Component Analysis and Precise Prevention and Treatment of Urinary Stones

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Abstract: Urinary stones are a common disease worldwide, and their incidence has continued to rise in recent years. This article systematically reviews the epidemiological characteristics, formation mechanism, clinical manifestations, and diagnostic treatment methods of kidney stones and ureteral stones, with a special focus on the latest advances in stone component analysis technology and its application value in precision prevention and treatment. Studies have shown that there are significant differences in the formation mechanism, physical properties and metabolic basis of stones of different components, and the accurate analysis of stone components through infrared spectroscopy and other technologies can provide patients with personalized prevention and treatment plans, reducing the recurrence rate from 50%-90% to 10%-15%. This paper also discusses the genetic association between urinary stones and systemic diseases such as metabolic syndrome and cardiovascular disease, as well as the application prospects of multi-omics technology in stone research. Finally, this paper looks forward to the future challenges and development directions in the field of stone prevention and control, including the development of novel drug targets, the establishment of artificial intelligence-assisted diagnostic systems, and the construction of multi-center collaboration networks.
Keywords**:** urinary stones; component analysis; infrared spectroscopy; precise prevention and control; relapse prevention; multi-omics technology

1. Introduction

Urinary stones , including kidney stones and ureteral stones, are one of the most common diseases of the urinary system, characterized by abnormal aggregation and deposition of crystalline material in the urinary system. Over the past 50 years, the incidence of urinary stones has continued to rise globally without significant population differences, and has become a major health problem plaguing the global healthcare system[1]. Stones can not only cause severe pain, urinary tract obstruction and recurrent infections, but also form a vicious circle with chronic kidney disease, cardiovascular disease, metabolic syndrome and osteoporosis, bringing heavy economic burden to patients and society[2].

The formation of urinary stones is a complex physicochemical process that is influenced by a variety of factors, including genetic factors, metabolic abnormalities, local anatomical factors, dietary habits, and environmental exposures. There are significant differences in the formation mechanism, risk factors and prevention strategies of stones of different components. Therefore, accurate analysis of stone composition has become a key prerequisite for formulating effective prevention and control strategies[3]. In recent years, with the continuous advancement of analytical technology and the deepening of multi-omics research, our understanding of urinary stones has deepened from the macromorphological level to the molecular mechanism level, providing new opportunities for the precise prevention and treatment of stones[4].

This paper aims to comprehensively summarize the component analysis technology and clinical application of urinary stones, systematically expound the formation mechanism, characteristics and relationship between different components of stones and systemic diseases, and look forward to the future development direction of stone research and prevention, so as to provide reference for clinicians and researchers.

2. Epidemiology and disease burden of urinary stones

Urinary stones are a global disease, but there are significant regional and population differences in their incidence and stone types. In general, the incidence of stones is higher in developed countries than in developing countries, and higher in tropical regions than in cold regions. According to statistics, the prevalence of stones in European and American countries is about 7%-13%, and the prevalence rate in Asian countries is about 1%-5%. In China, the prevalence of urinary stones is about 1.61%-5.95%, and there are obvious regional differences, with the southern region being significantly higher than the northern region, and the incidence of stones in Fengxian area is even significantly higher than that in Shanghai[5].

It is worth noting that the incidence of urinary stones also shows obvious seasonal changes. In summer and autumn, the risk of stone incidence increases due to hot weather, excessive sweating of the human body, and concentration of urine;

In winter, changes in vitamin D metabolism and urine concentration may also increase the risk of stones. This seasonal change is especially noticeable in hot regions.Urinary stones place a heavy burden on healthcare systems worldwide. It is estimated that global direct healthcare expenditures due to urinary stones amounts to $13 billion annually, not including indirect costs such as lost labor productivity due to patient visits and treatments. The main burdens faced by stone patients include: emergency visits, surgical treatment, long-term drug treatment, and follow-up monitoring. Especially for patients with recurrent stones, the cost of long-term prevention and treatment is more considerable[5-6].

