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Post-Menopausal Consequences in Nephrolithiasis

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Abstract

Nephrolithiasis is a chronic metabolic disease characterized by a number of physical and chemical processes including supersaturation, nucleation, development, aggregation, and retention of urinary calculi components inside the tubular cells. A remarkable rise in the prevalence of renal calculi has been reported across the world, however, in recent years, females have experienced this expansion more severely than males. According to sex-based observations, females are more likely to have hypercalciuria, hypocitraturia, low urine volume, hyperuricosuria, and urinary tract infections, which further increases the chances of developing nephrolithiasis. Prior studies also shows that pediatric renal stone disease occurs more in females as compared to males. Some life events like pregnancy and menopause as well as a combination of factors such as the impact of sex hormones, abnormalities in handling acid-base balance and urine pH, female hormone therapy, the composition of stones, and imbalance between promoters and inhibitors of calculi formation may also contribute to the risk profile for urolithiasis in females. In this review, we summarize the risk factors and mechanistic aspects contributing to the rising prevalence of urolithiasis in females.

Introduction

The development of stones in the urinary tract is known as urinary tract stone disease. It affects males between the ages of twenty and forty more frequently (12%) than females (6%) and its recurrence has been a major issue for decades [1,2]. The majority of recent studies have revealed that the difference in the occurrence of urinary stones disease between males and females has reduced [3].

The process of formation of renal stones is complicated and comprises long-term occurrences including crystal nucleation, crystal expansion, crystal accumulation, and crystal retention [1]. Several agents like calcium, phosphate, oxalic acid urate, and cysteine level in urine are responsible for the development of urinary calculi [4]. The most frequently occurring stones are calcium-containing stones such as calcium oxalate monohydrate (COM), Calcium Oxalate Dihydrate (COD), and basic Calcium Phosphate (CaP) followed by magnesium ammonium phosphate (Struvite), uric acid, and cystine [5]. Former studies have shown the influence of gender on stone composition. In males, the chances of occurrence of calcium oxalate and uric acid stones are higher, whereas in women the chances of calcium phosphate stones, apatite stones, struvite stones, and infection stones are more [6,7].

Lifestyle may also contribute to stone formation. Obesity is related to the production of idiopathic calcium oxalate residues in the kidney which further causes the development of renal stones [8]. Chronic kidney disorders, end-stage renal failure, obesity, diabetes, higher rates of hypertension, and cardiovascular diseases have all been linked to urolithiasis [9,10].

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Types of stones found in the kidney

Calcium stone (Calcium Oxalate and Calcium Phosphate)

Most kidney stones are composed of calcium oxalate (CaOx), which accounts for around 80% of all kidney stones [11] whereas calcium phosphate stones are relatively rare [1]. The composition of calcium stones may be explained by pure calcium oxalate (CaOx) (50%) or calcium phosphate (CaP, also known as apatite) (5%), or by a combination of both (45%) [9]. When the urine is acidic (pH of 5.0 to 6.5), CaOx stones are more likely to develop, whereas calcium phosphate stones are more likely to form in urine that is alkaline [1,2]. Calcium hydrogen phosphate or hydroxyapatite, often known as brushite, is the major component of calcium stones. Compared to other kidney stone types, calcium stones tend to recur more frequently [9].

Xu et al. [12] in their retrospective studies and NHANES findings, show that the proportion of females is raised among calcium stone former over three time periods from 24% to 42%. The increasing tendencies of urinary oxalate, urinary phosphate, and urinary sodium are also reported in calcium stone formers.

Struvite or magnesium ammonium phosphate stones

Kidney infections cause struvite stones. The struvite stone is composed of ammonia, magnesium, and phosphate and grows quickly within a month by urease which helps in breakdown of urea into urine and produces ammonia and carbon dioxide, the ammonia then combines with the urine (solvent) [13,2]. The increased ammonia production leads to the increase in urine pH and inhibition of phosphate solubility and therefore forming a struvite stone [11]. Additionally, bacteria including staphylococci, proteus, and haemophilus bacteria that cause urinary tract infections promote the production of excessive ammonia. While yeast, gram-negative and gram-positive bacteria form the urease that leads to the formation of struvite stones [14,2].

