CHAPTER 1

INTRODUCTION

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1.1 ROUTE OF DRUG ADMINISTRATION

The route through which a drug is given is typically categorized by the site of administration, such as orally or intravenously. The decision on which route to use is influenced by factors like convenience and patient adherence, as well as the drug's pharmacokinetic and pharmacodynamic properties.

1.1.1 Oral Route of Drug Administration:

This method involves placing the medication in the mouth and swallowing it. Also known as per oral, it is a convenient option for patients who are able to ingest and tolerate oral medications. Drugs with short half-lives can be administered orally in timed-release or sustained-release forms, allowing for gradual absorption over several hours. [1]

1.1.1.1 Advantages of the Oral Route

- **Convenient Administration:** Administering medication orally is straightforward and simple.
- **Patient Acceptance:** This method is widely accepted and preferred by patients.
- **Comprehensive Absorption:** Medication is absorbed throughout the entire gastrointestinal tract.
- **Cost-Effective:** Compared to many other parenteral methods, oral administration is generally more economical.

1.1.1.2 Disadvantages of the Oral Route

- **Inconsistent Absorption Rates:** The absorption of drugs can vary greatly.
- **Drug Degradation:** Some medications are broken down before they can be absorbed into the bloodstream.
- **Limited Permeability:** Many compounds cannot effectively cross the intestinal epithelial membrane to enter the bloodstream.
- **Low Solubility:** Many drugs are not soluble at the low pH levels found in the digestive tract.

- **Liver Inactivation:** Drugs can be inactivated by the liver before reaching systemic circulation.
- **Gastrointestinal Irritation:** Drugs can irritate the mucous lining of the gastrointestinal tract, although this can be mitigated somewhat by coating the drugs.

1.2 RESEARCH APPROACH TO HERBAL PRODUCTS:

Since they form the basis for all life on earth, plants hold a special place in the universe. In every food chain, they are the principal producers. 90% of the calories and 80% of the protein consumed by humans are directly derived from plants. Since the beginning of time, people have exploited plants as possible sources of medicine. The wealth of medicinal herbs originates from India, where people choose to use conventional medicine techniques. As a result, it is crucial that this vast natural resource be enhanced and used in line with the advancement of technology and human requirements.

The current millenium sets the objective of using nutraceuticals to provide treatment without adverse effects. The success of using various plants to treat ailments has increased interest in traditional medicine worldwide. For ages, the ethno-botanical practises of the people of Asia have included the use of medicinal herbs. Only after extensive chemical and pharmaceutical testing did the contemporary medical system diverge from folk medicine and the old medical system. Modern microbiological and chemical techniques can synthesis aromatic and therapeutic molecules, although the process is frequently expensive.

Many people opt for natural remedies from plants to avoid the potential side effects of synthetic drugs. It is estimated that around 20,000 plant species are utilized for medicinal purposes, as noted by Penos et al. [2] Furthermore, a study by Farnsworth et al. [3] in 1985 found that chemical research aimed at identifying the active components xresponsible for the traditional uses of 119 plant-based medications led to the discovery of these active ingredients in 74% of the cases.

The tropical, subtropical, and temperate species found in Asiatic flora serve as systems for herbal-based medicines and are crucial to the region's overall healthcare. According to Farnsworth et al., more than 80% of Asians still rely on traditional and folk treatments for their regular medical requirements. Of India's 1.1 billion people, more than 70% still use traditional herbal medication.[4] According to Scragg et al. [5], phytochemical investigation of plants that have historically been used to treat cancer has produced a variety of chemicals

having anticancer potential. Alkaloids with anti- HIV action have been found to accumulate in plants from many different families. Hussein disclosed a number of medicines and aromatic substances produced from plants [6] These include forskolin from Coleus root, which is used to prevent blood clotting and lower intraocular pressure in glaucoma cases, and anti-malarial drug from Artemisia annua. Forskolin helps the repair of damaged nerves after injury.

Reverse pharmacology, which stems from observational therapeutics, complements other methods in the development of natural drugs.

For a new to the area, the variety of plant usage in medicine can occasionally be overwhelming. However, the possibilities for research strategy offer strong motivation for the discovery of new pharmacophores for multidisciplinary research and a development network. New pharmacophores offer potential contributions to the field of herbal medicinal and preventative agents through the development of novel drug targets and the application of combinatorial chemistry. An example of this is seen in efforts to target curcumin chemically with combinatorial compounds. In India, the Council of Scientific and Industrial Research (CSIR) has initiated a nationwide network program aimed at creating herbal-based formulations for conditions such as diabetes, arthritis, and hepatitis, representing significant efforts in this area.[7]

1.3 DIAGNOSIS AND CONTEMPORARY THERAPEUTIC APPROACHES FOR THE TREATMENT AND MANAGEMENT OF URINARY STONES:

The process of diagnosing urinary stones is multifaceted, incorporating the patient's medical history, dietary patterns, complete blood cell counts, routine urine tests, and serum creatinine levels. Physical examinations are performed with a focus on symptoms commonly linked to urinary stone disease.[8] Furthermore, diagnostic procedures heavily rely on ultrasound and imaging techniques like X-rays and CT scans. Ultrasound is particularly advantageous because it can detect all types of kidney stones, including those that might not be visible on an X-ray. [9]

Urinary stones often pass spontaneously, prompting doctors to manage initial symptoms, primarily through pain relief. However, the rate at which stones pass varies significantly based on their size and location. If a stone cannot pass on its own, medical expulsive therapy is usually recommended. This approach may involve using antibiotics, calcium channel

blockers, pain relievers, and anti-inflammatory drugs. When conservative treatments are ineffective because of the size and complexity of the stones, or if the patient is unable to endure the pain while waiting for the stone to pass naturally, surgical intervention becomes necessary. [10-11]

Common surgical methods for treating kidney stones include extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), percutaneous nephrolithotomy (PCNL), and open surgery. Each of these techniques comes with its own set of advantages and drawbacks. The effectiveness of stone removal depends on various factors such as the patient's age, the size and location of the stones, the number of stones present, the radiological features of the kidneys, and any congenital abnormalities of the renal system. Moreover, both surgical and medical treatments must contend with the problem of stone recurrence. Research indicates that ESWL can lead to acute kidney injury due to the shockwaves and may also increase the risk of post-treatment infections. [12-15].

1.4 HERBAL MEDICINES FOR THE TREATMENT OF URINARY STONES

Numerous treatment plans for urinary stone disorders have been developed in recent decades. However, most of these treatments involve surgery, making them expensive and sometimes difficult to access. Consequently, many individuals opt for or are limited to using traditional herbal remedies. Herbal treatments for urinary stone issues are available in various traditional systems of medicine, including Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani.

