Review Article

Urolithiasis and Nephrolithiasis: The Two Wings of Analogous Urinary Tract Injuries

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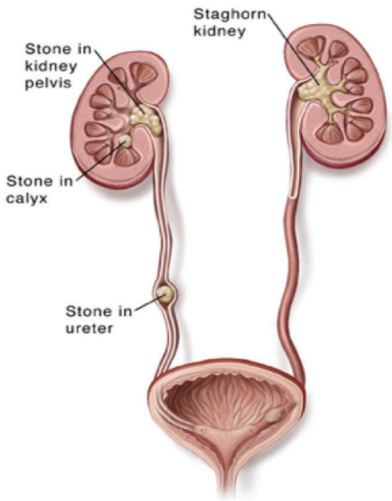
Introduction:

Commonly known as 'Kidney stones', are termed as 'renal calculi' in medical science. These calculi/stones are of hard masses of different sizes made of mineral crystals clumped together inside the kidneys.[1] Although they start to originate in the kidney, these hard masses (calculi) increase in size inside ureter or bladder. According to the anatomical location of these calculi, they are often termed as: 'kidney stone', 'ureteral stone', or 'bladder stone'. The stone forming procedure is known as 'urolithiasis', 'renal lithiasis', or 'nephrolithiasis'[2] which abstractly implicates 'The two wings of analogous urinary tract injuries'.[1,2]



Urinary stones in different locations of urinary tract[3]

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Brief History:

Looking back to the history, urinary stones (both bladder and kidney stones) were found in Egyptian mummies from 4800 BC. Being an age-old public health issue, the pathogenesis of urolithiasis had been studying**,** yet, its treatment strategies are being refined.[4] In 1901, Elliott Smith discovered a bladder calculus in the pelvis of an Egyptian mummy. The calculus has a uric acid nucleus with concentric laminations of calcium oxalate and ammonium magnesium phosphate.[5] An ancient Indian physician Sushruta, described urolithiasis in 6th century. During the 10th century an Arabian physician Abukasis prescribed the method of smashing stones in the urethra with an instrument devised by his own.[6] During the medieval period in Europe (1096–1438) there was little activity regarding the management of stone disease.[7,8]

Epidemiology in brief:

Both urolithiasis (urinary tract calculi or stones) and nephrolithiasis (kidney calculi or stones) are well-reported common occurrences among US population.[13] Recent epidemiological studies have suggested an increased frequency of kidney stone disease in all age groups during the last decades.[9]

In the western world about 0.5% people are diagnosed with urolithiasis, and it is the 3rd most common urological diseases affecting both the males and females worldwide.[10]

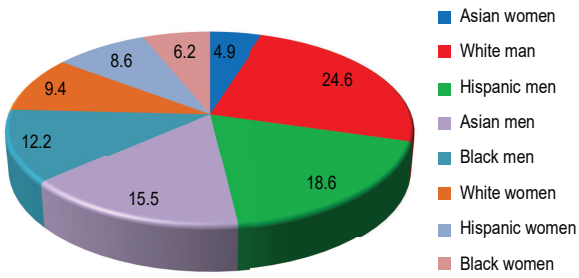

Figure: Prevalence of stone disease, specific to gender and race[28]

According to a report, almost 1 of 1,000 adults gets hospitalized in USA every year due to urolithiasis as this disease is more common in adults.[2]

Demographics:

In USA

Men: 140.6 per 100,000 population[11]

Women: 65.8 per 100,000 population[11]

In 2019, 115 552 140 incident cases were detected globally.[12]

Kidney stone belt on the globe:

In this zone the climatic and social conditions are favorable for stone formation. Some stones are associated with poverty, while others with affluence. In Europe and the USA, there has been a sharp, almost exclusively affluence-related rise in the occurrence of calcium oxalate and uric acid stones. Climate simulations for the USA show that the stone belt is likely to move northwards in the coming two decades.[13]

