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Calcium Oxalate Crystals: Epidemiology, Causes, Modeling Of Crystal Formation and Treatment Management

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Abstract

Background: Urolithiasis or nephrolithiasis is characterized by the presence of stones in the urinary tract and classically explained as the derangement in process of biomineralization involving the equilibrium between promoters and inhibitors of crystallization.
Urolithiasis is a relevent clinical problem in everyday practice, a common multifactorial disorder of etiology is not always clear and high rate of recoccurance
Content: A review of the current knowledge on urolithiasis based upon a molecular and genetic approach is reported underlying the stone formation are still unclear. A good number selected of abstracts and research articles (in total 72) published, so far, for evaluating calcium oxalate stone disease induced ethylen glycol in animal model
Summary: The latest strategies for preventing kidney stone formation and the occurrence of end-stage kidney disease by understanding the biomolecular mechanism of kidney stone formation is the key to successful therapy

Keywords: Calcium oxalate, ethylene glycol**,** animal model

INTRODUCTION

1. **Epidemiology**.

The formation of stone in the urinary system, i.e. in the kidney, ureter, and urinary bladder or in the urethra is called urolithiasis. 'Urolithiasis' = ouron (urine) and lithos (stone). Urolithiasis is one of the major diseases of the urinary tract and is a major source of morbidity. Stone formation is one of the painful urologic disorders that occur in approximately 12% of the global population and its re-occurrence rate in males is johri70-81% and 47-60% in female [1]

According to the latest report from the National Health and Nutrition Examination Survey (NHANES 2007-2010), the prevalence of kidney stones among American adults was 8.8%: 10.6% among men and 7.1% among women [2]. male: female = 2.4: 1, increase from 1977 (1.81) and 2006 (2.7: 1) [3]. Recurrence rates in 1 to 2 years is 10-20 %, 5 years : 35%, and 10 years : 60% [4]. According to Riskesdas 2013, prevalence data in Indonesia were 0.6%, Yogyakarta (1.2%), NAD (0.9%), Central Java (0.8%), West Java (0.8%), East Java (0.7%), and the lowest in Bangka Belitung. Prevalence increases with age, age 55-64 years (1.3%), 65-74 years (1.2%) and ≥ 75 years (1.2%). The prevalence of men (0.8%) and women (0.4%) [5].

It is anticipated that there will be an increase in kidney stones in the future due to global warming, lifestyle changes, diet and obesity [6]. The occurrence of kidney stones is costly due to both medical treatment and time lost from work [7], and is also associated with increased rates of chronic kidney disease, hypertension and myocardial infarction [8]. As most patients with stone disease have identifiable risk factors, it is worthwhile to evaluate for underlying causes of stone formation.

The stone type is named after its mineral composition. The most common stones are struvite (magnesium ammonium phosphate), calcium oxalate, urate, cystine and silica. [9] that is Ca stones (CaOx and CaP)-80%. Uric acid -9%, Struvite-10% and other-1%.

The most common type of kidney stones worldwide contains calcium. For example, calcium-containing stones represent about 80% of all cases in the United States; these typically contain calcium oxalate either alone or in combination with calcium phosphate in the form of apatite or brushite [10].

The problem of stone formation is considered as a medical challenge due to its multifactorial etiology and high rate of reoccurrence. One of the major problems with kidney stones is the high rate of recurrence: after an initial stone, there is a 50% chance of forming a second stone within 7 years if left untreated [11] Sutherland. Stone formation is also caused due to imbalance between promoters and inhibitors. Factors that promote the precipitation of oxalate crystals in the urine, such as primary hyperoxaluria, are associated with the development of calcium oxalate stones. [12]. The formation of calcium phosphate stones is associated with conditions such as hyperparathyroidism and renal tubular acidosis [13].

Calcium oxalate crystals in the urine are the most common constituent of human kidney stones, and calcium oxalate crystal formation is also one of the toxic effects of ethylene glycol poisoning. Hydrated forms of the compound occur naturally as three mineral species: whewellite (monohydrate, known from some coal beds), weddellite (dihydrate) and a very rare trihydrate called Ca oxite. Oxaluria is also increased in patients who consume increased amounts of oxalate (found in vegetables and nuts). Primary hyperoxaluria is a rare autosomal recessive condition which usually presents in childhood [14].

