

**School of Medicine and Health Sciences
Division of Basic Medical Sciences
Discipline of Biochemistry and Molecular Biology**

PLB SEMINAR

URINARY (RENAL) STONE FORMATION – An Overview

What are Urinary (Renal) Stones?

- ❑ Urinary stones (Nephrolithoisis or Renal calculi) are mineral buildups in the urinary system
 - Urinary stones are formed when various Salt or Mineral Crystals gradually build up on the Inner surfaces of Kidney or Urinary Tract
- ❑ Urinary stones (Renal calculi) may occur anywhere in Urinary tract and
 - Urinary stones are often jagged and sharp
- ❑ Piece of Stone may break off causing severe pain as it travels through the urinary tract, especially along the Ureter
 - Urinary stones are common causes of Pain, Obstruction and Secondary infection
- ❑ Many urinary stones pass without notice, but some are too large to pass and get imbedded in the wall of the ureter

What are Urinary stones made of?

- ❑ Most urinary stones are composed of one or more of the following substances:
 - ❑ Calcium Oxalate, Calcium Phosphate, Uric Acid, Cystine, Xanthine
 - ❑ A mixture of these with Magnesium Ammonium Phosphate (Struvite), or “Infection” stones
- ❑ All of the substances are poorly soluble, and for some, solubility is influenced to a major degree by the urinary pH
- ❑ These compounds crystallize within an Organic Matrix, forming stone
- ❑ Chemical analysis of urinary stones is important in investigation of their composition and why they have formed
- ❑ Stones may have characteristic Colors or Appearance, but Crystallographic Analysis should be used to determine the composition of the stones

How are Urinary stones formed?

- ❑ Many factors play a role in urinary stone formation, but exact mechanism of their formation, and what causes them to form is not fully know
- ❑ Most common theory used to explain formation is called “Super-Saturation Crystallization”
 - Dehydration can either cause Calcium Phosphates, Oxalates, Urea, Uric Acid, and/or other compounds to combine and crystallize
 - ❑ Other related factors are Age, Sex, and Family history of Stones, Water Consumption, Climate, Associated Medical Problems, and Dietary Patterns
 - Example, high doses of Vitamin C supplements on a regular basis (500mg or more) increase the risk of urinary stone formation in some individuals
 - Eating foods High in Oxalate may also trigger urinary stone formation
- ❑ Foods with Oxalate levels include Spinach, Rhubarb, Beets, Nuts, Chocolate, Wheat Bran, Tea, Strawberries
- ❑ Usually males suffer from urinary stones more often than women

What are some of the factors that can cause urinary stones to occur?

- Several reasons may cause urinary stones to occur:
 1. Occur due to Abnormal and Excessive Accumulation of Stone forming substances (such as, Calcium, Oxalate, Uric Acid, Cystine etc) in urine, which are normally soluble in the presence of substances (such as Citrate and Pyrophosphates) that inhibit the formation of urinary stones
 - a. Stone formation occurs when concentration of stone forming substances is very high and inhibitors are low
 2. Imbalance of factors affecting solubility of components in the urine
 3. Some inherited metabolic disorders may or may not result in stone formation,
 - a. Examples: Hypercalciuria, Hyperoxaluria, Cystinuria
 4. Less intake of fluids,
 - a. People living and working in hot conditions are liable to become dehydrated, and show a greater tendency to form renal stones, as the urine become more concentrated
 5. Urinary infection, because debris of Bacteria promotes crystal formation
 6. The pH of urine (altered both by bacterial activity and metabolic factors), alkaline urine formed due to infection with urea splitting organisms e.g., Proteus predisposes to formation of Magnesium Ammonium Phosphate stones (insoluble in alkali),
 7. Mucoproteins in urine provide Organic Nidus on which crystal deposition occurs
 8. Congenital anomalies of urinary tract with obstruction,
 9. Hyperparathyroidism, Renal Tubular Acidosis (RTA) can cause stone formation

Why do some individuals have multiple recurrences of urinary stones?

- Mechanisms responsible for multiple recurrences of urinary stones in some individuals are not completely understood but may involve multitude of factors including the following:
 - Low urine flow (low fluid intake)
 - Factors increasing the super-saturation of the urine with stone-forming salts, which include over excretion states and conditions that lead to inadequate amounts of urine
 - Absence, in individuals of substance or substances in the urine that, under normal circumstances, inhibit precipitation of insoluble agents (i.e., abnormal crystal growth inhibitors)
 - Occupation of the individual – as possible cause of dehydration
 - Nature of the diet of the individual
 - Medical conditions such as recurrent urinary infections, Gout, Cystinuria, family history of gout or urinary calculi

What are the characteristics of Calcium Oxalate stones?

