Chapter II

Brief Review on Urinary Calculi

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2.1 Introduction

The excruciating pain
that I am going thru
because of you,
oh my dear Kidney Stone!
Kept you safe
inside of me
for these whole long
four years, just like
one of my own
oh my dear Kidney Stone!
Feeling like a sharp knife
cutting me open and carving
it inside
your name all inside me
oh my dear Kidney Stone!
Ah ! ! ! How ungrateful of you
to give me all this horrible pain
I should have dumped you
long time ago
If I would have known
all this then
oh my dear Kidney Stone!
Some say it feels like giving birth
and some say losing virginity
but I don't really give a
Damn!
I would like to lose you
lose you right now
oh you painfully not so dear
Kidney Stone...

Khalid Hameed
The formation of urinary calculi, usually known as, renal stone or kidney stone is a serious, debilitating problem in all societies throughout the world. In medical language, the condition of having kidney stones is termed as nephrolithiasis, urolithiasis or ureterolithiasis, where the root word ‘lith’ means a stone. More specifically, Nephrolithiasis, urolithiasis and ureterolithiasis are the medical terms used to describe the different locations of the stones occurring in the Kidney, urinary tract and ureter, respectively. The term urinary calculi are synonymous with uroliths, kidney stones, renal calculi or crystals. To keep things simple, however, the term “Urinary calculi” is used throughout the thesis.

In India, the earliest Sanskrit documents like the Vedas, the Purāṇas and the Samhitās also described urinary calculi and their remedies [1]. The Charak Samhitā contains sufficient but scattered matter pertaining to anatomy, physiology and pathology of urinary calculi (Mutravaha aşhmari) as well as the diagnosis and treatment of its disorders. The Sushruta Samhitā is the pioneer text in surgery and it contains more descriptive explanations as far as the anatomy and physiology of Mutravaha aşhmari is concerned. The third chapter Aşhmari Nidāna of Sushruta Samhitā provides a scientific description of types, characteristics, etiology and symptoms of urinary calculi, where as the seventh chapter Aşhmari Chikitsita Sthanam explains the treatment of urinary calculi [2,3].

This chapter describes a brief review on urinary calculi, which covers various points related to urinary calculi like function of urinary system, types of kidney stones and epidemiology of urinary calculi all over the world. Various crystalline components of urinary calculi, pathophysiology as well as etiology
of urinary calculi including risk factors leading to the formation of urinary calculi and symptoms are briefly explained. At last the present techniques for diagnosis and management (line of treatment) of urinary calculi are discussed in brief.

### 2.2 Human Urinary System and Kidney Function

![Human Urinary System](image)

**Figure : 2.1 Human Urinary System** [4]

The urinary tract, or system, consists of two kidneys, two ureters, bladder and urethra. Figure 2.1 shows the human urinary system [4]. The system keeps or eliminates substances depending on the body's current needs. Each kidney continuously produces urine. Ureters are the tubes connecting each kidney to the bladder. A bladder is a triangle-shaped expandable, hollow muscular bag type organ in the lower abdomen that serves as a reservoir of urine. Normally the bladder can hold 250 - 450 cc of
urine. The bladder's elastic walls expand to store the incoming urine until it is eliminated from the body via another fibro-muscular tube called the urethra. Urethra varies from male to female. The male urethra is more complicated than the female urethra. The male urethra is usually 18 – 20 cm long and functions as a conduit for urine as well as seminal fluid. The male urethra is divided into three sections: prostatic urethra, membranous urethra, and spongy (penile) urethra. The upper portion, the prostatic urethra, passes through the prostate gland. Whereas female urethra is only 4 cm long. It begins at the internal urethral orifice at the neck of the bladder, roughly 5 cm behind the middle of the pubic symphysis. It runs downwards and forwards embedded in the anterior wall of vagina, traverses urogenital diaphragm and end at the external urethral orifice in the vestibule of vigin.

![Cross Section of Human Kidney](Source: Encyclopedia Britannica)

The kidneys are the main incredibly well-functioning organs of the urinary system. Figure 2.2 shows the cross sectional art of right Kidney [5].
The kidneys are two bean-shaped, fist-sized, reddish-brown organs on each side of spine located deep behind the abdomen below the ribs and toward the middle of the back. They are about 12.5 cm long and 7.5 cm wide. Grossly, the structure of the kidney consists of the cortex, medulla (inner and outer zones of outer medulla and papilla or inner medulla), pyramids, renal calyces and pelvis. Each kidney receives blood through a branch of the aorta, called the renal artery. Blood flows from the renal artery into progressively smaller arteries, the smallest being the arterioles. From the arterioles, blood flows into glomeruli, which are tufts of microscopic blood vessels called capillaries. Blood exits each glomerulus through an arteriole that connects to a small vein. The small veins join to form a single large renal vein, which carries blood away from each kidney.

![Figure: 2.3 Renal Malpighian Corpuscle and Nephron](source: Encyclopedia Britannica)

The process of urination begins in the kidneys. Figure 2.3 shows the renal malpighian corpuscle, which constitutes the beginning of the structural
and functional unit of the kidney i.e. nephron [6]. Nephrons are microscopic
functional filtration units that filter the blood and produce urine. Each kidney
contains about one million nephrons. Each nephron contains a filtering system
known as a glomerulus; and a tube through which filtered fluid travels. Each
glomerulus is a network of tiny blood vessels surrounded by a membrane
enclosed in a funnel-like bowl-shaped structure called Bowman's capsule. A
third part of the nephron is a collecting duct that drains urine from the tubule.
Each tubule has three interconnected parts: the proximal convoluted tubule,
the loop of Henle, and the distal convoluted tubule. The kidneys consist of an
outer part cortex and an inner part medulla. All glomeruli are located in the
cortex, while tubules are located in both the cortex and the medulla. The urine
drains from the collecting ducts of many thousands of nephrons into a cup like
structure calix. Each kidney has several calices, all of which drain into a single
central chamber renal pelvis. Urine drains from the renal pelvis of each kidney
into a ureter.

The primary function of the kidneys is to maintain the proper balance of
water and minerals including electrolytes in the body. The kidneys remove
extra water and dispose toxic substances from the blood by converting it to
urine. The kidneys play a role in controlling the acid-base balance in the body,
regulating electrolyte balance as well as helping to control blood pressure.
Another function of the kidneys is to produce hormones such as
erthropoietin, which regulates the production and release of red blood cells
from the bone marrow.

Body fluid is a pivotal element in digestion, circulation, elimination, and
regulation of body temperature. A critical function of the urinary system is the
maintenance of normal composition and volume of body fluid; this is accomplished by glomerular filtration, tubular reabsorption, and tubular secretion of soluble and filterable plasma components. By such means, urine contains water, electrolytes, minerals, hydrogen ions, end products of protein metabolism such as urea, uric acid, and creatinine.

2.3 Urinary Calculi

A urinary calculus, generally known as kidney stone, is a solid mineral like crystalline material that accumulates in the urinary tract when one or more calculogenic (crystal-forming) substances separate from the supersaturated urine. Urinary calculi (Plural of calculus) result from the growth of crystals into a larger lump of aggregates or stones [7]. Urinary calculi are compounds made up of salts, minerals, and other things found in urine and usually develop in the kidneys. However, they can form anywhere in the urinary tract. They grow slowly over several months or years. The composition of kidney stones may vary from person to person. Kidney stones vary greatly in size. Some are as small as a grain of sand or as large as a pearl or as big as golf balls. Sometimes it may fill the entire renal pelvis. They may be smooth, round, or jagged, spiky or asymmetrical. Most stones are yellow to reddish brown in colour. Passing of a kidney stone through a ureter or the urethra may be painless or may cause severe pain, depending on the size of the stone. When urinary calculi are quite tiny, they may pass unnoticed with the urine. Often calculi grow too large to pass easily through the urinary tract as well as some stones have rough or sharp edges, it can be quite painful when they pass through the urinary tract. In some cases, when kidney stones cannot pass on their own, a medical management is required. If untreated, it may
lead to substantial damage and in extreme case severe renal impairment or failure. Early detection of the occurrence of stone is beneficial in treatment.

2.4 Epidemiology

Urinary stone is one of the oldest and common afflictions of humans and remains a major public health burden. A large number of people are suffering from urinary stone problem all over the globe. Not only the humans but animals and birds also suffer from the urinary stone problem.

Generally, three terms, i.e., incidence, prevalence, and lifetime prevalence, are frequently used in the epidemiological studies of urolithiasis. The incidence of stone disease is defined as the number of new stone patients in a given population over a defined period of time (usually a year). The prevalence is defined as the number of stones present in a screened population at a particular point in time. Finally, the lifetime prevalence is defined as the presence of a stone at any point in a patient’s history.

Urolithiasis is a global problem spanning all geographic regions with an estimated annual incidence of 1%, prevalence of 3–5% and a lifetime risk of 15–25%. Once afflicted, urolithiasis tends to be recurrent in the majority of cases [8]. Recurrence rates after the first stone episode are 14%, 35%, and 52% at 1, 5, and 10 years, respectively. Approximately 50% of patients with previous urinary calculi have a recurrence within 10 years [9]. In a recent study the recurrence rates are estimated at about 10% per year, totaling 50% over a 5–10 years period and 75% over 20 years [10].

The incidence of urolithiasis varies in different countries. The risk of developing urinary calculi in adults appears to be higher in the western hemisphere than in the eastern hemisphere, although the highest risks of
20.1% have been reported in Saudi Arabia. It has been reported that the incidence rates of urolithiasis are 5–9% in Europe, 12% in Canada, 13–15% in the USA [11,12]. The incidence rate increases to 20–25% in the Middle East, because of increased risk of dehydration in hot climates [13]. According to the data of a nationwide survey on urolithiasis in Japan between 1965 through 1987, 5.4% of the population may be expected to develop a urinary calculus at least once in their life time [14].

The occurrence in some areas is so alarming that they are known as ‘Stone Belts’ [15]. The areas of high incidence of urinary calculi include British islands, Scandinavian countries, Central Europe, Northern Australia, Mediterranean countries. The Afro-Asian stone-forming belt stretches from Sudan, Egypt, Saudi Arabia, United Arab Emirates, Iran, Pakistan, India, Myanmar, Thailand, and Indonesia to the Philippines. In these areas of the world, the disease affects all age groups, from less than 1 year to more than 70 years old, with a male-to-female ratio of 2 : 1 [16].

Urolithiasis is a common disorder responsible to substantial human suffering and economic cost to society. Studies conducted over the last half century, suggest that the incidence has been steadily increasing [17,18]. Using data from the National Health and Nutrition Examination Surveys (NHANES) carried out by Centers for Disease Control and Prevention (CDC), USA, Stamatelou et al [18] demonstrated that the lifetime prevalence of a history of kidney stones among adults in the USA increased significantly by 37% between two periods, namely, 1976 to 1980 and 1988 to 1994. Recently, Brown [19] reported that the patients with urinary calculi account for nearly 1 million visits to emergency departments (EDs) in the United States annually.
Correspondingly, in one study the economic impact in the USA was estimated as US $ 2.1 billion (based on 2003) per year [20] and in another study as US $ 5.3 billion per year [21]. It has been found that in recent years there is an increase in the treatment and the money involved with urinary stone problems. In the last 10 years, the diagnosis of urolithiasis was increased approximately by a 50% [22].

In Germany there are approximately 7,50,000 cases of urolithiasis per year [23]. Recent reports suggest a continuing upward trend in stone rates in Germany. For example, between 1979 and 2000, the incidence increased nearly threefold (0.54–1.47%), with a resulting rise in prevalence from 4.0 to 4.7% among the population as a whole. Among German men aged 50–64 years, the prevalence was even higher at 9.7%, and over 40% of the stone formers were recurrent [17].

Studies in UK suggest that there has been a gradual increase in the annual incidence and a decrease in the age of onset of the urolithiasis perhaps due to the result of change in lifestyle and diet [24].

Based on epidemiological studies in Swedish stone patients, there was an expected recurrence rate of 70% after 10 years when those patients were considered who had formed at least 2 stones before the follow-up period [25].