2. Causes of urolithiasis

Dietary factors that increase the risk of stone formation include low fluid intake and high dietary intake of animal protein, sodium, refined sugars, fructose and high fructose corn syrup [15], oxalate [16], grapefruit juice, apple juice, and cola drinks. Stone formation commonly occur due to inadequate urinary drainage, foreign bodies in urinary tract, microbial infections, diet with excess oxalates and calcium, vitamin abnormalities like vitamin A deficiencies, excess vitamin D, and metabolic diseases like hyperthyroidism, cystinuria, gout, intestinal dysfunction etc. [17]. Calcium oxalate is considered as main constituent in the renal calculi.

Calcium is one component of the most common type of human kidney stones, CaOx. Unlike supplemental calcium, high intakes of dietary calcium do not appear to cause kidney stones and may actually protect against their development [16].

When the urine becomes supersaturated (when the urine solvent contains more solutes than it can hold in solution) with one or more calculogenic (crystal-forming) substances, a seed crystal may form through the process of nucleation. Heterogeneous nucleation (where there is a solid surface present on which a crystal can grow) proceeds more rapidly than homogeneous nucleation (where a crystal must grow in liquid medium with no such surface), because it requires less energy. Adhering to cells on the surface of a a renal papilla, a seed crystal can grow and aggregate into an organized mass. Depending on the chemical composition of the crystal, the stone-forming process may precede more rapidly when the urine pH is unusually high or low [14].

Normal urine contains chelating agents such as citrate that inhibit the nucleation, growth and aggregation of calcium-containing crystals. Other endogenous inhibitors include calgranulin (an S-100 calcium binding protein), Tamm-Horsfall protein, glycosaminoglycans, uropontin (a form of osteopontin), nephrocalcin (an acidic glycoprotein), prothrombin F1 peptide, and bikunin (uronic acid-rich protein). The biochemical mechanisms of action of these substances have not yet been thoroughly elucidated [18].

The salts and acids that normally crystallize in kidney stones do so because of their relative insolubility in urine. the urinary tract, it is almost impossible for it to re-dissolve. Its solubility is independent of urinary pH, unlike the solubilities of other common stone constituents such as cystine and uric acid (soluble in alkali) or calcium phosphate and magnesium ammonium phosphate (soluble in acid). However, the latter occurs only in the presence of infection involving a urea-splitting bacterium that produces high levels of ammonia (and ammonium ions, $NH4^{+}$) and an alkaline environment.

The various urinary risk factors associated with calcium-containing stones the risk factors are a low urine volume, a raised urine pH (>6.2), hypercalciuria, mild hyperoxaluria, hyperuricosuria, hypocitraturia, and low urinary magnesium excretion (19,20].

3. Modeling

Numerous models for hyperoxaluria in the rat have relied on exogenous administration of lithogenic materials including sodium oxalate, glycolic acid, ethylene glycol (EG), and hydroxy-L-proline (HLP) [21]. The delivery of these agents in the rat range from drinking water modification, enriched chow, gavage instillation, intraperitoneal injection and even subcutaneous implantation of oxalate-containing osmotic mini-pumps [22].

Ethylene glycol administration is a well-known model of nephrocalcinosis: EG metabolizes into glycolate, glyoxylate, and oxalate leading to COM crystals in both urine and kidneys [23]. However, multiple studies have shown EG to be a toxic agent that can cause multi-organ failure [24]. Yamaguchi, *et al*, demonstrated that the combination of EG and Ammonium Chloride (AC) is detrimental to rat health with rats having lower weights, worsening renal function, and increased urinary N-acetyl-b-D-glucosaminidase (NAG), an indicator of renal toxicity [25]. Other studies have also found that lipid peroxidation, increased free radicals, and metabolic acidosis

Administration of EG in drinking water has been shown to result in consistent induction of hyperoxaluria, crystalluria and calcium oxalate nephrolithiasis [26]. Delivering solely 0.75% EG to male rats eventually yielded persistent crystalluria at 12 days and renal crystal deposits at 3 weeks [26]. To enhance the development of crystal deposition, EG often has been combined with other agents such as AC to reduce urinary pH, as well as a vitamin D or calcium chloride to result in subsequent hypercalcemia and hypercalciuria [27]. This lithogenic combination decreased the time for crystalluria from 12 to 3 days, and detectable calcium oxalate nephrolithiasis from 3 weeks down to 1 week [28].