- ❑ Calcium oxalate stones:
 - ❑ Most common stones encountered
 - ❑ May be associated with either persistently concentrated urine or consistently increased excretion of urinary calcium or oxalate
 - ❑ Is not composed of pure Calcium Oxalate, but Calcium Oxalate predominates, with small quantities of Calcium Phosphate and Uric acid also present
 - ❑ Sometimes no abnormality is found in stone-forming individuals beyond a persistently small urine volume;
- ❑ Test for calcium and oxalate output in the urine of patients must be assessed to ascertain that the mechanism of urinary acidification is normal
- ❑ High fluid intake is beneficial, because it is effective in diluting Calcium and Oxalate preventing **Hypercalciuria**
- ❑ **All stone-formers should aim to pass at least 1.5L of urine per 24-hour**
- ❑ **A simple guide for the patient is to aim to keep the urine as colorless as possible;**
- ❑ **As a rule, the darker the urine, the more concentrated, hence the greater likelihood of crystal formation and subsequently stones**
- ❑ There are a number of diuretic drugs that can lower urine calcium excretion and prevent the super-saturation of urine with calcium oxalate
- ❑ Low calcium diet and sodium cellulose phosphate should be used cautiously, since there is a possibility of producing chronic negative calcium balance.

What is Hypercalciuria?

- ❑ **Hypercalciuria** is defined by an excretion rate of Calcium of about:
 - ❑ 300 mg/day (for men), 250 mg/day (for women) or 4 mg/kg for both male and female

What is Hyper-oxaluria?

- ❑ **Hyper-oxaluria** – is caused by enteric disease or excess ingestion of Oxalate-containing foods (e.g., spinach, cocoa, nuts, pepper, and tea)
- ❑ Amount of oxalate in the urine and clinical history will discriminate among the causes of hyper-oxaluria
- ❑ Usually suggested that Stone-formers with mild Hyper-oxaluria may consume diet high in Calcium **Why?**
 - Because calcium binds Free Oxalate in GIT and prevents its absorption and subsequently excretion in the urine
- ❑ Idea that stone-formers should eat more foods rich in Fiber content and hence Phytic Acid with the aim of binding Calcium in the GIT is not really a good suggestion, **Why?**
- ❑ Because this may make the Ingested Calcium less available to bind Oxalate
- ❑ An obvious strategy is to keep the diet low in Oxalate

What is Hyper-uricosuria?

- ❑ **Hyper-uricosuria** is defined as:
 - ❑ **Uric acid level in urine greater 750 mg/24hrs (in women) or 800 mg/24hrs (in men)**
 - ❑ **Uric acid crystals provide a nidus on which Calcium Oxalate crystals can orient themselves and grow**
- ❑ Hyper-uricosuria is mainly due to excess consumption of Purine, (what are the sources of Purine in the diet?)

What are the characteristics of Uric acid Stones?

- ❑ Uric acid stones can occur in patients with normal serum and urinary levels of uric acid
- ❑ Some patients with uric acid stones may either have been diagnosed as having Gout or be shown to have Gout during investigation
- ❑ Myeloproliferative disorders and Chemotherapy can cause uric acid stone
- ❑ Majority of patients with Uric Acid stones can be treated medically
- ❑ Treatment involves:
 - ❑ High fluid intake to maintain an output of at least 2 L of urine a day and the adjustment of urinary pH to 6.5 - 7.0.
 - ❑ Important to monitor urine pH with test strips and adjust medication accordingly
 - ❑ If increased hydration and adjustment of pH do not achieve dissolution or prevent recurrence, the latter usually due to patient non-compliance, then Allopurinol can be used to reduce the excretion of uric acid

What are some of the causes Uric acid stone?