In addition to the immediate financial burden, urinary stones can also lead to a decrease in patients' quality of life. Renal colic during an acute attack of stones has been described as "one of the most severe pains in life" and severely affects the patient's ability to live and work. In addition, recurrent stones and multiple surgical treatments can also bring psychological burdens to patients, such as anxiety and depression.What is more noteworthy is that urinary stones are often associated with a variety of systemic diseases, forming a vicious circle[7]. Large-scale studies have shown that patients with kidney stones have a 2-3 times higher risk of developing chronic kidney disease (CKD) than the general population, with mechanisms involving recurrent obstructive nephropathy and crystal-mediated tubular damage. In addition, the risk ratio (HR) for coronary heart disease in patients with stones was 1.19 (95% CI 1.05-1.34), which may be associated with shared metabolic abnormal pathways such as insulin resistance. In terms of bone metabolism, the average reduction of lumbar bone mineral density (BMD) in stone patients was 0.12 g/cm², suggesting the two-way harm of calcium homeostasis imbalance[7-8].

3. Formation mechanism and risk factors of urinary stones

3.1 Physicochemical basis of stone formation

The formation of urinary stones is essentially a physicochemical process that involves multiple stages such as urine supersaturation, crystal nucleation, growth, and aggregation. When the concentration of a certain stone component in the urine exceeds its solubility product, the urine is supersaturated and crystals form. Subsequently, the crystals grow aggregate with various organic matrices as the core, eventually forming clinically visible stones.Urine supersaturation is the driving force behind stone formation and is influenced by various factors, including urine pH, ionic strength, urine flow rate, and inhibitor activity[9]. Stones of different components form under different pH conditions: uric acid stones are closely related to persistent acid urine (pHcalcium phosphate stones are more common in alkaline environments (pH>6.5).Lack of crystal inhibitors is also an important factor in stone formation[10]. There are a variety of natural inhibitors in normal urine, such as citrate, magnesium, pyrophosphate, nephalcin, etc., which can increase the solubility of stone components or inhibit crystal formation. When these inhibitors are deficient, the risk of stone formation increases. For example, hypocitrateuria (urinary citrate< 320 mg/day) is an important risk factor for calcium stone formation[9-10].

3.2 ssification of risk factors

Risk factors for urinary stones can be divided into various categories such as metabolic, anatomical, hereditary, and environmental. Among them, metabolic factors play a central role in stone formation, especially for calcium stones. Hypercalciuria (urinary calcium >200 mg/day) is the most common metabolic risk factor for calcium stones, occurring in 30% to 60% of patients with calcium stones[11]. The mechanism of its occurrence includes increased intestinal calcium absorption, decreased renal calcium reabsorption, and increased bone calcium mobilization. Hyperoxaluria (urinary oxalic acid >40 mg/day) is another important risk factor, and increased oxalate can significantly increase calcium oxalate supersaturation. Other metabolic factors include low urine output (hypernatremuria, hypomagnesuria, and hyperuricuria, among others.Anatomical factors are also important triggers for stone formation. Urinary tract obstruction for various reasons (such as narrowing of the renal pelvis ureteral junction, prostatic hyperplasia, etc.) leads to poor urine flow, prolonged crystal retention time, and promotes stone formation. Congenital anomalies such as horseshoe kidney, sponge kidney, etc. also increase the risk of stones.In recent years, the role of genetic factors in stone formation has been increasingly emphasized. Mutations in specific genes can cause hereditary stone diseases, such as SLC34A3 variants that cause hereditary hypophosphatemic rickets with kidney stones (HHRH), a monogenic form that accounts for 15% of cases in children. Genome-wide association studies (GWAS) have identified multiple gene loci associated with stones, such as FTO, NEK4, etc.Environmental and dietary factors are just as important in stone formation. A diet high in protein, salt, sugar, and purines increases the concentration of uric acid and calcium ions in the urine, which promotes stone formation. Insufficient water intake leads to reduced urine output and concentration of urine, which is also an important cause of stone formation[12-14].

3.3 Systematic biological mechanisms of stone formation

Recent research suggests that urinary stones have a shared genetic architecture and molecular pathways with other systemic diseases. Large-scale GWAS data analysis revealed that kidney/ureteral stones (KUS) were significantly genetically correlated with cardiovascular disease (CVDs) and metabolic syndrome (MetS) (rg=0.133-0.223, p in KUS, hypertension (HPT) and obesity (OB). 0.968[15].At the molecular pathway level, tryptophan metabolism is the core pathway connecting KUS and hypertension ($p=6.37\times10-4$). As a key regulator of tryptophan-kynurenine metabolism, FTO gene may be an important regulatory node of this pathway. These findings provide a new perspective on understanding the intrinsic link between stones and systemic diseases.Multi-omics studies have further revealed the complex microenvironment in which stone formation occurs. Multi-omics analysis of patients with unilateral calcium oxalate kidney stones found significant alterations in the proteome and metabolome even in the contralateral "normal" kidney. The researchers identified 40 differential proteins (36 up-regulated and 4 down-regulated) and 10 up-regulated differential metabolites in renal pelvisuria, which are mainly involved in the processes of inflammatory response and oxidative stress. Among them, fibrinogen α chains and γ chains are key nodes in the regulatory network of stone formation and interact with many proteins[16].

