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Kidney stone, and their management: An update

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Abstract
Urolithiasis, or kidney stone development, is a complicated process that involves a series of physicochemical phenomena such as supersaturation, nucleation, growth, aggregation, and retention within the kidneys. It is a growing urological health problem that affects roughly 12% of the world's population. Kidney stones come in a variety of sizes, shapes, and colors. The stones must pass through ducts that carry urine from the kidneys to the bladder (ureters) and be expelled in order to be removed from the body. Kidney stones can take days to weeks to get out of the body, depending on their size. *Hassat-e-Kulya* (renal Stone) is abundant in ancient Unani literature, and Unani physicians addressed disease, manifestations, and treatment in broad terms. Several human studies have suggested that eating a diet rich in vegetables and fruits can help prevent kidney stones. Because of the drawbacks of surgical procedures and the restricted options for pharmacotherapy, it's worth looking into new pharmacological approaches for the treatment of kidney stones. Many Herbo mineral formulations (eg. *Qurs Kushta Hijrul Yahood; Majoon Hijrul Yahood, Majoon Sange Sarmahi*, etc) and medicinal plants/herbs (*Habbul Qilt, Kalonji, Jawakhar, Pathri Phori* etc) have been researched for the treatment of urolithiasis, albeit most of them have only been tested on a small number of people or in animal models.

Keywords: Renal calculi, kidney stones, dietary management, prevention

Introductions
Kidney stones are one of the most well-known and prevalent illnesses of the urinary tract, with a prevalence ranging from 1% to 20% [1]. Mineral deposits in the renal calyces and pelvis that are either free or adhering to the renal papillae are known as kidney stones. They are created when urine becomes supersaturated with respect to a mineral and contains both crystalline and organic components [2]. Urinary stones have troubled mankind for generations, reaching back as 4000 B.C [3]. The prevention of recurrence of renal stones is still a major issue in human health [4]. The prevention of stone recurrence necessitates a better knowledge of the mechanisms that lead to the creation of stones [5]. The passage of stones in the urinary tract system can produce a variety of symptoms, including pain, blockage, infection, and bleeding [6]. For the treatment and prevention of kidney stones, many phytotherapy, and herbal medications have been described [7].

Incidence/Prevalence
The global frequency and incidence of nephrolithiasis are said to be on the rise. We review data on stone incidence and prevalence from a worldwide viewpoint in this article [8]. Stone disease is most common in those between the ages of 20 and 40, while it affects people of all ages [9]. The male preponderance of stone disease may be waning, with recent data indicating that the male to female ratio is around 3:2 [10]. Calcium oxalate stones (the most prevalent type) had a recurrence rate of 10% at one year and 35% at five years following the initial episode of kidney stone illness in North America [11].

Risk factors
When urine crystals separate and accumulate within the kidney papillae, renal pelvis, or ureter, kidney stones form [12]. Calcium-containing stones, which are mainly made of calcium oxalate and less occasionally calcium phosphate, are the most prevalent type of stone. Uric acid, cysteine, and xanthine stones are examples of metabolic stones. Infectious stones, sometimes known as “struvite” stones, contain a mixture of magnesium, ammonium, and phosphate and are linked to urease-producing organisms like Klebsiella or Proteus species [13]. Dehydration, lifestyle, geographic location (dry arid environment), and some particular risk factors are all general predisposing factors for stone development.

Anatomical/structural anomalies (e.g., pelvic ureteric junction obstruction, urinary diversion surgery, horseshoe kidney, calyceal diverticulum), underlying metabolic disorders (e.g., cystinuria, oxaluria, gout), certain medicines, and urease-producing infective organisms are also possible causes [14].

Prognosis of Renal Calculi

With anticipatory treatment, most kidney stones pass within a few days (including adequate fluid intake and analgesia). Others may take longer to pass, in which case the monitoring time can be increased to 3-4 weeks [15]. Ureteric stones smaller than 5 mm in diameter pass spontaneously in 90% of patients, compared to 50% of ureteric stones between 5 mm and 10 mm in diameter [16]. Expectant (conservative) management is considered on an individual basis in people with asymptomatic, very small, or both stones (although stone size may not correlate with symptom severity), as well as in people with significant comorbidities, in whom the risks of treatment may outweigh the likely benefits. Stones may move despite or after therapy for their condition [14], Once in the ureter, it may or may not manifest clinically. Hydronephrosis and renal atrophy can be caused by stones impeding urine flow [12]. Urinary infection, perinephric abscess, or urosepsis are all life-threatening consequences that can occur. Drainage of an infected obstructed kidney is a medical emergency that, if left untreated, could end in death. Infection can also occur following invasive stone removal operations. Some of these issues can lead to kidney injury and impaired renal function. Eventually, 10-20% of all kidney stones will require therapy [10-16].