Struvite calculi are significant clinically even though they only make up 2% to 3% of stones from humans since they can induce sepsis and renal failure [15].

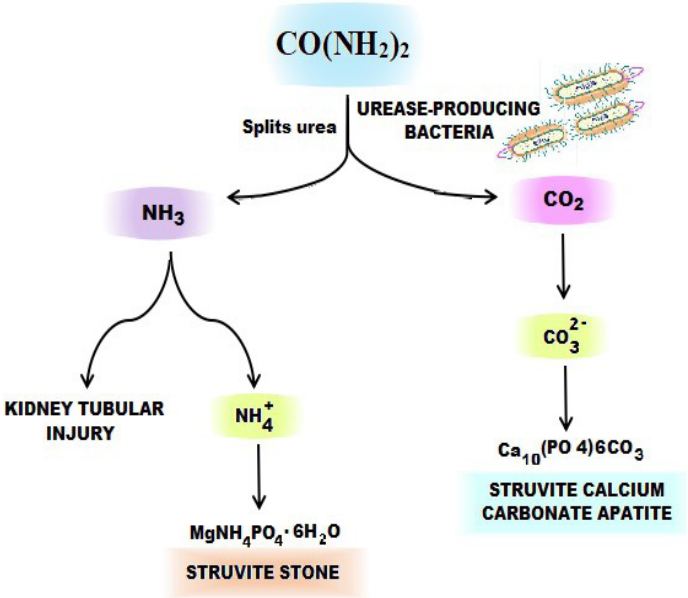

Figure 1: Role of urease-producing bacteria in the development of urinary calculi.

These bacteria split the urea into ammonium and carbon dioxide which further results in the formation of calculi and renal tubular injury [16].

Cystine stones

Cystinuria is responsible for up to 8% of urolithiasis in children and adolescents but fewer than 1% of urinary stones in adults. Cystine stone is a genetic disorder of the proximal tubular reabsorption of cystine and the dibasic amino acids arginine, ornithine, and lysine [17]. It is an autosomal recessive disorder that results from a defect in the rBAT gene on chromosome 2, which impairs cystine absorption by the renal tubules or causes cystine to leak into the urine. It causes the development of cystine stones because it does not dissolve in urine [9]. The SLC3A1 gene on chromosome 2 and the SLC7A9 gene on chromosome 19 have been identified as the two responsible genes [18].

Uric acid stones

Urine that is continuously acidic is more likely to develop uric acid stones. This might be associated to a diet rich in animal protein and purines [1]. The uric acid calculi that cause nephrolithiasis affect 9% of the renal stones. Uric acid stones develop as a result of hyperuricosuria (induced by a high consumption of dietary purines), dehydration, decrease in urine volume, and acidic pH in humans [19]. By converting hypoxanthine to xanthine as well as uric acid, the enzyme Xanthine Oxidase (XO) breaks down the purine to generate uric acid as an end result. Hyperuricosuric calcium urolithiasis and urate nephropathy are caused by high levels of uric acid, a byproduct of purine (Wiederkehr *et al.,* 2011). Numerous conditions, including metabolic disorders, diabetes, and obesity, increase the production of acid, leading to acidic pH of the urine. Additionally, the excess of H+ ion-forming buffer into the urate due to the deficiency or modification of renal ammonium excretion causes it to precipitate into uric acid stones [21,2].

Drug induced stones

The development of drug-induced calculi is primarily mediated by two mechanisms which can be divided into two categories,

1. Drugs or their metabolites induced renal calculi, where the calculi are entirely or partially made up of the drugs.
2. Metabolically induced renal calculi, where the drug interferes with the metabolism of calcium, oxalate, phosphate, uric acid, or purines, or urine pH which results into the formation of calculi [22].

