World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

SURVEY ON PROSPECTIVE OBSERVATIVE STUDY ON INCIDENT ON PREVALENCE OF KIDNEY STONE DISEASES BASED ON EFFECT ON LIFE STYLE

G. Sirisha[1], Dr. G. Nagaraju[1]* J. Gouthami[2], K. Ramya[3], M. Keerthi[4] and S. Vishnu[5]

[1]Assoc. Professor Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.
[1]*Principal of Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.
[2,3,4,5]B. Pharmacy IV Year Students of Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.

***Corresponding Author: Dr. G. Nagaraju**
Principal of Dhanvanthari Institute of Pharmaceutical Sciences, Sujathanagar, Kothagudem.

Article Received on 05/02/2025 **Article Revised on 25/02/2025** **Article Accepted on 17/03/2025**

ABSTRACT:
Kidney stone disease, also known as nephrolithiasis or urolithiasis, is a disorder in which urinary solutes precipitate to form aggregates of crystalline material in the urinary space. The incidence of nephrolithiasis has been increasing, and the demographics have been evolving. Once viewed as a limited disease with intermittent exacerbations that are simply managed by urologists, nephrolithiasis is now recognized as a complex condition requiring thorough evaluation and multifaceted care. Kidney stones are frequently manifestations of underlying systemic medical conditions such as the metabolic syndrome, genetic disorders, or endocrinopathies. Analysis of urine chemistries and stone composition provide a window into pathogenesis and direct ancillary studies to uncover underlying diseases. These studies allow providers to devise individualized strategies to limit future stone events. Given its complexity, kidney stone disease is best addressed by a team led by nephrologists and urologists with input from multiple other health professionals including dietitians, endocrinologists, interventional radiologists, and endocrine surgeons. In this instalment of AJKD's Core Curriculum in Nephrology, we provide a case-based overview of nephrolithiasis, divided by the individual stone types. The reader will gain a pragmatic understanding of the pathophysiology, evaluation, and management of this condition.

KEYWORDS: Kidney stones; Nephrolithiasis; Urolithiasis; Calcium phosphate; Calcium oxalate; Struvite; Uric acid.

INTRODUCTION

Kidney stones are mainly lodged in the kidney(s).[1] Mankind has been afflicted by urinary stones since centuries dating back to 4000 B.C.[2], and it is the most common disease of the urinary tract. The prevention of renal stone recurrence remains to be a serious problem in human health.[3] The prevention of stone recurrence requires better understanding of the mechanisms involved in stone formation.[4] Kidney stones have been associated with an increased risk of chronic kidney diseases[5], end-stage renal failure[3, 6], cardiovascular diseases[7, 8], diabetes, and hypertension.[9] It has been suggested that kidney stone may be a systemic disorder linked to the metabolic syndrome. Nephrolithiasis is responsible for 2 to 3% of end-stage renal cases if it is associated with nephrocalcinosis.[10]

The symptoms of kidney stone are related to their location whether it is in the kidney, ureter, or urinary bladder.[11] Initially, stone formation does not cause any symptom. Later, signs and symptoms of the stone disease consist of renal colic (intense cramping pain), flank pain (pain in the back side), haematuria (bloody urine), obstructive uropathy (urinary tract disease), urinary tract infections, blockage of urine flow, and hydronephrosis (dilation of the kidney). These conditions may result in nausea and vomiting with associated suffering from the stone event.[12] Thus, the treatment and time lost from work involves substantial cost imposing an impact on the quality of life and nation's economy.

PATHO PHYSIOLOGY

Environmental and genetic variables both influence the complexity and multifaceted nature of urolithiasis. The development of urinary stones involves various mechanisms, and the formation of Ca Ox stones differs from that of other types of stones. Impaired renal acidification, along with altered renal excretion or excessive absorption in the digestive tract, leads to the accumulation of stone-forming metabolites.[13]

Among the distinct pathophysiology mechanisms of Ca Ox stone formation, Randall plaques and mineral deposits, play a critical role[14 ,15] However, the emergence and pathophysiology of Ca Ox stones are still poorly understood, necessitating further research to identify effective prevention and treatment strategies. Recent studies suggest that the formation of interstitial apatite crystals may be an initial step in the development of Ca Ox stones.[16]

Reduced urine volume raises the concentration of stonecausing compounds, which in turn promotes crystallization and stone formation, making urine volume a critical factor in the pathophysiology of urolithiasis.[17] Kidney stones are more likely to form when urine volume is reduced, which can happen as a result of dehydration, some drugs, or medical issues that impact fluid balance or urinary function. One of the most prevalent causes of kidney stones is not drinking enough water.[18]

Certain medical conditions can increase the risk of developing kidney stones. Renal tubular acidosis is a condition in which the kidneys are unable to eliminate acids from the blood into the urine, leading to an increase in blood acidity. Other conditions, such as cystinuria, hyperparathyroidism, and recurring urinary tract infections, can also increase the chance of kidney stone formation.[19, 20] Further research is needed to fully comprehend the pathophysiology of these disorders and develop effective preventive and treatment strategies for urolithiasis.