Rats receiving EG-supplemented drinking water 0.75% vol/vol) develop hyperoxaluria and hypercalciuria one day after initiation [29]. Moreover, intra tubular crystal deposits are detected as soon as day 1 both in medulla and cortex altogether with tubular injury, dilatation, regeneration and interstitial inflammation. Several macromolecule such as OPN, bikunin or Tamm-Horsfall (TH) protein that could either inhibit or promote calcification are also induced [30]. Of notice, glycolate and glyoxylate metabolites seem to modify normal tubular epithelium into a crystal-binding epithelium [29]. This EG model is currently used to study crystal binding molecules, crystal clearance and the relevance of several macromolecular inhibitors such as OPN in crystal retention [31].

Despite the genomic advantages of the mice model, its overall accuracy and consistency in relation to human kidney stone disease remains controversial among researchers. Similar to other animal models, the majority of mice models rely on induction of hyperoxaluria. Except for primary hyperoxaluria patients, relatively few human kidney stone patients have hyperoxaluria. In addition, the prevalence of cystinuria is rare (less than 1% of urolithiasis patients), therefore these mice models

are not representative of the majority of humans who suffer from urinary stone disease [32].

4. Kidney Stones Formation

When the mice receives supplemented EG drink, EG metabolized by alcohol dehydrogenase to glycoaldehyde, by aldehydes dehydrogenase converted into glycolic acid, then dehydrogenated to glyoxylic acid and transformed into oxalic acid causing hyperoxaluria and hypercalciuria the day after initiation [29]. Hyperoxaluria and CaOx crystal deposition trigger morphological and pathophysiological changes in the kidney and affect the urine composition [33]. Glycolate and glyoxylate metabolites seem to modify the normal tubular epithelium into a crystal-binding epithelium [29].

Oxalate (Ox) with Ca rapidly forms CaOx crystals precipitate, dissolves and precipitates in the blood circulation, clogs the renal microcirculation and causes acute tubular necrosis and some are secreted with urine [34]. High levels are associated with increased risk of nephrocalcinosis and the number of stones, leading to pathological disorders such as hyperoxaluria, nefrolithiasis (calcination and accumulation of CaOx crystals in the kidney and nephrocalcinosis (renal calcification) [34,35].

The formed CaOx crystals can be excreted with urine or left behind in different parts of the urinary tract, causing blockade of renal tubules, lesions of different cells in the glomerular, tubular and intestinal compartments of the kidney, and disruption of cellular functions that produce renal injury and inflammation, impairment and impairment of renal function [36] and end-stage renal disease (ESRD) [37, 29].

Nephrocalcinosis is a risk factor for renal failure in primary hyperoxaluria. Nephrocalcinosis has been found in 34% of patients, including 41% with type 1 primary hyperoxaluria. Furthermore, intra-tubular crystal deposits are detected immediately the first day in the medulla and cortex together with tubular injury, dilatation, regeneration and interstitial inflammation. [38].

Reactive oxygen species (ROS) in response to Ox and CaOx crystals are partly produced with mitocondrial [39] and NADPH oxidase involvement [40] through activation of the renin-angiotensin renal system (RAS). NADPH oxidase is the main source of ROS in the kidney [41] especially the presence of Angiotensin II [42]. NADPH oxidase consists of six subunits, two transmembrane units, p22phox and gp91phox; and four cytosolic units, p47phox, p67phox, p40phox and small GTPase rac1 or rac2 [43]. Inhibition of NADPH oxidase by apocynin treatment reduces ROS production, excretion of kidney injury molecules (Kidney Injury Molecule, KIM) and precipitation of CaOx crystal kidney in hyperoxaluric mice [33].