As India comes under the stone belt region, urolithiasis affects about 2 million people every year and the incidence is comparatively low in southern India as compared to other parts of the country. In India, the "stones belt" occupies parts of Maharashtra, Gujarat, Rajasthan, Punjab, Haryana, Delhi and states of north-east [26]. Fewer occurrences of urinary calculi are found in southern India, which may be due to regular dietary intake of tamarind. A
recent study conducted by Ansari et al [27] at the All India Institute of Medical Sciences (AIIMS), New Delhi for upper urinary tract calculi; it was found that pure calcium oxalate is the most frequent stones. Prevalence of urolithiasis is high in many parts of India including Gujarat and Rajasthan [28-33]. The Saurashtra and Kutchchh region of Gujarat has higher prevalence of urinary stones. In India, 12% of the population is expected to have urinary stones, out of which 50% may end up with loss of kidneys or renal damage. Also, nearly 15% of the population of northern India suffers from kidney stones [34]. Singh et al [30] reported that the rate of incidence of urolithiasis, particularly staghorn calculi in Manipur is very high. Review of literature in urolithiasis in the recent past indicates that in India, there is an increased prevalence of the urolithiasis in north-western region [35]. Rao et al [36] reported a gradual increase of urolithiasis cases in Purnia division, situated in the northeastern part of Bihar during 1999-2001.

The epidemiologic studies have also shown a progressive increase in the incidence of pediatric urolithiasis over the last few decades, referred to as a "stone wave" [37]. VanDervoort et al [38] reported a fivefold increase in the prevalence of pediatric urolithiasis in North American children in the last decade. The incidence varies by region, but urolithiasis is most common in the southeastern region of the USA, where the states of Virginia, North Carolina, Georgia, Tennessee, and Kentucky are described collectively as the North American "stone belt" [39].

Recently, in the era of globalization, due to the use of melamine-tainted milk, milk powder as well as milk based food products such as cookies, candies and chocolates led to an emerging epidemic of nephrolithiasis and
acute kidney injury (AKI) among the people including children took place in East Asia, particularly in China, Taiwan, Hong Kong, and Macau [40]. Nearly 2,94,000 young children, most under 36 months of age, were diagnosed with urinary stones induced by melamine-tainted food in the mainland of China during the year 2008 [41].

Although nephrolithiasis is perceived as an acute illness, there has been growing evidence that nephrolithiasis is a systemic disorder that leads to end-stage renal disease [42]. The prevalence of this disease has been increasing among males and females of all ages, indicating a possible environmental cause in addition to genetic predisposition. Furthermore, the incidence of stone disease is increasing worldwide [43]. The lifetime risk of kidney stones is 6% for women and 12% for men [18]. For those with untreated stones, the risk at 5 years for forming another stone is 30% to 40%. Since all the epidemiological data show an increase in incidence and prevalence rates, the prevention and techniques for the medical management of urolithiasis requires further attention.

2.5 Crystalline Components of Urinary Calculi

Although the stone disease has been documented in ancient mankind [44] and indeed was avidly investigated by physicians and surgeons of advanced civilizations thousands of years ago, but much of the scientific analysis that rigorously investigated and accurately determined the components of urinary stone disease was carried out only within the past 200 years [45]. Urinary stone is usually a multiphase material; its compositions are complex and often found in a mixture of multiple mineral constituents. Knowledge of the composition of urinary stone is important because
urolithiasis is a recurrent disease in many people and preventive measures can be taken based on such information. There are several types of urinary calculi that differ in composition and pathogenesis. Major components of the urinary calculi are already listed in the literature [15, 45-47]. Majority of the calculi are composed of calcium salts, oxalates and phosphates. Table 2.1 shows the major components of the urinary calculi.

**Table 2.1: The Crystalline Components of Urinary Calculi**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Mineralogical Name</th>
<th>Formula</th>
</tr>
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<tbody>
<tr>
<td><strong>Oxalates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Oxalate Monohydrate (COM)</td>
<td>Whewellite</td>
<td>CaC$_2$O$_4$ . H$_2$O</td>
</tr>
<tr>
<td>Calcium Oxalate Dihydrate (COD)</td>
<td>Weddellite</td>
<td>CaC$_2$O$_4$ . 2H$_2$O</td>
</tr>
<tr>
<td>Calcium Oxalate Trihydrate (COT)</td>
<td></td>
<td>CaC$_2$O$_4$ . 3H$_2$O</td>
</tr>
<tr>
<td><strong>Phosphates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyapatite (HA)</td>
<td>Hydroxyapatite</td>
<td>Ca$_{10}$(PO$_4$)$_6$(OH)$_2$</td>
</tr>
<tr>
<td>Calcium Hydrogen Phosphate Dihydrate (CHPD)</td>
<td>Brushite</td>
<td>CaHPO$_4$ . 2H$_2$O</td>
</tr>
<tr>
<td>Unusual form of Calcium Phosphate</td>
<td>Whithlockite</td>
<td>Ca$_9$(Mg,Fe) (PO$_4$)$_6$(PO$_3$OH)</td>
</tr>
<tr>
<td>Tricalcium Phosphate</td>
<td></td>
<td>Ca$_3$(PO$_4$)$_2$</td>
</tr>
<tr>
<td>Ammonium Magnesium Phosphate Hexahydrate (AMPH)</td>
<td>Struvite</td>
<td>NH$_4$MgPO$_4$ . 6H$_2$O</td>
</tr>
<tr>
<td>Ammonium Magnesium Phosphate Monohydrate</td>
<td>Dittmarite</td>
<td>NH$_4$Mg PO$_4$ . H$_2$O</td>
</tr>
<tr>
<td>Magnesium Hydrogen Phosphate Trihydrate</td>
<td>Newberyite</td>
<td>MgHPO$_4$ . 3H$_2$O</td>
</tr>
<tr>
<td>Carbonate Apatite</td>
<td>Carbonate apatite</td>
<td>Ca$_{10}$(PO$_4$,CO$_3$,OH)$_6$(OH)$_2$</td>
</tr>
<tr>
<td>Octacalcium Phosphate</td>
<td>-</td>
<td>Ca$_8$H$_2$(PO$_4$)$_6$ . 5H$_2$O</td>
</tr>
<tr>
<td>Calcium Phosphate</td>
<td>Apatite</td>
<td>Ca$_9$(PO$_4$)$_3$(F,OH,Cl)</td>
</tr>
<tr>
<td><strong>Uric Acid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric Acid Anhydrous</td>
<td>Uricite</td>
<td>C$_5$H$_6$N$_4$O$_3$</td>
</tr>
<tr>
<td>Uric Acid Dihydrate</td>
<td>-</td>
<td>C$_5$H$_6$N$_4$O$_3$ . 2H$_2$O</td>
</tr>
<tr>
<td><strong>Urates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonium Acid Urate</td>
<td>-</td>
<td>C$_5$H$_3$N$_4$O$_3$NH$_4$</td>
</tr>
<tr>
<td>Sodium Acid Urate Monohydrate</td>
<td></td>
<td>C$_5$H$_3$N$_4$O$_3$Na . H$_2$O</td>
</tr>
<tr>
<td><strong>Cystine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystine</td>
<td></td>
<td>C$_3$H$_6$N$_6$S$_2$</td>
</tr>
<tr>
<td><strong>Purine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthine</td>
<td></td>
<td>C$_5$H$_6$N$_4$O$_2$</td>
</tr>
<tr>
<td>Melamine-associated urinary stones</td>
<td></td>
<td>C$_3$H$_6$N$_6$ + C$_5$H$_4$N$_4$O$_3$</td>
</tr>
</tbody>
</table>
The crystalline constituents of urinary calculi in the human are varied. Some of these occur geologically as a mineral, whereas others are found only in animal kingdom. To date over 200 components have been found in calculi; however, the most common constituents of kidney stones are as follows [45]:

**2.5.1 Whewellite \( \text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O} \)**

Calcium oxalate is the most common crystalline constituent of urinary stones. Usually, calcium oxalate occurs as three different phases: Calcium Oxalate Monohydrate (COM), Calcium Oxalate Dihydrate (COD) and Calcium Oxalate Trihydrate (COT). However, majority of them are of COM or COD.

Calcium oxalate monohydrate, also known as whewellite and synonymous with oxacalcite, is named after Professor William Whewell of Cambridge, England. Most calcium stones are formed when the calcium combines with oxalate. Occasionally, calcium may also combine with carbonate or phosphate. Calcium oxalate stones are the most common stone encountered by practicing emergency physicians [48]. All calcium stones are radio-opaque. Whewellite is one of the most common kidney stone minerals. It typically occurs as small, smooth, botryoidal to globular, yellow-green to brown, radially fibrous crystals and is traditionally hard to fragment.

**2.5.2 Weddellite \( \text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O} \)**

Calcium oxalate dihydrate (COD), also known as weddellite, is named after James Weddell. Like whewellite, weddellite is a calcium oxalate mineral. It differs from the whewellite in terms of amount of water included in its crystal structure, which gives very different crystal habit. Pure dihydrate stones are usually small and spherical consisting of a tan or yellow cluster of platelets. The platelets are sharp and are arranged in various orientations.
2.5.3 Calcium Oxalate Trihydrate $\text{CaC}_2\text{O}_4 \cdot 3\text{H}_2\text{O}$

Tomazic and Nancollas [49] reported that COT could be a precursor to COM and COD formation. There is supporting evidence that the COT is the first nucleated crystal phase of calcium oxalate. Subsequently, COT is converted to COD and then to COM [50].

2.5.4 Apatite

Hydroxyapatite, or hydroxylapatite, also known as apatite, is named from the Greek word apatō meaning “I am misleading”, in allusion to its similarity to other more valuable minerals such as the gems peridot and beryl. Apatite is a common mineral in nature. Chemically it is a complex calcium phosphate with varied, attached molecules of hydroxyl ($\text{OH}$), fluorine ($\text{F}$), and sometimes other elements. Apatite is the fundamental mineral component in bones and teeth, and when apatite has fluorine in its crystal structure, it is stronger. In kidney stones, the hydroxyl group is predominant, and carbonates ($\text{CO}_3$) substitutes for some of the phosphate, forming a mineral that is relatively poorly crystallized. Apatite often forms the nucleus on which other urinary minerals are deposited.

2.5.5 Brushite $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$

Calcium hydrogen phosphate dihydrate, also known as brushite, was named in 1864 by G. E. Moore, in honor of George Jarvis Brush. Brushite is a calcium phosphate compound that is very similar to the common mineral gypsum (calcium sulfate). Brushite is found as a common cave mineral in guano deposits and in phosphorites formed at low pH (acidic) by reaction of phosphate rich solutions with calcite and clay. It is a soft, silky mineral, usually honeybrown and showing a fine radial fibrous structure.
2.5.6 Whitlockite $\text{Ca}_3(\text{PO}_4)_2$

Tricalcium phosphate, or whitlockite, was named in 1940 for Herbert Percy Whitlock, who was a 20th century American mineralogist. Whitlockite is very rarely found in the urinary system and is usually found in prostate stones. It is a calcium phosphate with small amounts of magnesium, $\text{Ca}_9(\text{Mg,Fe})\text{H}(\text{PO}_4)_7$ or $\text{Ca}_9(\text{Mg,Fe})_6(\text{PO}_4)_6(\text{PO}_3\text{OH})$, and its occurrence may be stabilized by trace amounts of zinc, which perhaps accounts for its predilection for the prostate gland, which has a relatively high zinc content. The mineral is a resinous, brown material.

2.5.7 Struvite $(\text{NH}_4)\text{MgPO}_4.6(\text{H}_2\text{O})$

Ammonium Magnesium Phosphate Hexahydrate (AMPH), also known as struvite, is one of the fascinating inorganic phosphate minerals. It was first identified in the 18th century as a crystalline substance. The term “struvite” was introduced in 1845 by George Ludwig Ulex, a Swedish geologist [45]. It was named after geographer and geologist Heinrich Christian Gottfried von Struve of the Russian diplomatic service, consul at Hamburg, Germany.