MECHANISM OF STONE FORMTION

In individuals with risk factors for stone formation, such as high urinary supersaturation, low urinary volume, or low urinary pH, crystals may nucleate and aggregate into larger particles, potentially forming a stone. Stone formation can occur in various locations within the urinary tract, including the kidneys, ureters, bladder, and urethra. The development of stones can be influenced by several factors, including genetics, diet, lifestyle, and medical conditions such as urinary tract infections or metabolic disorders.[21, 22]

Once a stone has formed, it can continue to grow with the addition of new crystals and may also move within the urinary tract, leading to pain and other symptoms. The ability of a stone to move through the urinary tract can be influenced by its size and chemical makeup. While larger stones may require medical intervention for removal, smaller stones are more likely to pass spontaneously.[23, 24]

URINATION SUPERSATURATION

The initial stage of kidney stone formation is urinary supersaturation, which occurs when the concentration of certain substances in the urine, such as calcium, oxalate, and phosphate, exceeds their solubility limit. This leads to a state in which the urine becomes supersaturated, creating an environment conducive to the formation of crystals. Under these conditions, the excess solutes can no longer remain dissolved and begin to aggregate, resulting in the formation of small crystal particles.[26] These small particles can then combine and grow into larger crystals, eventually leading to the formation of kidney stones.

The degree of supersaturation, along with other factors such as urinary pH and the presence of inhibitors or promoters of crystal growth, can significantly influence the formation and growth of crystals, and ultimately the development of kidney stones. Understanding the factors contributing to urinary supersaturation and the subsequent crystal formation is important for the prevention and treatment of kidney stones.[25, 26]

CRYSTALLIZATION

The process of crystallization occurs when urine becomes oversaturated, leading to the formation of solid crystals. The specific type and characteristics of the crystals depend on the substances present in the urine and the conditions prevailing during their formation. Kidney stones, are a common result of this process, with types including Ca Ox, calcium phosphate, and uric acid stones, which are caused by high concentrations of these substances in the urine.[27]

The process of crystal formation is influenced by a multitude of factors, including the pH level of urine, the concentration of minerals that encourage stone formation, and the presence of inhibitors that hinder crystal growth. As crystals accumulate and grow, they can lead to the formation of urinary casts, which obstruct urine flow and promote further stone formation.[28]

The development of effective strategies for the prevention and treatment of kidney stone disease depends on our understanding of the mechanisms that influence crystal formation and growth.[29]

CRYSTAL NUCLEATION

The phenomenon of nucleation is a crucial aspect of crystal formation from a supersaturated solution. It involves the aggregation of solute molecules or ions to form a stable nucleus, which then serves as a basis for subsequent crystal growth. As a result, a crystal structure with a distinct lattice pattern is produced. Crystallization can occur in confined spaces within a solution, such as those present in certain regions of the nephron[30], and on surfaces such as cells and the extracellular matrix. Nucleation can occur through two main mechanisms: homogeneous nucleation, which arises spontaneously within the solution, and heterogeneous nucleation, which occurs on the surface of a foreign particle or solid surface.[31]

CRYSTAL GROWTH

After nuclei formation, crystals grow by adding new molecules to the crystal lattice. The rate of growth

depends on various factors, such as the concentration of salts that form stones, urine pH, and the presence of inhibitors or promoters of crystal growth.[32] Inhibitors of crystal growth, such as citrate and magnesium, help prevent crystal aggregation and growth by binding to crystal surfaces and inhibiting their further growth.[33] Promoters of crystal growth, such as calcium and oxalate, can facilitate the aggregation and growth of crystals by increasing their surface charge and promoting attachment to other crystals or surfaces.

