TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 14
Number 1 *Fall 2020*

79-85

2020

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Kidney Stones

Nephrolithiasis is the process of the aggregation of certain minerals in the urine due to super saturation, thereby causing the formation of kidney stones. What complicates matters, is, that there is no single cause that can be attributed to Nephrolithiasis. In fact, as research progresses, an abundance of causative agents are being linked. Outlined below is a comprehensive summary of the occurrence, recurrence, treatment and causative factors of kidney stones.

Kidney stones usually form in the renal pelvis and pass through the urine unnoticed. However, at times these stones can grow up to several centimeters. These large stones can cause blockages in different locations in the urinary system and can be very painful. Stones that do not obstruct passages cause no symptoms besides hematuria (blood in the urine). Passing a stone causes renal colic. The pain intensifies as the stone progresses downward. Pain is felt as the stone passes through the ureter. When a stone reaches the uretero-vesicular junction it may cause dysuria and urinary frequency. Unfortunately, colic is felt regardless of body position and motion. Stone size is a big determinant of treatment option. Stones smaller than five mm in diameter have a high possibility of passing. Those that are between five to seven mm have a 50% chance of passage. Stones that are greater than seven mm almost always require medical intervention (Coe, Evan and Worcester, 2005).

The prevalence of kidney stones is dependent on many different factors, including gender. About 5% of American women will develop a kidney stone at some point in their life. By contrast, about 12% of American men are likely to develop a stone. The peak age in men is 30 years old. In women stones are most common between the ages of 35 and 55 with peaks at both 35 and 55. Previous stone formers have a 50% chance of forming a second stone within five to seven years of the first. (Malvinder, 2004).

In recent years there has been an increase in the incidence of kidney stones. This has been associated with many different factors. For example; BMI, race, ethnicity and region of residence are strongly associated with stone formation. A seasonal disparity is also seen. Men have high urinary calcium oxalate saturation during the summer and women during the early winter. High levels of calcium oxalate in the urine are prone to solidify into stones. (Malvinder, 2004)

In the majority of cases, stones are passed without medical intervention. Even so, physicians will still prescribe strong pain killers to combat the typical pain that is experienced. In addition, anti-nausea medications as well as antibiotics may also be prescribed. Medicinal treatment is also an option. Alpha blockers may be prescribed, which relax the muscles of the ureter, allowing the stone to pass thereby mitigating the pain. If a stone is too large to pass, it may require a medical procedure to either break it up so that it can pass, or to completely remove it. In some situations, although the stone is small, it still requires medical intervention to remove it if it has lodged itself somewhere between the kidney and the urethra; usually in the ureters (Frassetto & Kohlstadt, 2011).

One method of treatment is using sound waves to break up stones. This is done through a procedure known as extracorporeal shock wave Lithotripsy (ESWL). ESWL shatters stones into very small pieces by use of shock (sound) waves that that create powerful vibrations. These stones can now pass more easily in the urine. This procedure is done under sedation or light anesthesia. It lasts around 45 minutes to an hour. Possible side effects include bruising on the back or abdomen and bleeding around the kidney and other nearby organs (Mayo Clinic, 2020).

Another method involves using a scope to remove stones. This is often done when the stones are smaller but have been lodged and can no longer pass on their own. The physician will pass a ureteroscope equipped with a camera through the urethra to the ureter. The stone will then be removed or broken into pieces. This is done under general anesthesia. Often a stent is placed in the ureter to relieve some of the swelling. The stent is left inside the ureter for a few days following the ureteroscopy to allow for further healing (Mayo Clinic, 2020).