Struvite is the main component of the infectious urinary stones and is associated with chronic urinary tract infection (UTI) with microorganisms that split urea into ammonium, which further combines with phosphate and magnesium. UTI does not resolve until stone is completely removed. Usually, the formations of struvite type calculi take place when the urine pH is typically greater than 7. Radiographs show that struvite stones are usually large, gnarled, and laminated ones. Struvite stones are among the most difficult and dangerous problems in stone disease because of the potential of life-threatening complications from infections.
Epidemiological studies from various countries continue to report a frequency of struvite stones of between 25% and 38% out of total observed cases with urinary calculi [51,52]. It was reported that struvite was present in 42.9% of stones in women in Sub-Saharan Africa, 13% in South America [51], 28.8% in Algeria [52]. Griffith [53] reported that struvite stones are relatively uncommon in the USA, making up to 15% - 20% of kidney stones. Durgawale et al [54] reported that uroliths obtained by surgical intervention at Krishna Institute of Medical Sciences and Research Centre, Karad, in Maharashtra, were of mixed heterogeneous type with struvite as predominant constituent having 71.2%. Pendse and Singh [55] reported that struvite was present in 78.2% stones out of 56 stones analyzed, which were collected from clinics of Udaipur in Rajasthan.

2.5.8 Dittmarite \( \text{NH}_4\text{Mg PO}_4 \cdot \text{H}_2\text{O} \)

It was named after William Dittmar (1833-1892), Professor of Chemistry, University of Glasgow, Glasgow, Scotland. Dittmarite is found rather infrequently in urinary calculi [56].

2.5.9 Newberyite \( \text{MgHPO}_4 \cdot 3\text{H}_2\text{O} \)

Magnesium hydrogen phosphate trihydrate, also known as Newberyite, is named in honour of James Cosmo Newbery (1843–1895), who was a 19th century Australian geologist and mineralogist. Newberyite is rare in kidney stones. It was first identified as a crystalline component of a kidney stone in 1956 [57]. It often occurs as tiny isolated globular crystals on the surfaces of apatite–struvite stones. This probably reflects an alteration of struvite to newberyite, or perhaps a change of conditions to more acidic solutions.
2.5.10 Uric acid stones

Usually, uric acid stones are found between 5 to 10% of all stones analyzed in a stone clinic. Uric acid is a product of metabolism. Generally, these stones are associated with urine pH less than 5.5. Uric acid stones are spherical with a smooth yellow-orange surface and nearly radiographically transparent unless mixed with calcium crystals or struvite. Approximately 25% of patients with uric acid stone have gout problem. There are three major factors for the development of uric acid stones, low urine volume, acidic urine pH, and hyperuricosuria.

2.5.11 Cystine Stones

Cystine stones account for only 1 to 3% of all kidney stones. They form in individuals with a rare inherited metabolic disorder that causes high levels of cystine in the urine. These stones can occur in childhood. Cystine is one of the essential amino acids, which are the building blocks of protein. Cystinuria is an uncommon genetic disorder that causes the kidney to excrete too much cystine type amino acid in the urine. The concentrated cystine leads to the formation of cystine kidney stones. Cystine is relatively insoluble, and appears in normal urine in small amounts that are insufficient to cause supersaturation, crystalluria, or stone formation.

2.5.12 Xanthine \( \text{C}_9\text{H}_4\text{N}_4\text{O}_2 \)

Chemically, xanthine is a purine. These stones are extremely uncommon and usually occur as a result of a rare genetic disorder. It can be caused by a deficiency of xanthine oxidase (enzyme necessary for converting xanthine to uric acid), which results in the production of xanthine and hypoxanthine rather than uric acid as an end product of purine metabolism.
Xanthine stones are radiolucent, but can be detected by using computed tomography. Inasmuch as xanthine stones are radiolucent they are frequently mistaken for the more common radiolucent uric acid stone. Usually, these stones tend to be small, round or oval in shape.

2.5.13 Matrix:

Matrix stone is a rare form of urinary calculi made of organic material muco-proteins. Usually they are radiolucent; however the radiologic aspect of these stones depends on the degree of mineral incrustations. The percentage of matrix, by weight, in urinary stones varies. In general, most solid urinary stones have a matrix content of about 3% by weight [59]. Matrix stones are non-crystalline and take on a variety of shapes and colors. The stones are composed of a variety of organic molecules including urinary macromolecules and membrane fragments.

2.5.14 Medication Related Stones

Unusual types of urinary calculi caused by ingestion of inappropriately large doses of medications are Ephedrine stones, Guaifenesin stones, Indinavir stones, Nelfinavir stones, Oxypurinol stones, Silicate stones, Sulfate stones, Topiminate-induced stones, Triamterene stones, Ammonium acid urate stones, Ciprofloxacin induced stones, etc [60].

Ephedrine stones: Ephedrine containing drugs have been used as bronchodilator for asthma, as a cough medicine, as a fat burner for weight loss, energy and sexual enhancement, as a stimulant and euphoria. But, excessive ephedrine intake can cause ephedrine nephrolithiasis and results in radiolucent ephedrine kidney stones. Usually, ephedrine is highly water soluble, however urine alkalinity decreases solubility.
Guaifenesin stones: Guaifenesin (glyceryl guaiacolate) is sold as pills or syrups and most often used as an expectorant, i.e., medication that helps bring up mucus and other material from respiratory tract including the lungs, bronchi, and trachea. Moreover, it is also used for the treatment of asthma, gout, fibromyalgia, to facilitate conception and as analgesic drug. But, excessive guaifenesin intake can cause guaifenesin urolithiasis and results in radiolucent guaifenesin kidney stones.

Indinavir (Crixivan) stones: Indinavir (Crixivan) is an antiretroviral (protease inhibitor) medication used in the treatment of HIV infections. It easily precipitates to form crystals. Due to the gelatinous nature of indinavir stones, they are not visible on plain radiographs. These calculi are difficult to detect by X-ray or CT scan. However, CT scan with contrast may demonstrate the presence of these stones. They are visible on an ultrasound. Indinavir crystals form at a pH of 7. Indinavir crystals are very distinctive, with a fan-shaped or starburst type of appearance. Pure indinavir stones are brown and have a pliable, puttylike consistency. Several other antiretroviral drugs such as ritonavir, nelfinavir, saquinavir, efavirenz and atazanavir have been reported to cause urinary calculi.

Nelfinavir Stone: Similar to indinavir stones, nelfinavir stones are radiolucent. However, in contrast to indinavir calculi, nelfinavir stones are visible on CT scan.

Oxypurinol Stones: The oxypurinol stone is seen in patients using high dose of allopurinol (600 mg/d). These stones are soft, yellow and radiolucent.

Silicate Stone: Silicate urinary calculi occur exclusively in patients taking large amounts of magnesium silicate antacids. They are extremely rare in
humans, but occurs in animals, when they are fed plants grown in sandy areas or water containing high levels of silica. In Japan, 46 adult patients with urinary silicate calculi have been reported in the literature [61].

**Sulfa Stones**: Sulfamethoxazole-trimethoprim is a commonly employed antibiotic. Sulfonamides, sulfadiazine medication commonly used to treat AIDS. Various sulfa compounds, such as sulfadiazine, acetylsulfasoxazole, acetylsulfamethoxazole, acetylsulfaguanadine and may precipitate in the urine and may lead to formation of sulfa stones. Usually, sulfa-induced calculi were found in the bladder and they are radiolucent on plain radiography.

**Triamterene Stones**: Triamterene is often used to treat edema as well as hypertension. Triamterene calculi are faintly radiopaque on plain radiography; however, they are detectable with CT scan. Triamterene is most commonly seen as a secondary component of calcium oxalate or uric acid stones, and has been described as a nidus for secondary stone formation. Triamterene calculi cannot be dissolved by pH manipulation and, rather, must be treated with conventional lithotripsy techniques.

**2.5.15 Rare types of Urinary Calculi**

There are certain rare types of urinary calculi which are summarized briefly as follows:

**Urostealith Calculi**: They are composed of fatty constituents and occasionally found in urinary concretions, but very rarely composing the entire calculus.

**Cholesterol Calculi**: They are usually yellow-green in color and are made mostly of hardened cholesterol.

In figure 2.4 photographs of different types of kidney stones are shown courtesy to L. C. Herring laboratory [62].
CHAPTER : II : Brief Review on Urinary Calculi

Growth and Characterization of Struvite and Related Crystals

<table>
<thead>
<tr>
<th>Calcium Oxalate Monohydrate</th>
<th>Calcium Oxalate Monohydrate</th>
<th>Calcium Oxalate Monohydrate</th>
<th>Calcium Oxalate Monohydrate with Apatite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Oxalate Dihydrate</td>
<td>Calcium Oxalate Dihydrate</td>
<td>Calcium Oxalate Dihydrate</td>
<td>Calcium Oxalate Monohydrate with superficial Dihydrate</td>
</tr>
<tr>
<td>Irregularly Laminated Oxalates &amp; Apatites</td>
<td>Calcium Oxalate Monohydrate irregularly laminated with Apatites</td>
<td>Calcium Oxalate Monohydrate deposited over Apatites</td>
<td>Carbonate Apatite</td>
</tr>
<tr>
<td>Brushite</td>
<td>Brushite</td>
<td>Brushite</td>
<td>Tricalcium Phosphate with Apatites</td>
</tr>
<tr>
<td>Struvite</td>
<td>Struvite</td>
<td>Uric Acid</td>
<td>Cystine</td>
</tr>
<tr>
<td>Xanthine</td>
<td>Calcium Carbonate</td>
<td>2,8-dihydroxyadenine</td>
<td>Cholesterol (Biliary)</td>
</tr>
</tbody>
</table>

Figure : 2.4 Photographs of Kidney Stones [62] [Source: L. C. Herring & Co. Laboratory]
2.6 General Pathophysiology of Urinary Calculi

The physical process of stone formation is a complex cascade of events. Kidney stones result from the growth of crystals into stones [7]. The process of stone formation depends on urinary volume; concentrations of calcium, phosphate, oxalate and sodium ions; concentrations of natural calculus inhibitors and urinary pH [63]. High ion levels, low urinary volume, low pH, and low citrate levels favor the formation of urinary calculi. The pathogenesis of urinary calculi formation is the end result of the following fundamental multi-step physicochemical processes:

Saturation $\rightarrow$ Supersaturation $\rightarrow$ Nucleation $\rightarrow$ Crystal aggregation $\rightarrow$
Crystal growth $\rightarrow$ Crystal retention $\rightarrow$ Stone formation

2.6.1 Supersaturation: The central event in stone formation is supersaturation. The term supersaturation refers to a solution that contains more of the dissolved material than could be dissolved by the solvent under normal circumstances. Supersaturation occurs when the concentration of substances forming urinary calculi increases in urine, or urine volume decreases, as well as the absence or reduction in urinary stone inhibitors occurs in urine. Supersaturation depends on urinary pH, ionic strength, solute concentration, and complexation. The level of supersaturation of a salt is expressed as the ratio between the actual ion-activity product ($A_P_{\text{salt}}$) and the solubility product ($S_P_{\text{salt}}$). The ion-activity of a salt is calculated from the free ion concentrations and the activity coefficients corresponding to the charge of the ions in the salt. The point at which saturation of a solution is reached, and crystallization begins is commonly known as thermodynamic solubility product ($K_{sp}$). Urine contains inhibitors of crystallization and can hold large
concentrations of solute above the $K_{sp}$, a metastable state. If the concentration of solute increases further and a point is reached where it cannot be held in solution, this concentration is known as $K_f$, which is the point of formation of product in urine [15,64]. Thus, supersaturation of the urine constitutes a driving force within the solution which can lead to crystallization and trigger a series of pathophysiologic events that include nucleation, crystal aggregation, growth, and attachment to epithelia. There are two stages of supersaturation. Once the solubility product exceeds in urine, a metastable process of supersaturation begins, which is followed by slow crystalline growth. This process is accelerated by preexisting crystals. If a critical limit of supersaturation is exceeded (formation product), large scale spontaneous precipitation of crystals occurs.

2.6.2 Nucleation: Urinary supersaturation alone cannot explain the formation of urinary stones. Nucleation is the formation of a solid crystal phase in a solution. It is an essential step in the formation of urinary calculi [65]. Nucleation involves the association of crystalloids in solution to form a submicroscopic particle. There are two types of nucleation; the homogeneous nucleation and the heterogeneous nucleation. The homogeneous nucleation results, when the process occurs spontaneously in a pure solution. Because impurities are always present in human urine, the homogeneous nucleation is unlikely to occur in vivo. Heterogeneous nucleation sites in urine can be epithelial cells, red blood cells, cell debris, urinary casts, other crystals and bacteria. The surfaces provided by the impurities can serve as a nidus in the nucleation process, leading to the heterogeneous nucleation. The heterogeneous nucleation will, generally, occur at a lower supersaturation
level than that required for the homogeneous nucleation [15]. The nucleation of crystalline components may occur in the lumens of renal tubules, in the basement membranes of tubule cells, or at both sites, perhaps depending on the type of stone.