Urolithiasis is considered a major health issue. In Ayurveda, urinary stones are known as "mutraashmari" (with "mutra" meaning urine and "ashma" meaning stone). Ayurvedic literature identifies four categories of urinary stones: phosphatic stones (sleshmaashmari), urate stones (pittaashmari), oxalate stones (vataashmari), and seminal concretions (sukraashmari). Ayurvedic treatment approaches for managing urinary stones include herbal remedies, alkaline drinks, and various surgical techniques.

Ayurveda offers various therapies for managing urinary stone diseases, including purification treatments (Shodhana) involving external and internal oleation and sweating induction, as well as alleviation therapies (Shamana). Additionally, Ayurveda recommends panchakarma procedures such as medicated emesis, purgation, and enemas to address these

conditions. This approach primarily involves the oral administration of herbal medications, including mutraladravyas (diuretics), ashmaribhedana (lithotriptics), and teekshnaushna (penetratives).[16].

Table No. 1.1: Medicinal Plants Used in Ayurveda to Cure Kidney Stones

Sr. No.	Botanical name and family	Sanskrit name	Part used	Dose/mode preparation
1.	*Aervalanata* (L.) Juss. (Amaranthaceae)	Gorakshaganja, Astmabayda, Bhadra, Pashanabheda, Pattura	Whole plant	Whole plant
2.	*Anisomelesma labarica (*L.) R. Br. ex-Sims (Lamiaceae)	Sprkka	Whole plant	3-5g, powder
3.	*Anogeissuslatifolia* Wall. Ex Guillem & Perr. (Combretaceae)	Dhava	Stem bark	30-50 ml, decoction
4.	*Apiumgraveolens* L. (Apiaceae)	Karaphsa	Root	5-7g, powder
5.	*Asparagus officinalis* L. (Liliaceae)	Dvipantara	Root	3-6g, powder
6.	*Baliospermm solanifolium* (Burm.) (Euphorbiaceae)	Satavari Hastidanti	Root	1-3g, powder
7.	*Benincasahispida* (Thunb.) Cogn. (C ucurbitaceae)	Kushmand	Fruits	5-10g, powder
8.	*Bergeniacilliata* (Haw.) Sternb. (Saxifragaceae)	Asmabhedaka	Rhizome	3-6g, powder

9.	*Buteamonosperma* (Lam.) Taub. (Lam.)(Leguminosae)	Palasah	Seed	0.5-1g, powder
10.	*Calamusrotang* L. (Arecaceae)	Vetra	Rhizome	50-100 ml, decoction
11.	*Caricapapaya* L. (Caricaceae)	Erandkarkati	Root	5-10g, powder

1.5 ROLE OF WHO IN HERBAL MEDICINE:

The World Health Organization (WHO) acknowledges the crucial contribution of traditional medicine to healthcare. In line with this recognition, the U.S. Congress established the Office of Alternative Medicine within the National Institutes of Health in 1989 to encourage scientific exploration of traditional medicine. That same year, the European Scientific Cooperative on Phytotherapy (ESCOP) was created to enhance the scientific validation and standardization of herbal medicines across Europe. These efforts resulted in increased funding for the study of herbal medicines. For example, in the fiscal year 2005, the National Centre for Complementary and Alternative Medicine at the U.S. National Institutes of Health dedicated about US$33 million to herbal medicine research. Similarly, in 2004, the National Canadian Institute invested close to US$89 million to investigate various traditional therapies. This funding, while modest compared to pharmaceutical industry budgets, highlights significant interest and support from the public, industry, and government in this field.[17]

The significant growth in global interest and utilization of traditional medicines presents two primary challenges. These challenges revolve around international diversity and national policies concerning the regulation, production, and usage of herbs and other complementary medicines. Moreover, they encompass ensuring the quality, safety, and scientific validation of health claims associated with these medicines. [18]

1.5.1 Global Herbal Market And Current Scenario:

The global herbal market is estimated to be worth approximately $62.0 billion. India's current market contribution stands at around $1 billion. Further details regarding India's

position in the global market can be found in Annexure 5. The European Union holds the largest market share in the herbal sector, accounting for 45% of the total global market.

The global market for herbal medicine reached a valuation of USD 151.91 billion in 2021. It is expected to grow from USD 168.86 billion in 2022 to around USD 437.59 billion by 2030, with a projected compound annual growth rate (CAGR) of 11.16% from 2023 to 2030.

Over the past decade, the popularity of herbal medicines and other alternatives to antibiotics has significantly increased. Both patients and healthcare providers are showing heightened interest in herbal products. According to the WHO, 10–50% of individuals in developed countries regularly use herbal products in some form. The primary appeal of herbal products lies in their ability to help the body combat illnesses more effectively than synthetic drugs. In developing countries such as China, Japan, India, Vietnam, South Africa, and Bangladesh, herbal medicines often serve as the only affordable treatment option. These remedies are commonly used to address conditions like coughs, colds, anxiety, gastrointestinal issues, and painful ailments such as joint pain, rheumatism, and stiffness. With the rising popularity of herbal supplements, the market is likely poised for significant growth.

Herbal medicines are increasingly sought after in developing countries for primary health care. This demand arises not only due to their affordability but also because they are culturally accepted, compatible with the human body, and have minimal side effects.

1.6 INTRODUCTION TO LITHOLYTIC ACTIVITY:

Urolithiasis, the formation of urinary stones anywhere in the renal system, is a longstanding chronic health condition documented throughout human history. Traditional medical systems like Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani include extensive literature detailing symptoms, indicators, and treatment approaches for urinary stone diseases. According to Ayurveda, urolithiasis ranks among the eight most challenging disorders. Urinary stone treatment in Ayurveda includes herbal formulae, alkaline drinks, and surgical methods. While, TCM advice using a combination of acupuncture, mexibustion, and multiherbal medications to treat urinary stones. Herbal treatments are still used today to treat and cure urinary stone illnesses among these medicines.

Urinary stones, medically known as calculi, are solid crystalline masses that can develop anywhere within the urinary tract. The condition of stone formation in this tract is termed urolithiasis. The formation of urinary stones typically occurs due to a reduction in natural inhibitors that prevent stone formation in urine or when urine becomes oversaturated with salts. Several environmental and dietary factors, such as low urine volume and diets high in animal protein, contribute significantly to urolithiasis. Metabolic changes like hypercalciuria and hyperuricosuria, as well as deficiencies in nutrients that inhibit stone formation such as citrate, magnesium, and glycosaminoglycans (GAG), also play a crucial role in promoting stone development [19]. Preventing urolithiasis can be challenging since it often manifests without symptoms and may remain unnoticed until it progresses significantly, particularly in cases of recurrence. Small urinary stones can pass spontaneously through urine, with reported spontaneous passage rates of 68% for stones 5 mm or smaller, and 47% for stones larger than 10 mm. [20]

Ancient medical texts such as those from Ayurveda, Chinese traditional medicine, and Greek medicine contain detailed descriptions of urinary stone symptoms, warning signs, and treatments. Common symptoms of urinary stone disease include pain in the back or lower abdomen, presence of blood in the urine, and discomfort during urination. Additionally, individuals may experience nausea, vomiting, and waves of pain that originate in the abdomen, often radiating to the groin, testicles, or vulva, and typically subsiding within 20 to 60 minutes. This type of pain is clinically referred to as renal colic.