When all other therapeutic options have been exhausted, a surgical procedure will be necessary. Smaller stones that did not respond to the aforementioned treatments and larger stones require surgery. This procedure is called percutaneous nephrolithotomy. It is the process of removing the kidney stone using small telescopes and other tools that are inserted through a small incision in the patient's back. The patient will be under general anesthesia at the time of the surgery and will remain hospitalized for a few days to recover (Mayo Clinic, 2020)

The Composition of Kidney Stones

Kidney stones are composed of different minerals that are found in urine. Calcium oxalate and Calcium phosphate comprise the composition of approximately 80% of stones. 19% are composed of struvite and uric acid. The remaining one percent are composed of cystine or ammonium acid urate. Kidney stones arise from the unwanted phase change of these substances from the liquid state to the solid state. The substances listed above exist in the urine as dissolved salts. However, at times, these salts can become super saturated. When a substance is super saturated no more of this solute can dissolve in solution and it will consequently precipitate out as a solid, forming hard granules. Super saturation is approximated by the ratio of

a substance's concentration in the urine to its solubility. At super saturation levels less than one, crystals of a substance will dissolve. But at super saturation levels greater than one, crystals can grow and form. The composition of stones correlates with the super saturation values from the urine produced (Coe, Evan and Worcester, 2005).

Calcium Oxalate Stones:
How/Why do they form?

The vast majority of Calcium Oxalate stone formers do not suffer from a systemic disease and are therefore described as idiopathic stone formers. In other words, they form stones spontaneously; the cause is unknown. The commonality found in many CaOx stone formers are disorders of calcium metabolism, resulting in abnormal levels of calcium. In addition, low urine citrate levels have been shown to permit CaOx stones. This is because urine citrate binds urine calcium in a soluble calcium citrate complex which reduces calcium super saturation (Coe, date unknown). However, when levels are low, calcium levels rise and ultimately stones may form. Furthermore, high urine uric acid excretion in men and women (above 750-800mg/d) is associated with idiopathic CaOx stones as well. These dissolved uric acid salts appear to reduce the solubility of calcium oxalate thereby promoting the formation of stones.

Disorders of Calcium metabolism range in severity and in the scope of their consequences. The most common cause of calcium metabolic irregularities is Primary Hyperparathyroidism, a systemic disorder in which an excess of Parathyroid hormone causes increased levels of calcium in the blood. In a healthy body, the kidneys lose calcium in the urine every day. In response, calcium receptors on the surface of the parathyroid glands cause the parathyroid glands to release PTH, a hormone that increases blood calcium levels. However, because of abnormalities, there is excess calcium and less reabsorption by the kidney leading to stone formation (Primary hyperparathyroidism).(Coe, date unknown). High calcium levels in the urine are also found in people with Idiopathic Hypercalciuria. Hypercalciuria results in increased intestinal absorption of calcium. High intestinal calcium absorption raises the amount of filtered calcium presented to the renal tubules in the kidney. It can also result in the reduction of the reabsorption of the renal tubules. Both of these mechanisms can increase the urinary calcium level. In certain instances, the excess calcium may solidify.

Other diseases linked to Hypercalciuria are of genetic natures. Dent disease is an X-lined hypercalciuric disorder found almost exclusively in males. In affected individuals, kidney problems result from damage to proximal tubules. The disorder is due to mutations in the gene (CLCN5) that codes for the voltage-gated endosomal chloride channel 5 (Heller & Pak 2002). Another type of genetic disorder is Barter Syndrome – specifically types I and II. In this syndrome renal calcifications are found in the cortex and the medulla. These calcifications come from problems in transport that reduce the capacity of the thick ascending limb of the kidney tubules which consequently reduces salt and calcium reabsorption. This results in a higher salt and calcium concentration leading to hypercalciuria (Heller & Pak 2002).

High Oxalate concentrations also lead to the formation of stones. Hyperoxaluria occurs when there is too much oxalate in one's urine. Hyperoxaluria can be caused by inherited-genetic disorders, because of intestinal disease or because of a diet of oxalate rich foods (Mayo Clinic, 2019). Primary hyperoxaluria is an autosomal recessive disorder caused by the overproduction of oxalate. This overproduction leads to calcium oxalate precipitation in the kidney and eventually to end stage renal disease (Ther, 2018). Enteric hyperoxaluria is caused by an increase in absorption of oxalate from foods. Several intestinal diseases including Crohn's disease and irritable bowel syndrome increase the absorption of oxalate from foods. This in turn increases the amount of oxalate excreted from the urine (Mayo Clinic, 2019). There are also many oxalate rich foods that can contribute to an overabundance of oxalate in the urine. These foods include beans, beer, beets, berries, chocolate, coffee, cranberries, dark green vegetables, nuts, oranges, sweet potatoes and tea. It has been proven that avoiding high oxalate foods can substantially help lower oxalate levels (Thomson, Husney, Romito, & Vachharajani, 2019)