2.6.3 Crystal Aggregation: The process in which crystal nuclei bind to each other to form larger particles is called aggregation. The initial nuclei can grow by further addition of desired salts. Aggregation of particles in solution is determined by a balance of forces, some with aggregating effects and some with disaggregating effects. A small inter-particle distance increases the attractive force and favours particle aggregation. Crystal aggregation plays an important role in stone formation.

2.6.4 Crystal Growth: Crystal growth is the next major step of the formation of urinary calculi. In this process atoms or molecules from solution are added to the solid phase of growing crystal in a geometrically precise arrangement. The driving force for crystallization is a reduction in the potential energy of the atoms or molecules when they form bonds to each other. The crystal growth process starts with the nucleation stage. Several atoms or molecules in a supersaturated liquid start forming clusters; the bulk free energy of the cluster is less than that of the liquid. The total free energy of the cluster is increased by the surface energy (surface tension), however, this is significant only when the cluster is small. Crystal growth is determined by the molecular size and shape, the physical properties of the material, the supersaturation levels, the pH of solution, and the defects present in the structure of crystal. The combination of crystal aggregation and crystal growth can explain the genesis of urinary calculi.
2.6.5 Crystal Retention: Another process that may lead to stone formation is crystal retention. None of the previously discussed elements, i.e., crystal precipitation, growth, and aggregation would result in urinary stone formation if the nucleated crystals were flushed out by urinary flow. Crystal retention is, therefore, a key factor. Crystal retention will result if the crystals grow large enough to be trapped in renal tubules.

2.6.6 Role of Promoters and Inhibitors

Urine is having several substances that change or modify the crystal formation [15]. These can further be divided into inhibitors, promoters and complexors. In general, the crystallization of stone-forming salts is due to an abnormal urinary composition that is either higher in crystallization promoters or lower in inhibitors or both [66].

Substances which prevent or reduce the crystallization are called inhibitors. Urinary inhibitors attach to the growth sites on crystals, retarding further growth and aggregation. Inhibitors exert their effects in multiple ways, including inhibition of primary and secondary nucleation and crystal growth and aggregation. Urinary inhibitors may be categorized into multivalent metallic cations, small organic or inorganic anions, or macromolecules.

Promoters promote the growth of crystals and facilitate the formation of urinary calculi. It may be possible that a substance may promote one stage of crystal formation such as growth and inhibits another stage such as aggregation.

Certain substances, which form soluble complexes with lattice ions of specific crystals, decrease the free ion activity of that ion and effectively decrease the state of saturation for that ion system. These substances are
known as complexers. Citrate is the potent complexor of calcium in urine and reduces ionic calcium concentration. Table 2.2 shows the promoters, inhibitors and complexors [15, 64, 66-71].

**Table : 2.2 : Urinary Stone Promoters and Inhibitors**

<table>
<thead>
<tr>
<th>Role</th>
<th>Substances in the urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoters</td>
<td>Calcium, Sodium, Oxalate, Uric Acid, Urate, Cystine</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Magnesium, Potassium, Pyrophosphate, Citrate, Glycosaminoglycans (GAGs)</td>
</tr>
<tr>
<td></td>
<td>kidney proteins such as Nephrocalcin (NC), Osteopontin (OPN), Tamm-Horsfall protein (THP), Muco-protein, Uropontin, Crystal matrix protein, Renal lithostathine, Urinary prothrombin fragment 1, Bikunin (Inter-alpha inhibitor), Calgranulin</td>
</tr>
<tr>
<td>Complexor</td>
<td>Citrate is the complexor for calcium ions.</td>
</tr>
</tbody>
</table>

Supersaturation takes place with low urine volume and abnormally high concentration of stone promoters as well as low concentration of stone inhibitors. When the balance of components in the urine is off, or a person is dehydrated, deposition is likely to occur on the walls of the kidneys, the ureter, or the bladder, forming crystals. In most cases, these crystals are removed from the body by the flow of urine, but they sometimes stick to the lining of the kidney or settle in places where the urine flow fails to carry them away. These crystals may aggregate and grow into a stone, ranging in size from a grain of sand to a golf ball. Most of the stones start growing in the kidneys. Some may travel to other parts of the urinary system, such as the ureter or bladder, and grow there. Mineralization in all biological systems has a common theme, in which the crystals and matrix are intertwined. Urinary stones are no
exception; they are polycrystalline aggregates composed of varying amounts of crystallite and organic matrix.

2.7 Etiology of Urinary Calculi

Etiology is the study of causes of disease. The development of stones in the urinary tract is a complex, poorly understood, multifactorial process. The formation of urinary calculi is a final manifestation of a broad range of etiologies and pathogenesis. A number of chemical and physical factors are known to play their roles. Kidney stones develop as a result of a complicated interaction of biologic events that are most likely triggered by genetic susceptibility coupled with dietary factors. Various etiologic factors play important role in the formation of urinary calculi. The primary known causes for the formation of urinary calculi are as follows:

2.7.1 Low Urine Volume

Low fluid intake greatly increases the risk of developing virtually all types of stones [72-74]. Urolithiasis is related to decreased urine volume as well as increased excretion of stone-forming components such as calcium, oxalate, urate, cystine, xanthine, and phosphate. Dehydration may also lead to formation of urinary calculi. When there is too little water in the body, the kidneys conserve water by forming less urine, and as a result the urine they produce is highly concentrated. People who live in hot climates may be susceptible to kidney stones if fluid is lost through perspiration [75].

2.7.2 Changes in the Urinary pH

Urinary pH is a major determinant for kidney stone formation. Changes in the balance of urinary pH can affect stone precipitation. Kamel et al [76] have suggested that urine pH approximately 6.0 reduces the risk of kidney
stone formation. However, the risk of uric acid and calcium stone formation increases progressively at urinary pH<5.5 and >6.5, respectively. Generally, some crystals are found exclusively in acidic urine, while the others are found exclusively in alkaline urine. Uric acid, calcium oxalates and cystine stones thrive in acidic urine, whereas calcium phosphate, calcium carbonates and struvite stones thrive in alkaline urine.

An elevated net acid excretion may occur due to increased endogenous acid production or because of dietary influences such as low dietary alkali or the increased consumption of acid-rich foods. Intake of high animal protein is known to reduce urinary pH and may lead to the formation of uric acid stones [77]. This happens due to the generation of protons during the oxidation of sulfur in animal proteins to sulfate [78].

2.7.3 Deficiency of Stone Inhibitors

The urinary constituents such as citrate, magnesium, zinc, glycosaminoglycans, pyrophosphate, various glycol-proteins and enzymes as listed in table 2.2 act as urinary inhibitors. At the physicochemical level, the urinary supersaturation capacity can be increased and crystal formation, growth, and aggregation can be delayed or prevented by micro and macromolecular urinary constituents. Inhibitors act by adsorption on the crystal surface, interfering with the formation of the crystal lattice and retarding the attachment of new ions, thus inhibiting nucleation, and most importantly, growth and aggregation into larger crystals. These compounds may protect against stone formation in various ways like allowing salt in the urine to be at higher-than-normal concentrations without forming crystals, preventing crystal formation, coating the crystals and preventing them for
adhering to the tube surface. Deficiencies in these protective substances therefore cause urinary calculi.

Nephrocalcin (NC), an acidic glycoprotein excreted in human urine, greatly reduce consumption of calcium and oxalate from metastably supersaturated solutions seeded with calcium oxalate crystals, a phenomenon usually referred to as inhibition of crystal growth. Urine and NC suppress self-nucleation \textit{in vitro} by adsorbing to the surface of COM crystals [79,80].

Tamm-Horsfall glycoprotein (THP) inhibits self-aggregation of COM crystals and may therefore be part of the natural defenses against deposition of COM in the kidney [81].

Glycosaminoglycans (GAGs) are well known macromolecular inhibitors found in urine. This growth inhibitor of COM is expected to affect at certain growth sites of crystal surface. The GAGs binds to crystal surfaces in a regular manner than at random, depending on the species. The binding sites are calcium sites on the faces matching negatively charged side groups on the GAG chains. The extensive study has been carried out to investigate the role of GAG in inhibition of COM by using Atomic Force Microscopy (AFM) [82,83].

Osteopontin (OPN), an aspartic acid-rich urinary protein, and citrate, a much smaller molecule, are potent inhibitors of COM crystallization at levels present in normal urine. Recently, extensive studies by James De Yoreo et al [84] on the combination of \textit{in situ} atomic force microscopy (AFM) analyses of the effects of citrate and OPN with molecular modeling have defined both the physical and stereochemical factors responsible for COM inhibition by citrate and OPN.
Low Urine Levels of Citrate (Hypocitraturia): Citrate (Citrate is the dissociated anion of citric acid) inhibits the growth of urinary calculi [85]. It is the primary agent for removal of excess calcium. Generally, citrate is excreted in normal urine at a mean of about 3.3 mmol/day (640 mg/day) in healthy individuals [86]. Hypocitraturia is defined as citrate excretion of less than 1.67 mmol/day (320 mg/day). Low level of citrate in the urine is a significant risk factor for calcium stones and also uric acid stones. Sometimes the Renal Tubular Acidosis (RTA) results in abnormalities in the acid and alkaline balance in the fluids of body, which causes a reduction of citrate in the urine. To make matters worse, the disorder also causes bone resorption and increases calcium levels in the blood.

Studies on the effects of urinary components, e.g., heparin (a highly-sulfated glycosaminoglycan) [83], phosphocitrate [87,88], nephrocalcin [89], and various surfactants [90] on the growth of calcium oxalate, struvite and hydroxyapatite are widely reported. These studies show a range of effects including inhibition of crystal formation, hydromorph selectivity, habit modification and promotion of the formation of metastable phases.

2.7.4 Use of Certain Medications

Urinary calculi may be induced by a number of medications used to treat a variety of conditions as discussed earlier in the section 2.5.14 of this chapter. These medications may lead to metabolic abnormalities that facilitate the formation of stones. Drugs that induce metabolic calculi include loop diuretics; carbonic anhydrase inhibitors; and laxatives, when abused. The formation of various types of urinary calculi due to overdose of certain medications for long periods have been reported in the literature [91-95].
Medication-induced calculi can be composed of the drug or one of its metabolites, and their formation may be promoted by the urinary supersaturation of these substances. Alternatively, the drug may induce physiologic changes that facilitate the formation of metabolic stones. The incidence of drug-induced urolithiasis is 0.44% [93].

Recently, a new cause of drug-induced acute kidney injury, namely, acute phosphate nephropathy, has been reported by Markowitz and Perazella [94] following the use of oral sodium phosphate bowel purgatives, which has lead to calcium phosphate type urinary calculi.

### 2.7.5 Excess Calcium in the Urine (Hypercalciuria)

The excessive calcium in the urine is known as hypercalciuria. Hypercalciuria is the most common etiology of urolithiasis in children as well as in adults [27,96]. It is responsible for about 70% of calcium-combining stones. A number of conditions may produce hypercalciuria. The development of hypercalciuria involves interactions between the gastrointestinal tract, bone and kidney, and a complex interplay of hormones, such as parathyroid hormone (PTH), calcitonin, and vitamin D. In a recent study, hypercalciuria is the most common risk factor, rounding about 40%, for the development of urolithiasis in children [97].

The conditions which can contribute to hypercalciuria are as follows:

**Overly Efficient Intestinal Absorption of Calcium** : In more than half of the cases, the source of excess calcium overload in urine is from the intestine, which may be due to a combination of genetic factors.

**Renal Calcium Leak** : This is a condition in which the filtering processes in the kidney fail, causing an increase of calcium in the urine.
**Increased Intake of Dietary Calcium** : Consumption of animal protein from meat, dairy, poultry, or fish increases urinary calcium. An increased level of urinary calcium also increases the risk of stone formation [98-100].

**Excessive Chloride** : Chloride has a negative charge and calcium has a positive one, so they are often used by the body to balance each other. The presence of excess chloride may lead to excess calcium. Many times it is found that a gene known as CLCN5 (chloride channel 5), which regulates chloride in the urine, is defective in the patients with calcium stones.

