LITHIASIS: THE CAUSATIVE SOURCES ARE UREATES AND OXALATES

Montu Barot, Urvashi Nayak, Khyati Pathak, Khushbu Patel and Prof. Dr. Dhrubo Jyoti Sen*

Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

ABSTRACT

A calculus (plural calculi), often called a stone, is a concretion of material, usually mineral salts, that forms in an organ or duct of the body. Formation of calculi is known as lithiasis. Stones can cause a number of medical conditions. Some common principles apply to stones at any location, but for specifics of the particular stone type in question. Calculi are not to be confused with gastroliths. Calculi in the urinary system are called urinary calculi and include kidney stones (also called renal calculi or nephroliths) and bladder stones (also called vesical calculi or cystoliths). They can have any of several compositions, including mixed. Principal compositions include oxalate and ureate.

Calculi of the gallbladder and bile ducts are called gallstones and are primarily developed from bile salts and cholesterol derivatives. Calculi in the nasal passages (rhinoliths) are rare. Calculi in the gastrointestinal tract (enteroliths) can be enormous. Individual enteroliths weighing many pounds have been reported in horses. Calculi in the salivary glands are called salivary calculi (sialoliths). Calculi in the tonsils are called tonsillar calculi (tonsilloliths).
Calculi are usually asymptomatic and large calculi may have required many years to grow to their large size.

- From an underlying abnormal excess of the mineral, e.g., with elevated levels of calcium (hypercalcaemia) that may cause kidney stones, dietary factors for gallstones.
- Local conditions at the site in question that promote their formation, e.g., local bacteria action (in kidney stones) or slower fluid flow rates, a possible explanation of the majority of salivary duct calculus occurring in the sub-mandibular salivary gland.
- Enteroliths are a type of calculus found in the intestines of animals (mostly ruminants) and humans and may be composed of inorganic or organic constituents.
- Bezoars are lumps of indigestible material in the stomach and/or intestines; most commonly, they consist of hair (in which case they are also known as hairballs). A bezoar may form the nidus of an enterolith.

In kidney stones, calcium oxalate is the most common mineral type (Nephrolithiasis). Uric acid is the second most common mineral type, but an in-vitro study showed uric acid stones and crystals can promote the formation of calcium oxalate stones.

Stones can cause disease by several mechanisms: Irritation of nearby tissues, causing pain, swelling and inflammation; Obstruction of an opening or duct, interfering with normal flow and disrupting the function of the organ in question; Predisposition to infection (often due to disruption of normal flow).

A number of important medical conditions are caused by stones: Nephrolithiasis (kidney stones), Can cause hydronephrosis (swollen kidneys) and renal failure, Can predispose to pyelonephritis (kidney infections), Can progress to urolithiasis, Urolithiasis (urinary bladder stones), Can progress to bladder outlet obstruction, Cholelithiasis (gallstones), Can predispose to cholecystitis (gall bladder infections) and ascending cholangitis (biliary tree infection), Canprogressto choledocholithiasis (gallstones in the bile duct) and gallstone pancreatitis (inflammation of the pancreas), Gastric calculi can cause colic, obstruction, torsion and necrosis, Diagnostic workup varies by the stone type, but in general: Clinical history and physical examination, Imaging studies, Some stone types (mainly those with substantial calcium content) can be detected on X-ray and CT scan, Many stone types can be detected by ultrasound. Factors contributing to stone formation (as in #Etiology) are often tested: Laboratory testing can give levels of relevant substances in blood or urine, Some stones can be directly recovered (at surgery, or when
they leave the body spontaneously) and sent to a laboratory for analysis of content.

Modification of predisposing factors can sometimes slow or reverse stone formation. Treatment varies by stone type, but, in general: Medication, Surgery (lithotomy), Antibiotics and/or surgery for infections, Extra corporeal shock wave lithotripsy (ESWL) for removal of calculi.

KEYWORDS: Calculi, Lithiasis, Nephrolith, Cystolith, Rhinolith, Enterolith, Sialolith, Tonsillolith, Urolith, Cholelith, Choledocholith, Bezoar.

INTRODUCTION

A kidney stone, also known as a renal calculus or nephrolith, is a solid piece of material which is formed in the kidneys from minerals in urine. Kidney stones typically leave the body in the urine stream and a small stone may pass without causing symptoms. If stones grow to sufficient size (usually at least 3 millimeters (0.12 in)) they can cause blockage of the ureter. This leads to pain, most commonly beginning in the flank or lower back and often radiating to the groin. This pain is often known as renal colic and typically comes in waves lasting 20 to 60 minutes.

Figure-1: Oxalate creating stones

Other associated symptoms include: nausea, vomiting, fever, blood in the urine, pus in the urine and painful urination. Blockage of the ureter can cause decreased kidney function and dilation of the kidney. Most stones form due to a combination of genetics and environmental factors. Risk factors include being overweight, certain foods, some medications and not drinking enough fluids. The diagnosis is usually based on symptoms,
urine testing and medical imaging. Blood tests may also be useful. Urinary stones are typically classified by their location in the kidney (nephrolithiasis), ureter (ureterolithiasis), or bladder (cystolithiasis), or by their chemical composition (calcium-containing, struvite, uric acid or other compounds). In those who have previously had stones, prevention is recommended by drinking fluids such that more than two liters of urine is produced per day. If this is not effective enough, thiazide diuretic, citrate or allopurinol may be taken. It is recommended that soft drinks containing phosphoric acid (typically colas) be avoided. When a stone causes no symptoms, no treatment is needed. For stones which are causing symptoms, pain control is usually the first measure, using medications such as nonsteroidal anti-inflammatory drugs or opioids. More severe cases may require procedures. For example, some stones can be shattered into smaller fragments using extracorporeal shock wave lithotripsy. Others require cystoscopic procedures. In the United States about 9% of the population has had a kidney stone. Slightly more men are affected than women. In 2013 kidney stones resulted in about 15,000 deaths globally.