Treatment

A new and developing form of treatment for CaOx stones is using a drug called Stiripentol. Stiripoentol is an antieplipetic drug used to treat children affected by Dravet syndrome. It has been shown to inhibit neuronal lactate dehydrogenase 5 enzyme. This isoenzyme is the last step in hepatic oxalate production and therefore can potentially reduce hepatic oxalate production and urine oxalate excretion. A young child affected by type I hyperoxaluria received this drug for several weeks, and her urine oxalate excretion decreased 66% (Dudal… Letavernier, 2019). Studies are still being conducted to ascertain the long term affects and the possibly harmful side effects that are accompanied by this drug.

In addition, a study was performed to see if there was an association between gut microbiome alterations and renal calcium oxalate stones. It was found that short chain fatty

acids may prevent stone formation. The research proposed that by regulating gut microbiome composition using short chain fatty acids, it may be possible to prevent kidney stones. Microbiome analysis was performed on 160 Chinese individuals some with recurring stones, some with one incidence of stone formation, and some non- stone formers. The results identified that recurrent stone formers and single time stone formers both exhibited higher fecal microbial diversity than the controls. While the mechanism of using short chain fatty acids to regulate gut microbiome is still unknown, the research has shown promising signs that this may be a cogent method to preventing and treating kidney stones (Wang…Li, 2019).

Recurrence

While there are many methods of treatment for kidney stones already in practice and many more in the development stages, recurrence of kidney stones reduces the effectiveness of many therapeutic methods. Following an initial stone event, the spontaneous five-year recurrence rate is 35 to 50 percent. As such it is imperative to institute a treatment plan that will change the whole nature of the kidney's function in order to be sure that renal calculi will not form yet again.

One such method is to alter the pH of the urine. Recently, the administration of potassium citrate has been considered as a therapeutic and preventative measure specifically for calcium oxalate nephrolithiasis. In a study conducted last year patients who underwent urolithiasis surgery were divided into subgroups. One subgroup in each category were given potassium citrate 40 mEq per day orally. The results were conclusive. The stone recurrence rate for the treatment subgroup was 1.72%, while it was 25.86% in the control subgroup. The difference was statistically significant. The treatment works because citrate inhibits the aggregation of calcium oxalate crystals by increasing the solubility by a mechanism mentioned above. It also inhibits urinary calcium stone formation due to change in urine pH. There are many other methods of prevention as well (Hosseini, Alipour, Omidbakhsh, and Ashraf, 2019).

Calcium Phosphate Stones:
Why/how do they form?

Calcium phosphate stones are not as common as calcium oxalate stones. Calcium phosphate stones may be caused by hyperparathyroidism, renal tubular acidosis, and urinary tract infections. Calcium Phosphate is present in urinary stones as either apatite, or brushite. What drives the development of brushite versus apatite stones is unknown. In patients of calcium phosphate stones, plugs of apatite fill the lumens of the terminal collecting duct. Epithelial cells are damaged and destroyed and around affected tubules, the interstitial area is inflamed and scarred. Besides for being hypercalciuric because of idiopathic hypercalciuria Calcium phosphate stone formers have a distinctive feature- their urine has a higher pH. This favors calcium phosphate crystallization by increasing the abundance of urine mono-hydrogen phosphate, the ion that combines with calcium. Urine pH rises progressively with increasing calcium phosphate percentage in stones. The mechanism of increased urinary pH in Calcium phosphate stone formers is unknown (Frassetto & Kohlstadt, 2011).