- ❑ **Uric acid stones** may occur because of increased urine acidity in which undissociated uric acid crystallizes
- ❑ Urate is far more soluble than uric acid
- ❑ Example:
 - ❑ **Urine at pH 7 can dissolve between 150 - 200 mg/dl of Urate, whereas urine at pH 5 can dissolve only about one-tenth as much Urate (i.e., between 15 - 20 mg/dl)**
 - ❑ **Normal urine usually has pH below 5.8**
 - ❑ **In urinary tract crystals are Sodium Urate anywhere Proximal to the site of Urine Acidification (Distal Tubules and Collecting Ducts) but Uric Acid at Distal sites**
- ❑ Since most stones of the urinary collecting system are composed of uric acid, stone formation can be reduced by Alkalinization of the urine
- ❑ Can be achieved by using either Sodium Bicarbonate tablets, or Citrate (Sodium or Potassium salt)

How can Uric acid stone formation be reduced?

- ❑ Intake of large amounts of food rich in Nucleic acids, (Sweet breads, Liver, Yeast, Kidneys, Sardines) raise Plasma Urate levels over 7 mg/dl (0.4 mmol/L) **Why?**
- ❑ Because dietary Purine bases are converted to Uric acid by Intestinal Xanthine Oxidase (enzyme that converts Hypoxanthine to Xanthine and Xanthine to uric acid)
- ❑ Purine-free diet would lower the Plasma urate level
- ❑ Diet adequate but not high in protein is advised, since high-protein foods might also contribute to an accelerated synthesis of Purine, because several amino acids are required for their synthesis
- ❑ Obesity contributes to Urate level because of the excessive amount of food required to maintain body weight
- ❑ Dehydration should be avoided, since urate crystallization is very dependent on concentration, thus the consumption of large quantity of water must be encouraged
- ❑ Alcohol causes diuresis leading to dehydration,
- ❑ High rate of alcohol metabolism may result in lactic acidosis, which might suppress tubular secretion of uric acid

What are some of the characteristics of Struvite stones?

- ❑ Struvite stones consist of Magnesium Ammonium Phosphate
- ❑ Struvite stones occur twice as commonly in women as in men **Why?**
 - Because Struvite stones are frequently associated with infection, although it is still unclear whether it is the stone that causes the infection or vice versa
 - Organisms associated with Struvite stones produce Urease, which splits Urea, thus raising urinary pH and causes precipitation
 - Organism that are commonly involved are Proteus, Pseudomonas and Klebsiella, but others, such as Staphylococcus, are occasionally responsible
- ❑ Urease inhibitors, such as Acetohydroxamic acid or Hydroxyurea, have been used to prevent Alkalinization of the urine and the precipitation of Struvite
- ❑ If the risk of recurrence is to be minimized, complete removal of the stone should be attempted and a high fluid intake should be maintained
- ❑ Agents that alter the urinary pH may have a role in the treatment of Struvite stones

What are the characteristics of Cystine stones?

- ❑ Cystine stones do not occur regularly, but correct diagnosis of Cystine stone is often delayed
- ❑ Family history is important as this condition is due to an Inherent Error in metabolism, characterized by increased excretion of the Amino Acids: Cystine, Ornithine, Arginine and Lysine
- ❑ Stones are composed mainly of Cystine, which is much less soluble in the urine than the other amino acids
- ❑ Cystine stones should be suspected in a patient that presents with a family history of stones, at an early age, and has not responded to common forms of treatment
- ❑ Diagnosis can be confirmed by either rapid screening using the Nitroprusside test or a high 24-hour Cystine excretion or Stone analysis
- ❑ Prevention of stone formation is adequate hydration (patient needs to produce more than 3 L of urine per 24 hours, which usually means drinking at least two glasses of water at night)
- ❑ Alkalinization of urine with large amounts of Bicarbonate
- ❑ Most patients find it difficult to maintain this regimen long-term and there is a high recurrence rate

What Chemical Investigations are carried on Patients with Renal Stones?

- ❑ Analysis of stone to identify some or all of its components
- ❑ Following tests may also be helpful in reaching a diagnosis:
 - ❑ Plasma Calcium, Albumin, Phosphate total CO₂, and Urate concentrations
 - ❑ Alkaline Phosphatase activity in plasma
 - ❑ Full acid-base assessment
 - ❑ Urine dipstick testing for pH and Protein,
 - ❑ 24-hour excretion of Calcium, Phosphate and Urate
 - ❑ Occasionally, urinary excretion of Oxalate, Cystine or Xanthine may be required
 - ❑ Urinary acidification tests
 - ❑ Renal function tests, or/and Plasma Creatinine concentration, and/or plasma concentration of Urea
 - ❑ Microbiological examination of urine