4. Stone composition analysis techniques and methods

4.1 Chemical Analysis

Chemical analysis is a traditional method of stone composition analysis that determines the composition of stones through a series of chemical reactions. The basic principle of this method is to use specific chemical agents to react with the components in the stone, resulting in visible phenomena such as color changes, gas formation, or precipitation formation, thereby inferring the chemical composition of the stone[17].

Although chemical analysis has the advantages of simple operation, low equipment requirements and low cost, its disadvantages are also very obvious: it requires a large sample volume, is destructive, has low sensitivity and poor specificity, especially for mixed stones, it is difficult to accurately determine the proportion of each component. As a result, chemical analysis has been gradually replaced by more advanced physical analysis methods in modern hospitals[18].

4.2 Physical Analysis Method

With the development of analytical technology, a variety of physical analysis methods have been applied to stone composition analysis, which are based on the interaction between substances and electromagnetic radiation, which can provide more accurate and detailed stone composition information. Commonly used physical analysis methods include:Infrared spectroscopy (IR) is the current "gold standard" for stone composition analysis. Its principle is based on the vibrational energy level transition of chemical bonds in molecules, absorbing specific wavelengths of infrared light to form a unique absorption spectrum. Different chemical components have characteristic spectral fingerprints, which can be accurately identified by comparing them with standard spectra. The modern automatic infrared spectroscopy stone analyzer can not only identify single-component stones, but also accurately quantify the proportion of various substances in mixed component stones, providing a more detailed basis for the adjustment of patients' prevention and treatment plans[19-22].

X-ray diffraction (XRD) is another high-precision stone analysis method, especially suitable for the analysis of crystal structure. The principle is based on the diffraction pattern produced by X-rays as they pass through crystals, each with a unique diffraction pattern, which can be used for accurate identification, just like a human fingerprint. The main advantage of XRD is the ability to distinguish between substances with the same chemical composition but different crystal structures (such as calcium oxalate monohydrate and calcium oxalate dihydrate).Polarized light microscopy uses the birefringence properties of crystals to analyze, and different crystals exhibit specific morphologies and interference colors under polarized light. This method requires relatively simple equipment but requires a high level of experience from the operator.Scanning electron microscopy (SEM) combined with Energy Dispersive X-ray Spectroscopy (EDS) can perform elemental composition analysis while observing the microscopic morphology of stones, providing detailed information about the structure and composition of stones[23].

4.3 Clinical classification of stone components

According to the results of component analysis, urinary stones can be divided into the following categories:Calcium oxalate stones are the most common type, accounting for about 70%-80% of urinary stones, and can be divided into two subtypes: calcium oxalate monohydrate (whewellite) and calcium oxalate dihydrate (weddellite). These stones are usually tan in color, with spinous protrusions on the surface, hard in texture, and clearly developed on radiographs[24].

Calcium phosphate stones include hydroxyapatite, carbonate apatite and dicalcium phosphate, accounting for about 5%-10% of stones. This type of stone is mostly grayish-white, with a smooth surface and a brittle texture, which is easy to form in alkaline urine.Uric acid stones account for about 5%-10% and are composed of anhydrous uric acid or uric acid dihydrate. These stones are yellow or reddish-brown, have a smooth surface, translucent X-rays, and are easy to form in acidic urine.Magnesium ammonium phosphate stones (infected stones) account for about 10%-15%, and the main component is magnesium ammonium phosphate hexahydrate. These stones are mostly grayish-white, crunchy in texture, and often form in urinary tract infections caused by urease-producing bacteria.Cystine stones are rare, accounting for about 1%-2%, and are caused by cystine reabsorption disorders by renal tubules. These stones are pale yellow, have a smooth surface, have a waxy appearance, and are not developed on X-rays[25].