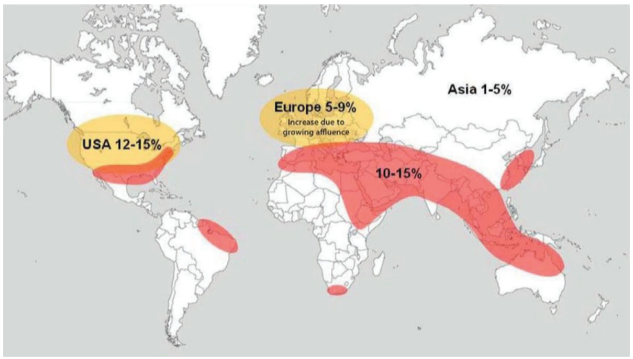

Figure: The kidney stone belt (red) extends all the way around the world and shows urinary stone prevalence of 10 to 15%.[14]

Urolithiasis vs Nephrolithiasis:

Urolithiasis is the process of forming stones anywhere in the urinary tract (kidney, bladder, and/or urethra),[15] whereas, nephrolithiasis specially refers to stone in the kidney.[16]

Etiology of and risk factors:

Though the etiology of renal stone is not well understood[10], multifactorial etiology has been related to this disease0.[9] Both genetic and environmental factors contribute to stone formation.[17]

The major causes of urolithiasis are:[18]

1) Hyperoxaluria, hypercalciuria, hypocitraturia, hyperuricemia, renal tubular acidosis, hypophosphatemia, cystinuria, etc.
2) Other causes include: urinary infections, impaired drainage (i.e. obstruction), post-bariatric surgery, foreign bodies, drugs, etc.

Types of urolithiasis:

The five commonest types of urinary stones are calcium oxalate (>50%), Ca Phosphate (10% to 20%), uric acid (8%), struvite (15%), cystine (3%).[19]

Figure: Major types of urinary stones

Generally, any physician, who is even not a urologist, can advise **preventive therapeutic measures** for reducing risk of recurrent kidney stones once anyone is at a risk of developing renal calculi.

Drug Induced Urolithiasis:

Indinavir calculi: Several drugs have been reported to cause urolithiasis. Among them, most frequent is indinavir, especially when administered with ritonavir.[5] Indinavir sulfate is currently one of the most widely used protease inhibitors used against HIV. The incidence of urolithiasis in patients taking indinavir is almost 20%.[20]

A study was conducted in 24 patients of urolithiasis who were taking protease inhibitors. Among them 14 were taking indinavir, three ritonavir, two nelfinavir, and five other drugs. Only in 4 patients of the 14 taking indinavir, the drug was found in kidney stone. Rest of the 10 patients underwent 24-hour urine collection and metabolic abnormalities were found in 80% of them. Five of them had hypocitraturia, four hyperoxaluria, four hypomagnesuria, three hypercalciuria, three supersaturation of calcium oxalate, and two hyperuricosuria. From this study, the authors deduced that metabolic abnormalities are more responsible for the formation of kidney stones than protease inhibitors.[21]

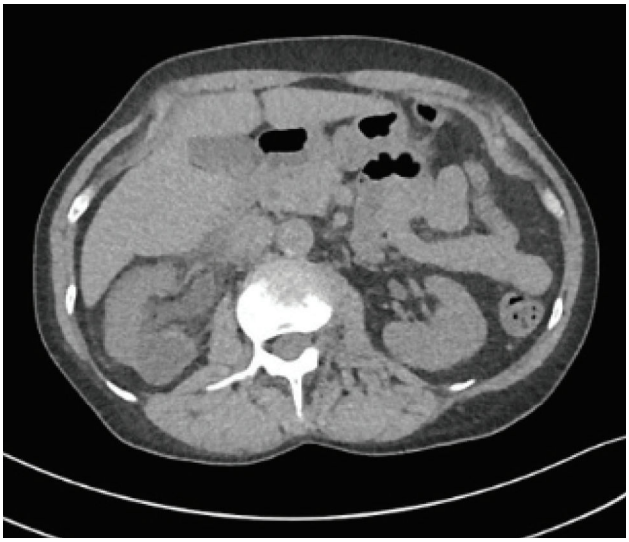

Figure: Pure indinavir calculi are radiolucent.[15]