Remarkably, Pregnant women have a double than average chance to form calcium phosphate stones compared with age-matched nonpregnant women. They are two to three times more likely to have calcium phosphate stones over oxalate stones. This can be attributed to the fact that women have an increased glomerular filtration rate and have higher urinary calcium during pregnancy. In late pregnancy, the urine tends to have a higher pH which can predispose women to calcium phosphate stones. Kidney stones during pregnancy increase the risk of urinary tract infections. Also, pregnant women with renal colic have a 50% higher risk of early delivery compared to women who do not have kidney stones (Frassetto & Kohlstadt, 2011).

Treatment

Thiazide diuretics such as hydrochlorothiazide can help the kidney absorb more calcium, leaving less of it in the urine where it can form stones. Thiazide diuretics are a type of diuretic drug. Diuretic drugs increase urine flow. They act directly on the kidney and promote urine flow by inhibiting the sodium/chloride cotransporter located in the distal convoluted tubule of a nephron. Thiazide decreases sodium reabsorption which increases fluid loss in urine. Potassium citrate is another medication that can bind to calcium and help keep calcium phosphate in the urine from forming stones (Mayo Clinic, 2019).

Brushite stones (calcium phosphate stones) are among the hardest to break, which, combined with the large size of the stones, results in poor outcomes with shock wave lithotripsy (SWL). In an experiment conducted, several shock waves were needed to break brushite stones. It was also discovered that pure brushite stones are harder to break than brushite stones that contain a mixed composition. Shock wave lithotripsy is not the optimal treatment for brushite stones. However, invasive imaging is needed to determine a stones composition and so it remains a challenge in deciding the best treatment plan (Williams… McAteer, 2012).

Uric Acid Stones:
Why/how do they form?
Uric acid stones form because of abnormally low-acidic pH of urine a pH below 5.5. low urinary volume and hyperuricosuria are also associated with the formation of uric acid stones, (Van Hattum, de Bie, and Somani, 2019). Low urine pH can be partly ascribed to low ammonia excretion. Low urinary pH and uric acid stones are common in patients with an assortment of disorders. Patients with high BMI, gout, diabetes mellitus, and the metabolic syndrome, may have reduced renal ammonia excretion. The reduced ammonia excretion may be due to insulin resistance which is common in these diseases. In addition, urinary pH is inversely proportional to body weight. As body mass increases, urinary pH falls and becomes more acidic. Chronic diarrhea also lowers urinary pH and causes uric acid stones. Uric acid gravel can obstruct ureters and produce acute anuric renal failure. Uric acid stones can fill the entire renal collecting system. Uric acid pebbles and stones are often orange or red, as they have absorbed uricine, a pigment of bilirubin breakdown. (Van Hattum, de Bie, and Somani, 2019).

Treatment/Recurrence
Prevention and even dissolution depend on the three main components of uric acid stone formation; an increase of urinary volume, prevention of hyperuricosuria and increase in urinary pH. By increasing daily fluid intake the urinary volume increases thereby decreasing the concentration of uric acid. There are different medications that can increase the pH of the urine thereby minimizing the risk of supersaturation and consequently stone recurrences. Medications such as potassium citrate, sodium citrate and sodium bicarbonate have been proven to increase the pH of urine (Van Hattum, de Bie, and Somani, 2019). Allopurinol is not usually required; however it can be used if one of the above three medications does not suffice (Coe, Evan, and Worcester, 2011).

Cystine Stones:
How/ why do they form?
Cystine stones are the most rare form of kidney stones. They constitute less than 1% of urinary tract stones. Cystine stones are often caused by Cystinuria. About 1 in 7000 people worldwide have cystinuria. Most people with cystinuria get their first stones in their twenties or thirties, but 30% get them in their teens. According to some research, 8-10% of kidney stones in children are cystine stones. Cystinuria is a genetic condition causing mutations in renal epithelial cell transporters that result in reduced reabsorption. This leads to an increased urine excretion of the dibasic amino acids, including cystine. Because of the high super saturation of cystine, stones form (Coe, Evan and Worcester, 2005).