Other rare types of stones include drug-related stones (e.g., indinavir, sulfonamides, etc.) and purine stones (e.g., xanthines, 2,8-dihydroxyadenine stones, etc.).

5. Clinical significance and personalized prevention and treatment of stone component analysis

5.1 Etiological characteristics of different stone components

ccurate stone composition analysis provides important clues to understand the root causes of stone formation. Stones of different components reflect different metabolic abnormalities and pathophysiological processes, which provides direction for targeted prevention and treatment[26].

Patients with calcium oxalate stones are often accompanied by metabolic abnormalities such as hypercalciuria, hyperoxaluria, hypocitrateuria, or hypouric output. Among them, hypercalciuria can be caused by a variety of mechanisms, including absorbed hypercalciuria (increased intestinal calcium absorption), nephrrhagic hypercalciuria (decreased renal calcium reabsorption), and reabsorbed hypercalciuria (increased bone calcium mobilization). In recent years, studies have found that there are significant changes in inflammatory response and oxidative stress in the renal pelvis urine of patients with calcium oxalate stones, such as the activation of complement and coagulation cascades and the formation of neutrophil extracellular traps.The formation of uric acid stones is mainly related to persistent acid urine and hyperuriuria. Uric acid is a weak organic acid (pKa=5.35), which has significantly reduced solubility in an acidic environment and is prone to crystallization[27]. Patients with uric acid stones are often accompanied by the characteristics of metabolic syndrome, such as insulin resistance, obesity and hypertriglyceridemia.The formation of magnesium ammonium phosphate stones (infected stones) is closely related to urinary tract infections caused by urease-producing bacteria. The urease produced by these bacteria breaks down urea into ammonia and carbon dioxide, alkalizing urine and promoting the supersaturation of magnesium ammonium phosphate and apatite carbonate and precipitation of crystals. These stones are common in patients with urinary tract malformations, neurogenic bladder, or long-term indwelling catheters.Cystine stones are caused by reabsorption of cystine, ornithine, arginine and lysine by the renal tubules, and are autosomal recessive diseases. The patient's urine cystine saturation increases, and when the solubility is exceeded, stones are precipitated to form[28].

5.2 Selection of control strategies based on component analysis

Personalized prevention and treatment under the guidance of stone component analysis is the key to reducing the recurrence rate of stones. Prevention and treatment strategies vary depending on different stone components and potential metabolic abnormalities.For patients with calcium oxalate stones, prevention and control measures include: increase water intake (maintain urine output >2.5 L/day), limit sodium intake (moderately restrict animal protein (0.8-1.0 g/kg/day), and limit oxalate-rich foods (such as spinach, nuts, chocolate, etc.). Drug prevention and control include thiazide diuretics (reducing urinary calcium excretion by 23%-45%) and citrate (increasing urinary citric acid by more than 35%). Recent studies have found that active ingredients in traditional Chinese medicine, such as forsythiaside, may reduce oxidative stress and apoptosis by activating the PPARγ/Nrf2/HO-1 signaling pathway, and have potential for prevention and control. For patients with uric acid stones, prevention and treatment strategies focus on alkalizing urine (maintaining urine pH 6.2-6.8) and reducing uric acid levels. It is recommended to limit purine intake in the diet (such as animal offal, seafood, etc.), and drug prevention and control include allopurinol (which reduces uric acid excretion by 200-300 mg/day) and uric acid oxidase[27-29].

The key to the prevention and treatment of magnesium ammonium phosphate stones is to thoroughly control the infection and remove stone residues. Sensitive antibiotics need to be selected based on susceptibility results, and sometimes long-term antibacterial therapy is required. In complex cases, surgery may be required to completely remove the stone and correct anatomical abnormalities in the urinary tract.Prevention and control measures for cystine stones include extreme increase in water intake (maintaining urine output >3 L/day), alkalizing urine (maintaining urine pH >7.5), and using thiols (such as α-mercaptopropionylglycine, D-penicillamine, etc.) to reduce urinary cystine concentration[30].