Dietary modifications and stone expulsive therapy often prove ineffective for many urinary stone patients due to the size of the stones or their location within the urinary tract. Consequently, these patients often require treatment with advanced interventional techniques. However, evaluating and selecting the most suitable interventional techniques can be challenging, particularly for patients prone to recurrent urinary stones. Alternatively, traditional herbal remedies have been identified as effective, accessible, and cost-effective options. Despite their long history of use and efficacy, widespread adoption of these herbal medications remains hindered, possibly due to inadequate scientific validation and support.[21]

1.6.1 Factors Responsible for formation of Urinary Stone

Urolithiasis has been a significant health concern for many years, yet our understanding of the underlying processes leading to urinary stone formation remains limited. A comprehensive comprehension of these mechanisms is essential for effective patient management, aiming to reduce both the morbidity associated with urolithiasis and related medical costs. Conventionally, it was believed that urinary stones arise from the super saturation of urine and subsequent crystallization of minerals. However, the formation of stones in the urinary tract is not solely attributed to the accumulation of stone salts in urine. The process of urolithiasis is intricate, involving stages such as crystal nucleation, aggregation, retention of crystals by the urothelium, urine saturation, super saturation, and the gradual growth of stones around retained crystals.[22]

It has been found that dietary habits, especially those contributing to metabolic syndrome or inherent abnormalities, are responsible for urine saturation or supersaturation.[20] Many epidemiological and metabolic investigations indicate that dietary habits contribute to the prevalence of urinary stones, influencing the composition of urine. Key dietary factors linked to increased risk include higher protein consumption, elevated intake of salt or oxalate, and reduced calcium intake. [23] Overconsumption of animal proteins in the diet can lead to problems with renal ammonia genesis and/or excretion. This can impair buffering capacity and exacerbate acidic urine due to increased acid excretion. Moreover, independent studies have shown a direct link between fructose consumption and a higher incidence of urinary stones. [24] Individuals with nephrolithiasis and comorbidities such as type II diabetes, obesity, or metabolic syndrome are at increased risk of developing uric acid stones.

1.6.2 Mechanism of Urolithiasis: Crystallization and Retention of Stones:

Urolithiasis becomes medically important when tiny stone fragments remain in the urinary tract and develop into larger stones.[25] The formation of urinary stones includes three main stages: urine oversaturation, crystallization, and the retention of stones within the urinary system.

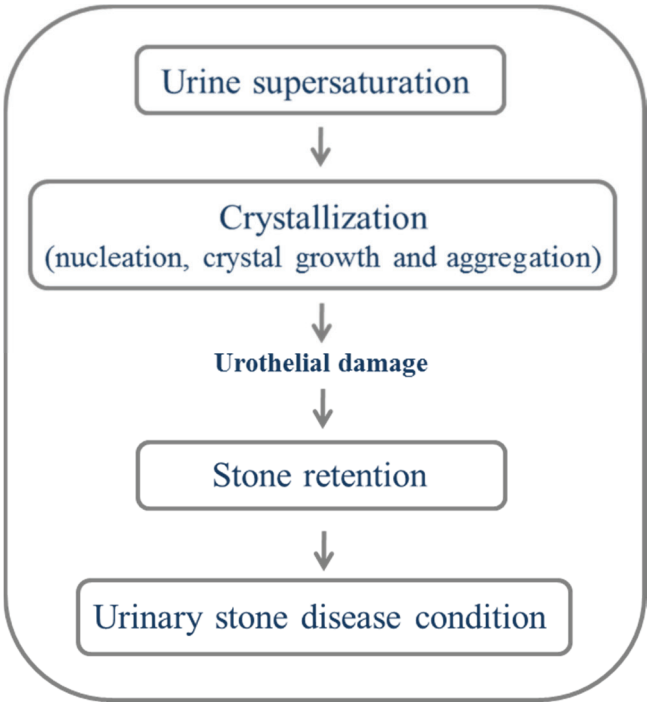


Figure No. 1.1: The overall mechanism of urinary stone formation

1.7 VARIOUS DISORDERS OF KIDNEY:

1.7.1 Chronic kidney diseases:

The most prevalent type of kidney disease is chronic kidney disease (CKD), which is a persistent condition that does not ameliorate with time. It is frequently linked to hypertension, or high blood pressure.

High blood pressure poses a significant risk to kidney health by increasing pressure on the glomeruli, the tiny blood vessels responsible for filtering blood in the kidneys. This sustained pressure can lead to damage over time, causing a gradual decline in kidney function. Eventually, kidney function may deteriorate to the extent that the kidneys are no longer able to adequately perform their functions. At this stage, individuals may require dialysis, a treatment that filters excess fluid and waste products from the blood. While dialysis can assist in managing kidney disease, it is not a cure. Depending on individual circumstances, a kidney transplant may be considered as another treatment option.

Diabetes significantly contributes to chronic kidney disease. It is characterized by elevated blood sugar levels, which gradually impair the blood vessels in the kidneys. Consequently, the kidneys lose their ability to filter blood efficiently, potentially leading to kidney failure due to toxin buildup in the body.[26]

1.7.2 Kidney Stone

Kidney stones represent a frequently encountered kidney issue. These stones form as a result of minerals and other compounds in the bloodstream crystallizing within the kidneys, resulting in the formation of solid masses. Typically, kidney stones exit the body during urination. Although passing kidney stones can be excruciatingly painful, they seldom lead to substantial complications.

Signs and Symptoms

The primary indication of a stone obstructing the ureter or renal pelvis is intense, sporadic pain that radiates from the flank to the groin or inner thigh.[27] This pain occurs due to referred signals from lower thoracic splanchnic nerves to lumbar splanchnic nerves during the passage of the stone from the kidney or proximal ureter to the distal ureter. This sensation known [28] as renal colic, this pain is often described as one of the most severe sensations of pain. Alongside pain, symptoms typically include urinary urgency, restlessness, hematuria, sweating, nausea, and vomiting. The pain recurs in waves lasting 20 to 60 minutes due to peristaltic contractions of the ureter as it attempts to expel the stone.[27]

The anatomical relationship between the urinary tract, reproductive system, and gastrointestinal tract contributes to the referral of pain to the genitals and the occurrence of nausea and vomiting frequently observed in urolithiasis cases.[29] Obstruction of urine flow through one or both ureters can lead to postrenal azotemia and hydronephrosis.[30]

Pain in the lower-left quadrant may resemble diverticulitis due to the overlap of the sigmoid colon and ureter in this region, posing challenges in precise localization of pain.