Table 1: Drugs that may cause renal calculi [22].

Class of drug	Examples
Antibacterial drugs	Sulphonamides, cephalosporins, aminopenicillins, quinolones, furan,
Antiviral drugs	Protease inhibitors, non nucleoside reverse transcriptase inhibitors
Analgesics	Amino-4-quinoleines
Anti-hypertensive molecules	Pteridines
Antacids	Silicium derivatives
Drugs for treatment of gout	benzobromarone, salicylic acid, probenecid
Diuretic	Carbonic anhydrase inhibitors

Risk factors responsible for nephrolithiasis in females

Menopause

According to several studies, the prevalence of kidney stone disease is about two times lower in females (15-49 years old) than in males of the same age but in postmenopausal age, this gap is less [23]. Due to low estrogen levels, stone formation may occurs more commonly in menopausal women as compared to premenopausal women as estrogen can affect urinary oxalate metabolism and therefore may be considered as an inhibitor of crystal deposition [24].

Protective role of estrogen against calculi formation

The hormonal status also plays a significant role in the sex difference in stone composition [22]. Estrogen enhances citrate excretion and also reduces the risk of developing renal stones in women, particularly during pregnancy [25]. Estrogen can lower uric acid, oxalate, and calcium levels in the urine and enhances cell proliferation and tissue healing, therefore may act as a protective hormone against the risk of urolithiasis in women [26,27].

Estrogen encourages cell migration and tissue healing

There are several findings that stone formation is linked with tissue injury, so the cell repairing or healing is essential for the inhibition of stone formation. The effect of estrogen in tissue healing and cell migration involves many pathways such as MAPK and PI3K pathway that have a significant role in cell proliferation, differentiation, apoptosis, and migration, and tissue healing [28].

Estrogen receptor β (ERβ) reduce oxidative stress

Estrogen activities are intermediated typically by 2 estrogen receptor subtypes, ERα and ERβ. Both subtypes are nuclear receptor superfamily members, however they are genetically and physiologically different [29]. Upon hormone binding, ERs undergo dimerization and migrate to the nucleus, where they interact with estrogen responsive elements (ERE) at target genes promoters, which regulate the transcription of those genes. More than 90% of estrogens target genes are regulated by this transcriptional pathway [30].

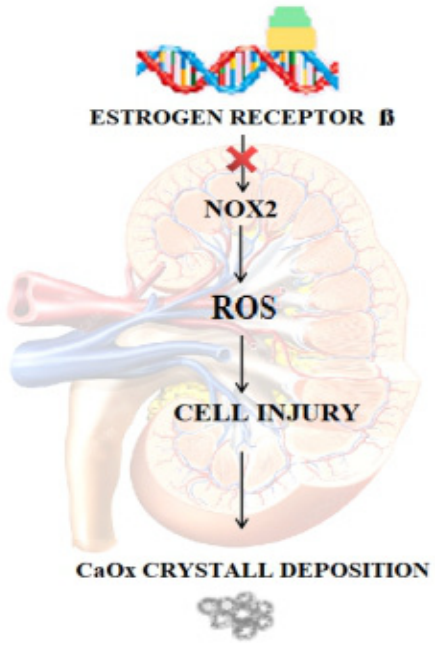

Figure 2: Regulation of CaOx crystal development in the kidney [29].

It is well known that calcium oxalate crystal adherence to renal tubules is significantly facilitated by oxalate-induced oxidative damage [31]. NADPH oxidase is a significant producer of ROS in the renal tubular epithelial cells [32]. An increase in oxalate concentration can quickly and significantly increase the expression of NADPH oxidase subunit 2 (NOX2) in renal cells. Previous studies have revealed that on the binding of estrogen response elements (EREs) to estrogen receptor β (ERβ), there is suppression of oxidative stress through transcriptional suppression of the NOX2, which further exerts a protective effect on calcium oxalate crystal deposition and also reduce cell injury [29].