Drug-Induced Nephrolithiasis:

1) Ephedrine calculi: Ephedrine and its metabolites (norephedrine, pseudoephedrine, and norpseudo-ephedrine) are sympathomimetic agents used for the treatment of enuresis, myasthenia gravis, narcolepsy, and rhinorrhea.[22] Ephedrine calculi are radiolucent.[23]

2) Indinavir calculi.

3) Guaifenesin calculi:

Guaifenesin is a widely used expectorant that has recently been reported to be associated with nephrolithiasis. They are found in patients consuming guaifenesin in excessive amount.[24]

4) Xanthine calculi. These stones occur due to a hereditary disorder called xanthinuria. The deficiency in xanthine oxidoreductase enzyme results in decreased levels of serum and urinary uric acid and high concentration of urinary xanthine that leads to formation of xanthine stone.[25] Patients who receive allopurinol treatment, also develop xanthine oxidoreductase deficiency, eventually causing iatrogenic xanthiuria that results in xanthine crystal formation.[25]

Summary table of drugs causing kidney stone disease:

Drug Induced Urolithiasis	Drug-Induced Nephrolithiasis
Indinavir	Ephedrine Guaifenesin
Ritonavir	Indinavir Xanthine

Size of urinary tract stones:

Associated Symptoms of Urolithiasis:

1) Pain:

While tiny urinary tract stone(s) may not cause any symptoms[1,2], larger calculi may cause sharp pain in the side and back, below the ribs, radiating to the lower abdomen and groin[1]

Renal colic: Stones obstructing the ureter or renal pelvis or any of kidney's drainage tubes may cause back pain or renal colic characterized by an excruciating intermittent pain, usually in the area between the ribs and hip on one side, radiating across the abdomen and often extends to the genital area. The pain is likely to come in waves, gradually increasing to a peak intensity, then fading, over about 20 to 60 minutes.[2]

2) Urine:

The colour may be pink, red or brown, may look cloudy or foul-smelling and the patient feels persistent need to void urine more often than usual but in small amounts.[1]

3) Other signs & symptoms:

Other symptoms include nausea vomiting, restlessness, sweating, passing out stone/piece of stone with the urine. Fever and chills also can present if there is an infection.[1]

Diagnosis of Urinary tract Stone:

Physicians usually suspect stones in people with renal colic, tenderness over the back/pain or in genital area without any obvious cause. Presence of blood in urine support the diagnosis. Sometimes symptoms and physical examination remain so distinctive that additional tests are often not needed, especially for the patients with a history of urinary tract stones.[2]

Imaging techniques used to diagnose urolithiasis:

1) Non-contrast computed tomography: Non-contrast CT or CT-KUB are most often used in patients with nephrolithiasis. CT creates a 3D image of the stone and the surrounding tissues, which can be reconstructed into multiple viewing planes. The sensitivity of CT for detecting kidney stones is the highest among all the imaging techniques (~95%). Limitations of CT: radiation exposure, double cost compared to USG.[26]

2) Ultrasonography: Ultrasonography is a low-cost imaging modality that does not depend on ionizing radiation, thus sparing the patients from the risk of radiation exposure. Although ultrasonography is less