Oxalate (IUPAC: ethanedioate) is the di-anion with the formula \( \text{C}_2\text{O}_4^{2-} \), also written \((\text{COO})_2^{2-}\). Either name is often used for derivatives, such as salts of oxalic acid, for example sodium oxalate \( \text{Na}_2\text{C}_2\text{O}_4 \), or dimethyl oxalate \(((\text{CH}_3)_2\text{C}_2\text{O}_4)\). Oxalate also forms coordination compounds where it is sometimes abbreviated as ox.

Many metal ions form insoluble precipitates with oxalate, a prominent example being calcium oxalate, the primary constituent of the most common kind of kidney stones. In the body, oxalic acid combines with divalent metallic cations such as calcium (Ca\(^{2+}\)) and iron(II) (Fe\(^{2+}\)) to form crystals of the corresponding oxalates which are then excreted in urine as minute crystals. These oxalates can form larger kidney stones that can obstruct the kidney tubules. An estimated 80% of kidney stones are formed from calcium oxalate. Those with kidney disorders, gout, rheumatoid arthritis, or certain forms of chronic vulvar pain (vulvodynia) are typically advised to avoid foods high in oxalic acid. Methods to reduce the oxalate content in food are of current interest. \(^{[1]}\) Magnesium (Mg\(^{2+}\)) oxalate is 567 times more soluble than calcium oxalate, so the latter is more likely to precipitate out when magnesium levels are low and calcium and oxalate levels are high. Magnesium oxalate is a million times more soluble than mercury oxalate. Oxalate solubility for metals decreases in the order Mg > Ca > Cd > Zn > {Mn, Ni, Fe, Cu} > {As, Sb, Pb} > Hg.
The highly insoluble iron (II) oxalate appears to play a major role in gout, in the nucleation and growth of the otherwise extremely soluble sodium urate. This explains why gout usually appears after age 40, when ferritin levels in blood exceed 100 ng/dl. Beer is rich in oxalate and iron and ethanol increases iron absorption and magnesium elimination, so beer intake greatly increases the risk of a gout attack. Cadmium catalyzes the transformation of vitamin C into oxalic acid. This can be a problem for people exposed to high levels of cadmium in their diets, in the workplace, or through smoking. In studies with rats, calcium supplements given along with foods high in oxalic acid can cause calcium oxalate to precipitate in the gut and reduce the levels of oxalate absorbed by the body (by 97% in some cases.) Oxalic acid can also be produced by the metabolism of ethylene glycol ("antifreeze"), glyoxylic acid, or ascorbic acid (vitamin C). Powdered oxalate is used as a pesticide in beekeeping to combat the bee mite. Some fungi of the genus *Aspergillus* produce oxalic acid. Some preliminary evidence indicates the administration of probiotics can affect oxalic acid excretion rates in a positive manner (and presumably oxalic acid levels, as well).

About 80% of kidney stones are partially or entirely of the calcium oxalate type. They form when urine has been persistently acidic. Some of the oxalate in urine is produced by the body. Calcium and oxalate in the diet play a part, but are not the only factors that affect the formation of calcium oxalate stones. Dietary oxalate is an organic molecule found in many vegetables, fruits and nuts. Calcium from bone may also play a role in kidney stone formation. Spinach (*Spinacia oleracea*) is an edible flowering plant in the family Amaranthaceae. It is native to central and western Asia. It is an annual plant (rarely biennial), which grows to a height of up to 30 cm. Spinach may survive over winter in temperate regions. The leaves are alternate, simple, ovate to triangular, very variable in size from about 2–30 cm long and 1–15 cm broad, with larger leaves at the base of the plant and
small leaves higher on the flowering stem. The flowers are inconspicuous, yellow-green, 3–4 mm diameter, maturing into a small, hard, dry, lumpy fruit cluster 5–10 mm across containing several seeds. Common spinach, *Spinacia oleracea*, was long considered to be in the family Chenopodiaceae, but in 2003, that family was merged into the family Amaranthaceae in the order Caryophyllales. Within the family Amaranthaceae, Amaranthoideae and Chenopodioideae are now subfamilies, for the amaranths and the chenopods, respectively.[2]

Spinach, along with other green leafy vegetables, is rich in iron. For example, the United States Department of Agriculture states that a 180-g serving of boiled spinach contains 6.43 mg of iron, whereas a 170-g ground hamburger patty contains at most 4.42 mg. However, spinach contains iron absorption-inhibiting substances, including high levels of oxalate, which can bind to the iron to form ferrous oxalate and render much of the iron in spinach unusable by the body. In addition to preventing absorption and use, high levels of oxalates remove iron from the body. Spinach also has a moderate calcium content which can be affected by oxalates, decreasing its absorption. The calcium in spinach is among the least bioavailable of food calcium sources. By way of comparison, the human body can absorb about half of the calcium present in broccoli, yet only around 5% of the calcium in spinach. Unless you have kidney stones, or are at risk of having them, there’s no evidence that eating lots of raw spinach has any harmful side effects. If you are at risk of certain types of kidney stones, however, eating raw spinach may raise the likelihood of developing them because it’s high in oxalates -- a waste product that makes up certain kidney stones. Talk to your doctor about the dietary changes necessary to reduce your risk of kidney stones.

**Figure-3: Kidney stone and MRI Kidney Stones**
About 1 million Americans get kidney stones each year, according to the University Of Pennsylvania School Of Medicine. Roughly 70% of these stones are made of a mixture of calcium and oxalate. Kidney stones are pebble like material that forms on the walls of your kidneys. While most stones are small enough to pass through your urinary system without causing problems, some stones can grow large and cause excruciating pain.