**Excessive Sodium** : Calcium absorption in the kidney tubules follows the absorption of sodium and water. High urinary levels of sodium then results in increased levels of calcium. Defects in the kidney tubules transport system can cause imbalances in sodium and phosphate that result in elevated calcium level in the urine. A high salt diet can also produce this effect.

**Disorder** : Certain cancers and sarcoidosis (a chronic disorder marked by small lumps on organs) can cause excess calcium.

**Medications** : Many drugs, including thyroid hormones and loop diuretics (drugs that increase urination), can increase calcium concentration in urine. Stones are an uncommon side effect of these medications.

**Idiopathic Hypercalciuria** : Idiopathic hypercalciuria (IH) is the most common metabolic abnormality in patients with calcium kidney stones. It is characterized by normocalcemia, absence of diseases that cause increased urine calcium, and calcium excretion that is greater than 250 mg/day in women and 300 mg/day in men [101]. The IH occurs with normal serum calcium and in the absence of any systemic diseases [102].

Figure 2.5 shows the classification of hypercalciuria.
Absorptive Hypercalciuria: Absorptive hypercalciuria (AH) is a disorder involving the excessive absorption of calcium by the intestines which increases the body's calcium levels and inhibits the functioning of the parathyroid gland. Normal calcium intake averages approximately 900–1000 mg/day. Approximately one-third of this is absorbed by the small bowel and out of that approximately 150–200 mg is obligatorily excreted in the urine [103]. The AH can be subdivided into three parts.

- Type I absorptive hypercalciuria is dietary independent. Patients have elevated urinary calcium levels with a high or low calcium diet.
- Type II absorptive hypercalciuria is dietary dependent and patients will have elevated urinary calcium levels only while consuming a high calcium diet.
- Type III absorptive hypercalciuria is secondary to a phosphate renal leak. The decreased phosphate results in a secondarily increased parathyroid hormone level and an increase in vitamin D production. The increased vitamin D results in increased phosphate, which further
increases calcium absorption, thus it is named as absorptive hypercalciuria.

**Resorptive Hypercalciuria**: Resorptive hypercalciuria is the result of a rare metabolic disorder, which causes the body to produce too much parathyroid hormone (hyperparathyroidism), causing bone tissue to dissolve. The dissolved tissue creates excessive calcium in the blood that accumulates in the kidneys and produces calcium stones [104].

**2.7.6 Excess Oxalate in the Urine (Hyperoxaluria)**

The excessive oxalate or oxalic acid in the urine, known as hyperoxaluria, is responsible for about 30% of calcium stones and is a more common cause of stones than excessive calcium in the urine [105]. Oxalic acid combines with calcium to form calcium oxalate which is the most common stone-forming compound. The hyperoxaluria is encountered in 8–50% of kidney stone formers [106].

The conditions which can contribute to hyperoxaluria are as follows:

**Primary hyperoxaluria (type I or type II)**: A rare cause of hyperoxaluria is the inherited condition known as primary hyperoxaluria [107]. Among disorders causing hyperoxaluria, the primary hyperoxaluria is the most severe, ultimately leading to the end-stage renal failure and if untreated, death in most of the patients. It is a hereditary metabolic disorder of amino acid metabolism that leads to increased production and excretion of oxalate (> 40 mg / day) even on oxalate-restricted diets. It is characterized by recurrent nephrolithiasis leading to renal failure [108]. In this condition, the hepatic enzyme that converts glyoxalate to glycine is deficient. As a result, there is increased production of oxalate from glyoxalate. This is an inherited disorder.
associated with kidney stones. These conditions are typically present with multiple stones in childhood and may cause renal failure, although presentation in adulthood is also possible [109].

**Deficiencies of Pyridoxine (Vitamin B6)**: Severe vitamin B6 deficiencies can result in overproduction of oxalic acid. Vitamin B6 deficiency leads to an increase in urinary calculi as a result of elevated urinary oxalate [110].

**Short Bowel Syndrome**: This disorder is the inability of the intestines to absorb fat and nutrients. In such cases, calcium may bind to unabsorbed fat instead of to oxalates. This leaves excess oxalate, which is absorbed by the intestine and excreted into the kidney.

**Dietary Oxalates**: Whether eating foods rich in oxalates or taking too much vitamin C plays any major role in hyperoxaluria is unproven. Many foods contain oxalate; however, only a few—spinach, rhubarb, beet greens, nuts, chocolate, tea, bran, almonds, peanuts, strawberries, tomatoes, beans, beets and radishes—appear to significantly increase urinary oxalate levels [111].

**Hormones**: Androgens (male hormones) are associated with a higher risk for calcium oxalate formation, while estrogens (female hormones) decreased it.

**2.7.7 Excessive Calcium in the Bloodstream (Hypercalcemia)**

Hypercalcemia is an abnormally high level of calcium in the blood, usually more than 10.5 mg / dL of blood, which also plays an important role in the formation of urinary calculi [112]. Hypercalcemia generally occurs when bones break down and release too much calcium into the bloodstream. This is a process called resorption, which can occur because of following reasons:

**Hyperparathyroidism**: Overactive parathyroid glands are the causes of about 5% of calcium stones. And people with this disorder have at least a
20% chance of kidney stones. Women are more likely to have this disorder than men are.

**Renal Tubular Acidosis**: Renal Tubular Acidosis (RTA) is a disease that occurs when the kidneys fail to excrete acids into the urine, which causes a patient’s blood to remain too acidic. It not only increases calcium in the bloodstream, but it also reduces citrate levels.

**2.7.8 Excessive Amounts of Uric Acid (Hyperuricuria)**

Uric acid \([C_5H_4N_4O_3 - \{7,9\ \text{dihydro-1H-purine-2,6,8(3H)-trione}\}]\) is a weak organic acid and major metabolite of purine nucleotides. Excessive amounts of uric acid, i.e., the hyperuricuria may also play a role in the formation of urinary calculi. Uric acid stones most often form out of high concentrations of uric acid. The two major factors that promote uric acid precipitation are a high urine uric acid concentration and an acidic urine pH, which drives the following reaction toward the right, converting the relatively soluble urate salt into insoluble uric acid.

\[
H^+ + \text{Urate}^- \rightarrow \text{Uric acid}
\]

In some cases, urate (anion of uric acid or the salt formed from uric acid) creates a crystal nidus, around which calcium oxalate crystals form and grow. Such stones tend to be severe and recurrent. Hyperuricuria occurs after eating purine-rich foods or because of uric acid overproduction \([113]\). A uric acid stone is an end product of purine metabolism.

Generally, urinary uric acid solubility is limited to 96 mg / L in normal urine. In humans with the urinary uric acid excretion of 600 mg / day, generally, exceeding the limit of solubility, is susceptible to precipitation \([114]\). Moreover, the urine pH is another important factor in uric acid solubility. The
ionization constant of uric acid is 5.35 [114, 115]. Therefore, at the urine pH less than 5.35, the urinary environment becomes supersaturated with sparingly soluble, undisassociated uric acid that precipitates to form uric acid stones [116].

2.7.9 Defect in Renal Ammonia Secretion

In some patients very low urine pH is caused by a defect in renal ammonia secretion that results in less buffering of secreted hydrogen ion and lower urine pH. Sakhaee et al [116] suggested that very low urine pH is in some way related to the insulin resistance. Uric acid is insoluble (15 mg / dL) in urine at pH 5.0, but becomes significantly more soluble (150 mg / dL) in urine at pH 7.0. Any combination of low urine pH, concentrated urine, and increased urinary uric acid excretion make one at risk for uric acid stone.

2.7.10 Inappropriate Renal Phosphate Transport

The control and balance of serum phosphate concentration, which is carried out by kidneys, is mandatory to avoid the occurrence of severe metabolic disorders. Inappropriate renal phosphate transport may alter serum phosphate concentration and bone mineralization and as a result increase the risk of urinary calculi [117]. Hypophosphatemia is also associated with bone demineralization and increased risk of occurrence of urinary calculi [118].

2.7.11 Urinary Tract Infections (UTI)

Urinary calculi may also result from long-standing urinary tract infections (UTI), which affects as many as 50% women at least once during their lifetime [119]. Generally, struvite and carbonate apatite type urinary calculi form as a result of UTI. Struvite calculi are formed due to UTI with various urease producing urolithic microorganisms like Proteus (most
commonly), *Pseudomonas*, *Klebsiella*, some *Escherichia coli*, and *Staphylococcus* species, that split urea and cause persistently alkaline urine [47,53,113,120].

2.7.12 Genetic Abnormalities

Some other urinary calculi, like cystine and xanthine, are usually due to genetic abnormalities. Cystine stone disease occurs in individuals who have an inherited genetic disorder that causes abnormal transport in the kidney and gastrointestinal system of the four amino acids, namely, cystine, ornithine, lysine, and arginine (COLA). Cystine type urinary calculi arise from excessive cystine excretion [121]. The cystine is the most insoluble in normally acidic urine and thus precipitates, crystallizes and forms stones [122,123]. The cystine is normally absorbed by the kidney. When there is defective absorption, large amounts of this amino acid are excreted in the urine and may crystallize and form large stones.

2.7.13 Vitamin Abnormalities

Vitamin abnormalities, e.g., vitamin A deficiencies, excessive vitamin D, are also responsible for the formation of urinary calculi.

2.7.14 Other Risk Factors of Urinary Calculi

A variety of intrinsic and extrinsic factors influence urolithiasis in individuals. Urolithiasis is a multifactorial disorder arising essentially from an abnormal combination of a number of urinary risk factors. Epidemiologic data, particularly, differences in occurrence rates among populations, strongly suggest that various environmental factors such as diet, climate, geographical factors and fluid consumption play a strong etiologic role [15, 124].
Inherited Factors: Inherited factors account for 45% of all cases of kidney stones. A person with a family history of kidney stones may be more likely to develop stones [125-126]. More than 70% of patients with adequate hereditary disease called renal tubular acidosis develop kidney stones.

Age: Stone occurrence is relatively uncommon before the age of 20 years but peak in incidence occurs in the fourth to sixth decades of life. The prevalence of stone disease increases with age until of 70 years. The incidence of nephrolithiasis exhibits peak between the ages of 20 and 60 years and 50% of stone formers will have a recurrence within 5 years [127]. The intestinal absorption of many nutrients that influence stone formation, such as calcium, may be reduced in the elderly persons [128,129]. In men, the incidence of kidney stones declines markedly after 60 year of age [99,130] suggesting that the pathophysiology of nephrolithiasis is different in the elderly person.

Gender: Urinary calculi are common, with some estimates suggesting that they affect 12% of men and 5% of women in industrialized countries by age of 70 years [131]. Nephrolithiasis typically affects adult men more commonly than adult women, with a male to female ratio of 2 or 3:1 [20]. There are several reasons for high incidence of urinary calculi in men than women. Men generally have a larger muscle mass than women. Hence they have more of the daily breakdown and rebuilding of tissue that result in metabolic waste. And an increase in metabolic waste pre-disposes people to stone formation. Men generally eat more meat than women do.

As mentioned earlier in section 2.2, the male urinary tract is more complicated than the female urinary tract. Occasionally men suffer with
narrowing of penile urethra. The enlargement of the prostate gland, i.e.,
Benign Prostatic Hypertrophy (BPH) {the condition arise due to the
enlargement prostate gland, which makes it difficult to empty the bladder
completely, so that some urine remains in the bladder at all times.} and
prostatitis (an inflammation of the prostate gland causing acute symptoms
such as an urgency to urinate, frequent need to urinate and a very weak
stream) are responsible to invite urinary complications. Anatomically, the
urethra is larger than the ureter, so most stones that reach the bladder usually
pass easily from that point [132].

Race : Disease prevalence varies by race, with the highest prevalence in
white men, followed by Asian, Hispanic, and African American men [133].

Geography : Many epidemiological studies have recorded a geographic
variability in the prevalence of stone disease. It has been postulated that this
variability may be owing to variations in climate and sun exposure [134].
Higher prevalence of stone disease is found in hot, arid, or dry climates such
as the mountains, desert, or tropical areas. Uric acid stones are subject to the
most pronounced geographical variation. In Scandinavian countries uric acid
stones occur with a frequency of not more than 4-5%, while the frequency
might be as high as 30-40% in the Mediterranean and Arabic countries [135].