CRYSTAL AGGRIGATION

Over time, crystals can aggregate to form larger particles, which may lead to the formation of stones. The aggregation of crystals can be influenced by several factors, including the concentration and composition of the stone-forming salts, the pH of the urine, and the presence of organic and inorganic molecules that can act as bridging agents or inhibitors of crystal aggregation.[32, 34] The formation of stones can also be influenced by urine flow rates; slower flow rates allow for increased crystal aggregation and growth, whereas faster flow rates promote the flushing out of crystals, thereby preventing their aggregation.[35]

CRYSTAL CELL INTERACTION

The interaction between crystals and renal epithelial cells is a critical factor in the pathogenesis of kidney stones. When crystals adhere to the cell surface, they can cause injury and inflammation. This process can further promote crystal growth and aggregation, as well as the recruitment of immune cells and the release of inflammatory mediators. The attachment of crystals to renal cells occurs through various mechanisms, including electrostatic interactions, surface receptors, and extracellular matrix proteins. Once attached, crystals can cause cellular injury through multiple pathways, such as membrane disruption, oxidative stress, and mitochondrial dysfunction. These changes lead to the release of danger signals and the activation of inflammatory pathways, further exacerbating crystal-induced injury and inflammation. The interaction between crystals, renal cells, and immune cells can also lead to the formation of urinary casts, which may obstruct urine flow and promote stone formation. In addition to renal epithelial cells, immune cells such as macrophages and T cells can contribute to the progression of kidney stone disease by releasing inflammatory cytokines and chemokines. This cycle of injury and inflammation can promote the growth and aggregation of stones, contributing to the development and progression of kidney stone disease.[27]

DIAGNOSIS

Diagnosing and developing effective prevention strategies requires both understanding the metabolic background that promotes lithiogenesis and assessing the patient's risk of CKD and metabolic bone disease (MBD). Metabolic evaluation of patients with stones aims to estimate the propensity of the urine to crystallize, investigate the metabolic mechanisms of nephrolithiasis, diagnose underlying systemic causes of nephrolithiasis, determine the risk of CKD and MBD and to achieve insights on nutritional habits.

Specific software for estimating the urine propensity for crystallization have been proposed (for example, the EQUIL and JESS programs)73,178. These programs calculate the urinary supersaturation of numerous salts by considering the concentration in the urine of different ionic species. The probability of stone formation can also be evaluated by algorithms based urine excretion of a limited number of parameters140. Although these methods can be of help, they are not compulsory for a successful metabolic assessment and follow up.

LIFESTYLE AND HABIT MODIFICATIONS

Obesity and overweight are also considered as risk factors for KSD. Hence, weight loss to maintain the normal body mass index (BMI) is recommended by the EAU and UAA to reduce risk of KSD. An in vivo study has also revealed that weight loss by food restriction and exercise can increase urinary citrate excretion and reduce risk of KSD. Physical activity and exercise can reduce and protect several diseases and disorders. A large cohort study of almost 90,000 women has suggested that physical activity (regardless of its intensity) may prevent KSD, as evidenced by the association of physical activity with a lower risk of KSD in postmenopausal women. A meta-analysis from 3 large prospective cohorts comprising >200,000 participants in total has reported the association of a lower risk of incident kidney stones with a higher level of physical activity in women. However, there is no independent association found after multivariate adjustment. Similarly, a later meta-analysis has also shown no association between physical activity and risk of KSD. However, an analysis of questionnaire survey in patients with KSD from Southern China has revealed that physical activity is one of the protective factors for KSD. An inverse correlation of physical activity and KSD prevalence is found in both genders. In addition, some protective factors, such as high urinary magnesium, are found in athletes. On the contrary, several risk factors for kidney stone formation (such as dehydration, high urinary calcium, uric acid and sodium concentrations, and low urinary citrate concentration) are also found in these athletes. From these data, the true benefit of physical activity and exercise on KSD remains controversial and needs further elucidations with adjustments on several variables or confounding factors. Another factor that should be also considered is hydration status during and after heavy physical activity and exercise, which can induce profound sweating and water loss.

