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Review Article

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A REVIEW ARTICLE ON URO LITHIASIS IN RATS FOR EXPERIMENTAL STUDY

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ABSTRACT

Urolithiasis is a common problem afflicted for many centuries with high recurrence. Stone formation in kidney is the oldest and the most widespread medical affliction known to human. The aim of this review is to provide comprehensive information about formation of stone in rats for experimental study. The present study was done to assess the pathophysiology of stone formation. Lithiasis (stone formation) induced by oral administration of 0.75% ethylene glycolated water to adult male albino wister rats for 14 days. The ionic chemistry of urine was altered by ethylene glycol, which elevate the urinary concentration of ions eg. Calcium, oxalate, phosphate, there by contributing renal stone formation. Also discuss about stone forming promoters and inhibiters.

KEYWORDS: Urolithiasis, Male Albino Wister Rats, Ethylene Glycol ETC.

INTRODUCTION

Lithiasis is a common disorder estimated to occur in approximately 12% of the population. Most calculi in the urinary system arise from a common component of urine eq. calcium, oxalate, phosphate, most commonly CaOx representing up to 80% of analyzed stone. The present day medical management of lithiasis includes lithotripsy and surgical procedures. Mechanism of formation of stone depends on concentration of phosphate, calcium, sodium, oxalate and uric acid ions; urinary volume, concentration of natural inhibitors of calculi and pH of urine. There are main three factors which determine stone formation by assessing **urinary compositions**: quantity of inhibitors (glycoaminiglycan, citrate etc), increase in level of stone forming elements and promoters (i.e.- sodium, urates etc**)** in urine. Promoters of stone formation are calcium, sodium, oxalate, urates, cystine, low urine pH and inhibitors of stone formation are divided in two parts, inorganic (magnesium, pyrophosphate, and citrate) and organic (nephricalcin, protease inhibitors, glycosaminoglycans and high urine flow).

Review of Literature

Lithiasis

Lithiasis (Stone formation) refers to the growth of hard, solid and non-metallic minerals in the urinary tract.

Lithiases are typically classified by their location:-

a. Nephrolithiasis (kidney)

In this stone is formed in the kidneys.

b. Ureterolithiasis (ureter)

In this stone is formed in the ureter.

c. Cystolithiasis (bladder)

In this stone is formed in the urinary bladder.

In most of the patients, stones are unilateral (one-sided) but some have bilateral (two- sided). There are some common sites for the formation of stones are renal pelvis, calyces and in the bladder. The stones have a tendency to be small (2-3mm) up to big (12-13mm) seize. A kidney stone is a hard and crystalline material formed in the kidney or urinary tract. A kidney stone is a common cause of blood in the urine and pain in the abdomen, flank or groin. Kidney stone are some time called **renal calculi**.

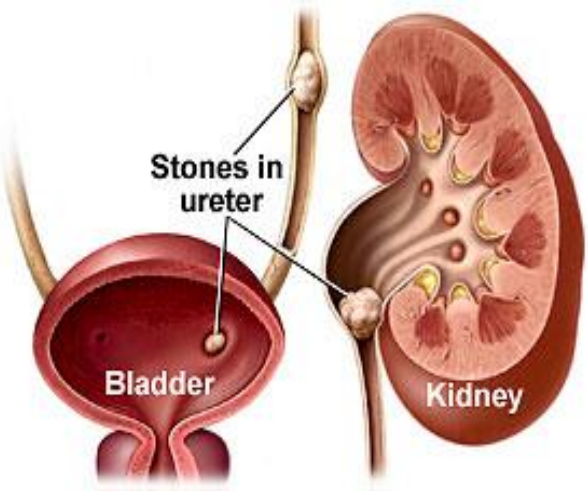


Figure. 1.1 Stone in Urinary Tract.

Epidemiology

Epidemiology of lithiasis varies according to the geographical area and socioeconomic conditions. Urinary calculi are much more likely to be found in individuals who have sedentary occupation. It is fairly common in developing and under developed countries, Urinary stone disease continues to occupy an important place in everyday urological practice. Metabolic abnormalities such as hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and gouty diathesis can change the composition or saturation of the urine so as to boost stone formation. Hyperoxaluria is the main initiating factor for Urolithiasis.

- In general UTI is believed to be predisposing factor for the Urolithiasis.
- Calcium oxalate stone are associated with chronic diarrheal symptoms.
- Menopause, postmenopausal hormone use and risk of this incidents kidney stones.