Food Habit Factors : Dietary factors play an important role in kidney stone
formation [46,136], because it influences urinary constituents and pH, which
may affect stone nucleation and growth [73]. Both malnutrition and obesity
increase the risk of urolithiasis. People whose diets are high in animal protein
and low in fiber and fluids may be at higher risk for stones [137]. In general,
certain foods increase the risk for stones only in people who have genetic or
medical susceptibility. The effects of diet on the formation of urinary calculi may be different for the people of different age groups, because the metabolism of many dietary factors may change with age [138]. Oxalate-rich foods may be a risk factor for formation of calcium oxalate monohydrate calculi.

A diet rich in animal protein is associated with a low urinary pH, which leads to uric acid crystal formation that can act as a heterogeneous nucleant for calcium oxalate crystals [139,140]. The increase in dietary protein also increases the risk of the formation of calcium oxalate stones [141]. Protein consumption in children in Europe and USA is three to five times higher than the recommended intake [142].

Dietary sodium increases the risk of the formation of urinary calculi. Salt intake expands intravascular volume, which can increase urinary calcium level likely by decreasing renal tubular calcium reabsorption. Increase in salt intake can also induce mild systemic metabolic acidosis, which can lower urinary citrate levels, and increases the risk of calcium precipitation [143].

High glucose can also increase the risk of urolithiasis through an increase in urinary oxalate levels [144]. Fructose intake may increase the urinary excretion of calcium, oxalate, uric acid, and other factors associated with kidney stone risk [145]. Fructose intake may also increase insulin resistance, which is associated with the low urinary pH, a major risk factor for uric acid [146]. Sucrose increases the urinary calcium and oxalate concentrations. A lack of dietary fiber is also thought to contribute to stone formation [147].
Use of Melamine-contaminated Food: Use of melamine-contaminated milk products led to melamine nephrotoxicity, which is characterized by nephrolithiasis, acute kidney injury (AKI), or both. It was found that both melamine and cyanua were combined to form insoluble crystals, which results in urinary calculi. Most melamine associated stones were irregular, nubby in shape, and were mainly localized to the renal pelvis [41]. In December 2008, World Health Organization (WHO) published a detailed report on “Toxicological and Health Aspects of Melamine and Cyanuric Acid” and considering melamine as one of the risk factors for urolithiasis, set a standard for acceptable human consumption, i.e., Tolerable Daily Intake (TDI) of melamine at 0.2 mg / kg of body mass and gave several recommendations to control the epidemic induced by melamine contaminated food [148].

Soft Drink Habits: The findings of some [149] but not all [150] studies suggest that consumption of soft drinks may increase the risk of forming a kidney stone. The phosphoric acid found in these beverages is thought to affect calcium metabolism in ways that might increase risk of urolithiasis.

Medical Conditions: Many medical conditions, including but not limited to high blood pressure, gout [151], inflammatory bowel diseases [93], hyperparathyroidism [104], tubular acidosis [152], kidney disease, UTI [120], blockage of the urinary tract, chronic diarrhea, being bedridden for a long period, spinal cord injury [153], certain cancers [154], and sarcoidosis [155], put people at higher risk for stones.

Obesity Factor: Recent studies have confirmed that people with overweight and obesity may be at higher risk for urolithiasis [156-158]. The prevalence and incidence of urinary calculi have been reported to be associated with
body weight and body mass index (BMI) [159], although the magnitude of this association is greater in women than in men [160]. Obesity may sometimes cause uric acid stones by producing renal insulin resistance that in turn reduces urinary pH [161].

**Stress Factor**: Najem et al [162] reported the association between stressful lifestyles and urolithiasis. People who had a major, stressful life experience were more likely to develop stones than those who had not. Stressful lifestyles have been shown to increase lithogenic urinary constituents like calcium, oxalate and uric acid [163]. This increased risk may be due to a hormone called vasopressin, which is released during stress. Among its other functions, vasopressin increases the concentration of urine.

### 2.8 Symptoms of Urinary Calculi

This chapter starts with the poem – ‘*Ode to a Kidney Stone*’ by Khalid Hameed, which describes the symptoms of the kidney stone disease. The symptoms of urinary calculi disease can sometimes be excruciating and unbearable pain. It was reported that the presence or absence of symptoms does not significantly alter the presence and extent of urinary deposits in the urinary stone patients [164]. In many cases, kidney stones develop without producing any symptoms. If they become lodged in the ureter, nevertheless, the symptoms can be very severe. Often, they vary depending on the location of stone and then its progress.

- Usually, the first symptom of a kidney stone is extreme pain. Although side pain or flank pain are the most common symptoms in nephrolithiasis, the abdominal pain, back pain, and groin pain are other presenting symptoms encountered in the patients [19]. The pain often
begins suddenly when a stone moves in the urinary tract, causing irritation or blockage. Typically, a person feels a sharp, cramping pain in the back and side in the area of the kidney or in the lower abdomen. Later, pain may spread to the groin, testes, or tip of the penis, depending on the location of obstruction.

• If the stone is in the kidney or upper urinary tract, the pain usually occurs in one flank area.

• If the stone is too large to pass easily, pain continues as the muscles in the wall of the tiny ureter try to squeeze the stone along into the bladder.

• As stone grows or moves, blood may appear in the urine.

• The patient cannot become comfortable and usually stands, sits, paces, or reclines in a vain search for a position that will bring relief.

• It should be noted that the size of the stone does not necessarily predict to the severity of the pain; a very tiny stone with sharp edges or spiky nature can cause intense pain, while a larger round stone may not be as distressing as the spiky small one.

• As the stone moves down the ureter closer to the bladder, one may feel the need to urinate more often or feel a burning sensation during urination.

• Sometimes nausea and vomiting may occur.

• If fever and chills accompany any of these symptoms, an infection may be present.

• Sometimes urine passes with cloudy or foul-smelling.

• Large calculi can cause obstructions anywhere within the urinary tract, eventually causing organ damage and even renal failure.
It is interesting to note that the present author has experience the urinary stone pains.

2.9 Diagnosis of Urinary Calculi

Recurrence of urinary calculi appears to have increased in recent years despite the development of more effective surgical techniques [11,165], emphasizing the importance of laboratory analyses of urinary stones. Investigation of urinary calculi has been an important part of clinical chemistry for more than a century [166]. The majority of routine clinical laboratories only perform a qualitative analysis of the calculus by means of wet chemistry kits or infrared spectroscopy of the whole pulverized calculus, omitting details concerning minoritary components, percentages of different compounds or internal structure. The information obtained with wet methods or infrared spectroscopy is valuable on setting up therapeutic advice but is not valid for guidance on the concrete etiological causes of the lithiasis [167]. At present it is accepted that no single method provides total information on the structure and composition of the stone, and at least two different methods have to be combined for accurate study of calculi.

**Diagnostic steps for urinary calculi:**

- By using physical examination and imaging techniques, establish the presence or absence of kidney stones.
- If a kidney stone is present, using imaging techniques, determine whether the stone is obstructing the urinary tract.
- By urine and blood tests, determine the substance forming the crystal so that appropriate treatment and preventive measures can be taken.
By using the tests for urine and blood chemistries, determine any metabolic abnormalities in patient with recurrent stones.

Stone analysis may be carried out to determine the stone composition.

2.9.1 Physical Examination:

The physician will press against abdominal areas to know the locations that might indicate the presence of the stone.

2.9.2 Medical History:

A medical history may help predict which crystal has formed the stone. The physician may need to know the following:

- The physician may ask / collect the previous kidney stone attacks to determine whether first stone or recurrent.
- History, including, family history and dietary history.
- Histories of cancer, sarcoidosis, or small bowel disease.
- The patient should be sure to inform the physician of any medications being taken, including non-prescription substances, particularly high doses of vitamins D or C and calcium-containing antacids.
- Urinary tract infection with organisms possessing urease.

2.9.3 Imaging Techniques:

A number of imaging techniques, including plain abdominal radiography, i.e., X-Rays, ultrasonography, Intravenous Pyelography (IVP), helical Computed Tomography (CT) scanning and Magnetic Resonance Imaging (MRI) can be used to detect urinary calculi in the renal tract.

X-Rays: A standard plain x-ray film of abdomen comprising of the kidneys, ureter, and bladder, commonly referred to as a KUB, may be a first step for identifying urinary calculi, since most of them are opaque on x-rays. Calcium
stones can be identified on x-rays by their white color. X-ray is quick and inexpensive technique that can give the location, size and number of stones present. The use of KUB can result in a much lower radiation burden for the patient. However, small stones less than 2 mm may not be identified. KUB film may be affected by obesity or too much gas in the large intestine. Figure 2.6 shows the location of calculi in x-ray KUB [168].

Table 2.3 shows the radiographic characteristics of urinary calculi. For conventional radiography, a sensitivity of 57% and specificity of 71%, as well as a poor detection rate of 50–70%, are reported [169]. The main disadvantage of a KUB is that overlying bowel gas and bone can obscure the identification of a calculus.

### Table 2.3 : Radiographic Characteristics of Urinary Calculi

<table>
<thead>
<tr>
<th>Radiopaque</th>
<th>Poor Radiopaque</th>
<th>Radiolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>Struvite</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>Cystine</td>
<td>Xanthine</td>
</tr>
<tr>
<td>Calcium phosphate (different)</td>
<td>Triaterene stone</td>
<td>Matrix calculi</td>
</tr>
<tr>
<td>Carbonate</td>
<td></td>
<td>Urate</td>
</tr>
<tr>
<td>Brushite</td>
<td></td>
<td>2,8 dihydroxyadenine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug stones like Ephedrine stone, Indinavir stone, Guaifenesin stone, Nelfinavir stone, Oxypurinol stone, Sulphonamide</td>
</tr>
</tbody>
</table>

**Ultrasonography**: This test, generally known as sonography, uses ultrasonic sound waves rather than x-rays to produce pictures of internal organs. The
frequencies used in diagnostic ultrasonography are typically between 1 and 6 MHz. Sonography as an imaging alternative is mainly used for imaging the kidneys and the proximal parts of the ureters. It also can detect the presence of stones and it shows both calcified radiopaque stones and non-calcified radiolucent stones. Ultrasonography may detect all types of renal stones if the stone is larger than 3 to 5 mm. Ultrasound can also detect obstruction in the urinary tract. Ultrasound can be used to obtain information about the presence, size and location of a stone as well as the grade of dilatation and obstruction. It also detects signs of abnormalities likely to increase the probability of stones. But, it is not useful to detect very small stones. The quality of the sonography images depends on many factors that cannot be influenced by the radiologist (e.g., intestinal gas, obesity), and sonography detects only 50–60% of ureteral calculi [170]. Oner et al [171] reported that ultrasonography failed to identify stones in more than 40% of pediatric patients. Nevertheless, it is the preferred imaging method for kidney stone patients who are pregnant since it does not use any ionizing radiation. Moreover it does not use any intravenous contrast agents. Figure 2.7 shows the ultrasound image of calculus [172].

Figure : 2.7 Ultrasound Image of Urinary Calculus [172]
**Helical Computer Tomography** : A helical (or spiral) Computed Tomography, commonly, known as a CT scan, is a significant advance for diagnosing urinary calculi. Figure 2.8 shows the CT scanner [173] and CT scan image [174].

![CT Scanner](image1)

![CT Scan Image](image2)

**Figure : 2.8 (a) CT Scanner (b) CT scan image of the abdomen showing both kidneys and small calcified stones (arrowheads).**

At the present time, helical computed tomography without contrast is the procedure of choice for the initial radiographic investigation. It is now the standard imaging technique for detecting as well as characterizing urolithiasis. The main advantage of CT scan is that it offers rapid and excellent visualization of all opaque and non-opaque stones regardless of their size and location together with additional information about all urinary system. Non-contrast spiral CT seems to be a very effective and reliable imaging tool in the diagnosis of pediatric urolithiasis especially in detection of ureteral stones and stones smaller than 5 mm. Spiral CT is more efficient than ultrasonography [171]. It is noninvasive technique and provides detailed and accurate images. Moreover, the anatomic status of the urinary tract can be clarified and other possible non-stone cause for the patient’s symptoms or signs may be identified [175]. In normal radiation dose CT, the sensitivity and specificity are 94–100% and 97%, respectively [176]. Notwithstanding, the main
disadvantage of CT is that it exposes patients to a relatively high radiation dose and the potential effects of the radiation exposure from CT examinations have raised concern among some physicians [177]. However, the mean effective radiation dose for an excretory urography examination is reported as 2.6 mSv (millisievert) {The SI unit of the equivalent dose of radiation is sievert (symbol: Sv), which is named after Rolf Maximilian Sievert - a Swedish medical physicist renowned for work on radiation dosage measurement and research into the biological effects of radiation.} [178], which is less than one third of the effective radiation dose of routinely used CT protocols for the detection of urolithiasis [179] ranging between 8 and 16 mSv. The dose-reduced studies carried out by Niemann et al [180] envisaged that applied maximum effective doses of 0.7–2.8 mSv.