SYMPTOMPS

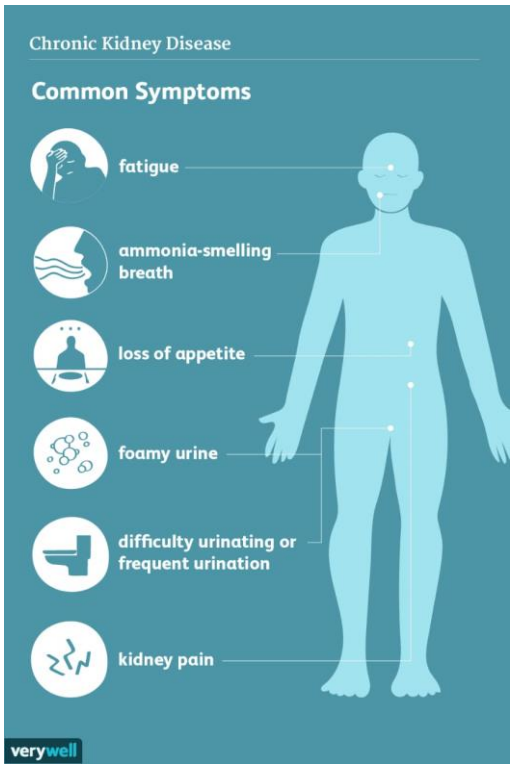
A kidney stone usually will not cause symptoms until it moves around within the kidney or passes into one of the ureters. The ureters are the tubes that connect the kidneys and bladder. If a kidney stone becomes lodged in the ureters, it may block the flow of urine and cause the

kidney to swell and the ureter to spasm, which can be very painful. At that point, you may
experience these symptoms:

- Severe, sharp pain in the side and back, below the ribs
- Pain that radiates to the lower abdomen and groin
- Pain that comes in waves and fluctuates in intensity
- Pain or burning sensation while Urinating

Other signs and symptoms may include:

- Pink, red or brown urine
- Cloudy or foul-smelling urine
- A persistent need to urinate, urinating more often than usual or urinating in small amounts
- Nausea and vomiting
- Fever and chills if an infection is present
  Pain caused by a kidney stone may change — for instance, shifting to a different location or increasing in intensity — as the stone moves through your urinary tract.



TREATMENT

Stone size influences the rate of spontaneous stone passage. For example, up to 98% of small stones (less than 5 mm (0.2 in) in diameter) may pass spontaneously through urination within four weeks of the onset of symptoms, but for larger stones (5 to 10 mm (0.2 to 0.4 in) in diameter), the rate of spontaneous passage decreases to less than 53%. Initial stone location also influences the likelihood of spontaneous stone passage. Rates increase from 48% for stones located in the proximal ureter to 79% for stones located at the Vesicoureteral junction, regardless of stone size. Assuming no high-grade obstruction or associated infection is found in the urinary tract, and symptoms are relatively mild, various nonsurgical measures can be used to encourage the passage of a stone. Repeat stone formers benefit from more intense management, including proper fluid intake and use of certain medications, as well as careful monitoring.

PAIN MANAGEMENT

Management of pain often requires intravenous administration of NSAIDs or opioids. NSAIDs appear somewhat better than opioids or paracetamol in those with normal kidney function. Medications by mouth are often effective for less severe discomfort. The use of antispasmodics does not have further benefit.

MEDICAL EXCLUSIVE THERAPY

The use of medications to speed the spontaneous passage of stones in the ureter is referred to as medical expulsive therapy. Several agents, including alpha adrenergic blockers (such as tamsulosin) and calcium channel blockers (such as nifedipine), may be effective. Alpha-blockers likely result in more people passing their stones, and they may pass their stones in a shorter time.[107] People taking alpha-blockers may also use less pain medication and may not need to visit the hospital. Alpha-blockers appear to be more effective for larger stones (over 5 mm in size) than smaller stones. However, use of alpha-blockers may be associated with a slight increase in serious, unwanted effects from this medication. A combination of tamsulosin and a corticosteroid may be better than tamsulosin alone. These treatments also appear to be useful in addition to lithotripsy.

PREVENTION

To be the cause for stone formation. Preventive Options for Urolithiasis Effective kidney stone prevention depends upon addressing the cause of stone formation. Generally, to prevent the kidney stone formation or its secondary episodes, proper management of diet and the use of medications is required. Primary prevention of kidney stone disease via dietary intervention is low-cost public health initiative with massive societal implications. us, nutritional management is the best preventive strategy against urolithiasis. Regardless of the underlying Aetiology and drug treatment of the stone disease, patients should be instructed to increase their water intake in order to maintain a urine output of at least 2liter per day. A simple and most important lifestyle change to prevent stone disease is to drink more water/liquids. Enough fluid intake reduces urinary saturation and dilutes promoters of Ca Oxalate crystallization. Dietary recommendations should be adjusted based on individual metabolic abnormalities. For absorptive hyperoxaluria, low oxalate diet and increased dietary calcium intake are recommended A high sodium intake boosts stone risk by reducing renal tubular calcium reabsorption and increasing urinary calcium. Restriction of animal proteins is also Encouraged since animal proteins provide an increased