Theories of Stone Formation

There are four major theories have been proposed to explain stone formation and growth. These are-

1. Nucleation or crystallization.
2. Supersaturation.
3. Reduction of Inhibition.
4. Anatomical abnormalities..

1. Nucleation or crystallization.

The nucleation or crystallization theory states that when the ions or molecule i.e. organic material forms the core for crystalloid material formation, in a dissociated state binds and forms crystals. These clusters of crystal form lattice structure, which leads crystal are nucleated and grow by aggregation.

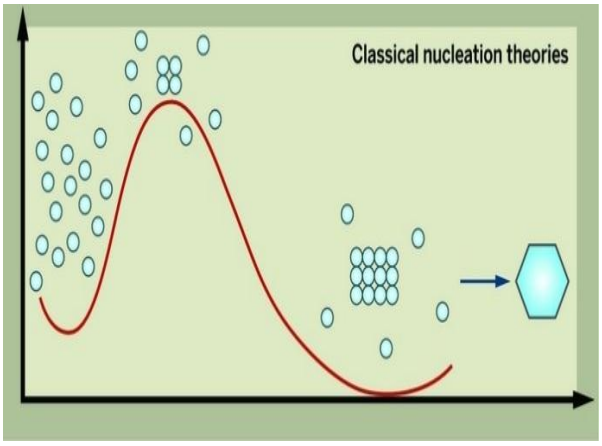


Figure. 1.2: Nucleation Theory.

2. Supersaturation Theory

The super saturation theory is based upon binding of stone forming crystalloid, calcium, oxalate and urea. This situation comes after a definite concentration of ions or salts is obtained in urine. When the concentration of salt is minus, compounds remain in the urine. On the other hand, if salt or ions concentration excess, the compound precipitates. Temperature & pH of a solution as well effects the solubility. It indicates that formation of crystals is the reason of supersaturation of urine.

3. Reduction of Inhibition

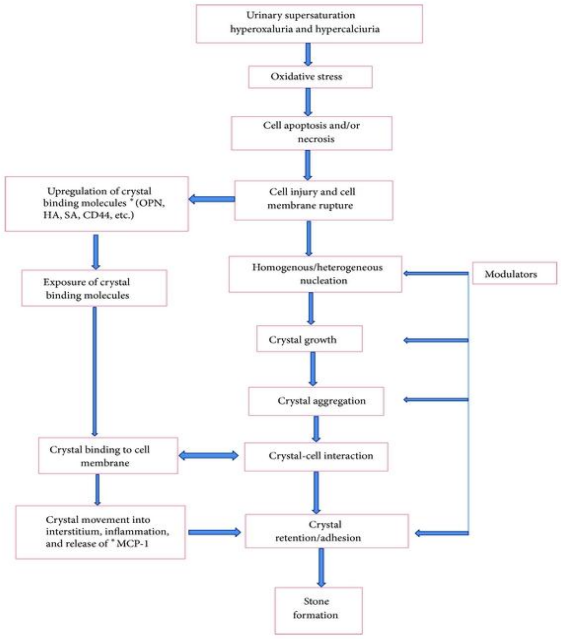
In this hypothesis, if there is a decline of crystalloids inhibitors that are the material that modify or alter crystal growth. whereas urine may be supersaturated with ions or salts, these inhibitors prevent the stone formation. Citrate is the most important urinary stone inhibitor, magnesium and phosphate are other important stone inhibitors. These molecules work by forming complex among active surface compounds, which reduces their binding of calcium to oxalate. The nonexistence or **reduction** of these inhibitors can assist in the production of stone formation.

4. Anatomical abnormalities.

Functional or an anatomic defect can also cause an obstruction of the flow of urine & the retention of urinary crystals. This crystal binds in the direction of epithelium & cause further crystal to aggregation into stone.

Pathogenesis of Stone

After that physio-chemical change in state of supersaturation and abnormal crystalluria, crystals aggregations, crystals growth is formed – stone formation.



Pathogenesis of Stone Formation

Material

Experimental Animal

Animals: Albino rats of wistar strain weighing 180 -220 gm were used. They were housed in group of six under standard in well ventilage cages of polypropylene maintained labratory conditions of temperatureat (25 ± 2^0 C) under 12 hr light – dark cycles. Animals had

free access to standard pellet diet and water. Laboratory animal handling and experimental procedure were performed in accordance with the OECD guidelines.

S. No.	Animal Name	Sex	Weight Range
1	Albino wistar rat	Male	180-220gm

Experimental Animal
Drugs and Chemicals Used
1. 0.75% ethylene glycol solution
2. Drinking water

List of Instruments
1. Metabolic cage
2. Digital weighing balance.

METHOD
For in-vivo study male rat of albino wistar rats were used. The animal were placed in polypropylene cages under hygenic condition & were provided standard animal feed and water. The animals were maintain in these condition for a one week before the experiment. All procedures were done in accordance with ethical guidelines for care and use of laboratory animals and were approved by the Institutional Animal Ethical Committee (IAEC).