**Intravenous Pyelogram (IVP)**: An intravenous pyelogram (IVP, also known as intravenous urogram or IVU) is a radiological procedure used to visualize abnormalities of the urinary system, including the kidneys, ureters, and bladder. If no stones show up but the patient has severe pain indicative of urinary calculi, the next step is to proceed to an IVP test.

![Figure 2.9 (a) Injecting Contrast material into the patient's vein, and (b) IVP Radiograph](image)

*Figure 2.9 (a) Injecting Contrast material into the patient's vein, and (b) IVP Radiograph*
In the IVP procedure, the patient is injected with contrast material (a radiopaque dye) and a series of moving X-rays (called fluoroscopy) are taken as the dye travels through the urinary tract. Figure 2.9 shows the injecting contrast material for IVP procedure [181] and IVP radiograph [182]. This procedure is performed to confirm the presence of urinary calculi, although some calculi may be too small to be seen. This test should not be used on patients with kidney failure. There is also a risk for an allergic reaction to standard dyes. IVP is the most cost-effective method for detecting stones to date, but it is invasive and take a very long time if the blockage to the kidney is severe.

**Retrograde Pyelogram** : It is a procedure in which a cystoscope, which is an endoscopic instrument especially designed for urological use, is inserted into the urethra to visualize the lower urinary tract. The contrast agent is injected directly into this opening and an x-ray is taken to locate the urinary calculi. The flow of contrast (up from the bladder to the kidney) is opposite to the usual flow of urine, hence the name retrograde. This procedure eliminates the risk for an allergic reaction to the contrast agent because the dye does not reach the bloodstream, but it may require anesthesia. It is the most reliable method for visualizing the urinary system and detecting stones. Retrograde pyelography is generally done when IVP or contrast CT scan cannot be done because of renal disease or allergy to intravenous contrast.

**Magnetic Resonance Imaging (MRI)** : MRI uses three electromagnetic fields, namely, a very strong static magnetic field to polarize the hydrogen nuclei; a weaker time-varying field for spatial encoding; and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce
measurable signals, collected through an RF antenna. MRI techniques are showing promise for diagnosing urinary tract obstruction, but do not yet accurately reveal non-obstructive or small stones. Unlike x-ray and CT scan, it does not use any harmful ionizing radiation. MRI is an important modality due to its ability to obtain multiplanar images and excellent contrast resolution without the use of ionizing radiation.

2.9.4 Urinalysis (Urine Tests):

Urine samples are required to evaluate features of the urine, such as its acidity, the presence of red or white blood cells, whether infection is present, presence of any crystals, and elevated or decreased components that inhibit or promote stone formation. Urinalysis helps the clinicians or urologists to know the concentration of sodium, potassium, citrate, chloride, urea, nitrogen, creatinine, pH, calcium, oxalate, phosphate, Glucose, White Blood Cells (WBC), Red Blood Cells (RBC), ketones and bacteria, yeast cells, or parasites if any.

Clean-Catch Urine Sample for Culturing: A kidney stone patient is usually given a collection kit, including filters, to try to catch the stone or gravel as it passes out. A clean-catch urine sample is always required for culturing.

Twenty-Four Hour Urine Collection: A 24-hour urine collection may be needed to measure urine volume, urine pH, i.e., the levels of acidity, calcium, sodium, magnesium, uric acid, oxalate, citrate, and creatinine.

Test for Blood in the Urine: A dipstick for blood in the urine is typically performed when patients appear in the emergency room with flank pain. About a third of kidney stone patients, however, do not show blood in the urine, so other tests are needed.
Testing the Acidity of Urine: Testing whether urine is acid or alkaline helps to identify the specific stone. The levels of acid or alkaline in any solution, including urine, are indicated by the pH scale:

- A pH value of 7.0 is neutral.
- A solution with a low pH (below 7.0) is acidic. (A low pH favors uric acid and cystine stones.)
- A solution with a high pH (above 7.0) is alkaline. (A high pH favors calcium phosphate and struvite stones.)

2.9.5 Microscopic Examination

The kidney stones obtained from the sample are examined under a microscope. The crystal morphologies are often specific enough so that the physician is able to identify the substance causing the stone:

- Calcium oxalate crystals are eight-sided (octahedral), while calcium phosphate crystals tend to have irregular shapes.
- Uric acid stones are sometimes described as pear- or diamond-shaped.
- Struvite have very specific shapes commonly described as "coffin lids."

2.9.6 Blood Tests

Blood tests may help determine levels of blood urea nitrogen, creatinine, calcium, phosphate, and uric acid for patients with known or suspected calcium oxalate stones.

Parathyroid Tests: Tests to detect parathyroid hormone levels are needed if the physician suspects hyperparathyroidism.

Tests for Infection: If a test result shows a high white blood cell count, which might indicate infection. But such results could be misleading, since
white cells could also increase in response to the extreme physical stress of a kidney stone attack.

2.9.7 Analysis of Urinary Calculi

Various techniques usually employed for the urinary calculi analysis are as illustrated in figure 2.10.

![Flowchart showing various techniques for the analysis of urinary calculi]

**Figure : 2.10 Various techniques for the analysis of urinary calculi**

The study of the calculus begins through the direct observation of its external aspect, using a stereoscopic microscope. The surface characteristics are evaluated for color, texture, crystallinity, size, presence of layers, homogeneity, presence of foreign bodies, and any other notable features.
Afterwards, the calculus is sectioned in two parts along a plane as near as possible to its geometric centre, to be able to establish the internal structure. When the calculus is supplied after fragmentation, its all fragments are observed by stereoscopic microscopy to establish its original complete form and as a consequence, its internal structure.

**Fourier Transform Infrared Spectroscopy (FT-IR)**: The quantity of sample needed for FT-IR can be less than one microgram. If inspection of the superficial and cross-section of the stone reveals a homogeneous appearance, the identification of calculus composition can be performed by powdering the whole stone and taking an average sample for FT-IR study. But if inspection reveals a heterogeneous appearance such as areas of differing colors or textures, lamination or other structural details, it may become necessary to scrape off bits of calculus material from the different regions with a scalpel and perform several identifications by FT-IR. Identification is very simple if a reference spectrum that matches that of the unknown material is found. When an exact reference spectrum match cannot be found, a band by band assignment is necessary to determine the composition of the solid. The main advantages of FT-IR use in the identification of calculi components are the speediness, simplicity and specificity for the identification of rare components and the availability of the instrument. FT-IR technique is less expensive than SEM, and does not require highly qualified technicians.

The FT-IR spectroscopic method was used to investigate urinary calculi [183], it was found that calcium oxalate was the most common constituent with the presence of phases of hydroxyl and carbon apatite. There are reports of upgraded infrared techniques to analyze the urinary calculi, for
instance, the use of partial least squares regression in the analysis program enables better quantitation of stone components [184] by use of Fourier transform infrared spectrophotometer coupled with computer and photoacoustic detector. Spectra analysis was carried out by quantitative analysis program PLS (Partial Least Squares) Quant. Moreover, Volmer et al [185] carried out FT-IR analysis of urinary calculi by use of Golden Gate Single Reflection Diamond Attenuated Total Reflection (ATR) sample holder, a computer library, and an Artificial Neural Network (ANN) for spectral interpretation. FT-IR spectroscopy study of urinary calculi procured from South India has been reported [186,187]. A review is written on the application of infrared and Raman spectroscopy to urinary calculi by Carmona et al [188]. They suggested that some characteristic bands are useful for analytical purpose. Recently, the application of FT-IR and FT Raman spectroscopy in analysis of urinary calculi is reported [189].

**X-Ray Diffraction** : Unique X-diffraction pattern was explored to characterize and identify different urinary calculi, as early as in 1947 by Prien and Frondel [190]. In 1962 Herring [191] studied 10,000 urinary calculi with x-ray diffraction. The x-ray diffraction is even enabling to determine the proportional rate of particular crystalline components forming the calculus. Moreover, it provides a well organized reliable facility, which can give clinicians reliable results within a few hours [192,193]. Combining crystal-optical and x-ray diffraction methods many urinary calculi have been analyzed with their core and shell examinations separately [194].

The powder XRD technique is also popular to characterize urinary calculi. A difficulty in the identification of different components of mixed urinary
calculi is reported [195]. Moreover the internal standard method and powder XRD has been applied to the quantitative determination of urinary stone constituents. The study has indicated that the XRD analysis, nevertheless, alone can not be regarded as a routine technique for quantitative characterizations for urinary calculi, but the semi-quantitative XRD analysis supplements accurate quantitative elemental data is more suitable for precise determination of true stone composition [196]. Attempts were made to study the urinary calculi constituents by the powder XRD [197]. A mineralogical study was carried out for the calculi collected from the south India by using XRD [186].

**Thermal Analysis**: The thermal analysis is a popular technique to estimate the presence of water molecules. The presence of different ions and molecules can be estimated easily by the wet chemical methods. The difficulties appear in the differentiation of hydrates of calcium oxalates, not with standing, the thermal technique was found more useful [198]. Thermal study was carried out on various calculi obtained from south India [186,187] employed Differential Scanning Calorimetry (DSC) and identified COM, COD and the mixture of the two urinary calculi. Moreover, Thermogravimetric Analysis (TGA) is an important analytical technique for urinary calculi, which has suggested that some stones had less than 80 % calcium oxalate [199]. It was found that the level of the presence of COM and COD was different in the core region and the surface layer region. Earlier many workers [198-201] have carried out thermal analysis as an alternative method for quantitative determination of the two types of calcium oxalate in urinary stones. The thermo-balance and FT-IR were coupled through a heat transfer line, which
helped to analyze urinary calculi, particularly, in the case of complex mixtures [202].

**Scanning Electron Microscopy (SEM)**: The SEM provides three outstanding improvements over the optical microscope: it extends the resolution limits so that picture magnifications may be increased up to 30000x to 60000x, it improves the depth-of-field resolution more dramatically, by a factor of approximately 300, and finally, it entails the observation of several surfaces of a sample because of the possibility of rotating the sample in several directions. But in addition to image formation, this instrument may provide elemental analysis of micron-sized areas of the specimen observed when coupled with a special device for energy dispersive X ray microanalysis. SEM provides information about the nature of crystalline compounds, shape of the crystals, internal structure, location of components, crystalline conversions, crystallite size distribution, characteristics of the aggregates and some data about intimate relations between crystals and organic matrix or relationships between different crystalline species [203].

The appearance of urinary calculi by SEM permits identification based on textural grounds [204-206].

**Energy Dispersive Analysis by X-rays (EDAX)**: The EDAX technique has been employed to investigate the composition of different types of urinary calculi [205,206], viz., calcium oxalate, and / or calcium phosphate containing stones, infection stones, uric acid containing stones, cystine containing stones and containing rare substance (brushite, whitlockite, xanthine, etc) and elements (C, N, O, Na, S, Mg, Al, Si, Cl, K, Ca, Mn, Fe, Ni, Zn). The elemental
analysis of urinary calculi is also reported by Laser Induced Plasma Spectroscopy (LIPS) [207].

**Micro Computed Tomography** : Clinical laboratory assessment of urinary calculi is typically conducted using destructive methods of analysis. Micro CT is a potential *in vitro* imaging method for the analysis of urinary stone composition and morphology in a nondestructive manner at very high resolution [208,209]. Micro CT gives excellent structural detail within urinary calculi and these results demonstrate the feasibility of identifying and localizing most of the common mineral types found in urinary calculi.