Epidemiology of Kidney Stones

Kidney stone disease frequency and recurrence rates are rising worldwide 69, despite a lack of effective treatments. Urolithiasis affects roughly 12% of the world's population at some point during their lives [17]. It has an impact on people of all ages, genders, and races, but is more common in men than in women between the ages of 20 and 49 [18]. The relapse rate of secondary stone forms is expected to be 10–23% each year if patients do not use metaphylaxis, 50% in 5–10 years, and 75% in 20 years if patients do not use metaphylaxis. Although the incidence of nephrolithiasis is increasing among girls, the lifetime recurrence rate is higher in males. As a result, preventive care is critical in the treatment of urolithiasis [16, 17].

According to recent studies, the prevalence of urolithiasis has risen in both industrialized and developing countries during the last few decades. This rising trend is thought to be linked to lifestyle changes such as lack of physical exercise and food habits, as well as global warming [18]. Kidney stones afflict one out of every eleven people in the United States. Urinary stones affect 600,000 Americans each year, according to the CDC. Urinary stones are projected to affect roughly 12% of the Indian population, with 50% of those who develop them losing kidney function [19].

Types of Kidney Stones

The chemical composition of kidney stones is determined by anomalies in urine chemical composition. The size, form, and chemical content of stones vary (mineralogy) [20]. Kidney stones are usually categorized into five kinds based on differences in mineral content and etiology [21].

Calcium Stones: Calcium Oxalate and Calcium Phosphate

Calcium stones are the most common kidney stones, accounting for nearly 80% of all urinary calculi [17]. Calcium stones can be made up of pure calcium oxalate (CaOx) (50%) or calcium phosphate (CaP, also known as apatite) (5%), or a combination of both (45 percent) [18]. Brushite (calcium hydrogen phosphate) or hydroxyapatite are the major components of calcium stones [16, 17]. CaOx monohydrate (COM, also known as whewellite, $CaC_2O_4H_2O$) and CaOx dihydrate (COD, weddellite, $CaC_2O_{42}H_2O$) are the most common forms of calcium oxalate discovered in kidney stones, accounting for more than 60% of the total [19]. The most thermodynamically stable type of stone is COM. In clinical stones, COM is seen more commonly than COD [20].

Hypercalciuria (resorptive, renal leak, absorptive, and metabolic disorders), hyperuricosuria, hyperoxaluria, hypocitraturia, hypomagnesuria, and hypercystinuria are all variables that lead to CaOx stone development [21]. CaOx stones are most commonly caused by urinary pH of 5.0 to 6.5, whereas calcium phosphate stones are caused by pH more than 7.5. Calcium stones return more frequently than other types of kidney stones [22].

Struvite or Magnesium Ammonium Phosphate Stones

Struvite stones, also known as infection stones and triple phosphate stones, are seen in 10–15 percent of people [22]. It occurs in people with urease-producing chronic urinary tract infections, the most frequent of which is Proteus mirabilis; other bacteria that are less prevalent include Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter aerogenes [23]. Urease is required to split/cleave urea into ammonia and CO_2, causing urine to become more alkaline, raising pH (usually > 7). Because phosphate is less soluble at alkaline than acidic pH, it precipitates on insoluble ammonium compounds, forming a huge staghorn stone [24]. Women are more likely than men to produce this form of stone. Escherichia coli cannot split urea and is not linked to the formation of struvite stones [25].

This sort of stone makes up about 3–10% of all stone types [11]. Purine-rich diets, particularly those including animal protein such as meat and fish, cause hyperuricosuria, low urine volume, and a low urinary pH (pH 5.05) that exacerbates the production of uric acid stones [12]. Gouty arthritis patients may develop kidney stones (s). Idiopathic uric acid nephrolithiasis is the most common cause, and uric acid stones are more common in males than in women [13].