Model: Ethylene Glycol (0.75 %) induced lithiasis.

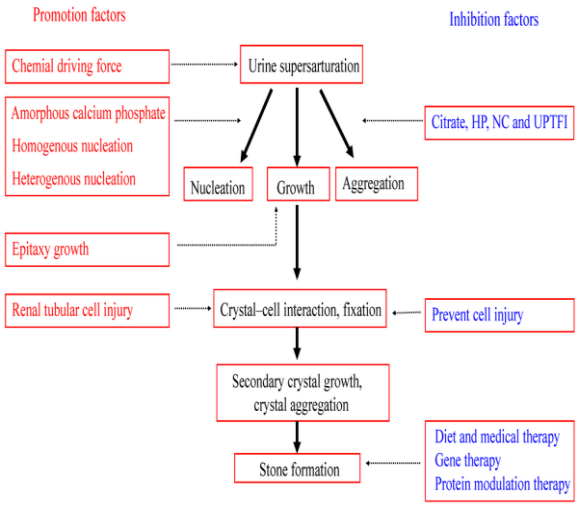
a. ***Principle:*** Ethylene glycol is rapidly absorbed and metabolized in liver via alcohol dehydrogenase and aldehyde dehydrogenase to glycolic acid.[82] This is oxidized to glyoxylic acid which is further oxidised to oxalic acid/oxalate by glycolate oxidase/ lactate dehydrogenase, thus promoting hyperoxaluria.[81] Which increases the calcium absorption in kidney. Administration of EG to rats results in hyperoxaluria, after this CaOx crystalluria occurs and this results occasional deposition of CaOx crystals in the kidney.[87] However, various crystal deposition rats have been reported with EG. Hyperoxaluria is the major risk factor for lithiasis.[88] Toxicity from EG is produced from the metabolites such as Glyceraldehydes and oxalate, producing wide spread tissue injury in the kidney. Dose: 0.75% v/v in drinking water for 14 days.[78]

b. Requirements
i. Animals: Male albino wistar rat.
ii. Chemicals**:** Ethylene Glycole 0.75% v/v.

c. Procedure
1. Experimental model
The animal were maintained these conditions for 1 week before the experimental session. This study was approved by our Institutional Animal Ethical Committee.[89]

Stone Formation Promoters and Inhibitiors
Kidney stone formation is a complex process that occurs due to imbalance between promoters and inhibitors in the kidneys. The waste product from the blood is filter by the kidney and excreted them to through the urine that the kidney produce. When waste materials do not dissolve completely in the urine, crystals or kidney stone are form means lithiasis occurs. Renal calculi form when there is a high level of calcium (hypercalciuria), oxalate (hyperoxaluria), and uric acid (hyperuricosuria) occurs in the urine. Kidney stones are formed by end products of metabolism i.e. uric acid, phosphates and oxalates which precipitate and take figure of stone. A lack of citrate in the urine or insufficient water in the kidney to dissolve waste products also leads formation of renal calculi. If dehydration occurs, increased urinary concentrations of calcium, oxalate and uric acid, may form crystal that slowly builds up into kidney stones.

Normally, urine contains chemicals like citrate, magnesium, pyrophosphate, Glycosaminoglycans. All these chemicals prevent formation of crystals and low level of these inhibitors contributes to the formation of kidney stone. Often these, citrate is trough to be most important because citrate or citric acid is an ordinary component of our diet, which is present in high amounts in citrus fruits.



Effect of Promoters and Inhibitors in Stone Formation.

A. Citrate
Citrate acts in the tubular lumen by combining with calcium to form a non-dissociable but soluble complex and this result in availability of a smaller amount free calcium to combine with oxalate. In addition, citrate also appears to inhibit the important process of crystal agglomeration, in which individual calcium oxalate crystals combine, to form a stone. Finally, it makes the urine less acidic, which inhibits the developments of both calcium oxalate or uric acid stones.

From the point of view of Urolithiasis, a condition increasing the urinary calcium in the urine will leads the condition for crystal formation. Despite what is known about renal calcium handing, the idiopathic form of hypercalciuria is the most common. It occurs in about

50% of calcium oxalate stone formers so, there are two main mechanisms have been proposed. The first is absorptive hypercalciuria. The serum calcium is normal and the suspected mechanism is enhanced gastrointestinal calcium absorption.

The second mechanism is renal hypercalciuria. In this renal hypercalciuria, fasting urinary calcium excretion is elevated, where as it is normal in absorptive hypercalciuria.