Estrogen decreased the expression of calcium oxalate (CaOx) crystal receptors

The majority of data have demonstrated that alteration in the expression of calcium oxalate crystal receptors level on the cell plasma membranes can affect the cell's ability to bind with crystal [33,34]. Annexin A1 and α enolase are two CaOx crystal receptors and estrogen might regulate their gene expression through the indirect mechanism (Figure 8). Annexin A1 and α enolase do not contain estrogen response element (ERE) within their genomic sequences [28].

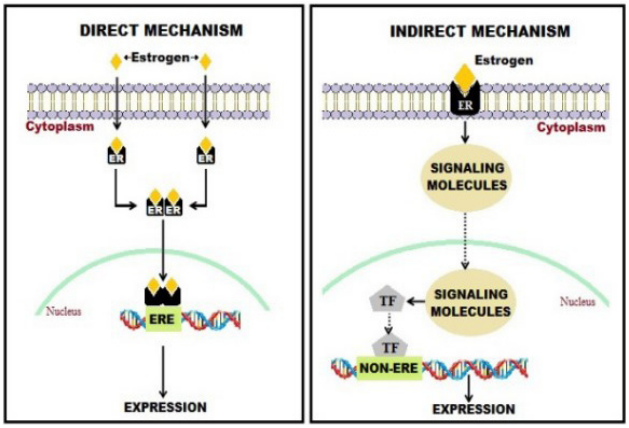

Figure 3: Role of estrogen in protein gene expression. Estrogen Receptor, ER; Estrogen Response Element, ERE; Transcription Factor, TF [28].

Annexin A1 (calcium-binding protein) is elevated by high-calcium therapy, increasing the ability of renal tubular cells to bind crystals [33]. α enolase is a glycolytic having numerous roles in pathophysiology. Its surface expression as a calcium oxalate receptor may be stimulated by high-oxalate circumstances in addition to enhancing its ability to bind CaOx crystals [28,34]. According to several studies, in estrogen-treated cells, the level of Annexin A1 and α enolase has reduced and therefore ability to bind with crystal also reduced. Estrogen may reserve the activity of these receptors to the baseline if upregulated by high calcium and oxalate therapy [28].

Estrogen can regulate adenosine triphosphate (ATP) synthesis

ATP is a currency for intracellular energy and glycolysis is a major pathway that contributes to ATP production. α enolase and Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH) are the two main enzymes involved in the glycolysis pathway and both these enzymes are seen to be reduced in estrogen-treated cells concerning the reduced level of intracellular ATP [28].

Several studies have demonstrated that oxidative stress, increases ROS levels, and tissue injury is associated with ATP overproduction [28]. Thus, the decreased intracellular ATP level is considered as the defensive role of estrogen to protect the

tissue from calcium oxalate induced oxidative stress and injury normally associated with nephrolithiasis [35].

Female hormone therapy

In postmenopausal women due to the decline in the level of estrogen majority of women experience some menopausal symptoms and hormone therapy is used to target these symptoms [36]. Female hormone therapy may also associate with the development of renal calculi [37]. Many studies have found that estrogen may have protective role against urolithiasis [38]. Increased urine uric acid excretion with estrogen use, which may cause heterogeneous calcium oxalate nucleation, is one possible explanation for the development of stones associated with hormone therapy. Estrogen therapy may accelerate renal tubular calcium reabsorption in postmenopausal females [38].

Pregnancy

Kidney stone disease during pregnancy is a complicated situation and requires special care as there is a risk to both the mother and foetus [39]. It has been reported that urinary stone is more common in women who had two or more pregnancies [37]. Several physiological changes with pregnancy could explain the rise in risk of renal stone development [40]. In pregnant females, due to hormonal changes, the lithogenic factors such as the level of calcium, uric acid, oxalate, and sodium in urine are found to be increased and this rise is joined by an increase in inhibitory factors such as urinary citrate, magnesium, nephrocalcin and glycosaminoglycans. While citrate is considered as an inhibitor of stone formation, it also elevates the urinary pH, due to which the risk of calcium phosphate stones may increase by alteration in supersaturation point of calcium phosphate crystallization [39].