Cystine Stones

These stones make up less than 2% of the total number of stone types [14]. It's a condition that affects the transfer of an amino acid and cystine in the body. It causes cystinuria, an autosomal recessive condition caused by a mutation in the rBAT gene on chromosome 2, which causes reduced renal tubular absorption of cystine or cystine leakage into urine [4]. It does not dissolve in urine, resulting in the production of cystine stones [15, 26]. Cystinuria is caused by the excretion of more than 600 millimoles of insoluble cystine per day by those who are homozygous for the disease [9]. The only

clinical sign of cystine stone disease is the formation of urinary cysteine [27].

Drug-Induced Stones

This accounts for about 1-2% of all stone types [1]. Drugs such as guaifenesin, triamterene, atazanavir, and sulfa drugs induce these stones. For instance, people who take the protease inhibitor indinavir sulfate, a drug used to treat HIV infection, are at risk of developing kidney stones [100]. Such lithogenic drugs or their metabolites may deposit to form a nidus or on renal calculi already present. On the other hand, these drugs may induce the formation of calculi through its metabolic action by interfering with calcium oxalate or purine metabolisms [2-7].

Kidney Stone Compositions

The chemical compositions of urinary stones include crystals and noncrystalline phases of the organic material.[2] The organic matrix of urinary stones consists of macromolecules such as glycosaminoglycans (GAG's), lipids, carbohydrates, and proteins [3]. These molecules play a significant role by promoting or inhibiting the processes of kidney stone development [4]. The main components of the stone matrix are proteins (64%), nonamino sugars (9.6%), hexosamine as glucosamine (5%), water (10%), and inorganic ash (10.4%). The matrix acts as a template participating in the assembly of kidney stones [28]. The matrix of all stones contains phospholipids (8.6%) of the total lipid, which in turn represents about 10.3% of stone matrix. Cell membrane phospholipids, as part of organic matrix, promote the formation of calcium oxalate and calcium phosphate stones and albumin is the major component of the matrix of all stone types [29].

Causes of Kidney Stones

Kidney stone production is a multifaceted process that includes both intrinsic (such as age, sex, and inheritance) and extrinsic (such as geography, climate, food, mineral composition, and water intake) components [1, 6, 7, 30].

Management of Renal Stone

Medicinal plants having diuretic, antispasmodic, and antioxidant properties reduce crystallization, nucleation, and aggregation of crystals, making them effective for urolithiasis treatment [31, 32]. Kidney stones can be prevented by increasing fluid intake and making dietary modifications. Increasing urine volume to at least 2 L/day OR 2 lit/day has been found in numerous studies to prevent the recurrence of stone disease by up to 40%–50% [33]. Water should be the primary fluid consumed. Because oxalate is present in tea and coffee, milk (which binds free oxalate) should be added. However, increasing urine volume has the drawback of lowering urinary citrate levels [34]. Cucumber, green peppers, beetroot, spinach, soya bean, chocolate, rhubarb, popcorn, and sweet potato are all high in oxalate; hence, oxalate-rich foods including cucumber, green peppers, beetroot, spinach, soya bean, chocolate, rhubarb, popcorn, and sweet potato should be avoided. Calcium restriction has been linked to an increased risk of stone disease in numerous studies, hence it is not recommended [35].

Dietary interventions are being considered as potential kidney protection approaches, either in conjunction with or independent of hereditary or genetic variables. Nutritional plants are effective dietary therapies that can reduce the chance of calcium oxalate stone recurrence. The following section discusses a variety of dietary herbs, food additives, fruits, and vegetables that have been shown to protect against urolithiasis [36].