B. Magnesium

In the urine, the magnesium is also one of the crystal inhibitor. It acts by inhibiting calcium absorption or calcium solubility (in urine). It can help to prevent especially calcium oxalate containing kidney stone. It is thought those calcium oxalates are most likely to form in people who are magnesium deficient, so it may just correct that deficiency.

C. Pyrophosphate

Inorganic pyrophosphate is a potent inhibitor, which appestat affects calcium phosphate more than calcium oxalate crystals. Other uric inhibitors in urine that appear are glycoprotein's, which strongly inhibit the calcium oxalate crystals. As a consequence of the presence of these inhibitors, can slow the crystal grows in the urine.

D. Glycosaminoglycans (GAG)

Glycosaminoglycans are a class of complex long chain of polysaccharides made up of reciting disaccharides having alternative uronic acid and hexosamine residues. Glycosaminoglycans have been found as a macromolecule present in calculi matrix. Hyaluronic acid & heparin sulphate were removed through urine. GAGs are thought to play a major function in calcium oxalate crystallization. (Roberts SD and Resnick MI, 1986) In the growth of crystal and by zeta-potential measurements, glycosaminoglycans ware manifested to work as preventers of calcium oxalate minerals deposition & development by preventing the development areas and stop adhering of crystal to kidney cells.

Hyaluronic acid (HA) is an extremely large GAG. Hyaluronic acid is a best crystal combining a group of atoms breason of its size & capability to make hydrated gel. Mineral combining to Hyaluronic acid results into NC & to a production of Randall's plaques. (Verkoelen CF, 2006). Low level of these inhibitors can contribute to the formation of kidney stone.

Promoters

Promoters decrease the formation of super saturated solution. On the kidney cell surfaces, aggregates of protein, cell debris & other crystals can provide functionally same place for nucleation. The nucleation places can reduce super saturation which is needed to start crystallization and promote CaOx crystallization.

A) Calcium

Oxalate & calcium are major promoters of renal calculi production. Urine is a super saturated solution and few particulars are prone to nephrorolithiasis. So, the super saturated situation is not sufficient to precipitate calculus but aggregation & crystallization of those lithogenic materials results into formation of calculi.

B) Uric Acid

Uric acid is induced by xanthine oxidase from hypoxanthine and xanthine, which in turn are produced from purine. Uric acid is highly toxic to tissues than either hypoxanthine or xanthine. Increased or decreased concentrations of uric acid in blood and urine are not medical conditions, but are related with different medical conditions. Aroundly one third of volunteers with CaOx calculi have raised removal of urinary uric acid. Two possible mechanisms ware suggested: excessive dietary protein intake & endogenous uric acid over formation.

C) Oxalate

Oxalate is a final substance of glyoxylate & ascorbate biotransformation which is a usual constituent of renal calculi. Hyperoxaluria is marked risk factor in process of formation of calculi. Major oxalate in urine finds to be induced by biosynthesis of endogenous substances from precursors of oxalate which might or might not be a source of diet. Glycolic acid is a quick forerunner of oxalate which forms in regular food, divides markedly to the developing from inside biosynthesis of oxalate & is able for elevating urinary oxalate removal. CaOx mineral production is a toxic action of EG poisoning.

D) pH

pH < 5.5 increases risk of uric acid precipitation cause uric acid stones, pH > 6.7 increases risk of calcium phosphate precipitation and pH > 7 -7.5 increases urinary tract infection. pH between 5.8-6.2 considered normal and safe in prevention of stone prevention (Moe *et al.*, 2010).

CONCLUSION

Urolithiasis is a complex process that results due to some physiochemical events including supersaturation, crystal nucleation, crystal growth, aggregation and retention within the kidneys. In this way induced ethylene glycol help in lithiasis and so that experimental study can held out for several researches.

REFERENCES

1. Short practice of surgery-Baily and Love's with Chapman and Hall, 2013 26rd edition.
2. Text book of surgery Published by Dr.S.Das Calcutta 8th edition, 2014.
3. Devrao Awari, Vaishali Mute. Evaluation of antilithiatic effect of cucurbita pepo linn seed extract on ethylene glycol induced nephrolithiasis in rats, 2009.

4. Devrao Awari, Vaishali Mute. Antilithiatic effect of stem bark of butea monosperma on ethylene glycol induced lithiasis in male albino wister rats, 2009.
5. Pooja Tiwari, Preeti Kothiyal, Parminder Ratan Antiliurolithiatic effect of some polyherbal formulations used in experimentally induced urolithiasis, 2017.
6. Kidney stone- medical & surgical management ed.: Coe, Favus, Pak, Parks, perminger Lippincott-Raven, 1996.
7. Park S, Pearle MS. Pathophysiology and management of calcium stones. Urologic Clinics of North America, 2007 Aug 31; 34(3): 323-34.