5.3 Recurrence risk assessment and long-term management

Recurrence risk assessment based on stone composition analysis and metabolic assessment is an important part of long-term stone management. A comprehensive metabolic evaluation should include a serum electrolyte test and a 24-hour urine composition analysis to assess the levels of various risk factors for stone formation.[30]

For patients at high risk of recurrence, a comprehensive prevention and treatment strategy is required, including dietary intervention, medication and regular monitoring. Monitoring indicators include imaging examination (to assess stone recurrence or enlargement) and urine metabolism parameters (to evaluate the effectiveness and compliance of prevention and control measures).It is worth noting that urinary stones are a lifelong metabolic disease, with a 5-year recurrence rate of up to 50% and a 10-year recurrence rate of up to 90% in patients who have not been effectively prevented and treated. Through accurate component analysis and personalized prevention and treatment plans, the recurrence rate can be reduced from 50%-90% to 10%-15%, achieving a real breakthrough in stone prevention and control[31].

6. Future development directions and challenges

Despite significant progress in the research and prevention of urinary stones, there are still many challenges and development opportunities. Future research directions include:Technological innovation and multi-omics research: With the rapid development of multi-omics technology, stone research is deepening from macroscopic phenomenon description to molecular mechanism[28]. Proteomics, metabolomics, and transcriptomic analyses will reveal more refined mechanisms of stone formation[28]. For example, multi-omics studies have found an important role in the tryptophan metabolism pathway in stone formation. At the same time, stone analysis techniques are also advancing, and new technologies such as spectroscopic imaging, Raman spectroscopy, and mass spectrometry imaging may provide more accurate compositional and structural information.Novel drug development: The research and development of new drugs based on the molecular mechanism of stone formation is another important direction[29]. Natural active ingredients such as forsythiaside show anti-stone potential by mitigating oxidative stress and apoptosis through the PPARγ/Nrf2/HO-1 signaling pathway. Other potential targets include seven core genes such as NEK4 and GLT8D1, which show pleiotropicity in a variety of diseases and are mainly involved in mitochondrial function and glycosylation processes.Minimally invasive technology innovation: In terms of treatment, minimally invasive technology continues to innovate and improve. Retroinsertion-free tubeless PCNL technology realizes the three advantages of "no ureteral intubation, no indwelling stent tube and no nephrostomy tube", reducing patient pain and complications. The flexible ureteroscopic negative pressure suction sheath technology improves stone clearance efficiency and controls intrarenal pressure[31]. These technological innovations have made stone treatment more minimally invasive, safe, and efficient.Interdisciplinary cooperation and comprehensive prevention and treatment model: The close association between urinary stones and metabolic syndrome, cardiovascular disease and bone metabolic disease requires the establishment of an interdisciplinary cooperation model. In the future, it is necessary to collaborate with multiple disciplines such as urology, endocrinology, cardiovascular medicine, nutrition and nephrology to establish a comprehensive prevention and treatment system of "stone-metabolism-bone disease", break down specialist barriers, and provide overall solutions.Data Sharing and AI Applications: The establishment of large-scale multicenter registry systems and data sharing are crucial for stone research. Using artificial intelligence and machine learning technology to analyze clinical big data, new risk patterns and predictors may be discovered, and early identification and precise intervention of stone risk can be realized.Population health education and prevention strategies: Finally, strengthening population health education and prevention strategies is the fundamental way to reduce the incidence of stones. Public education should focus on the promotion of adequate drinking water, reasonable diet, and healthy lifestyle. For high-risk groups, such as family history of stones, metabolic abnormalities, and chronic diseases, early screening and intervention strategies should be implemented to prevent problems before they occur[30-33].

7. Conclusion

Urinary stones are a complex multifactorial disease characterized by high incidence and high recurrence rates, placing a heavy burden on patients and society. Stone composition analysis is a key link in understanding the mechanism of stone formation and guiding personalized prevention and treatment, among which infrared spectroscopy, as the current gold standard method, can provide accurate and detailed composition information.Stones of different components reflect different metabolic abnormalities and pathophysiological processes, such as calcium oxalate stones, uric acid stones, infection stones, and cystine stones, each with its own unique formation mechanism and clinical characteristics. Personalized prevention and treatment strategies based on stone composition analysis and metabolic assessment can significantly reduce the recurrence rate of stones, from 50%-90% to 10%-15%.

In the future, with the continuous development of multi-omics technology, minimally invasive surgical technology and artificial intelligence analysis, as well as an in-depth understanding of the mechanism of the association between stones and systemic diseases, the prevention and treatment of urinary stones will be more accurate, efficient and comprehensive, and ultimately reduce the health burden caused by this disease.

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