Hydronephrosis occurs in about 90% of women during pregnancy and is responsible for stasis due to which the contact time between lithogenic metabolites such as calcium in urine increased, leading to crystallization and further resulting in stone formation [40]. The risk of infection is also associated with stasis and due to which urinary pH also increases [39]. Furthermore, the glomerular filtration rate also rises in pregnant women. Because of this, various lithogenic factors such as hypercalciuria, an increase in the pH of the urine, and intestinal absorption of calcium increases, favouring salt supersaturation in the urine [41].

In pregnant women, due to the increased level of 1,25-dihydroxy vitamin D, the gastrointestinal absorption and bone mobilization of calcium are increased. The elevated level of 1,25-dihydroxy vitamin D also suppresses the parathyroid hormone due to which kidney reabsorbs the less filtered calcium. Vitamin D and calcium supplements are also suggested for pregnant women which can further lads to hypercalciuria. Progesterone-induced chronic respiratory alkalosis can also increase the urinary pH [40].

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS), which affects 5-18% of females in this life span, particularly adolescent girls, is an endocrine disorder of females in fertile age and causes metabolic and reproductive complications [42,43]. It is characterized by chronic anovulation, clinical or biochemical evidence of hyperandrogenism symptoms (such as acne, hirsutism, oligomenorrhea, and amenorrhea) [43], increase infertility and polycystic ovaries on ultrasound examination [44,45]. A higher risk of type-2 diabetes, hypertension, dyslipidemia, and subclinical atherosclerosis is linked to PCOS. PCOS is associated with hyperandrogenism and also abdominal adiposity which further may contributes to calculi development [46,47].

Urinary tract infection

Urinary tract infections (UTI) may lead to the development of calculi consisting of struvite (magnesium ammonium phosphate) and variable amounts of calcium-phosphate or calcium-oxalate [7]. Females have high risk of occurring UTI which is further leads to increase in urinary pH because of infection caused by urease containing bacteria and may results into hydroxyapatite supersaturation [48]. Several studies show that there is a link between bacteria and urinary stones, together with the increased frequency of Urinary Tract Infections (UTIs). E. coli and Pseudomonas spp. are the primary bacteria found in stone cultures, followed by the urease-splitting bacteria which contributes to struvite stone development [49]. Female stone formers are generally at higher risk of UTI, due to which urinary pH may increase [6].

Pediatric renal calculi

Several earlier investigations have shown that pediatric nephrolithiasis likely to affect more females than males [50,51]. The composition and risk factors of pediatric stones differ from those found in adult stones. Although the age of the patient has a linear relationship with the creation of renal stones, children tend to form more calcium-based stones than adults. On the other hand, uric acid stones are less common in children [52].

According to Gabrielsen et al. [53] females had considerably more calculi in the eleven to eighteen year age group and had a greater percentage of calcium phosphate-containing stones at the one to five and fourteen to eighteen year age ranges compared to males in the same age ranges.

Schwaderer et al. [54] in their studies, also found that pediatric urinary stone disease occurs more in females as compared to males due to unknown mechanisms involved. These findings were further validated by a study by Fang et al. [44] which discovered an increase in the incidence of female pediatric urolithiasis in females due to having more dietary and urinary risk factors than males in 24-hour urine samples.

Mechanism of stone formation

Calculus formation is a complex procedure which involves urinary biochemical conflicts that promote crystal nucleation, aggregation, and potentially adhesion [21]. Renal cell injury, crystal retention, cell apoptosis, Randall's plaque, and associated stone inhibitors or promoters play important roles for kidney stone formation [9]. It was shown that renal Randall plaques may contribute to the development of calcium oxalate calculi but not uric acid calculi.. Hyperuricosuria (described as daily urine uric acid surpassing 750 mg/d in females and 800 mg/d in males) and hypovolemia and low urinary levels are among the urinary abnormalities that affect the development of uric acid calculi. The key reason is persistently low urinary pH [21].

