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REVIEW ARTICLE

Review on Role of Oxalates in Nephrolithiasis

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Abstract

Nephrolithiasis is defined as the occurrence of crystalline stones (calculi) in the urinary system. These are also known as renal stones and are composed of different amounts of calcium and oxalate in an organic matrix. Oxalate is a metabolic end product of glyoxylate and ascorbate. Oxalates reach the kidneys through blood and are excreted through urine. However, if present in large quantities, they become a hazard as they form insoluble crystals on combining with calcium. Oxalates are produced in our body through both endogenous and exogenous (dietary) sources. *Oxalobacter formigenes* is a bacterium that degrades oxalate and colonizes the large intestine. The absence of this bacteria from GIT causes a primary deficiency of Oxy-decarboxylase enzyme responsible for degrading dietary oxalates into easily digestible forms. Different researches on oxalate metabolism point towards an oxalate-rich diet as the most important contributory factor for raised oxalate levels in the blood. The incidence of urinary oxalate excretion and nephrolithiasis is elevated by higher levels of lipids and lower levels of calcium and magnesium in the diet. Increasing fluids in the diet along with enough number of fruits with vitamin C reduce the risk of developing nephrolithiasis.

Keywords: *Oxalobacter*, Oxalate rich diet, Oxydecarboxylase, Renal stones, Urinary system

Introduction

Kidneys are the bean-shaped paired organs in the abdomen. There are million tiny filters (nephrons) in each kidney, which are the functional units of the kidney. They help in eliminating the waste products from the body, help in the filtration of the blood and maintaining the chemical balance of the body. After removal of waste and excess salt and water, the purified blood gets circulated back. The waste fluid thus collected gets converted to urine and is stored in pelvis region in kidney, which is a funnel-shaped structure that drains into a tube called the ureter.

Nephrolithiasis is a huge burden globally. Its prevalence (history of stone disease) in an area, varies with age, sex, race, and geographical region whereas incidence of nephrolithiasis, (the first stone event), varies with sex, age and race. The burden of kidney stone disease has been quantified by epidemiologic studies. These studies have also expanded the understanding of risk factors (Taylor and Curhan, 2015). In India, 12% of the total population has been found to be prone to urinary stones. Out of this 12%, 50% of the population is severely affected by renal damage, which even leads to a complete loss of kidneys (Guha *et al*., 2019). Nephrolithiasis which is also known as kidney stones is hard deposits of salts and minerals that are formed inside the kidneys (Worcester and Coe, 2008). Nephrolithiasis has been generally attributed to lack of water intake on daily basis, oxalate-rich diet, obesity, family history, sex-specific factors (more common in men), and environmental factors. Seventy-five per cent of the renal stone disease are calcium-based calculi. The incidence of calcium-based calculi is increasing, which suggests that dietary and environmental factors work upon a preexisting genetic background (Sayer, 2017). Kidney stones generally occur in 1 out of every 10 persons in a lifetime (Rodgers, 2017). The symptoms of nephrolithiasis include severe pain in the lower abdominal and lower side back region with nausea, haematuria, urinary tract infections, blockage of urine flow and vomiting. Symptoms depend upon their location, whether stones are present in the urinary bladder, kidneys or ureter (Alelign and Petros, 2018).

One of the waste products filtered by the kidney is oxalate. Oxalate, a metabolic end product is formed as a byproduct of ascorbate and glyoxylate metabolism and is excreted out in urine. But because of the insolubility of its calcium salt, it causes a hazard leading to kidney stones. The patients with extreme hyperoxaluria and idiopathic calcium oxalate nephrolithiasis have an elevated plasma oxalate level (Lu and Bonny, 2015). Oxalic acid is highly oxidized compound that is synthesized by a wide range of micro-organisms, plants and animals. Oxalates are naturally present in many foods. Paralysis of the nervous system, precipitation of blood calcium and corrosion of skin may be caused by ingestion of gram quantities of

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oxalate. During digestion in the stomach and intestines, oxalates bind to the calcium and leave the body through faeces. Unbound oxalate travels from the blood to the kidneys as a waste product and leaves the body through urine. Kidney stones are formed when these fragments stick together to form larger crystals. Damage to renal tissue and a decrease in renal function may occur as a result of stone formation (Knight *et al.*, 2016a). During the process, increased urinary supersaturation (hyperoxaluria, increased pH) leads to crystal nucleation, crystal growth, crystal aggregation, crystal retention within the kidney and ultimately stone formation. Supersaturation of urine is the key step in the formation of stone (Fig. 1).