**Spinach, Oxalates and Risk**
Your doctor may recommend a controlled-oxalate diet if you are at risk for calcium oxalate kidney stones. A low-oxalate diet often involves limiting your oxalate consumption to less than 50 milligrams per day. To do so, you need to avoid foods high in oxalates. Spinach is very high in oxalates and is known to increase kidney stone formation and urinary oxalate content, according to the Cleveland Clinic. A 100-gram serving of spinach, or about 3.5 ounces, contains approximately 645 milligrams of oxalate.

**Cooking Spinach Decreases Oxalates**
Researchers found that steaming and boiling were effective cooking methods for decreasing the oxalate content of spinach and other vegetables. Boiling appears to be more effective; it reduced the soluble oxalate content by 30% to 87%. They found that steaming lowered oxalates 5% to 53% in their study. Cooking also decreased insoluble oxalate content anywhere from zero to 74%.

**To Eat or Not to Eat Spinach**
Study concluded that boiling and steaming may be an effective cooking strategy to decrease the risk of high urinary oxalates in people who are at risk of developing kidney stones. But talk to your doctor about whether you can have cooked spinach and if so, how much. It may be challenging to tell how much oxalate is left in the spinach after cooking. Your doctor may recommend avoiding spinach if you're on a low-oxalate diet that restricts you to less than 50 total milligrams per day. Low-oxalate green vegetables include lettuce, cabbage, endive, broccoli and Brussels sprouts. They contain little to no oxalate. Spinach can be eaten raw in salads, steamed or added to stir-frys and soups. Low in calories but high in vitamins, minerals and fiber, it is a versatile addition to a healthy diet. In rare cases, consuming excessive amounts of spinach can lead to kidney stones, issues with iron absorption and gastrointestinal difficulties. Maintaining a balanced, varied diet will help you avoid these problems.\(^3\)
Nutrition in Spinach
A cup of cooked and drained spinach offers 41 calories and 4.3 g of fiber. Its high mineral content includes 245 mg of calcium, 6.43 mg of iron, 157 mg of magnesium, 101 mg of phosphorous and 839 mg of potassium. It also contains 17.6 mg of vitamins C, 263 μg of folate, 11,319 μg of β-carotene, 35.5 mg of choline, 20,354 μg of lutein and zeaxanthin and 18,866 IU of vitamin A.

Kidney Stones
Spinach contains a naturally occurring substance called oxalate. In rare cases, eating extreme amounts of oxalate-rich foods like spinach, nuts, pepper and rhubarb can lead to a condition called hyperoxaluria, in which oxalate crystals combine with calcium in the kidney and form kidney stones. Kidney stones can cause sharp pain in the lower back, genitals or inner thigh, urinary problems, nausea and abdominal bloating. If you notice these symptoms, see your doctor.

Iron Absorption
Although spinach contains high levels of iron, plant-based iron or non-heme iron can be difficult for the body to absorb. The oxalate in spinach can combine with iron, interfering with the body’s ability to absorb it. Try eating spinach with citrus fruit or juice, since vitamin C can help counteract this effect and increase absorption. Calcium-rich foods and whole grains can also keep the body from absorbing nonheme iron, so it may help to avoid eating these foods at the same time as spinach.

Gastrointestinal Problems
Dietary fiber like the fiber found in spinach is essential to healthy digestion, but when eaten in excess, it can cause gastrointestinal distress, including gas, cramps, bloating, constipation or diarrhea. If you experience any of these symptoms after eating spinach, introduce it to your diet more slowly. Eat smaller portions until your digestive bacteria become accustomed to the additional fiber. If your symptoms persist, speak with your doctor. A mummy that had been preserved for a couple of thousand years in the high desert of Chile was discovered upon X-ray examination to have a very large oxalate stone in the kidney, about the size of a golf ball. The discovery of this ancient sufferer is testimony to the fact that kidney stones and oxalate toxicity have afflicted humans for a very long time.
Oxalates (the salt form of oxalic acid) are extremely painful when deposited in the body. About eighty % of kidney stones are caused by oxalates and they are by far the most common factor in kidney stone formation. There is also a large degree of genetic variability in the ability to detoxify the chemicals that produce oxalates. Perhaps twenty % of the population has a genetic variance that increases their likelihood of producing oxalates, even when not consuming a high-oxalate diet.[4]

![Figure-4: Oxalate stone Stone](image)

Oxalates can form all throughout the kidney and the urinary tract, and can also form in the ureter as well as in the bladder. These star-shaped crystalline stones cause pain as the pressure in the urinary filtrate builds up, and perhaps also by tearing into the walls of the urinary tract itself.

Some kidney stones acquire a stag horn shape, while some oxalate crystals resemble pieces of coral. The crystals do have a lot of calcium in them just as coral does. Oxalate crystals appear in different colors. Some are black and almost look the color of Indian arrowheads made of obsidian. On page 41 is shown a picture of a kidney with one of the oxalate crystals imbedded in it. You can see that the crystal is very pointed. Some of these have extremely sharp ends that cause severe pain. Kidney stones are one of the most common medical ailments—ten to fifteen % of adults will be diagnosed with a kidney stone in their lifetime. One million Americans develop kidney stones each year and most of these are oxalate related. Seventy-five to ninety % of kidney stones are made of oxalic acid bound to another compound, usually calcium. Once you have experienced a kidney stone attack, you have a very high chance of having another unless you change your way. The common symptoms are pain in the side and the back below the ribs. The episodes of pain last between twenty to sixty minutes, and it is common to hear women who have suffered kidney stones claim that they are more painful than childbirth. The pain radiates from the
side and the back to the lower abdomen and groin. There may be bloody, cloudy and foul-smelling urine. If there is infection, there may also be fever and chills. Pain with urination may accompany nausea and vomiting, and the sufferer may have a persistent urge to urinate.