There can be basic two aspects involved in the pathogenesis of kidney stone like as

(a) Increased urinary flow of stone forming constituent elements like calcium, uric acid, oxalate and cysteine etc.

(b) Stone formation is affected by physicochemical factors such as urine's pH, stone matrix, and protective material [63].

Table 2: Summary of key findings included in this study.

Theme	Reference	Key findings
Stone composition	[6]	Females have more chances of apatite, struvite stones, and infection stones
	[55]	There was a significant increase in uric acid stones (7.6-10.2%) and calcium oxalate monohydrate stones (55.8-64.3%) in women
	[37]	In women, obesity and metabolic syndrome rate have increased, which are also associated with various types of kidney stone
	[56]	A study on the Norwegian population found that carbonate apatite stones more frequently occur in females as compared to males
	[57]	Young females are more prone to developing hydroxyapatite stones.
Menopause	[26]	Estrogen serves as a protective hormone against the kidney stones
	[28]	Effect of estrogen in tissue healing and cell migration involving MAPK and PI3K pathways and decrease the surface expression of CaOx crystal receptors
	[29]	Estrogen receptor β (ERβ) is involved in the suppression of oxidative stress
	[58,35]	Estrogen can regulate the intracellular ATP level.
Female hormone therapy	[37]	Female hormone therapy is also linked with the development of renal calculi.
Pregnancy	[37]	Urinary stone occurs more commonly in women who had two or more pregnancies.
	[40]	Hydronephrosis occurs in about 90% of women during pregnancy and is responsible for stasis which may also contribute to stone formation. In pregnant women, due to increased levels of 1,25-dihydroxy vitamin D, the gastrointestinal absorption and bone mobilization of calcium are increased.
Role of microbes	[49,59]	Struvite stones formation occurs as an outcome of urinary tract infection (UTI) with urease-producing bacteria namely Proteus, Klebsiella, Pseudomonas, and Staphylococcus bacteria.
	[60]	P. Mirabilis and nanobacteria are also associated with UTIs and the further formation of infection stones.
Polycystic ovary syndrome (PCOS)	[24,46]	PCOS is associated with hyperandrogenism which further contributes to urinary calculi development.
	[47]	Abdominal adiposity is usually related to PCOS which further can lead to calculi development.
Pediatric urolithiasis	[49]	Pediatric urinary stone disease occurs more in females as compared to males.
	[61]	An increase in the incidence of female pediatric urolithiasis in females is observed due to having more dietary and urinary risk factors than males in 24-hour urine samples.
Promoters and inhibitors of kidney stones	[62]	Females excrete more citrate (inhibitor of stone formation) than males. Citric excretion varies with the estrus cycle and level of estrogen secretion.

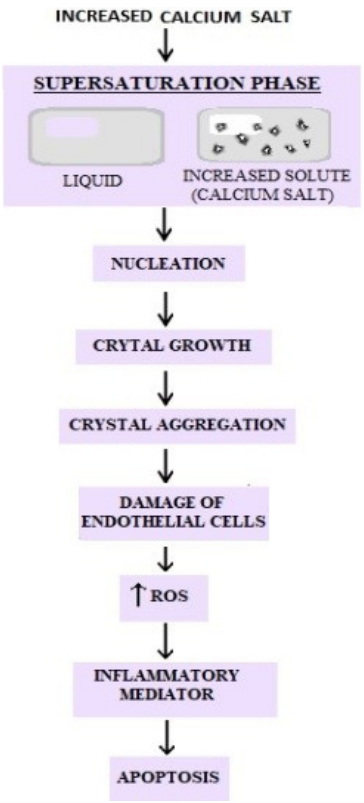

Figure 4: Steps involved in stone formation [2].