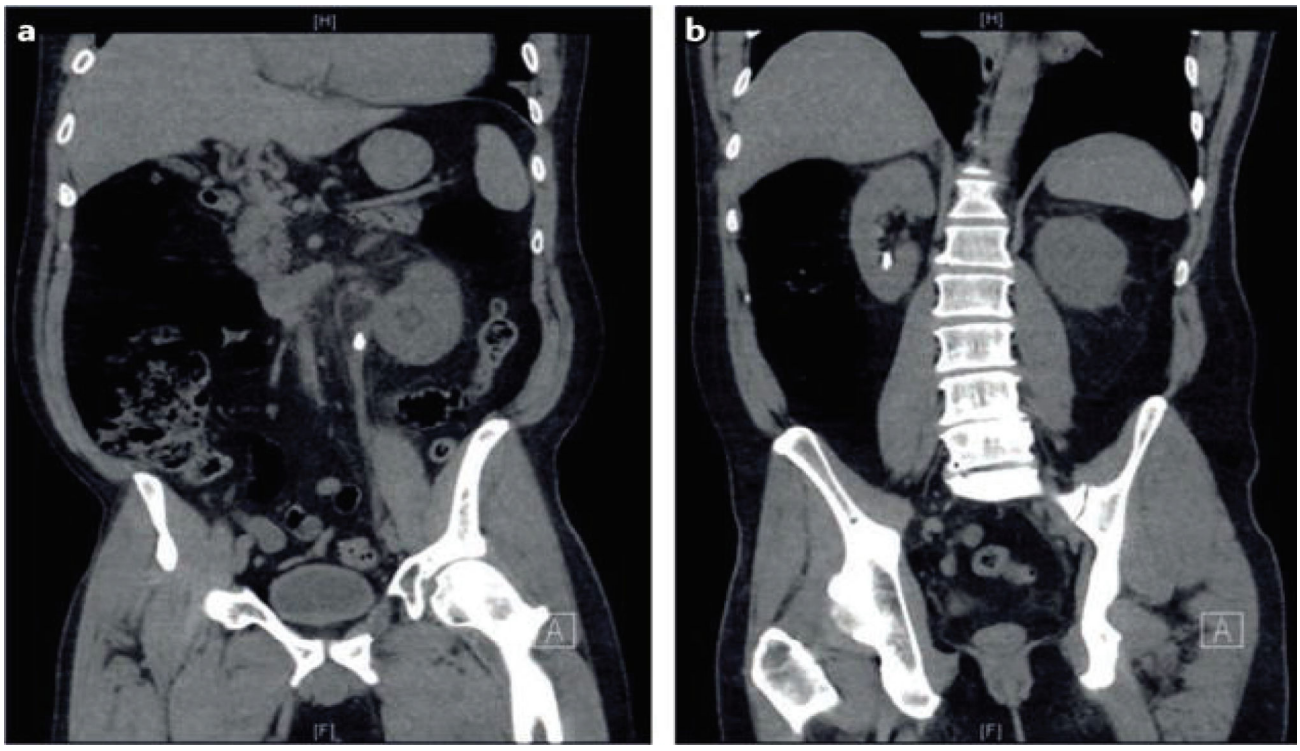

Figure: A coronal demonstration of bilateral 8 mm nephrolithiasis on non-contrast CT[26]

sensitive and specific than CT imaging for detecting and sizing of stones, it has good diagnostic ability, and can effectively detect hydronephrosis. USG is recommended as the first-line imaging modality for pregnant and paediatric patients (<14 years old). Modern ultrasonography has a sensitivity of about 80%.[26]

3) KUB radiography: KUB radiography allows relatively low ionizing radiation exposure to patients compared with CT (0.15 mSv) and it is cost effective. Nevertheless, as radiography views stones only at one angle, accuracy is decreased that causes reduced sensitivity and specificity and, therefore, limiting its usefulness. Many stone types can be visualized using KUB radiography; although cystine and struvite stones often are poorly visible on KUB radiography, and uric acid and matrix stones are not visible at all.[26]

4) MRI: The sensitivity of MRI (82%) is higher than that of USG and KUB radiography but less than that of CT.[26]

5) Excretory urography: (previously known as intravenous urography or intravenous pyelography) It is a series of x-rays taken after a radiopaque contrast agent is injected intravenously. This test can detect stones and accurately determine the degree to of blockage of the urinary tract caused by the stone. But it is time-consuming and involves the risks of exposure to the contrast agent.[2]

Complications of Urolithiasis:[27]

1) Acute renal failure secondary to obstruction.
2) Anuria.
3) Urinary tract infection with renal obstruction.
4) Sepsis.