This last symptom is a common factor in autism. Autism is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior. Parents usually notice signs in the first two years of their child’s life. These signs often develop gradually, though some children with autism reach their developmental milestones at a normal pace and then regress. The diagnostic criteria require that symptoms become apparent in early childhood, typically before age three. It has been noted that many children with autism urinate perhaps fifty times a day, but only release a small amount of urine each time. The behavior arose because these children were suffering from kidney stones and high oxalate concentrations. The children would urinate only a small amount at a time since when urinating normally the pressure of the stream causes pain. Frequently releasing small amounts of urine causes much less pain to the child.[5]

**Not just in the kidneys**

Even though oxalate crystals are most common in the kidney, they also can form in virtually any other tissue in the body, including the brain and the blood-brain barrier. Oxalate crystals resembling pieces of glass can form in the heart muscle. As the heart muscle contracts, these pieces of oxalate crystals actually tear into the tissue. If these crystals are deposited in skeletal muscle, normal movement and exercise can be very painful. I’m convinced this is also one of the factors responsible for fibromyalgia. Oxalates may also cause thyroid disease as they react in thyroid tissue.

![Figure-5: Painful stones](image-url)
Star-shaped kidney stones can cause great pain in the kidneys and bladder. Typical stag-horn shaped kidney stone. A kidney stone resembling glass embedded in the kidney. Oxalate stones resembling glass embedded in the heart. Oxalate crystals can form in the bone. The oxalate crystals can become so dense they actually push the bone marrow cells out of the bones, leading to severe anemia. Deficiencies of red blood cells as well as white blood cells may result due to the oxalate depositions in the bones. Oxalates can likewise cause osteoporosis. The oxalates form in the bone marrow and alter the structure of the bone matrix so the bone is much weaker and prone to breakage. Other diseases in which oxalates may play a role include arthritis, joint pain and interstitial cystitis.[6]

Properties of oxalates
The shape of the crystal will depend on which metal the oxalate combines with. Calcium is one of the most common but it can combine with virtually any metal. There are cobalt oxalates and zinc oxalates. The cobalt ones are spear shaped whereas the zinc oxalate resembles thin disks. These are extremely thin and very sharp. Oxalates in the gastrointestinal tract have a tendency to bind essential elements. If you have a lot of oxalates, you won’t be able to utilize essential elements like calcium, magnesium and zinc because they will also form deposits with oxalates. If you have excess oxalates, you may have to increase your intake of calcium, magnesium and zinc. In addition, rather than acting as antioxidants, oxalates are pro oxidants, so they encourage the oxidation of your fats, forming rancid fats in your body.

A fungal origin
An unexpected finding is the fact that oxalate crystals are produced in very high amounts by molds and fungus. Aspergillums—a common organism that causes infection in humans and also is found in the black fungi that you see in your bathroom—produce oxalates. The stalactites in this case were formed from calcium oxalate. Aspergillums produce these oxalates, and these stones will form any place that has infection by the fungus. In the case of sinus infection, mold and fungus, not bacteria, are the most common causes of infection. A colleague of mine, who is an eye, nose and throat specialist, X-rayed a patient’s sinuses and found large oxalate crystals in her sinuses, which disappeared after anti-fungal treatment. Large oxalate crystals have also been isolated from the lungs of people who had Aspergillums infection of the lungs. The deposits can also form in the skin where they create black areas and necrotic lesions in people with very high oxalate levels.
**Oxalates and autism**

Children often manifested gastro-intestinal symptoms such as diarrhea and stomach pain. They may also have pain in the urinary tract. That pain is relieved when a low oxalate diet is instituted. Owens also found that children had improved cognitive, academic and motor skills once the amount of oxalates in their diets was sharply reduced. The same dietary measures helped reduce pain in their muscles and feet, and also brought about a reduction in abnormal behavior and self-abuse as well.

Eighty % of people with genetic diseases that cause them to produce kidney stones die before the age of twenty. These genetic diseases, which belong to a class of disorders called hyperoxaluria, are frequently fatal unless the victim receives both a liver and a kidney transplant. Sometimes even after the transplants people die because the oxalates are deposited in tissues all throughout the body. The oxalates will come out of the bones or the muscles and then form in the transplanted kidneys and still kill the person.

More than a third of children with autism have oxalate values as high as people who have these rare genetic disorders, even though these autistic children do not have the disorders. The question naturally arose: If they don’t have this genetic disorder, why are their oxalates so high? We correlated the amount of oxalate in autistic children with other biochemical parameters and found there was a high correlation with the sugar arabinose, which is a Candida marker. It appears that the main reason for the high oxalates in children with autism is because of the Candida problem, which is prevalent in autism. Arabinose is very low in normal children and very high in those with autism. We found in my earliest research that treatment with the anti-fungal drug Nystatin markedly decreased this compound. In addition, autistic symptoms such as hyperactivity, lack of eye contact, and aggressive behavior markedly decreased as well. Because of the dramatic reduction in symptoms, anti-fungal treatment has become one of the most common therapies in autism in the world today. [7]