Risk Factors

Dehydration resulting from insufficient fluid intake significantly contributes to the formation of kidney stones.[27,31] Individuals living in warmer regions are particularly susceptible due to increased fluid loss. Factors that elevate the risk include being overweight, leading a sedentary life, and reduced mobility. [32] Consuming diets high in animal proteins[27], salt, sugars (such as honey, refined sugars, fructose, and high fructose corn syrup) [33] , and large amounts of fruit juice can contribute to kidney stone development by increasing the excretion of uric acid and urinary oxalate. Conversely, beverages like tea, coffee, wine, and beer may lower this risk. Several metabolic disorders, including distal renal tubular acidosis[34], Dent's disease[35] , hyperparathyroidism[36],

primary hyperoxaluria [37], and medullary sponge kidney[38,39], can also cause kidney stones. Medullary sponge kidney affects about 3-20% of individuals prone to developing kidney stones.[38-39] People with Crohn's disease are more susceptible to kidney stones due to hyperoxaluria and magnesium malabsorption associated with the condition.[40-41] Individuals experiencing recurrent kidney stones should undergo screening for these disorders, typically involving a 24-hour urine collection to analyze factors contributing to stone formation.[30]

1.7.3 Glomerulonephritis:

Glomerulonephritis involves the inflammation of glomeruli, small kidney structures crucial for blood filtration. This condition may develop due to factors such as infections, medications, or congenital issues. Often, glomerulonephritis resolves on its own.[42]

1.7.4 Polycystic Kidney Disease:

Polycystic kidney disease (PKD) is an inherited disorder characterized by the formation of multiple fluid-filled cysts in the kidneys. While individual kidney cysts are generally benign and pose little threat, PKD significantly impairs kidney function and can lead to kidney failure. It is crucial to distinguish between solitary kidney cysts, which are usually harmless, and PKD, a more severe condition with serious implications for kidney health.

1.7.5 Urinary tract infections (UTIs):

Urinary tract infections are bacterial infections affecting any portion of the urinary system, with the bladder and urethra being the most frequently affected areas. These infections are typically straightforward to treat and seldom result in further health complications. Nevertheless, untreated cases can escalate, potentially spreading to the kidneys and triggering kidney failure**.**

1.8 TYPE OF KIDNEY STONE:

Kidney stones primarily consist of four major types: calcium stones (comprising 7585% of cases), struvite stones (2-15%), uric acid stones (6-10%), and cystine stones (1-2%). The prevalence and distribution of these stones vary depending on geographical location and the demographics of the population studied. In rare cases, long-term medication use can also contribute to the formation of kidney stones, accounting for approximately 1% of cases. [43].

1.8.1 Calcium Stones:

Calcium stones such as calcium oxalate, calcium urate, and calcium phosphate are linked to hypercalciuria, which can be caused by conditions such as hyperparathyroidismDiseases that enhance calcium absorption from the intestine can result in the kidneys excreting more calcium or phosphate. This condition is often accompanied by elevated levels of uric acid, oxalate, and reduced levels of citrate and magnesium in the urine.[44].

Calcium stones typically consist of calcium oxalate, often mixed with calcium phosphate or calcium urate.[45] Factors contributing to the formation of these stones include elevated calcium levels in the urine (hypercalciuria), reduced urine volume, and low levels of citrate in the urine (hypocitraturia). Hypercalciuria is frequently linked to conditions causing elevated blood calcium levels, such as hyperparathyroidism, certain cancers, sarcoidosis, and high vitamin D intake.[46] When no specific cause is identified, it is termed "idiopathic hypercalciuria," a condition that often runs in families and is influenced by multiple genetic factors, though rare single-gene disorders like Dent's disease can also cause it. This disease is characterized by hypercalciuria, kidney calcification (nephrocalcinosis), and potential kidney failure. Furthermore, alkaline urine can increase the risk of calcium phosphate stone development [47]. Hyperoxaluria, which can result from bowel diseases (enteric hyperoxaluria) or genetic disorders affecting oxalate metabolism (primary hyperoxaluria), also raises the risk of calcium oxalate stone formation.[48]

Dietary oxalate plays a crucial role in kidney stone formation. Foods like spinach, beets, and rhubarb are rich sources of oxalate, which can increase urinary oxalate excretion and raise the risk of developing calcium oxalate stones. Furthermore, excessive intake of vitamin C can lead to increased oxalate production since ascorbic acid is metabolized into oxalate. Calcium can reduce oxalate absorption in the colon by forming insoluble calcium oxalate complexes. [49]

1.8.2 Struvite Stones:

Struvite stones, alternatively referred to as triple phosphate stones or infection stones, arise from upper urinary tract infections triggered by bacteria such as Proteus and Klebsiella that produce urease. Under normal circumstances, urine does not contain high levels of ammonium phosphate. However, struvite stones develop due to heightened ammonia production and an increased urine pH, which lowers phosphate solubility. The presence of

bacterial urease is crucial in struvite stone formation because it raises levels of ammonium and carbonate ions while simultaneously increasing urinary pH.

Struvite stones are composed of magnesium ammonium phosphate and have the potential to grow large enough to occupy the renal collecting system, forming partial or complete staghorn calculi. The formation of these stones is associated with persistent urinary tract infections caused by Gram-negative bacteria that produce urease, including species like Proteus, Pseudomonas, and Klebsiella.[50]

1.8.3 Uric acid stones:

Uric acid stones form due to factors such as high purine intake from diet or medications, and conditions involving rapid cell turnover like malignancy, often seen in patients with gout. These stones typically develop in slightly acidic urine with a pH around 5.5 and are generally not visible on X-ray due to their radiolucent nature. Instead, they can be detected using ultrasound or computed tomography (CT) scans.