Urinary supersaturation and crystallization

Supersaturation is the initial stage in the formation of almost all types of stones. Less water consumption and an increase in the solute (calcium salt) cause the solvent to become saturated and crystallize, which causes nephrolithiasis and a decrease in the crystallization inhibitor's concentration. The next step is nucleation. It is a process where the salt mixture begins to produce crystals and the nuclei of the formed crystal do not disintegrate [2]. The individual microcrystals combine into larger forms i.e., crystal growth, which, in turn, can group together to form massive, solid deposits i.e., crystal aggregation [64]. In the following stage, the crystals may interact with the renal tubular epithelial cells and induce nephrolithiasis [65].

The formation of calcium oxalate calculi, as the most prevalent type, comprises a multi-step pathophysiology that includes nucleation, development, accumulation, and eventually retention of crystal [67]. Hyperoxaluria, which elevates urine oxalate and endorses calculi development, and crystallizes CaOx, is considered a major contributor to the development of idiopathic calcium oxalate stones [68]. Hyperuricosuria also contributes to the development of calcium oxalate stones as uric acid may induce heterogeneous nucleation of calcium oxalate and may also reduce the solubility of calcium oxalate and therefore resulting in increasing its rate of precipitation [69]. The increase in urine pH and calcium elimination is also linked with calcium oxalate and calcium phosphate calculi [48].

Cell injury and oxidative stress

It has been observed that exposing renal epithelial cells to oxalate disrupts the basic processes of the epithelium, alters gene expression, impairs mitochondrial function, produce reactive oxygen species and thus, decreased cell viability [70].

Membrane injury is may lead to binding of calcium oxalate crystal and serves as a trigger for the production of calcium crystals [71,65]. When calcium oxalate crystals get to adhere to the epithelial cells, (nicotinamide adenine dinucleotide phosphate) NADPH oxidase may generate the superoxide and then there will be activation of cyclophilin D in mitochondria [72] which increases the mitochondrial permeability transition and then mitochondrial collapse. This may result in the formation of Reactive Oxygen Species (ROS). Due to this many events like apoptosis, cell injury, and osteopontin expression get activated. Then, distorted mitochondria and fragmented microvilli fall off into the urine and result into renal calculi [5].

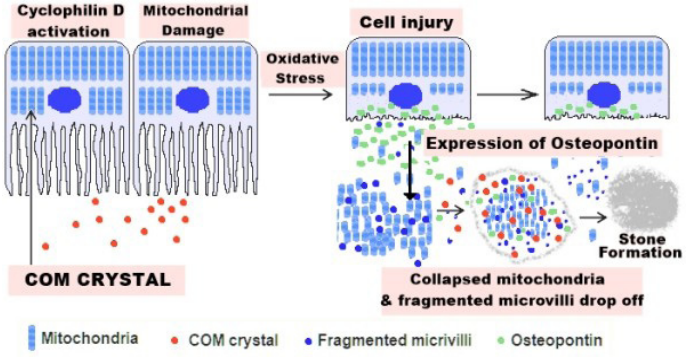

Figure 5: Pathway of renal calculi development. The Calcium Oxalate Monohydrate (COM) crystals get attached to renal tubular cells and activate the cyclophilin D resulting in mitochondrial collapse as well as oxidative stress and then, collapsed mitochondria and fragmented microvilli fall off into the urine and lead to renal calculi formation [5].

Randall's plaque and calcium oxalate stone development

Randall's plaque, which is a calcium plaque that has accumulated in the renal papilla's interstitial tissue, serves as a nidus for the development of urinary calculi [73]. Randall's plaques are composed of a variety of cellular breakdown products, including membrane-bound vesicles, calcium phosphate deposits, and collagen fibres [74].