Mitochondria are generally the most common source of superoxide and H_2O_2 in most cells and tissues. Deposition of hyperoxaluria and CaOx crystals in rat kidneys causes mitochondrial damage. Mitochondrial damage due to pore opening of the mitochondrial permeability transition (mPTP). The opening of mPTP depends on the activation of cyclophilin D in the mitochondrial matrix by ROS produced by NADPH oxidase and inhibited by cyclosporine A (CSA) [44]. CSA prevents mitochondrial membrane depolarization, decreased SOD expression, increased 4-hydroxy-2-nonenal (4HNE) and release of cytochrome-c into the cytosol in NR52E renal epithelial cells affected by COM crystals in vitro

According to Umekawa *et al*, [2004] that Ox can activate RAS and upregulation of OPN is a mediated part through RAS renal. Hyperoxaluria and crystal formation in renal tubules cause stress in tubular epithelial cells and increase ROS, activate RAS so that angiotensin II rises, increases ROS, and increases the synthesis of OPN [45].

Evidence of experimental crystal deposition in the kidneys is associated with ROS production, the development of oxidative stress [34], renal and inflammatory lesions [46]. There is also evidence of activation of the renin-angiotensin system and nicotinamide adenine dinucleotide phosphate NADPH oxidase when cells are exposed to high oxalate (Ox) and CaOx / CaP crystals [47,48].

Some markers in the kidney increase during oxidative stress. Research has shown that there is greater excretion of 8-Isoprostane, PGF2α, and malondialdehyde (MDA) by long-term infusion of Angiotensin (ANG) II in mice [49], ANG II is a bioactive peptide of the renin-angiotensin-aldosterone system (RAAS) and plays an important role in cell growth, differentiation, apoptosis, induction of pro-inflammatory cytokines, and fibrogenesis [50].

Studies have also shown that animals significantly secrete higher amounts of thiobarbituric acid (TBARS) reactive compounds in urine, generally as lipid peroxidation byproducts and indications of oxidative stress in the kidneys [51], it was also reported that angiotensin production reduction, by inhibition of angiotensin converting enzyme (ACE) blocked angiotensin receptor, increased expression of renin, decreased osteopontin (OPN) expression, crystal deposition and related inflammatory response [45].

Some macromolecules such as OPN, bikunin or Tamm-Horsfall (TH) that can inhibit or promote calcification are also induced [30]. OPN is synthesized in the kidney [52], and is in urine at a level that effectively inhibits CaOx crystallization [53]. OPN expression of mRNAs is regulated in stone formation [54]. OPN, a stone matrix constituent, also known as monocyte chemoattractant specific to renal interstitium [55].

The decrease in OPN concentrations has been documented in the urine of patients with kidney stone disease [56]. In vitro data suggest that urinary OPN may inhibit the calibration, growth and aggregation of CaOx crystals and directly inhibit the CaOx crystal bonds in culturally renal epithelial cells [57,58]. Reduction of OPN expression is associated with significant reduction and crystal deposition. Specific suppression of OPN expression of mRNA in renal mouse hyperoxaluria leads to decreased OPN production and simultaneously inhibits renal crystal deposition [31]. OPN will increase CaOx crystal formation and aggregation in several experiments [59]. OPN also directs the crystallization of CaOx to the CaOx dihydrate phase (COD), which is significantly less than that of CaOx monohydrate (COM) [60]. On the other hand, some

researchers propose the role of OPN as a stone-forming promoter, probably acting to support withdrawal from CaOx crystals and cell membranes [61]

The induced OPN causes infiltration of inflammatory interstitium cells and crystal attachment to tubular epithelial cells, subsequent to formation of disposition and formation of lesions in the renal tubulointerstitial. [39]. Data show that OPN is a critical inhibitor of crystalline formation and CaOx retention in the in vivo kidney [61], implicated in the pathogenesis of kidney stone disease 3n humans [62].

Angiotensin II mediates the synthesis of OPN, which is involved in macrophage recruitment and CaOx crystallization, synthesis and OPN production increases with hyperoxaluria but less in the Candesartan-treated hyperoxaluria mice. These results suggest that for the first time Ox may activate RAS of the kidneys and that oxalate-induced upregulation of OPN is a mediated portion of the RAS kidney [43]. Treatment of hyperoxaluria mice with ANG II type I receptor blockers (ARB) reduced lesion formation, since Ang II mediated the synthesis of osteopontin (OPN), which was involved in macrophage recruitment and CaOx crystallization, suspected that ARB acts via OPN [43]. Inhibition of the AT1 receptor will inhibit aldosterone so that no sodium retention stimulation and cardiac or renal fibrosis occur. [64].