Pure uric acid calculi are radiolucent on plain radiographs but visible on ultrasound or CT scans, and they tend to occur in individuals with hyperuricosuria. About 1520% of patients with uric acid stones have a history of gout. A diet high in animal protein, which increases uric acid production during catabolism due to its high purine content, can elevate the risk of uric acid stone formation. Uric acid solubility decreases significantly when urinary pH is below 5.5 but improves above 6.5.[51-53]

1.8.4 Cystine Stones:

Cystine stones are caused by cystinuria, an inherited metabolic disorder affecting the renal tubule's ability to reabsorb cystine.[54] These stones can be challenging to detect on Cystinuria is a rare genetic disorder, estimated to affect approximately 1 in 15,000 adults in the United States, and it represents only about 1% of all cases of nephrolithiasis. It follows an autosomal recessive inheritance pattern and is characterized by excessive excretion of cystine in the urine due to abnormal transport in the renal tubules. Symptoms typically appear as early as the first decade of life and can continue into the fourth decade. These symptoms often include the formation of kidney stones, which tend to be large, numerous, and can affect both kidneys. Diagnosis involves identifying hexagonal crystals in the urine. Patients commonly experience complications such as urinary tract infections,

kidney stone-related obstructions, and recurrent stone formation occurring every 1 to 4 years.[55-56]

1.8.5 Drug-Induced Stones:

Some medications have been linked to the formation of renal stones, which may serve therapeutic purposes in other diseases. Examples of these medications include indinavir, atazanavir, guaifenesin, triamterene, silicate-containing antacids, and sulfa drugs. Although rare, these stones are typically identifiable on X-rays.[56]

1.9 PATHOPHYSIOLOGY:

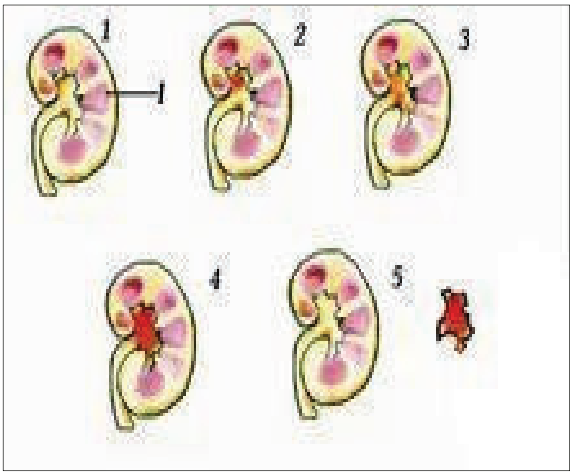


Figure No. 1.2: Pathophysiology of Kidney stone

Kidney stones, typically composed of calcium oxalate crystals measuring around 4–5 mm in size, form within the kidneys. Larger stones, known as staghorn kidney stones, can grow considerably bigger.

- The process begins with calcium and oxalate combining to form the initial crystal nucleus, facilitated by conditions of supersaturation or inhibition.
- These crystals then continue to accumulate at the renal papillae, leading to the gradual growth of kidney stones.
- As kidney stones increase in size, they can accumulate debris. Severe cases involve stones blocking all paths to the renal papillae, causing intense pain and discomfort.
- Complete staghorn stones can form, causing retention. Small fragments breaking off may get lodged in urinary ducts, contributing to further discomfort.

- Stones that dislodge may travel through the ureter. If they cannot be naturally fragmented, surgical intervention becomes necessary for their removal.

1.9.1 Supersaturation of urine:

When urine contains excessive amounts of substances that can form crystals, such as calculogenic substances, tiny crystals known as seed crystals may develop through nucleation. Heterogeneous nucleation, which occurs on solid surfaces, typically progresses more rapidly than homogeneous nucleation, which occurs within a liquid medium without solid surfaces, due to lower energy requirements. Once these seed crystals adhere to cells on the surface of a renal papilla, they can grow and accumulate, eventually forming a structured mass. The rate of stone formation can vary based on the pH of the urine, which may be unusually high or low depending on the chemical composition of the crystals.[57]

The likelihood of uric acid dissolving in urine, and thus the potential for uric-acid stone development, is greatly influenced by the pH level of the urine. For example, when the urine pH is 7.0, uric acid solubility is around 158 mg per 100 mL. However, if the pH drops to 5.0, the solubility significantly decreases to less than 8 mg per 100 mL. This means that the formation of uric-acid stones requires both high levels of uric acid in the urine (hyperuricosuria) and a low urine pH; high uric acid levels alone are not sufficient if the urine pH is not acidic. It's essential to understand that while urine supersaturation is necessary, it is not the only factor needed to cause urinary stones. Although supersaturation is a key factor in the formation of uric acid and cystine stones, calcium-based stones, such as calcium oxalate stones, may have more intricate causes.[58-59]

1.9.2 Randall's plaque:

Randall's plaque, first identified by Alexander Randall in 1937, is composed of calcium phosphate deposits located in the papillary interstitium. These plaques are thought to act as the initial site (nidus) for the development of kidney stones. Although urine supersaturation can lead to crystalluria, it does not inevitably lead to stone formation because the crystals may not attain the necessary size for attachment within the kidneys[60][61]. Furthermore, Randall's plugs can develop within the Duct of Bellini, and this, along with Randall's plaques, can contribute to the formation of stones by producing reactive oxygen species.[62-64]

1.9.3 Pathogenic bacteria:

Some types of bacteria play a role in the development of stones in the urinary tract. For example, Proteus mirabilis, which is urease-positive, generates an enzyme called urease. This enzyme transforms urea into ammonia and carbon dioxide [65], leading to an increase in urinary pH levels. The higher pH levels create a favorable environment for the formation of struvite stones. Moreover, bacteria that do not produce urease can supply components that facilitate the crystallization of calcium oxalate, although the exact mechanism behind this phenomenon remains unclear. [66][67]

1.9.4 Inhibitors of stone formation:

Normal urine contains chelating agents such as citrate, which help prevent the formation and aggregation of calcium-based crystals. Other inhibitors found naturally in urine include calgranulin, a calcium-binding protein from the S-100 family; Tamm-Horsfall protein; glycosaminoglycans; uropontin (a form of osteopontin); nephrocalcin, an acidic glycoprotein; prothrombin F1 peptide; and bikunin, which is rich in uronic acid. Although the precise biochemical pathways through which these substances act are not entirely clear, a deficiency in these inhibitors can lead to crystal aggregation and kidney stone formation.[68] Ensuring adequate intake of magnesium and citrate through the diet can help prevent the development of calcium oxalate and calcium phosphate stones. Additionally, magnesium and citrate work together to inhibit kidney stone formation, though the effectiveness of magnesium in reducing stone formation and growth depends on the administered dosage.[69]

1.9.5 Hypocitraturia:

Hypocitraturia, a condition where urinary citrate excretion is low (commonly defined as under 320 mg/day), is a contributing factor in many kidney stone cases. Citrate is beneficial in preventing stone formation by decreasing the urinary supersaturation of calcium salts through the formation of soluble complexes with calcium ions and by inhibiting the growth and aggregation of crystals. To increase urinary citrate levels and reduce the risk of kidney stones, potassium citrate therapy is often prescribed. Additionally, alkali citrate, which comes in pill, liquid, or powder forms, can be used to boost urinary citrate levels and is available both by prescription and over-the-counter.[70][71]