acid load because of its high content of sulphur containing amino acids. protein intake reduces urine pH and the level of citrate and enhances urinary calcium excretion via bone reabsorption. therefore, if you have very acidic urine, you may need to eat less meat, and poultry and avoid food with vitamin D. Instead, an increase intake of fruits and vegetables rich in potassium is recommended. People who form calcium stones used to be told to avoid dairy products and other foods with high calcium content

CONCLUSION

Despite considerable improvements in the development of new therapies for the management of urinary stones, the incidence of urolithiasis is increasing worldwide. Many aspects of renal stone formation remain unclear. However, it is certain that renal cell injury, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitors or promoters play important roles for kidney stone formation. These seem to be critical targets that lead to developing a novel strategy to prevent kidney stone disease and drugs against kidney stones. In addition, the identification of novel treatment targets on the basis of molecular and cellular alterations in relation to stone formation will help develop better drugs. Moreover, better understanding of the mechanisms of urolithiasis associated with stone inhibitors or promoters will be critical for stone-removing medications. Furthermore, understanding the underlying pathophysiology, pathogenesis, and genetic basis of kidney stone formation will hopefully lead to discover novel drugs and strategies to manage urolithiasis in the near future.

REFRENCES

1. Giannossi L., Summa V. A review of pathological biomineral analysis techniques and classification schemes. In: Aydinalp C., editor. An Introduction to the Study of Mineralogy. InTech, IMAA-CNR, Italy: In Tech Open; 2012. http://www.intechopen.com/books/ [Google Scholar]
2. Lopez M., Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatric Nephrology, 2008; 25(1): 49–59. doi: 10.1007/s00467-008-0960-5. [DOI] [PMC free article] [PubMed] [Google Scholar]
3. Mikawlrawng K., Kumar S., Vandana R. Current scenario of urolithiasis and the use of medicinal plants as antiurolithiatic agents in Manipur (North East India): a review. International Journal of Herbal Medicine, 2014; 2(1): 1–12. [Google Scholar]
4. Khan S. R., Pearle M. S., Robertson W. G., et al. Kidney stones. Nature Reviews Disease Primers, 2016; 16008. doi: 10.1038/nrdp.2016.8. [DOI] [PMC free article] [PubMed] [Google Scholar]
5. Sigurjonsdottir V. K., L.Runolfsdottir H., Indridason O. S., et al. Impact of nephrolithiasis on kidney function. BMC Nephrology, 2015; 16(1): 149. doi: 10.1186/s12882-015-0126-1. [DOI] [PMC free article] [PubMed] [Google Scholar]
6. El-Zoghby Z. M., Lieske J. C., Foley R. N., et al. Urolithiasis and the risk of ESRD. Clinical Journal of the American Society of Nephrology, 2012; 7(9): 1409–1415. doi: 10.2215/cjn.03210312. [DOI] [PMC free article] [PubMed] [Google Scholar]
7. Rule A. D., Roger V. L., Melton L. J., et al. Kidney stones associate with increased risk for myocardial infarction. Journal of the American Society of Nephrology, 2010; 21(10): 1641–1644. doi: 10.1681/asn.2010030253. [DOI] [PMC free article] [PubMed] [Google Scholar]
8. Worcester E. M., Coe F. L. Nephrolithiasis. Primary Care, 2008; 35(2): 369–391. doi: 10.1016/j.pop.2008.01.005. [DOI] [PMC free article] [PubMed] [Google Scholar]
9. Taylor E. N., Stampfer M. J., Curhan G. C. Obesity, weight gain and the risk of kidney stones. Journal of the American Medical Association, 2005; 293(4): 455–462. doi: 10.1001/jama.293.4.455. [DOI] [PubMed] [Google Scholar]
10. Courbebaisse M., Prot-Bertoye C., Bertocchio J., et al. Nephrolithiasis of adult: from mechanisms to preventive medical treatment. Revue Medicale International, 2017; 38(1): 44–52. doi: 10.1016/j.revmed.2016.05.013. [DOI] [PubMed] [Google Scholar]
11. Kumar S. B. N., Kumar K. G., Srinivasa V., Bilal S. A review on urolithiasis. International Journal of Universal Pharmacy and Life Sciences, 2012; 2(2): 269–280. [Google Scholar]
12. Teichman J. M., Joel M. H. Acute renal colic from ureteral calculus. New England Journal of Medicine, 2004; 350(7): 684–693. doi: 10.1056/nej
13. Yasui T, Okada A, Hamamoto S, Ando R, Taguchi K, Tozawa K et al Pathophysiology-based treatment of urolithiasis. Int J Urol., 2017; 24: 32–38.
14. Khan SR, Canales BK, Dominguez-Gutierrez PR Randall's plaque and calcium oxalate stone formation: role for immunity and inflammation. Nat Rev. Nephrol., 2021; 17: 417-433. https://doi.org/10.1038/s41581-020-00392-1
15. Alelign T, Petros B Kidney stone disease: an update on current concepts. Adv Urol., 2018; 3068365. https://doi.org/10.1155/2018/3068365
16. Siener R, Hesse A Fluid intake and epidemiology of urolithiasis. Eur J Clin Nutr., 2003; 57(Suppl 2): S47-51. https://doi.org/10.1038/sj.ejcn.1601901.
17. Sohgaura A, Bigoniya P A review on epidemiology and aetiology of renal stone. Am J Drug Discov Dev., 2017; 7: 54–62.
18. Emmett M, Kelepouris E (2015) Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance. UpToDate. last updated: Jun 30. Accessed 23 Sept 2016.
19. Emmett M, Kelepouris E (2015) Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance. UpToDate. last updated: Jun 30. Accessed 23 Sept 2016
20. Yasui T, Okada A, Hamamoto S, Ando R, Taguchi K, Tozawa K et al Pathophysiology-based treatment