**Vulvodynia**

Another condition associated with oxalates is vulvodynia, or pain in and outside the vagina. The oxalate crystals act like tiny pieces of glass, which are deposited in the tissue. The oxalate is extremely acidic so it is corrosive as well. The pain is often described as burning or stinging, with a feeling of rawness or irritation. One of the published studies on the treatment of this condition states that this is due to a reaction with yeast. There is
indeed a connection of vulvodynia with yeast, most often Candida. There are about a
dozen different species of Candida yeast normally associated with humans, the most
common of which is Candida albicans. It was found that the main way to treat
vulvodynia was anti-fungal treatment to get rid of Candida, along with a low-oxalate diet.
These two approaches have been very effective in correcting this condition. Children who
take oral antibiotics will frequently have much higher amount of oxalates. Antibiotics
severely disrupt the balance of normal flora in the gut, with a consequent exponential
proliferation in the growth of Candida, which is resistant to antibiotics. Oral antibiotics
first appeared in the early 1950s, and the pharmaceutical companies actually included
antifungal drugs along with the antibiotics because they knew about this problem. The
FDA disallowed the addition, declaring that there was no approval for the prophylactic use
of anti-fungals, thereby washing their hands of the whole business. It is significant to note
that if individuals are given the same amount of antibiotics intravenously, their oxalate
values do not rise because there was no effect on the GI tract. In some ways the old medical
treatment—a shot of penicillin—was a lot safer.\[8\]

![Figure-6: Vulvodynia and Fibromyalgia Fibromyalgia](image)

Yeast is a common factor in chronic fatigue and fibromyalgia, and antifungal therapy is
very useful in treating these problems. Jacob Teitelbaum has written several books about the
treatment of fibromyalgia and indicates two-thirds of individuals improved their chronic
fatigue and fibromyalgia after anti-fungal therapy.

A Dr. Eaton in England found that individuals who had chronic fatigue would actually
produce alcohol from their sugar intake. He describes patients who would do a baseline
blood-alcohol test, then take some glucose dissolved in a flavored drink, and measure the
blood alcohol one or two hours later. The blood alcohol would be substantially higher if the
person had a severe Candida problem.

The OH component readily attaches to minerals like calcium, zinc and mercury, forming
oxalates. Oxalates in the body come from food, can be formed in the gut by yeasts and
fungi, or can result from an interruption in the glycolate pathway. Nutritional deficiencies and inborn errors of metabolism cause the formation of oxalates rather than the protein glycine.

Eaton found that by using this test he could monitor patients undergoing different treatments for chronic fatigue and fibromyalgia and found that 42 % of patients improved just with sugar restriction alone. If he combined a low-sugar diet together with anti-fungal drugs, he had about a 78 % success rate. The most comprehensive study was that of a Dr. Jessop in California, who treated over one thousand people with chronic fatigue and fibromyalgia using a single anti-fungal drug, ketoconazole. Eighty-four % of the patients improved. Of the 1,100 patients, 685 were on disability payments. After the treatment with anti-fungal treatment, only twelve remained on disability. It was an extremely effective treatment."^{9}\)

**Zellweger syndrome**

High amounts of oxalates have also been found in persons with a metabolic disorder called Zellweger syndrome, which causes the reduction or absence of an intracellular organelle called peroxisome, leading to mental retardation and severe metabolic problems. In one study, nineteen of twenty-three patients exhibited high amounts of oxalate, and there was a direct relationship between the degree of mental impairment in children and their levels of oxalates. The children with the highest amounts of oxalates were the ones who were the most mentally impaired.

**Oxalates and cancer treatment**

Oxalates also come into play in cancer treatment. One of the drugs used to treat cancer, oxaliplatin, contains a combination of platinum and oxalate. In many of the people taking this drug, their cancer improved, but they also experienced severe neurotoxicity and nerve damage. While undergoing treatment, patients developed high amounts of oxalates which were coming from the drugs. Researchers found the effect was specific to the oxalates. If they gave the drug without the oxalate the toxicity did not occur; the toxicity was a result of the oxalate combined with the drug."^{10}\)

![Figure-7: Oxaliplatin](image-url)
Research has also found that people with genetic variations called polymorphisms experienced much more neurotoxicity when exposed to this drug. Alanine-glyoxylate aminotransferase (AGXT) is the enzyme responsible for moderating the production of oxalates in the body. People with a genetic variation that leaves them deficient in AGXT are much more likely to suffer severe reactions. They suffer peripheral neuropathy, the disease of the peripheral nerves that causes superficial and deep sensory loss; sensory ataxia, which means not feeling a sense of balance; and functional impairment.

**Oxalates in food**

People who are vegetarians really have to be aware of all the oxalates they take in. The biggest culprit for all vegetarians is soy protein, and the second is spinach. Virtually everybody who eats a large spinach salad every day is going to succumb to kidney stones. I’ve tested them over and over again and the people who have the highest oxalate values invariably tell me that a cornerstone of their daily diet is a large spinach salad. If they add nuts to their salad and textured soy protein, both of which are very high in oxalates, you’ve got a cocktail made to produce kidney stones. Spinach is so high I would not recommend eating it even cooked, as a main course. Lettuces, by the way, are very low in oxalates. The biggest problem vegetarians face is eating a diet high in soy protein and spinach.\(^{[11]}\)