The nutritional and medicinal plant Dolichos biflorus (horse gram) is native to India, where its seeds are used to make soup. The seeds are said to have litholytic, free radical-scavenging, and anti-nephrotoxic properties in ayurvedic literature [36, 37]. The presence of several phytoconstituents in the seeds, such as phenolic chemicals (such as quercetin), alkaloids, phytosterols (such as -sitosterol), saponins, and glucosides (such as -galactosidases and -mannosidase), can be ascribed to the plant's positive effect. In experimental kidney stone models, several extracts from seeds, including aqueous, chloroform, and benzene, dissolved calcium oxalate stones. When compared to other extracts, aqueous extract demonstrated the most stone disintegration [38]. The hydro-alcoholic extract of seeds inhibited the nucleation and aggregation of calcium oxalate monohydrate crystals in a synthetic urine system for calcium oxalate crystallization. Patients with calcium oxalate renal calculi who were given D. biflorus had a lower recurrence of calcium oxalate stones and had a better outcome than those who were given potassium citrate [39].

Nigella sativa has been utilized to treat urinary stones in Iranian traditional medicine [40, 41]. In ethylene glycol-induced lithiasis rats, ethanolic extract of seeds reduced the amount of calcium oxalate deposits and decreased the calcium oxalate concentration in the urine [42]. The main component of the seeds, thymoquinone, has both preventative and therapeutic effects in rats with ethylene glycol-induced renal calculi. The size and number of calcium oxalate deposits in the renal tubules of rats were reduced by this phytochemical substance [43].

Oliganum vulgare has been widely used as a spice and as a lithotriptic, diuretic, and antispasmodic in traditional medicine [44]. The crude aqueous-methanolic extract of O. vulgare's aerial component inhibited the nucleation and aggregation of calcium oxalate crystals *in vitro*, as well as the number of crystals formed in calcium oxalate metastable solutions. The extract of the aerial part of O. vulgare displayed antiurolithic activity in rats with ethylene glycol and ammonium chloride-induced urolithiasis, possibly through inhibition of calcium oxalate crystallization, renal epithelial cell protection, antioxidant, and antispasmodic characteristics. Flavonoids, terpenes, coumarins, saponins, alkaloids, sterol, and tannins are among the active phytochemicals that may have a protective impact [11, 36].

Anti-lithotriptic action has been documented in several Unani formulations, including *Qurs kaaknaj, kushta Hajr-ul-yahood, Majoon Aqrab, Qurs kushta Hajr-ul-yahood, Sharbat Aaloo Balu, Jawarish Zarooni saada, Jawarish Zarooni Ambari, Kushta Hajr-ul-Yahood, Majoon Aqrab* [45, 46].

Faridi P *et al*. reported that *Lapis judaicus* significantly reduced the size of kidney stones when given orally at the dose of 2 g on 30 patients for 10 weeks, and another 30 patients received a placebo for the same period. Contrary to the placebo group, the size of kidney stones was reduced significantly in the treatment group after oral administration of *Lapis judaicus*. This preliminary study confirms traditional knowledge of the efficacy and safety of *Lapis judaicus* in kidney stone diseases and suggests a new method to treat calcium kidney stones [47]. An open

prospective clinical trial was carried out by Ahmed NZ *et al*. on 107 subjects of renal calculi of 3-7 mm diameter diagnosed by Ultrasonogram-KUB (USG-KUB) and the drug was *Safūf Hajar-al Yahūd.* Substantial reduction (53%) in the size of calculi confirmed by USG-KUB and considerable lowering of VAS score (75%) were observed with the active intervention in the majority of the cases, and the researcher concluded the trial has revealed that the Unani pharmacopoeial formulation *Safūf Hajar-al Yahūd* was well tolerated and has the therapeutic potential in the reduction and expulsion of renal calculi [49]. *Safoof-e-Pathar phori* (SPP) is an Unani poly-herbomineral formulation, which has for a long time been used as a medicine due to its antiurolithiatic activity, as per the Unani Pharmacopoeia, and Ahmad W *et al*. (2021), reported that the usefulness of SPP as an antiurolithiatic and an antioxidant agent, and long-term daily oral consumption of SPP was found to be safe in albino Wistar rats for up to 3 months. Thus, SPP may be safe for clinical use as an antiurolithiatic formulation [50].

Conclusion

Renal calculi are a painful condition that affects people all over the world. Every day, the prevalence rises. Males, on the other hand, are more likely than girls to develop renal calculi. According to the concept of the Unani system of medicine, *Su-e-Mizaj Gurdah, Qarha, Ghaleez Madda*, and their stationery, responsible for renal calculi. Kidney stones can be prevented by increasing fluid intake and making dietary modifications.

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