1.10 DIAGNOSIS:

Diagnosis of kidney stones relies on information gathered from the patient's medical history, physical examination, urinalysis, and radiographic studies. Typically, clinical diagnosis hinges on assessing the pain's characteristics, often described as colicky and intermittent, to determine its location and severity. Pain in the back can indicate obstruction caused by calculi in the kidney. Moreover, during a physical examination, clinicians may observe symptoms such as elevated body temperature and sensitivity around the costovertebral angle on the affected side.[72-74]

1.10.1 Imaging studies:

Calcium-containing stones are relatively radiodense and can often be identified using a traditional radiograph of the abdomen, which includes imaging of the kidneys, ureters, and bladder (KUB film). However, while a KUB radiograph is valuable for monitoring stone size or passage in stone formers, its sensitivity in acute settings may be limited. Approximately 60% of all renal stones are radiopaque. Calcium phosphate stones typically exhibit the highest density, followed by calcium oxalate and magnesium ammonium phosphate stones. In contrast, cystine calculi are minimally radiodense, whereas uric acid stones are generally radiolucent.. [75-79]

People under 50 years old who have a previous history of kidney stones and symptoms indicating their presence, but lacking alarming signs, generally do not require a helical CT scan for imaging.[80].

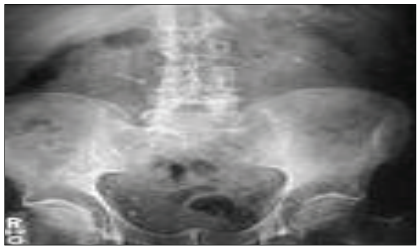
Moreover, CT scans are typically discouraged for pediatric patients [81]. Nonetheless, in cases where imaging is necessary, a non-contrast helical CT scan with 5-millimeter (0.2-inch) sections is preferred for diagnosing kidney stones and confirming kidney stone disease. Most types of kidney stones are detectable via CT scans, except for those composed of specific drug residues in urine, like indinavir.

When a CT scan is unavailable, an intravenous pyelogram (IVP) can be performed to confirm the diagnosis of urolithiasis. This procedure involves injecting a contrast agent into a vein, followed by obtaining a KUB (kidneys, ureters, bladder) radiograph. The contrast agent improves the visibility of uroliths in the kidneys, ureters, or bladder. Alternatively, stones can be identified using a retrograde pyelogram, where a similar contrast agent is

injected directly into the distal ostium of the ureter, the point where the ureter enters the bladder. [82]

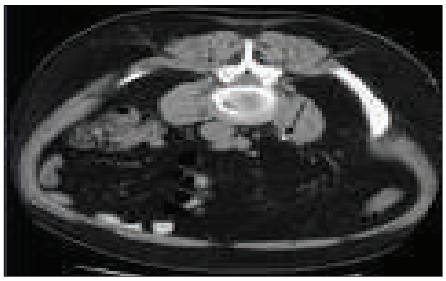
Renal ultrasonography can be beneficial in clinical practice due to its ability to provide insights into the presence of hydronephrosis, indicating potential obstruction of urine flow by stones. Unlike KUB, ultrasound imaging can detect radiolucent stones that are otherwise invisible on X-rays. Additionally, renal ultrasonography is advantageous because it is cost-effective and does not expose patients to radiation. It is particularly valuable in populations where radiation exposure is a concern, such as children and pregnant women. In 2009, renal ultrasonography was not considered a replacement for noncontrast helical CT scans in the initial assessment of urolithiasis. This limitation arises because ultrasound may be less effective than CT scans in detecting small stones, especially in the ureters, and may fail to identify other significant underlying conditions that could be causing the symptoms. [83-85]

In contrast, according to a 2014 study, ultrasonography was recommended as the primary diagnostic imaging test. Additional imaging studies should be conducted based on clinical judgment by the physician. Opting for ultrasonography over CT scans initially leads to reduced radiation exposure with comparable clinical outcomes.[86]



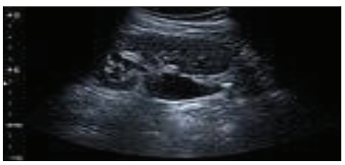
(A)

This KUB radiograph reveals kidney stones on both sides. Additionally, there are phleboliths located in the pelvis, which might be mistaken for bladder stones.



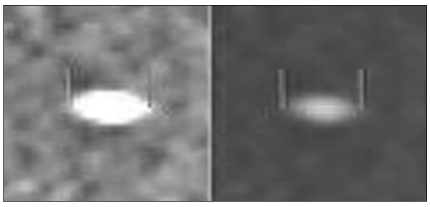
(B)

An axial CT scan of the abdomen without contrast reveals a 3-mm stone located in the left proximal ureter, clearly indicated by an arrow.



(C)

Renal ultrasound revealed a stone positioned at the junction between the renal pelvis and the ureter, alongside signs of hydronephrosis.



(D)

Detection of a kidney stone measuring 5.6 mm using soft tissue rather than skeletal CT window.

Figure No. 1.3: Ultrasonography showing presence of Kidney stone. A: Bladder stone, B: left proximal ureter stone, C: Stone located at the pyeloureter junction, D: 5.6 mm large Kidney stone in soft tissue.

1.11 KIDNEY STONE COMPOSITION AND RECURRENCE:

Calcium-containing stones are the predominant type of kidney stone worldwide [84]. In Olmsted County, Minnesota, a study found that calcium stones constituted 94% of all kidney stone cases, with 76% primarily composed of calcium oxalate, 18% of calcium phosphate, 5% uric acid stones, 1% struvite magnesium ammonium phosphate, and 0.1% cystine stones [85]. Similar trends were noted in Germany, where an analysis of 45,783 urinary stones from 2007 to 2020 identified calcium oxalate (CaOx) as the most prevalent type at 71.4%, followed by calcium phosphate at 10.2%, and uric acid at 8.3%.[86]

Uric acid nephrolithiasis constitutes approximately 8–10% of kidney stone cases and its prevalence is increasing globally. It is frequently observed in individuals who are obese or have metabolic syndrome. This rise in incidence correlates with the increasing rates of metabolic syndrome, obesity, and diabetes worldwide. Uric acid stones are more prevalent

among older adults. Hyperuricosuria is not the primary cause; instead, it is the acidity of the urine that plays a crucial role. [87].