Once after I gave a talk a physician came up afterwards and told me that a few months earlier he had decided to get healthy. He decided to forswear all the McDonald’s and the like. He was going to start eating healthy and eating healthy meant a very large spinach salad with lots of pecans on it every day. Within two months he had kidney stones. Cooking does not destroy the oxalates; they are extremely stable. Cooking may reduce the oxalates in foods as they precipitate into the cooking water, and if you discard that water you are likely reducing the oxalates remaining in the food. If you drink that pot liquor, however, you will absorb the full amount. Peppercorns are very high in oxalates, but not many people eat a pound of black pepper every day. However, if you like pepper-coated steaks, pepper may contribute to your oxalate load. The same goes for parsley, it’s very high in oxalates but you don’t eat very much of it. Peanuts and peanut butter are problematic because some kids eat them every single day. Peanut butter is not a poison, so eating it occasionally isn’t going to bother you. The problems come when you make a few highoxalate foods the staples in your diet. Dr. Massey at Washington State University found that textured soy protein is very high in oxalates. There are 638 milligrams of oxalate per 85-gram serving, which is
about the size of one of these small soy burgers and as much as you would find in a typical serving of spinach. The recommended amount of oxalate for people who have kidney stones is less than 30 mg a day. One soy burger contains twenty times the recommended daily dose in just one single portion. This, I would say, is a major problem for the soy producers. The soy cheese does not have nearly as much. It’s the textured soy protein, the soy burgers, the soy bacon that have such high levels. Some soy companies recommend that you pour textured soy protein on your breakfast cereal. You really don’t want to do that. How much oxalate is in the typical diet? There’s a very large range—from 97 to 930 mg a day. To reduce kidney stones you should consume less than 30 to 50 mg a day.\textsuperscript{[12]}

\textbf{Treatment}

Even though we can avoid the worst offenders—soy foods and spinach—if you are enjoying a varied diet, it is difficult to reduce dietary oxalate levels to near zero because they occur in so many foods—grains, nuts, vegetables and fruits. The most effective way to get rid of oxalates is the use of calcium citrate. This supplement exerts a double potency action in eliminating oxalate. The calcium part of calcium citrate binds to the oxalate and causes it to precipitate out in the stool so it will not be absorbed. But part of the oxalate escapes. The citrate is a second line of defense, which competes directly with the oxalate for absorption. For the treatment to be effective, the calcium citrate must be taken at the same time as the oxalate-containing food. If you have problems with any of conditions caused by oxalates—kidney stones, autism or vulvodynia—then taking calcium citrate with each meal can be very effective. If there is an adequate amount of calcium in the diet—if supplementing with calcium citrate, for example—it will combine with the oxalate in the GI tract, precipitate out in the stool, and then be eliminated in the stool. The optimum dosage is approximately 300-350 mg calcium as calcium citrate for a total of 1000 mg (one gram) of calcium a day. If you’re taking this you don’t need additional sources of calcium. An even better approach would be to use magnesium citrate. The adult dosage is about 300-400 mg a day. Some practitioners recommend up to 1000 mg but many people report problems with diarrhea if they exceed 400 mg. Again, a divided dose would be best, taking the magnesium citrate with each meal. Some other supplements that can be very useful include probiotics and anti-fungal medication to help to control Candida. The probiotic bacteria have enzymes that break down oxalates. The amino acid arginine helps to prevent the depositing of oxalates in the tissues. The omega-3 fatty acids and cod liver oil are also very effective in preventing oxalate deposition. The omega-6 fatty acids,
mostly from commercial vegetable oils, behave in the reverse, and accelerate the deposition of oxalate. The supplement that is most helpful is vitamin B6. This costs only pennies a day and is extremely safe. I take 100 mg every single day. I recommend just the pyridoxine form. I know the type called P5P is also used but personally I don’t think you get the additional benefit by the P5P. There are a number of medical tests for oxalate status that we use at Great Plains Laboratory. We have a urine panel to measure oxalates and we can also test for yeast markers. We typically find that where the yeast marker is very high, the oxalate marker is also very high. We also test for vitamin B6. With these measures, kidney stones are largely preventable. This is good news because oxalate buildup can do a lot of damage.[13]

**Sidebars the chemistry of oxalates**

Oxalate refers to the salt form of oxalic acid. All acids follow the same convention of nomenclature. The salt of citric acid is citrate, for example. The salt form simply means it is missing hydrogen atoms. Instead, the salt form has a negative charge attached to it. When the acid has the hydrogen attached to it, it has the suffix. When the hydrogen atoms are removed so that it is negatively charged, it has the suffix –ate. The critical thing about this, from the chemist’s point of view, is that the pH, which is a measure of the acidity of the molecule, of oxalates is the lowest of all the organic acids. (A low pH rating corresponds to a high level of acidity.) It’s the most acidic, most corrosive organic acid there is because of its very low pH value. For example, citric acid might have a pH of 5—mildly acidic in comparison, and hundreds of times less acidic than oxalate. The molecule of oxalic acid could lose two hydrogen atoms so it can become doubly negatively charged and this is the form in which oxalate is predominantly found in the blood and the urine. This form in which there are two negative charges makes it much more likely to bind to a number of metals. Calcium, zinc and mercury are examples. What is very interesting from the chemist’s point of view is the fact that oxalate binds most tightly to toxic metals such as mercury and lead. One might think this strong chelating action is beneficial, but it is quite the opposite. Once oxalate binds with mercury or lead it immediately becomes insoluble and precipitates out of the bloodstream and forms crystals in the bones and other tissues. Rather than attaching to these toxic metals and escorting them out of the body, the oxalate traps the toxic metals within the body. This is one aspect of oxalates that I believe should be more closely examined as it may explain why oxalates are associated with so many diseases. They will trap heavy metals and enhance their toxicity. The oxalate itself is water soluble, but once it binds with a metal ion it becomes insoluble and then precipitates
out to be deposited in tissue. In a comparison of the different strengths of reaction of oxalates with various metals, the metal with the highest reactivity is mercury. When oxalate reacts with mercury, even if there is only a tiny amount present, it will preferentially bind with mercury compared to calcium or other metals. The oxalate almost seems to seek out and trap toxic metals. The reactivity of oxalate with calcium and magnesium, on the other hand, is very low, and the lowest reactivity is with magnesium. One of the treatments to help people get rid of excess oxalates is to take very high doses of magnesium, or in some cases, actually give intravenous infusions of magnesium. Because it has the least solubility with oxalates magnesium will help to dissolve them, so to speak.