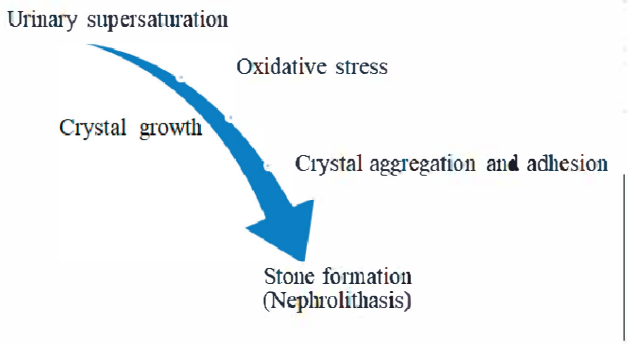

Fig. 1. Formation of stone in kidney

Oxalate Sources

Endogenous Oxalates

Glyoxalate is the primary precursor of oxalate which is the intermediatory product in the metabolic pathway of oxalate synthesis from glycolate via enzyme lactate dehydrogenase in the liver. Thus making liver the major source of endogenous oxalates in bloodstream. Glyoxalate is formed by the oxidation of glycolate by glycolate-oxidase in peroxisomes. Glyoxalate is also formed through the breakdown of hydroxyproline, which increases urinary oxalate. The metabolism of glyoxylate to glycine, catalyzed by enzyme alanine glyoxylate aminotransferase (a pyridoxine dependent enzyme) helps in keeping the concentration of glyoxalate low in the blood (Wood *et al.*, 2019). An intermediate in amino acid metabolism, the urea cycle and gluconeogenesis, serine is formed on glycine metabolism. The reduction of glyoxylate into glycolate occurs in cytosol, with the help of D-glycerate dehydrogenase, enzyme widely present in the body.

Protein transporters help in the entry of oxalate into erythrocytes. However, blood oxalate proportion carried in erythrocytes for oxalate synthesis is unknown. Metabolism of exogenous glyoxal to glycolate is effectively carried out by erythrocytes. This conversion depends upon glyoxal concentration (Holmes *et al.*, 2001). Erythrocytes take up exogenous glyoxal and convert it to glycolate because they contain low levels of glyoxal, glyoxylate, oxalate glycolate and methylglyoxal. The rate of conversion to oxalate is approximately 1%. The glyoxalase system converts most of the glyoxal to glycolate, which is taken up by the erythrocytes which utilize glutathione as a cofactor, but only a small amount of this is converted to oxalate. Oxalate synthesis is reduced when glutathione in the cells increases and oxalate synthesis is decreased when aldehyde dehydrogenase activity lowers. Thus, oxalate synthesis is increased by oxidative stress in tissues (Knight *et al.*, 2016b).

Catabolism of ascorbate (vitamin C) in urine or blood is another source of non-dietary oxalate. Ascorbate catabolizes non enzymatically to oxalate, carbon dioxide and L-erythrulose or L-threonate after being oxidized by enzymatic and non-enzymatic pathways to dehydroascorbate. Ascorbate reduces the risk of nephrolithiasis by increasing oxalate excretion, and binding to calcium. Hence decreasing the supersaturation of urinary calcium oxalate (Siener *et al.*, 2013). Circulating ascorbic acid acts as an antioxidant in the cells and tissues, where it can result in the formation of the ascorbyl radical. Dehydroascorbate is formed by the loss of one more electron. Two ascorbyl radicals can change to ascorbic acis and dehydroascorbate. Ascorbic acid can be formed from dehydroascorbate through interaction with reduced glutathione. One of the enzymes that help in this reduction is glutaredoxin. A small amount of the dehydroascorbate irreversibly forms open chain diketogulonic acid (DKG), a highly unstable molecule which can break down to oxalate. The condition that promotes or limits the breakdown of both dehydroascorbate and DKG has not been well characterized. Therefore it remains a major limitation in deciding the contribution of ascorbic acid in metabolism to oxalate synthesis (Grano and Tullio, 2007). Ferraro *et al.* (2016) suggested that oral administration of ascorbate results in a lower incidence of kidney stone formation.