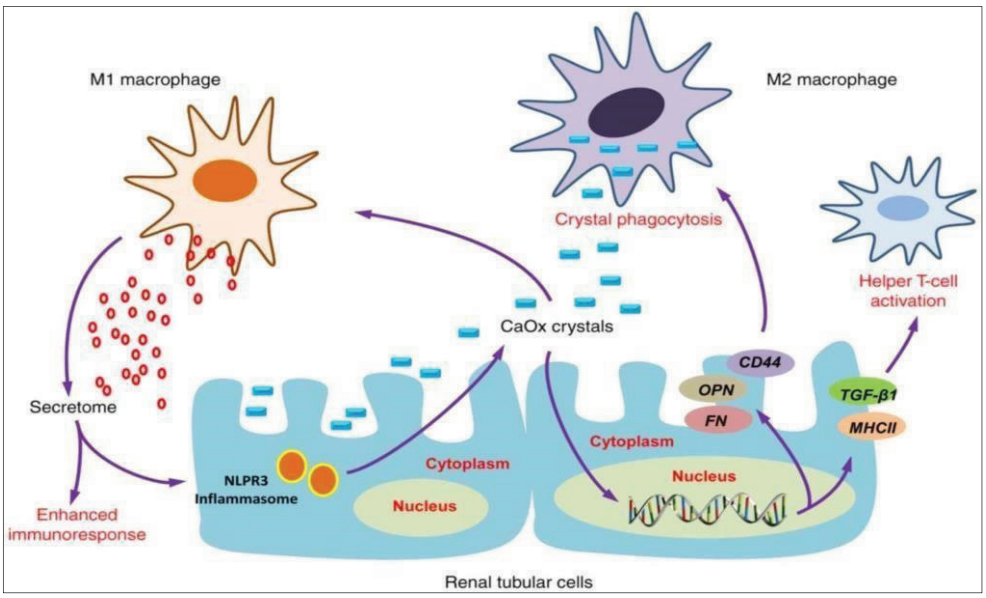


Figure No. 1.4: Mechanism of Kidney Stone Formation

In a retrospective study conducted at a major stone center in the United States, researchers observed a significant rise in the prevalence of uric acid stones among 1516 patients between 1980 and 2015. Initially accounting for 7% of kidney stones, uric acid stones increased to 14% during this period. The study found that individuals with uric acid stones tended to be older, had higher BMI, and lower urinary pH compared to those with calcium stones [88].

Another study across seven states in the US, involving 4339 kidney stone cases, reported a 12% incidence of uric acid stones. It noted that stone composition varied minimally between regions except for Florida [47].

Norwegian surgical data over four decades revealed an increase in uric acid stones from 2.0% to 9.1% during the 2014–2017 period [89,90]. Struvite stones, which are associated with infection due to urea-splitting bacteria, constitute 7–8% of kidney stones worldwide [91].

Certain rare inherited metabolic disorders, such as cystinuria, primary hyperoxaluria, distal renal tubular acidosis (RTA), xanthinuria, Lesch–Nyhan syndrome, Dent disease, and adenine phosphoribosyltransferase (APRT) deficiency, frequently manifest as kidney stones in early childhood and pose a significant risk of recurrence.

Cystinuria, the most prevalent among rare monogenic disorders, causes approximately 6% to 8% of kidney stones in children and 1% to 2% in adults [92]. Primary hyperoxalurias, estimated to affect about 1 to 3 individuals per million population, are crucial to identify [93]. Left untreated, these conditions can lead to recurrent kidney stones, especially in primary hyperoxaluria type 1, which may progress to kidney failure. Currently, epidemiological data highlight uric acid and other rare stones as posing the highest risk for symptomatic recurrence, underscoring the importance of understanding stone composition for effective disease prevention.

Stone recurrence is broadly defined to encompass both symptomatic stones that are clinically evident and asymptomatic changes detected through radiographic imaging of kidney stone burden [94] There has been inconsistency in terminology and classification in this field, alongside varying reported rates of recurrence. Earlier studies have suggested recurrence rates for nephrolithiasis as high as 50%.[95, 96] A community-based study conducted in Minnesota and Florida with a 5-year follow-up found that 19% of patients experienced symptomatic recurrence, while 25% reported recurrence, albeit self-reported. Radiographic evidence revealed asymptomatic recurrence, including new stone formation in 35% of patients, stone growth in 24%, and spontaneous stone passage in 27%.[97] The study proposed a novel "rule of halves" based on its findings: "half of initial symptomatic stone formers have an underlying asymptomatic kidney stone at baseline, half of whom will pass the stone within the next 5 years, and half of these will experience symptoms (pain or gross hematuria) during stone passage.[98].

In a study of symptomatic kidney stone recurrence in Olmsted County, Minnesota, the rates per 100 person-years following initial episodes were as follows: 3.4 (95% CI, 3.2–3.7) after the first episode, 7.1 (95% CI, 6.4–7.9) after the second episode, 12.1 (95% CI, 10.3–13.9) after the third episode, and 17.6 (95% CI, 15.1–20.0) after the fourth or subsequent episodes ($p < 0.001$ for trend). Several independent risk factors for increased recurrence were identified, including younger age, male sex, higher body mass index, family history of stones, pregnancy, and a history of brushite, struvite, or uric acid stones [99].

A systematic review encompassing twenty-one studies from 1976 to 2011 reported a median five-year recurrence rate of 26% among first-time kidney stone formers [100]. Furthermore, a comprehensive meta-analysis that included 40 retrospective and 13 prospective studies involving 488,130 patients identified twelve risk factors associated with kidney stone

disease recurrence: younger age, higher BMI, family history of kidney stones, personal history of kidney stones, hypertension, uric acid stones, white race, suspected prior kidney stone episode, previous surgery, presence of concurrent asymptomatic stones, presence of pelvic or lower pole kidney stones, and completion of a 24-hour urine test [101-102]

1.12 ROLE OF HERBAL MEDICINES IN MANAGEMENT OF KIDNEY STONE:

Urolithiasis is recognized as one of the eight major health issues, and in Ayurveda, urinary stones are commonly referred to as mutraashamari (mutra for urine, ashma for stone, and ari for enemy). Ayurvedic texts describe four main types of urinary calculi: phosphatic stones (sleshmaashmari), urate stones (pittaashmari), oxalate stones (vataashmari), and spermoliths or seminal concretions (sukraashmari). Ayurvedic medicine employs herbal remedies, alkaline beverages, and surgical techniques to effectively treat and manage urinary stones.

To address urinary stone illnesses, Ayurvedic treatments typically include Shodhana therapies (involving external and internal oleation and induction of sweating), Shamana therapy, and Panchakarma procedures like medicated emesis, purgation, and enemas. These treatments involve the oral administration of herbal medicines such as mutraladravyas (diuretics), ashmaribhedana (lithotriptics), and teekshnaushna (penetrative).[103]

1.13 ROLE OF PARATHYROID HORMONE AND CALCITONIN IN MANAGEMENT OF CALCIUM LEVEL IN BLOOD AND URINE:

Calcitonin plays a crucial role in maintaining calcium and phosphate levels in the bloodstream. Its mechanism involves counteracting the effects of parathyroid hormone, thereby lowering calcium levels in the blood. Additionally, calcitonin decreases the excretion of calcium and magnesium in urine by enhancing reabsorption within the loop of Henle.