Hydronephrosis:

It is a clinical condition where the kidney becomes distended due to obstruction in urine outflow. Urine flows back behind the obstruction and remains trapped inside renal pelvis, eventually causing a distended kidney.[28]

Etiology of Hydronephrosis:

- In children: Structural abnormalities - congenital anomalies such as posterior urethral valves and other constrictions that narrow or block the ureter or urethra
- In young adults: Large stones in a kidney or in ureter or elsewhere in the urinary tract.
- In older adults: Benign prostatic hyperplasia (BPH) or prostate cancer, tumors, and stones.

As BPH is so common in older males, obstruction is more common among men. Another common cause of obstruction might be stricture (narrowing caused by scar tissue) of the ureter or urethra that can develop after radiation therapy, surgery, or any procedure done on the urinary tract.[28]

A urinary tract infection may result when micro-organisms, especially bacteria become trapped in urine around a blockage by any/few stone(s), for a longer period of time when urine backs up in the tubes inside the kidney, causes hydronephrosis.[29]

Management of Urolithiasis:

Conservative management: Small stones that are not causing any symptom, blockage or infection of urinary tract are likely to pass with urine. Larger stones (over 5 mm) and those that are closer to the kidney are less likely to pass on their own. Several medications (tamsulosin or calcium channel blockers) may increase the likelihood of spontaneous stone passage.[2]

History of urinary tract stone removal: In 1561, Pierre Franco performed the first suprapubic lithotomy. In 1874, a lithotrite was developed by Bigelow, which was which was introduced into the bladder under anaesthesia (called as ***"litholopaxy"***). Young was first reported to use ureteroscopy in 1929. With the introduction of intracorporeal lithotripsy techniques, ureteroscopy became the treatment of choice for ureteric stones. In 1976, Fernstrom and Johannson initiated percutaneous access to remove a renal stone. However, with the introduction of the first extracorporeal shock wave machine in 1980 stone management was changed significantly.[30]

Nowadays, the following methods[31] are used for urinary stone removal:

1) Shock wave lithotripsy can be used to break up a stone in the renal pelvis or uppermost part of the ureter that is ½ inch (1centimeter) or less in diameter.

2) A **ureteroscope** (a kind of endoscope) can be inserted into the urethra, through the bladder and up the ureter to remove small stones in the lower part of the ureter.

3) Percutaneous nephrolithotomy is used to remove some larger kidney stones.

Recurrence of urolithiasis:

On average, around 30% to 50% of patients, show a probability of recurrence or another stone attack within 3 to 5 years.[31]