![Oxalate pathway](image)

**Figure-8: Oxalate pathway Oxalate pathways**

About fifty % of oxalate comes from the diet and the other fifty % comes from what your body makes itself. Oxalic acid in the diet is first converted to glycolate, then glyoxylate, and then at this point glyoxylate can either bind to a mineral to form oxalate or it can be transferred and form glycine. If you have a genetic deficiency in the enzyme AGXT, the glyoxylate primarily forms oxalate because reduced amounts of AGXT do not function adequately to override this process. One in five people in the population has this genetic variant in which they cannot detoxify this compound. Instead it predominantly forms oxalate. It has been found that one third of the people with oxalate toxicity have this genetic variant, and 53 % of them are likely to have acute, very severe neurotoxicity versus only 4 % in those with normal genotype expression. Probably a high %age of people who have kidney stones are in this group of 20 % of individuals with this genetic variant. One of the body’s energy production factories called glycolysis is inhibited by oxalates. The enzyme pyruvate kinase is involved in the last step in the body’s energy production and is strongly inhibited by oxalate. It is very interesting that the same enzyme inhibition is largely responsible for Tourette syndrome. People with Tourette syndrome, however, have strep
antibodies that inhibit this enzyme. Oxalates also strongly inhibit the same enzyme. The critical factor here is that this enzyme works much better in the presence of high amounts of vitamin B6. This is another one of the holistic treatments for people with kidney stones. In fact, vitamin B6 treatment is also used by the mainstream medical community for people with kidney stones.\[14\]

**Vitamin C, copper and oxalates**

What about the controversy surrounding vitamin C therapy? Vitamin C has been shown to be very helpful in kids with autism, although theoretically vitamin C can form oxalates. I say theoretically. Vitamin C can increase your risk of kidney stones if you take extremely high doses, in the range of 100 grams (100,000 mg) a day.

A double-blind study found that very high doses of vitamin C were very effective in reducing autistic symptoms. A study showed that a person taking 2000 mg (2 grams) of vitamin C a day for ninety days did not cause a significant effect or change in oxalate levels. Another study evaluated forty-five thousand men who took vitamin C and vitamin B6 over six years and examined the effect this supplementation had on their kidneys. In the six years of follow up they found 751 cases of kidney stones out of 45,000 men. There was no association, however, of vitamin C or vitamin B6 intake with the kidney stones. In fact, men who took more vitamin C had less risk of kidney stones than men who took less than 250 mg vitamin C. The real problem with vitamin C is the metals that the person may be taking. If one is taking high amounts of copper or iron, these can accelerate the breakdown of vitamin C to form oxalates. Someone with high copper or iron levels may be at risk for higher oxalate formation if also supplementing with vitamin C. The vitamin C may be broken down to form dehydroascorbate and then oxalate. Knowing your copper and iron status can be very important. If, for example, you have copper pipes in your home, which is very common, and you have acidic water, that water will dissolve your copper pipes so that most of the water coming out of your faucet will contain high amounts of copper. In turn, the high copper may cause you to degrade your vitamin C. There is a problem with forming extra oxalates, but this also means that even if you take high doses of vitamin C, it may not be useful because the copper can degrade it so rapidly. It is the free copper that is so toxic. Copper is bound to a protein in the blood called ceruloplasmin. In some individuals with autism this can be most significant; but this copper-zinc imbalance is important in almost every chronic disease: ADD, schizophrenia, arthritis, chronic fatigue,
and many others. When you have too much copper and not enough zinc, vitamin C will not be utilized, it will be destroyed.[15]

CONCLUSION

*How does diet affect the risk of developing kidney stones?* Kidney stones can form when substances in the urine—such as calcium, oxalate and phosphorus—become highly concentrated. The body uses food for energy and tissue repair. After the body uses what it needs, waste products in the bloodstream are carried to the kidneys and excreted as urine. Diet is one of several factors that can promote or inhibit kidney stone formation. Certain foods may promote stone formation in people who are susceptible, but scientists do not believe that eating any specific food causes stones to form in people who are not susceptible. Other factors that affect kidney stone formation include genes, environment, body weight, and fluid intake.

*Four major types of kidney stones can form:* Calcium stones are the most common type of kidney stone and occur in two major forms: calcium oxalate and calcium phosphate. Calcium oxalate stones are more common. Calcium oxalate stone formation may be caused by high calcium and high oxalate excretion. Calcium phosphate stones are caused by the combination of high urine calcium and alkaline urine, meaning the urine has a high pH. Uric acid stones form when the urine is persistently acidic. A diet rich in purines—substances found in animal protein such as meats, fish, and shellfish—may increase uric acid in urine. If uric acid becomes concentrated in the urine, it can settle and form a stone by itself or along with calcium. Struvite stones result from kidney infections. Eliminating infected stones from the urinary tract and staying infection-free can prevent more struvite stones. Cystine stones result from a genetic disorder that causes cystine to leak through the kidneys and into the urine, forming crystals that tend to accumulate into stones. Why is knowing which type of kidney stone a person has important?

The first step in preventing kidney stones is to understand what is causing the stones to form. This information helps the health care provider suggest diet changes to prevent future kidney stones. For example, limiting oxalate in the diet may help prevent calcium oxalate stones but will do nothing to prevent uric acid stones. Some dietary recommendations may apply to more than one type of stone. Most notably, drinking enough fluids helps prevent all kinds of kidney stones by keeping urine diluted and flushing away materials that might form stones.
How does a health care provider determine the type of kidney stone? If a person can catch a kidney stone as it passes, it can be sent to a lab for analysis. Stones that are causing symptoms can be retrieved surgically or with a scope inserted through the urethra into the bladder or ureter, then sent to a lab for analysis. Blood and urine can also be tested for unusual levels of chemicals such as calcium, oxalate, and sodium to help determine what type of kidney stone a person may have had.