Parathyroid hormone (PTH) plays several critical roles in regulating calcium and phosphate levels in the body through its actions on the kidneys. In the nephron, the majority of calcium reabsorption occurs in the proximal convoluted tubule and the ascending loop of Henle. PTH primarily acts on the distal convoluted tubule and the collecting ducts of the nephron,

where it enhances calcium reabsorption directly. By doing so, PTH reduces urinary calcium loss. Additionally, PTH stimulates the activation of vitamin D in the kidneys, which further aids in calcium absorption from the intestines. Importantly, PTH inhibits phosphate reabsorption in the proximal convoluted tubule. This action is crucial because phosphate ions in the blood tend to form insoluble salts with calcium, thereby reducing the level of ionized calcium in the bloodstream. Therefore, by reducing phosphate reabsorption, PTH helps to maintain adequate levels of ionized calcium in the blood.[104]

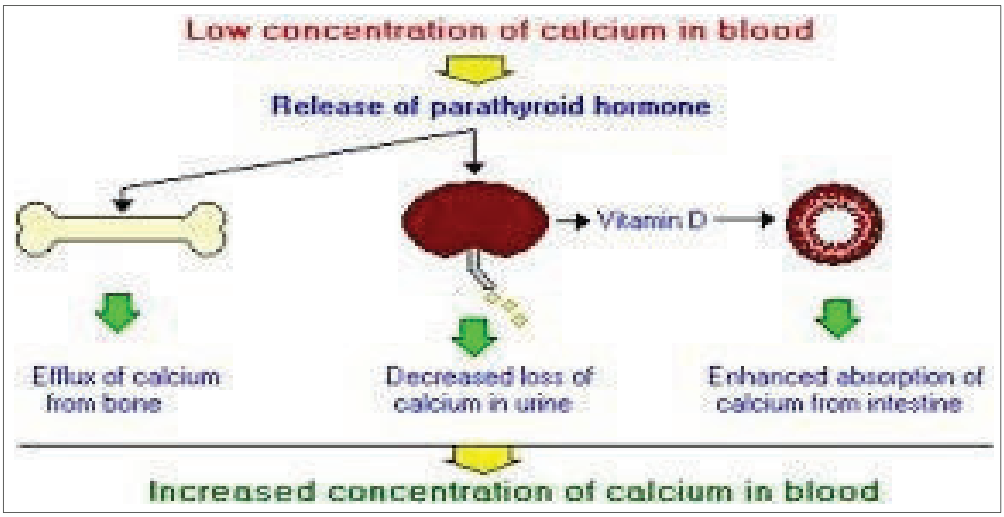


Figure No. 1.5: Role of Parathyroid Hormone in Blood

Calcitonin is involved in regulating calcium and other mineral levels within the kidneys. It inhibits phosphate reabsorption by the kidneys and enhances the reabsorption of calcium and magnesium, thereby increasing calcium excretion through urine.

Parathyroid hormone (PTH) initiates its action at the kidneys by promoting the synthesis of 1 alpha-hydroxylase in the proximal convoluted tubule. This enzyme is crucial for converting inactive vitamin D (25-hydroxycholecalciferol) into its active form, 1,25-dihydroxycholecalciferol. Active vitamin D facilitates calcium reabsorption in the distal convoluted tubule through calbindin-D, a vitamin D-dependent calcium-binding protein. In the small intestine, vitamin D promotes calcium absorption via both an active transcellular pathway requiring energy and a passive paracellular pathway that utilizes tight junctions.[105]

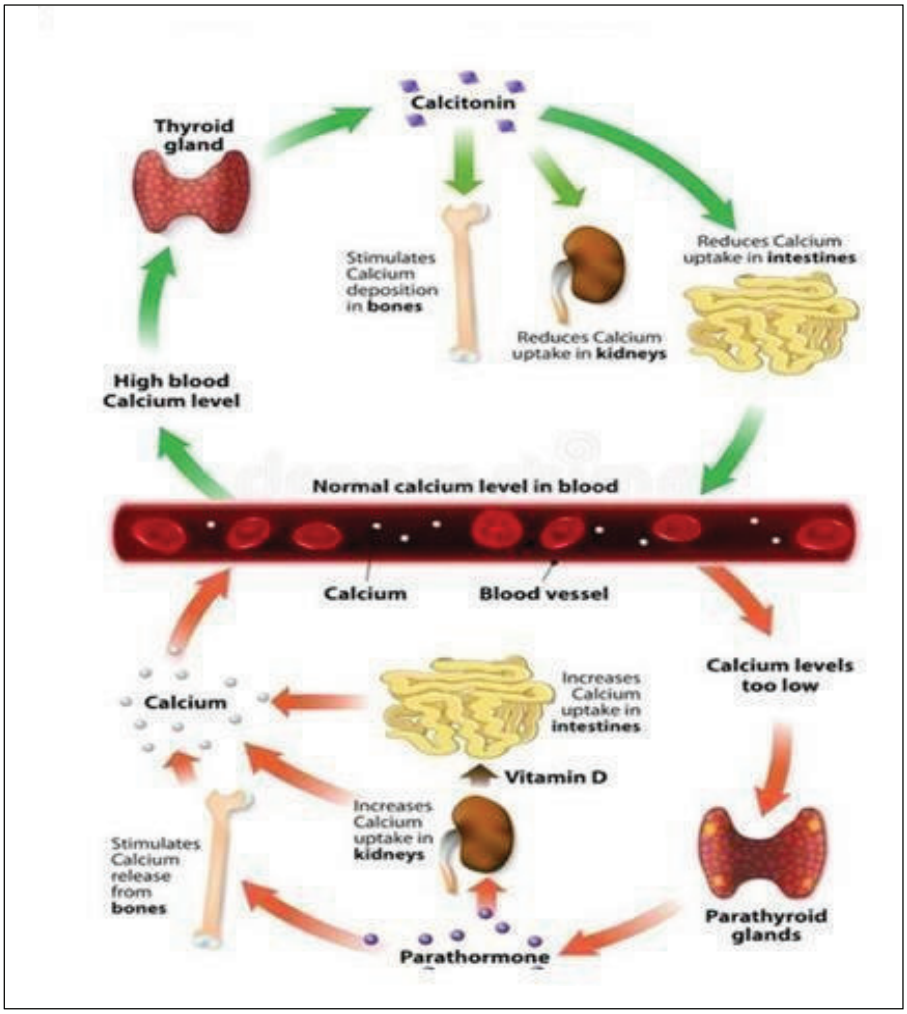


Figure No. 1.6: Role of parathyroid hormone and calcitonin in management of calcium level in blood