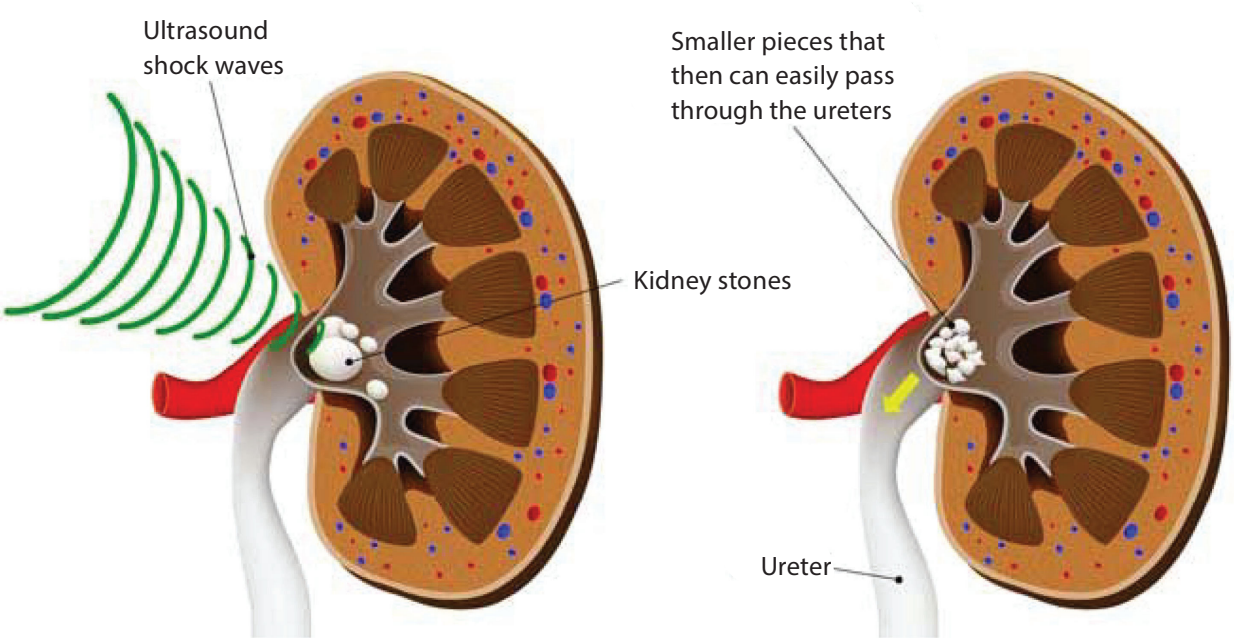

Figure: Shockwave lithotripsy[31]

Prevention of Urolithiasis:[32]

1) Drinking plenty of water.
2) Avoiding excessive intake of salt.
3) Increasing consumption various types of nuts.
4) Limiting the intake of animal protein.
5) Eating citrus fruits.

Kampo Medicine in Urinary Stone Disease

Kampo medicine originated in China had been used for the cure and the prevention of urinary calculi for years, but the effect and the mechanism of this use of kampo medicine are unclear.[16]

Urolithiasis in pregnancy:

Urolithiasis in pregnancy is an important health issue. It is one of the most common causes of non-obstetrical abdominal pain and hospital admission during pregnancy.[33]

1 in 3300 pregnancies show symptomatic urolithiasis that complicates pregnancy.[34]

Urolithiasis during pregnancy requires multi-disciplinary approach concerning both department of urology and department of obstetrics and gynaecology.[35]

The first choice of treatment is conservative management and trial of passage with hydration and analgesia. NSAIDs are generally avoided during pregnancy and narcotics are usually administered. This pathway requires a solitary stone <1cm, no infection, adequate oral pain control ability to tolerate food and fluid. The success rate is 70%–80% and 50% of those without spontaneous passage during pregnancy are likely to pass their stones after delivery.[36-42]

Childhood Urolithiasis - A Paradigms Shift:

Despite being recognized in children for centuries, the clinical features, evaluation and management of urolithiasis are still evolving. Approximately 7% of all stones occur in children younger than 16 years.

In the past, urolithiasis used to be characterized by bladder stone in children in developing countries; with the incidence of upper tract calculi mostly occurring in industrialized areas, being much lower in children than adults.Nowadays, the incidence of upper tract calculi in children is experiencing a rise globally**,** and the patterns are also changing**.** Smaller endoscopic instruments and the refinement of extracorporeal shock wave lithotripsy (**ESWL**) technology have made treatment of **pediatric stone disease** easier.[4]

However, pediatric urolithiasis is being studied in Ad-Din Women's Medical College, Dhaka, Bangladesh by Prof. ARML Kabir.

Salient features:

- Although all the urinary tract stones start to originate inside the kidneys, they are named as per their location, thus urolithiasis and nephrolithiasis remain two analogous terms for urinary calculi.
- Multiple factors facilitate the stone forming process.
- CT scan is the choice of diagnosis option.
- Conservative management is the major approach to treat smaller stones, but larger stones require surgical management.
- There is a chance of recurrence in 30-50% patients.

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