Exogenous (Dietary) Oxalates

Hyperoxaluria is the major cause of kidney stones which is mostly contributed by oxalate-rich foods (Asplin, 2002). Vegetables, nuts, fruits, and grains are sources of dietary oxalate. Dietary (exogenous) sources contribute to 20 to the 40% of blood oxalate. Processing of ingested food during its preparation determines the bioavailability of the oxalates. Amount of free oxalates in the gut is also affected by presence of other ions. Calcium oxalate stone formation is dependent on the quantity of oxalate excreted in urine (Mitchell *et al.*, 2019). Dietary oxalates also affect the risk of formation of kidney stones. Normal intake of dietary calcium and a reduced intake of high-oxalate-

containing foods have shown positive responses in calcium oxalate supersaturation and thereby limit the formation of oxalate kidney stones. The amount of dietary oxalate excreted in urine is about 50% of the dietary oxalate ingested through the food items containing oxalate (Holmes *et al.*, 2001). Most common diets contain around 200-300 mg of oxalate. A reasonable goal of 100 mg of oxalate daily is required for stone prevention. An ideal amount of oxalate would be about 50 mg daily if that can be accomplished (Harris, 2021).

The role of gut microbiota on the formation of renal stones have been focused in the recent studies. Healthy gut microbiota has been associated with no history of urinary stones. It was also observed that a particular strain of bacteria *Oxalobacter formigenes* is a key micro-organism that proved healthy in oxalate degradation (Knight *et al.*, 2016b). *Oxalobacter formigenes* that colonizes in the large intestine of humans, is an oxalate-degrading bacterium. There is a beneficial symbiotic effect between *O. formigenes* and humans. These microbes develop an obligate or facultative relationship with the host and help in the production of certain enzymes that are good for gut and metabolical activities (Sadaf *et al.*, 2017). *O. formigenes* is a strict anaerobe and gram-negative bacteria found in the gut that uses the carbon sources from the degradation of oxalate for its survival. Antibiotic consumption kills O. formigenes. When there is lack of this bacterium in a persons GIT, then the GIT cannot degrade dietary oxalates because it lacks the primary source for the Oxy-decarboxylase enzyme, which on digestion gets easily absorbed and excreted in the kidney, where it precipitates as calcium oxalate stone. The absence of *O. formigenes* also increases the absorption of dietary oxalate in the colon and decreases the secretion from endogenous sources. Thus, predisposition to calcium oxalate calculus formation is increased because of higher oxalate excretion in urine. Patients with renal calculi and hyperoxaluria have lower amount of *O. formigenes* in faecal sample, as compared to the control subjects (Kaufman *et al.*, 2008). It was concluded that individuals with secondary to high oxalate nephropathy and oxalate-rich diet have little or no *O.formigenes* in their gut microbiota (Nazzal *et al.*, 2020). A recent study shows that oxalate homeostasis is maintained more by a symbiotic community of bacteria rather than isolated species and its role in oxalate homeostasis by the intestinal microbiome and hence in urinary kidney stone (Miller *et al.*, 2019). Studies that have assessed the efficacy of intake of probiotics that provide bacteria with oxalate-degrading capacity have led to promising but generally mixed results (Lieske, 2017).

Dietary Influences on Nephrolithiasis

The risk of stone formation is greatly influenced by dietary, non-dietary, and urinary risk factors, which in turn vary with sex, age and body mass index (Taylor and Curhan, 2015). Food rich in oxalates must be avoided in excess consumption especially among the ones who have a history of stones. A few foods with high oxalate content listed in Table 1 are plant-based foods- spinach, sweet potatoes, almonds, cashews, okra (ladyfinger), beets, pumpkin, eggplant, soy, tofu, beans, raspberries, brans, shredded cereals, stevia sweeteners, cocoa powder, beverages including tea leaves, baked potatoes with skin and French fries. Animal-based foods- chicken, beef, eggs, cheese and fish (Trinchieri, 2013). Risk of developing kidney stones also increases on consumption of sodium rich canned, packaged, and fast foods. High dietary intake of sodium chloride is directly associated with urinary calcium excretion as both share the same transport system in the kidney. Therefore, a high sodium diet can increase the chance of developing urinary calculi (Damasio *et al.*, 2011).

