consequence, kidney stone disease is a clear medical concern for people aged 65 years or more, given their frequent comorbidities such as insulin resistance, type 2 diabetes mellitus, obesity, and cardiovascular disease. While the entire decision-making process should take in due account not only such known comorbidities but also the potentially occult ones, particularly immunosenescence, age per se should not preclude effective treatments.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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