of urolithiasis. Int J Urol., 2017; 24: 32-38. https://doi.org/10.1111/iju.13187
21. Alelign T, Petros B Kidney stone disease: an update on current concepts. Adv Urol., 2018: 3068365. https://doi.org/10.1155/2018/3068365
22. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H (2021) Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. https://doi.org/10.3892/ijmm.2021.4982
23. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M et al EAU guidelines on interventional treatment for urolithiasis. Eur Urol., 2016; 69: 475-482. https://doi.org/10.1016/j.eururo.2015.07.041
24. Preminger GM, Tiselius H-G, Assimos G, Alken P, Buck C, Gallucci M, et al. 2007 guideline for the management of ureteral calculi. The Journal of urology, 2007; 178: 2418-34.
25. Ratkalkar VN, Kleinman JG Mechanisms of stone formation. Clin Rev Bone Miner Metab., 2011; 9: 187–197. https://doi.org/10.1007/s12018-011-9104-8
26. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H (2021) Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. https://doi.org/10.3892/ijmm.2021.4982
27. Alelign T, Petros B (2018) Kidney stone disease: an update on current concepts. Adv Urol., 2018; 1–12. https://doi.org/10.1155/2018/3068365
28. Schwaderer AL, Wolfe AJ The association between bacteria and urinary stones. Ann Transl Med., 2017; 5: 32. https://doi.org/10.21037/atm.2016.11.73
29. Olszta MJ, Odom DJ, Douglas EP, Gower LB A new paradigm for biomineral formation: mineralization via an amorphous liquid-phase precursor. Connect Tissue Res., 2003; 44(Suppl 1): 326–334.
30. Ratkalkar VN, Kleinman JG Mechanisms of stone formation. Clin Rev Bone Miner Metab., 2011; 9: 187–197. https://doi.org/10.1007/s12018-011-9104-8
31. Evan AP, Coe FL, Lingeman JE, Shao Y, Sommer AJ, Bledsoe SB et al Mechanism of formation of human calcium oxalate renal stones on Randal l's plaque. Anat Rec Adv Integr Anat Evolut Bio., 2007; l290: 1315–1323
32. Rimer JD, An Z, Zhu Z, Lee MH, Goldfarb DS, Wesson JA et al Crystal growth inhibitors for the prevention of l-cystine kidney stones through molecular design. Science, 2010; 330; 337–341. https://doi.org/10.1126/science.1191968
33. Khan SR Renal tubular damage/dysfunction: key to the formation of kidney stones. Urol Res., 2006; 34: 86–91. https://doi.org/10.1007/s00240-005-0016-2
34. Trinchieri A. Epidemiology of urolithiasis: an update. Clin Cases Miner Bone Metab., 2008; 5: 101.