A study was conducted where subjects were introduced to take DASH (Dietary Approaches to Stop Hypertension)-style diet for decreasing the risk of kidney stone formation. DASH scores were given on eight components namely high intake of nuts and legumes, vegetables, fruits, whole grains and low-fat dairy products, and low intake of red and processed meats, sweetened beverages and sodium. DASH scores were assigned to every individual according to their dietary intake and results concluded that subject with high DASH score has lower chances of developing the kidney stones as compared to the one with low DASH scores. It was concluded that a marked decrease in kidney stone risk is associated with the consumption of a DASH-style diet (Taylor *et al.*, 2009). A study conducted on postmenopausal women for the intake of fiber rich diet containing high fiber sources shows a lower incidence of nephrolithiasis (Sorensen *et al.*, 2014).

A cross-sectional study was conducted at Nephrology Department, Hospital de Santa Cruz by Laranjinha et al. (2019), where serum magnesium levels were studied and results showed a high prevalence of kidney stones in individuals with low levels of serum magnesium. Reduction in the absorption of oxalate in the GIT occurs when oxalate binds with magnesium, thereby decreasing supersaturation of calcium oxalate in urine. Up to 18 stone formers exhibited low magnesium levels. Studies have reported that stone formation risk is reduced by 30% in males on higher dietary magnesium consumption. A study was conducted among women where they were asked to keep a check on their daily intake of Vitamin B6. Results revealed that a lower prevalence of kidney stones

was associated a good intake of vitamin B6. Vitamin B6 deficiency increases oxalate production and urinary oxalate excretion as vitamin B6 is a cofactor in oxalate metabolism. Results have shown that in women, stone formation risk is decreased by a higher intake of vitamin B6.

Oxalate absorption is decreased by higher levels of magnesium and calcium as they bind the oxalate. Whereas, the free oxalate concentration increases when unabsorbed lipid binds the calcium. So, high level of lipids and lower levels of magnesium and calcium in the gut, increase the risk of nephrolithiasis (Miller *et al.*, 2019).

Excess of Vitamin-C that is beyond 500 mg per day must be avoided as it can lead to over production of oxalate (Knight *et al.*, 2016a). A study concluded that obese individuals with high BMI and waist-hip circumference have more chances of developing kidney stones. Individuals with normal BMI have lower urinary risk factors for stone formation like calcium, oxalate, and urate excretions as compared to overweight and obese patients (Poore *et al.*, 2020). Nephrolithiasis is associated with high urinary oxalate/ calcium/ uric acid, low fluid intake and low urinary citrate. These findings can be the basis for devising treatment plans to reduce stone recurrence.

Table 1. Oxalate content of common foods (IFCT, 2017)

S.No.	FOOD ITEM	OXALATE CONTENT (mg/100g)
1	Cardamom black	2472
2	Cardamom green	1961
3	Niger seeds	1913
4	Cloves	1845
5	Poppy seeds	1631
6	Turmeric powder	1531
7	Bathua leaves	1077
8	Amaranth spined leaves	1073
9	Cumin seeds	817
10	Coriander seeds	809
11	Amaranth leaves (green)	779
12	Amaranth leaves (red and green)	676
13	Spinach	592
14	Lotus root	364
15	Almonds	344
16	Mango ginger	307
17	Ginger fresh	259
18	Pomegranate seeds	253

Source: Indian Food Composition Tables, 2017. (Longvah *et al.*, 2017)

Dietary Guidelines to Prevent Nephrolithiasis

Decrease the oxalate rich foods in diet like spinach, okra, sweet potatoes.

Increase the intake of calcium rich foods like curd, milk, broccoli, finger millet.

Proper intake of enough amount of fruits with Vitamin-C must be included.

Increase the intake of fluids and water i.e.at least 10-12 glasses per day.

Good quality and amounts of probiotics must be included in diet like yogurt, fermented soy, milk and cabbage products, kimchi, kombucha, traditional buttermilk and miso a traditional Japanese seasoning.

A low sodium diet must be taken on a daily basis.

Include home remedies like Basil leaves juice, Cranberry juice, Lemon juice, Wheatgrass juices, Apple cider Vinegar.

A weight management diet must be taken.

Avoid processed and canned foods like canned tuna, processed meats.

Avoid foods high in saturated fats (Lieske, 2017).

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