Dietary Changes to Help Prevent Kidney Stones: People can help prevent kidney stones by making changes in fluid intake and, depending on the type of kidney stone, changes in consumption of sodium, animal protein, calcium, and oxalate. Drinking enough fluids each day is the best way to help prevent most types of kidney stones. Health care providers recommend that a person drink 2 to 3 liters of fluid a day. People with cystine stones may need to drink even more. Though water is best, other fluids may also help prevent kidney stones, such as citrus drinks.

How much fluid should a person drink to prevent kidney stone formation? People who have had a kidney stone should drink enough water and other fluids to produce at least 2 liters of urine a day. People who have had cystine stones may need to drink even more. The amount of fluid each person needs to drink depends on the weather and the person’s activity level—people who work or exercise in hot weather need more fluid to replace the fluid they lose through sweat. A 24-hour urine collection may be used to determine the volume of urine produced during a day. If the volume of urine produced is too low, the person can be advised to increase fluid intake. Drinking enough fluid is the most important thing a person can do to prevent kidney stones. Some studies suggest citrus drinks like lemonade and orange juice protect against kidney stones because they contain citrate, which stops crystals from growing into stones.

How does sodium in the diet affect kidney stone formation? Sodium, often from salt, causes the kidneys to excrete more calcium into the urine. High concentrations of calcium in the urine combine with oxalate and phosphorus to form stones. Reducing sodium intake is preferred to reducing calcium intake.

How can a person limit sodium intake? Learning the sodium content of foods can help people control their sodium intake. Food labels provide information about sodium and other nutrients. Keeping a sodium diary can help a person limit sodium intake to 2,300 mg. When
eating out, people should ask about the sodium content of the foods they order. Some foods have such large amounts of sodium that a single serving provides a major portion of the RDA. Foods that contain high levels of sodium include: hot dogs, canned soups and vegetables, processed frozen foods, luncheon meats fast food. People who are trying to limit their sodium intake should check labels for ingredients and hidden sodium, such as monosodium glutamate, or MSG; sodium bicarbonate, the chemical name for baking soda; baking powder, which contains sodium bicarbonate and other chemicals; disodium phosphate; sodium alginate; sodium nitrate or nitrite.

*How does animal protein in the diet affect kidney stone formation?* Meats and other animal protein—such as eggs and fish—contain purines, which break down into uric acid in the urine. Foods especially rich in purines include organ meats, such as liver. People who form uric acid stones should limit their meat consumption to 6 ounces each day. Animal protein may also raise the risk of calcium stones by increasing the excretion of calcium and reducing the excretion of citrate into the urine. Citrate prevents kidney stones, but the acid in animal protein reduces the citrate in urine.

*How does calcium in the diet affect kidney stone formation?* Calcium from food does not increase the risk of calcium oxalate stones. Calcium in the digestive tract binds to oxalate from food and keeps it from entering the blood, and then the urinary tract, where it can form stones. People who form calcium oxalate stones should include 800 mg of calcium in their diet every day, not only for kidney stone prevention but also to maintain bone density. A cup of low-fat milk contains 300 mg of calcium. Other dairy products such as yogurt are also high in calcium. For people who have lactose intolerance and must avoid dairy products, orange juice fortified with calcium or dairy with reduced lactose content may be alternatives. Calcium supplements may increase the risk of calcium oxalate stones if they are not taken with food.

*How does oxalate in the diet affect kidney stone formation?* Some of the oxalate in urine is made by the body. However, eating certain foods with high levels of oxalate can increase the amount of oxalate in the urine, where it combines with calcium to form calcium oxalate stones. Foods that have been shown to increase the amount of oxalate in urine include: spinach, rhubarb, nuts, wheat bran. Avoiding these foods may help reduce the amount of oxalate in the urine.
What diet plan should a person follow to prevent future kidney stones? A diettian can help a person plan meals that lower the risk of forming stones based on the type of stone the person formed in the past. A person with a history of kidney stones may want to talk to a diettian who specializes in kidney stone prevention or nutrition for people with kidney problems. A diettian can also help overweight people plan meals to help them lose weight. Studies have shown that being overweight increases the risk of kidney stones, particularly uric acid stones. Diets that are low in carbohydrates have been shown to further increase the risk of uric acid stones and should be avoided.

**Points to Remember:** Kidney stones can form when substances in the urine—such as calcium, oxalate, and phosphorus—become highly concentrated. Diet is one of several factors that can promote or inhibit kidney stone formation. Four major types of kidney stones can form: calcium stones, uric acid stones, struvite stones, and cystine stones. Drinking enough fluid is the most important thing a person can do to prevent kidney stones. People who have had a kidney stone should drink enough water and other fluids to make at least 2 liters of urine a day. Sodium, often from salt, causes the kidneys to excrete more calcium into the urine. High concentrations of calcium in the urine combine with oxalate and phosphorus to form stones. Reducing sodium intake is preferred to reducing calcium intake. Meats and other animal protein—such as eggs and fish—contain purines, which break down into uric acid in the urine. Calcium from food does not increase the risk of calcium oxalate stones. Calcium in the digestive tract binds to oxalate from food and keeps it from entering the blood, and then the urinary tract, where it can form stones.

A diettian can help a person plan meals that lower the risk of forming stones based on the type of stone the person formed in the past. Clinical trials are research studies involving people. Clinical trials look at safe and effective new ways to prevent, detect, or treat disease. Researchers also use clinical trials to look at other aspects of care, such as improving the quality of life for people with chronic illnesses.

**REFERENCES**