However, it is exhaustive to give complete survey of various stone analysis technique. Louis C. Herring Laboratory [210] performs urinary calculi analysis professionally by using various sophisticated techniques. The predecessor of the present author [211] has analyzed urinary calculi collected after surgery by FT-IR, TGA, SEM, powder XRD and EDAX. Some of the results were presented by Joshi et al [212] using powder XRD technique.

It has been found in the majority of cases that no single technique is capable enough to give complete stone analysis, many times, more than one technique are used.

### 2.10 Management of Urinary Calculi

In the present time the management of urolithiasis is not only stone removal but also to prevent its recurrence. Medical management or treatment of urinary calculi was once entirely surgical, but recent technological advances allow stones to be treated with less-invasive methods, including Extracorporeal Shock Wave Lithotripsy (ESWL), ureteroscopic and percutaneous procedures. Treatment decisions are based upon suspected
stone type, size, location, renal anatomy, and renal function. A previous study by Tann et al [213] identified that 90% of stones less than 4 mm and 50% of stones 4–7 mm will pass spontaneously while 8 mm and larger stones will rarely pass without intervention. Comprehensive management of urinary calculi necessitates collaborative efforts between various disciplines.

2.10.1 Medications

Physician usually prescribes the drugs such as allopurinol, thiazides, potassium citrate, magnesium citrate and potassium-magnesium citrate depending on the cause of stone formation [214].

2.10.2 Lithotripsy

This procedure is effective for stones in the kidney or upper ureter. It uses an instrument to break the stone into tiny particles that can pass naturally through urine. Lithotripsy is not appropriate for patients with very large stones or other medical conditions. There are various types of techniques available.

2.10.3 Ultrasonic lithotripsy

Ultrasonic lithotripsy uses high frequency sound waves delivered through an electronic probe inserted into the ureter to break up the kidney stone. The fragments are passed by the patient naturally or removed surgically.

2.10.4 Electro-hydraulic Lithotripsy (EHL)

Electro-hydraulic lithotripsy (EHL) uses a flexible probe to break up small stones with shock waves generated by electricity. The probe is positioned close to the stone through a flexible ureteroscope. Fragments can
be passed by the patient or extracted. EHL requires general anesthesia and can be used to break stones anywhere in the urinary system.

2.10.5 Extracorporeal Shock Wave Lithotripsy (ESWL)

"Extracorporeal" means "outside the body" and "lithotripsy" means stone-breaking. All ESWL procedures deliver shock waves from outside the body to break the stones, which are then more easily passed through the ureter and out of the body in the urine. This innovation has eliminated the need for open surgical removal of urinary calculi in the vast majority of patients. ESWL is the most frequently used procedure for most simple stones located in the kidney or upper urinary tract, including struvite stones. It is not used for cystine stones. ESWL is generally not successful for stones larger than three centimeters in diameter.

**Figure 2.11** (a) Extracorporeal Shock Wave Lithotripter [215]  
(b) Shock waves Break the Urinary Calculus in Kidney [216]

**ESWL Procedure**: The Lithotripter used for ESWL procedure is as shown in figure 2.11 (a) [215]. Most ESWL procedures use some anesthesia, although they are often done on an outpatient basis. The patient is positioned in a water bath or on a soft cushion. The procedure uses ultrasound to generate shock waves that travel through the skin and body tissues until they hit the
dense stones. The stones are crushed into tiny sand-like pieces (Figure 2.11 b [216]) that usually pass easily through the urinary tract. The shattered stone fragments may cause discomfort as they pass through the urinary tract. In such cases, the doctor may insert a small tube called a stent through the bladder into the ureter to help the fragments pass. This practice, however, has not proved to speed up passage of the stones in most cases and is not used routinely. Success rates range from 50% to 90% depending on the location of the stone and the surgeon's technique and level of experience. Recovery time is short, and most people can resume normal activities in a few days.

**Complications of ESWL** : The most common complication is blood in the urine, which lasts for a few days after the treatment. To reduce the chances of bleeding, doctors usually advise patients to avoid taking aspirin, which can promote bleeding, for seven to 10 days before the treatment. Bruising and minor discomfort due to the shock waves are common in the back or abdomen. Sometimes the stone is not completely fragmented with one treatment, and then additional treatments may be required. Its safety for small or abnormal kidneys is not fully known. Recently, Xue et al [217] reported through an animal model experiment that ESWL treatment is associated with a high rate of recurrent renal calculi. Shock wave therapy can result in renal epithelial cell injury, which in turn is a most important factor in calculus formation. It is not known if this complication has any long-term consequences. Experts recommend minimizing as much as possible the impact and number of shocks in young people. If more than one treatment is needed, there should be a waiting period of at least 15 days.
2.10.6 Percutaneous Nephrolithotomy (PCNL)

This surgical procedure is performed under local anesthesia and intravenous sedation. Percutaneous means ‘through the skin’ and lithotomy means ‘removal of kidney stones’. It is accomplished through the most direct route to stones through the kidney. Percutaneous nephrolithotomy may be used when ESWL is not available or effective, e.g., if the stone is very large, in an inaccessible location, or is a cystine stone. It is more effective for patients with severe obesity. It appears to be safe for the very elderly and the very young. Long-term effects are unknown. It is also preferred over ESWL for stones that have remained in the ureter for more than four weeks.

**Figure : 2.12 Percutaneous Nephrolithotomy Procedure [218, 219]**

**PCNL Procedure :** As shown in figure 2.12 [218, 219], the surgeon makes a tiny incision in the back and creates a tunnel directly into the kidney. The surgeon then inserts an instrument called a nephroscope through the tunnel. The stone is located and removed. An advantage of percutaneous nephrolithotomy over ESWL is that the surgeon is able to remove the stone fragments directly instead of relying on their natural passage from the kidney. For large stones, some type of energy device (ultrasound, a pneumatic drill-like device, or a special device called a holmium laser lithotripter) may be
needed to break the stone into small pieces. The holmium laser literally melts the stones and can be used on nearly all stone types. Of concern are studies reporting that the holmium laser produces cyanide as a by-product of uric acid stone fragmentation. No poisoning has been reported in any patient after this procedure; nevertheless, the device has an excellent safety record. It should be used sparingly, cautiously with large uric stones until more is understood about this effect. Generally, patients stay in the hospital for five or six days and may need a small tube called a nephrostomy tube left in the kidney during the healing process. Success rates have been reported to be about 98% for kidney stones and 88% for ureteral stones. They are slightly lower in children, although the procedure can be used safely.

Complications of PCNL: Complication rates are about 3% and serious problems are rare. Some scarring occurs, but studies indicate that it does not impair kidney function, even if the patient requires repeat surgery. The procedure also poses a risk for blood loss during and after the procedure, and, in some cases, it can be significant. Other complications encountered are imbalances in the fluid used to irrigate the tunnel, collapsed lung, and injuries to areas outside the kidney but within the operative area, such as the abdomen or chest.

2.10.7 Ureteroscopic Stone Removal

Ureteroscopy may be used for mid- and lower ureter stones. In this procedure no incision is made, but general anesthesia is still required. The surgeon passes a small fiber optic instrument called a ureteroscope through the urethra and bladder into the ureter. The surgeon then locates the stone or stones. Smaller ones are grasped and removed with tiny forceps. Large ones
are shattered with lasers or pneumatic drill-like devices. A small tube, or stent, may be left in the ureter for a few days after treatment to help the lining of the ureter heal. Complication rates range from 10% to 20% with major problems occurring in between 0% and 6%, with the risks being highest in less experienced surgeons and if stones are found in the kidney. The risk for perforation of the ureter is higher the longer the operative time.

2.10.8 Open Surgery (Nephrolithotomy)

Open surgery involves incisions through the patient's flank and into the kidney. The kidneys are cooled down using ice and x-rays are used during the procedure to locate specific areas and the stone. The arteries in the kidney are identified and isolated away from the surgical region. The surgeon locates the collecting system and retrieves the stone. If the surgeon finds any blockage, this is corrected. The surgery is very invasive and is now restricted to the patients with very large or complex stones that cannot be removed using less invasive measures and for very obese patients.

The procedure is not appropriate for the following patients:

- Those with bleeding or clotting disorders.
- Those with untreated widespread infection.
- Those with severe and chronic kidney insufficiency.

Surgery should be reserved as an option for cases where other approaches have failed. Surgery may be needed to remove a kidney stone if ...

- It does not pass after a long period of time and causes constant pain.
- It is too large to pass on its own or is caught in a difficult place.
- It blocks the flow of urine.
- It causes ongoing urinary tract infection.
• It damages kidney tissue or causes constant bleeding.
• It has grown larger.
• Because cystine stones frequently are large and resistant to disruption via shock wave lithotripsy, the surgical treatments are required [220].

Until 30 years ago, surgery was necessary to remove a stone. It was very painful and required a recovery time of 4 to 6 weeks. Today, treatment for stones is greatly improved, and many options do not require major surgery.

2.11 Prevention of Urinary Calculi

Prevention of progressive or recurrent stone formation is best managed by diet, adequate fluid intake, and in some cases, dietary supplements or medications. The modest progress in understanding the pathophysiology has hampered successful development of targeted therapy. Current regimens are based mostly on rational alteration of urinary biochemistry and physical chemistry to lower the risk of precipitation. In terms of pharmacotherapy, there are drugs to successfully improve hypercalciuria, hypocitraturia, aciduria, hyperuricosuria, and hypercystinuria. But due to the space limitation, complete description with exhaustive citation is not possible.

Several authors have written detailed reviews on the etiology, epidemiology, constitutions, theories, characteristics, therapies, medical managements and metabolic factors of urinary stones [15,24,45,56,60,124, 132,134,221,222]. The predecessors of the present author [211,223,224] have written detailed reviews on urolithiasis, therefore, it is avoided in greater details in the present thesis. The author has attempted to mainly include recent studies and the studies carried out mostly in last one decade.
2.12 *In Vitro* Growth Inhibition

The occurrence of urinary calculi is taking place in a dynamic environment in a body where urine is constantly flowing. The growth of urinary calculi in a body is a complex process and depends on many factors. This has already been discussed earlier in this chapter.

Nevertheless, it is important to study the growth of urinary type crystals *in vitro* and study various parameters affecting the growth. The gel growth technique is found the most suitable one to mimic the growth occurring in a body in a simplified manner. This gel growth technique will be discussed in chapter – III.

The *in vitro* growth dissolution and inhibition is again important to study because the normal dissolution differs from it. In the normal dissolution, the stone or urinary crystal is dissolved in a suitable solvent. But in growth dissolution, the dissolution is achieved under the growth condition by maintaining the constant supply of nutrients for the growth. This type of condition mostly desired in a body to dissolve the stone. If the dissolution of stone or crystal is not achieved by the growth is retarded then it is known as inhibition. The gel based *in vitro* growth inhibition study is important as it provides a simple screening model to identify different inhibitors. The inhibitors may be chemical compounds present in urine or different herbal extract solutions or fruit juices for *in vitro* studies. There are large numbers of herbal drugs as well as Ayurvedic drugs available for different therapeutic use [225,226], the possibilities of testing certain selected ones for pilot *in vitro* study is required to be explored. This has lead several researchers to address the issue of urinary stone problem and many other ailments from reverse
pharmacology point of view [227-229]. The reverse pharmacology can be defined as a transdiscipline that initiates drug discovery and development from the traditional knowledge / practice at the beside through robust and objective experimental documentation. The path of reverse pharmacology is cost effective and time saving unlike the long and expensive direct path of drug development from natural products.

Earlier, Natarajan et al [230] employed gel growth of a few urinary stone constituents and studied inhibitory role played by some extracts or juices of natural products in crystal growth.

In the present authors laboratory the earlier workers have studied growth inhibition of different urinary crystals in vitro by using gel growth technique with different inhibitors; for instance, growth inhibition of calcium oxalate monohydrate crystals by herbal extracts of Tribulus terrestris Linn and Bergenia ligulata Linn [231]; brushite by citric acid, lemon juice, artificial reference urine and natural urine [232, 233], by herbal extracts of Tribulus terrestris Linn and Bergenia ligulata Linn [234] by tartaric acid and tamarind [235], and by unripe mango juice, pomegranate juice and grape juice [223]. The present author has carried out extensive studies on growth inhibition of struvite crystals which will be discussed in chapter VI and published several research papers as listed after the last chapter on page number 412.
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