ANG II and other factors such as oxidative stress conditions are thought to be capable of causing fibrosis via TGF-ß1, leading to the formation of Tumor necrosis factor (TNF)-α. in tubular epithelial cells (TEC) [65]. TNF-α futher triggers *caspase*-3 to cause oxidative stress in the mitocondria, affect cytochrom C and apoptosome so that triggers apoptosis. Apoptosis can be inhibited by the presence of antioxidants. [66].

Administration of vitamin E improves the level of tissue antioxidant enzymes, decreases injury and completely eliminates CaOx crystal deposition in kidney [67]. CaOx crystal deposition was associated with total cellular glutathione reduction in the kidney and increased lipid peroxide [47]. Rats were given ACE inhibitors (losartan), oxidative stress reducers (oxydative stress, OS), showed significant increases in glutathione levels and decreased active compounds of thiobutyric acid (TBA) in the kidney. [68].

The Ethylene Glycol model is currently used for the study of crystalline binding molecules, crystal clearance. Use of apocyanin, antioxidant and inhibitor NADPH oxidase, hydroxypropline (HPL) induced hyperoxaluria rat almost completely reverses the effects of hyperoxaluria [46], CaOx kidney crystal deposition was also significantly reduced, and excretion of OPN, KIM, MCP-1 urine was reduced without affect on hyperoxaluria.

CaOx crystal deposition causes inflammation and attracts many inflammatory cells including leukocytes, monocytes, and macrophages [46], and multinucleated giant cells are identified around the crystals.

The use of EG is a model of nephrocalcinosis causing COM (calcium oxalate monohydrate) crystals in urine and kidney [23]. The current EG model is used for the study of crystal binding molecules, crystal clearance and the relevance of some macromolecular inhibitors such as OPN to crystal retention [31].

5. Medical Management of Recurrent kidney stones

A. Non Pharmacological Treatment

- Adequate dietary calcium intake (calcium and oxalate intakes must be in balance)
- Reduce animal protein intake
- Reduce salt intake
- Increase fruits and vegetables intake (rich in potasium)
- Increase fluid intak (at least > 2 L/day)

B. Pharmacological Treatment

The mainstay of prevention of recurrence for kidney stones is represented by increased water intake, which, together with diet and lifestyle changes, represents the first-line of treatment, Sodium intake restriction, decreased supersaturation and stone extraction surgery methods

The DASH (Dietary Approach to Stop Hypertension) diet, also known as the Mediterranean diet, which emphasizes a higher proportion of fruit and vegetables, low-fat dairy products and whole grains, and contains only small amounts of meat, sweets and sugar- containing beverages, has been shown to lower the risk of kidney stones and has other health advantages [69].

In patients with recurrent or active disease, diuretik thiazides (to reduce calcium excretion in patients who are hypercalciuric), potassium citrate (to boost within tissues, cells coordinating need a proper citrate excretion and offset potassium losses from diuretic use) or allopurinol (for uric acid stones) can be tried [70],

However, the use of pharmacological methods of treatment and treatment has some limitation, ie persistent rock fragments causing injury and increased recurrence of stones with ESWL and development of diabetes and hypertension on long-term use, in ESWL CaOx use will turn into a more solid CaP [71]. The use of long-term thiazid diuretics can result in K depletion (hypokalemia), fatique, diiziness, impotence, and guccal muculoskeletal.

Aside from calcium, other electrolytes appear to influence the formation of kidney stones. For example, by increasing urinary calcium excretion, high dietary sodium may increase the risk of stone formation. A reconsideration of the 1988 National Institute of Health (NIH) Consensus Statement on prevention and treatment of kidney stones had been well covered elsewhere [72]. That is

1. HCT/Chlortalidone/Indapamide (potasium citrate may be added)
2. Potasium citrate
3. Allupurinol or potasium citrate
4. Pyridoxine
5. Alphamercaptopropionylglycine (tiopanin) or d-penicilamine or ACE inhibitor
6. Potasium citrate
7. Antibiotics

CONCLUSION

Various studies related to the pathogenesis and mechanism of kidney stone formation are still complex and contradictory, but involve various crystallization processes namely nucleation, growth, aggregation, and crystal retention. This review is intended to understand the process of Calcium oxalate stone formation induced by the presence of ethylene glycol, in order to find the latest strategies for preventing kidney stone formation and the occurrence of end-stage kidney.

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