It is well known that crystal retention is a significant factor in stone formation as there won't be any stone formation if the nucleated crystals are flushed out with urine flow. However, when the crystals develop large enough to get caught in the renal tubule or get attached to the urothelium prior to elimination, it will result in crystal retention and may cause injury by receptor activation and toxicity [73]. These processes may lead to the production of osteopontin, inter-α-trypsin inhibitor, and fibronectin which can regulate inflammation and mineralization. The adhered crystals may also be endocytosed into intestinal area and get attached to tissue macrophages (that are activated by epithelial cell damage and cytokine production). Anti-inflammatory macrophages destruct crystals by lysosomal processing. But chronic interaction with crystals may change the macrophage to a pro-inflammatory phenotype and alteration in pro-inflammatory macrophage will result in reducing anti-inflammatory macrophages, which endorse the crystal nucleation and adhesion in a self-perpetuating cycle. The pro-inflammatory macrophages epithelial cells and inflammation contribute to the formation of calcifying vesicles and enhance mineralization and collagen deposition which further results into Randall's plaques formation [74].

Several studies have shown that the frequency of calculi development associated with Randall's plaque is increasing. It has been reported that the frequency of the development of calcium oxalate calculi on Randall's plaque is rising among both men and women, but is mostly noticed in young women. Furthermore, the portion of papillary tissue covered by Randall's plaque is correspond to the quantity of stones [75].

Promoters and inhibitors of nephrolithiasis:

Stone formation is the result of an imbalance between the promoters (calcium, oxalate) and inhibitors (citrate, magnesium) of crystallization [2]. The rise in the level of stone promoters and a decline in the level of stone inhibitors results in the supersaturation of the crystallizing stone [76,2].

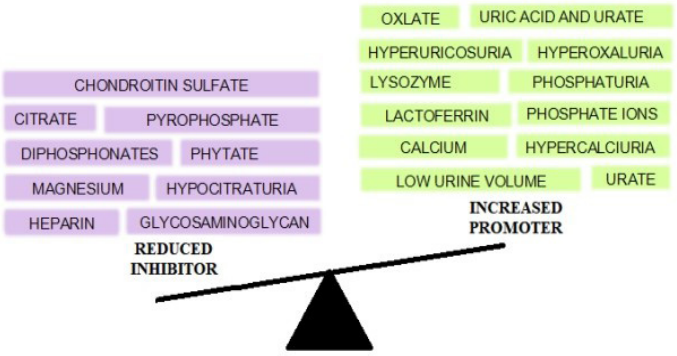

Figure 6: Imbalance of promoter and inhibitor involved in stone formation [16].

Several studies have revealed that females excrete more citrate than males. Urinary citrate, as an inhibitor of stone formation, has the chelating property against calcium ions and prevents supersaturation concerning the creation of CaOx.

The urinary citric excretion varies with the estrus cycle and increased with an increase in the level of estrogen secretion and is also associated with the variation of acid-base equilibrium [62,69].

Conclusion

Gender disparities can influence not only the risk parameters and susceptibility but also the kind of stones typically found. In females, more chances of occurrence of apatite, struvite stones (result of UTI caused by urease-producing bacteria), COM, and hydroxyapatite stones have been noticed. Despite the fact that the pathophysiology of urolithiasis involves complicated pathways, the primary cause of almost all calculi is the urine supersaturation with regard to the constituents of calculi; parameters influencing solubility which involve urine volume, pH, and overall solute excretion. Significant advancements have been made over the past few decades in the pathogenesis of calculi development, including the upgrading impact of Randall's plaque in calcium-containing stones, and the decline of estrogen hormone that put postmenopausal women at risk of forming urinary stones. Combinations of elements such as the impact of sex hormones, abnormalities with urine pH and acid-base management, female hormone therapy, the composition of stones, and an imbalance between elements that encourage and prevent calculi formation also contribute to the stone formation. These elucidations may enable us to comprehend the fundamental cause of the rising incidence of urolithiasis among

women which will aid in the development of new medications that address the fundamental metabolic imbalances that prevent stone formation.

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