Treatment
Cystine stones can be removed in the same manner as other kidney stones. They can be removed by nephrolithotomy, a procedure where an instrument is inserted through the skin and into the kidney to either take the stone out or break it apart. Ureteroscopy is another method. It involves sticking a tiny instrument into the bladder and then up the ureter to remove the stone. A third method, is Extracorporeal shock wave lithotripsy (ESWL). This is a procedure that uses shock waves to break up larger stones into smaller pieces so that they are passable. This method however, does not work as well for cystine stones as it does on other types of stones (Frassetto & Kohlstadt, 2011).

Recurrence
Being that Cystinuria is a lifelong condition, the recurrence of cystine stones is quite high. To combat this, the patient must be sure that the super saturation concentration of cystine is below one. To begin with, patients try to attain a urine volume of three to five liters a day which can dissolve the cystine that is excreted. Some also require a medication to raise the pH of the urine. In addition, reduction of sodium and protein intake reduces cystine excretion in the urine. It is for this reason that attention to diet is an essential part of the treatment process. If increasing fluid levels and lowering the pH of the urine by diet does not work, there are medications that can be used. D-penicillamine, α- mercaptopropionylglycine, or captopril, all form soluble heterodimers with cysteine and so they can be used. However, these medications may have severe side effects such as loss of taste, fever and proteinuria, and so the former mentioned methods are more desirable (National Kidney Foundation, 2016).

The Effect of the Seasons
When attempting to connect seasonal changes with occurrence of kidney stones a huge number of factors must be taken into account. There have been many studies done on this topic and the results have been confusing. In one study, research has shown no difference in urine volume from the summer to the winter. In another study, during the winter months when vitamin D intake is limited, urinary calcium excretion was found to be much higher. This being the case, it would seem that kidney stones would more likely form in the winter (Attalla, De, Sarkissian, and Monga, 2018) .

Dietary patterns may fluctuate as well with the changing

seasons. With a reliance on packaged and processed food during the winter, urinary sodium may be increased. With an increase in urinary sodium, urinary calcium will subsequently increase as well. Also, weight fluctuations may complicate the analysis further. With less opportunities for physical activity during the winter months, coupled with the indulgent eating during the holiday season, urinary calcium may be increased. Also, lower levels of vitamin D have been associated with weight gain (Attalla, De, Sarkissian, and Monga, 2018) . All these factors point to the winter months having a high propensity for stone formation.

In contrast to the research above, William Haley, a Mayo Clinic nephrologist, has found that heat, humidity, and lack of proper hydration all lead to a higher prevalence of kidney stones in the summer. In the summer there is a greater likelihood of dehydration and thereby the possibility of a decrease in urine volume. This would consequently raise the possibility of nephrolithiasis (Sparks, 2015).

Socioeconomic Status

A study was done to ascertain if socioeconomic status can affect nephrolithiasis. The study used the Distressed Communities Index (DCI) which takes into account employment status, education level, poverty rate, median income, and business growth. Diabetes and hypertension were more prevalent in the group of people from severely distressed communities. Patients from these communities needed more invasive treatment and 13% needed staged surgery versus 9% from the non-severely distressed communities. Men from the severely distressed community had a significantly larger stone size; 12.5mm vs 9.7mm. The men also had a higher prevalence of stones greater than 20 mm. Interestingly, there was no difference in stone size between the two different groups of women. Socioeconomic status seems to correlate with stone size, but appears to have more of an effect in men than in women(Quarrier, Li, Best, Hedican, Penniston, and Nakada, 2020)

Obesity

Obesity contributes to the risk of kidney stones more than dietary factors. Maladaptive changes associated with obesity are disturbed thermogenesis and dehydration. This is because body fat is hydrophobic, so the proportion of body water decreases with increasing obesity and this can lead to dehydration. Also, the decrease in body surface area compared to body volume complicates heat exchange and metabolic functions. Obesity is often associated with electrolyte imbalances and altered urine chemistry. All evidence points to obesity being a great risk factor for kidney stones.

It would seem logical and apparent that weight loss would be the solution to the abovementioned complications. However, it is not that simple. Weight loss has to be done in a healthy and reasonable fashion. A high animal protein diet, quick loss of lean tissue, or insufficient hydration can actually increase the likelihood of kidney stone formation. Diets high in acid can increase the risk of uric acid stones. The patient must make his or her dietary choices in an informed manner taking into account, his specific propensities to stone formation (Frasseto & Kohlstadt, 2011)

Serial soda drinkers may be at an increased risk for kidney stones. An experiment was done with a sample of males who ingested 200 grams of fructose daily for two weeks. Research showed that fructose intake greatly increases the chances of kidney stones. This is because fructose affects urate metabolism, urinary pH and affects oxalate. Since fructose is present in so many of the foods that the average American consumes, it can play a major role in increasing the risk of forming stones. Moreover, a randomized trial stated that a 10% reduction in stone recurrence for those who could reduce their soft drink intake to less than 24 ounces a week (Johnson, Perez-Pozo Lillo, 2018)

Occupation-"You are what you do"

Studies have shown that people with certain occupations have a higher probability of developing kidney stones. Some forms of work don't allow for proper fluid intake leading to a saturated urine concentration. Individuals who are more active when they work, especially if they work outdoors, perspire more, leading to more concentrated urine. However, those who have more sedentary jobs are also in danger. Since they have a higher chance of metabolic syndrome, they also have a higher risk of forming stones. Since Astronauts work in environments without gravity, they assemble calcium from their bones, leading to greater calcium levels and consequently a higher risk of stone disease (Malieckal & Goldfarb, 2020).

Removal of Kidney Stones- A Wild Ride

In 2016 two physicians came up with a rather unique method to dislodge a kidney stone after hearing about this interesting phenomenon from their patients. One patient reported passing renal calculi after each of 3 consecutive rides on the roller coaster. Many other patients reported passing renal calculi within hours of leaving the amusement park, and all of them rode the same roller-coaster during their visit. They used three renal calculi, based on real life measurements. The renal calculi were suspended in the urine model and taken for 20 rides

on the Big Thunder Mountain Railroad roller coaster at Disney World in Orlando. When the model was sitting in the front seat of the roller coaster, there was a passage rate of 4 out of 24. When sitting in the back there was a passage rate of 23 of 36. Sitting in the rear, different kidney stone location had different passage rates. An upper calyceal calculi passage rate of 100%, a middle calyceal passage rate of 55.6% and a lower calyceal passage rate of 4%. Although the data written above is encouraging, physicians must determine if a roller coaster ride is the correct form of treatment for their patients, as size and location may complicate the situation (Mitchell &Wartinger, 2016).

Corona Virus and the Kidney:

There has been emerging connections between corona virus and kidney failure but why this happens is still unclear. Many doctors have proposed different theories. One theory is that the virus directly attacks the kidneys by its way of infiltration. A study published in March shows that Corona virus infiltrates the body by binding to the ACE2 cell receptors. The kidney contains these ACE2 receptors, and in this way is under direct attack. Yet another theory states that the kidneys are affected secondary to the virus. Because the lungs are so hard hit, the body is unable to deliver adequate oxygen to the body. In turn organs are damaged and functionality is reduced. The virus also effects the blood, which can lead to clots. The kidney, being the biggest blood filter in the body is not susceptible to blood clots within its thousands of capillaries and vessels of filtration. Also blood clotting has an effect on the body's immune system possibly triggering a cytokine storm in which the body attacks its own cells and tissues. Furthering the potential damage to the kidneys and other essential organs (Edwards, 2020)

Conclusion

As more research is done on kidney stones it becomes abundantly clear that even more research is needed. There are an innumerable amount of factors to take into account when determining the best course of treatment for persons with renal calculi. The patient's occupation, ethnicity, BMI, family history, and region of residence are all contributing aspects. Stone composition may be very varied from case to case. Treatment that was successful for one may be detrimental for the other. There is no one-size-fits-all solution. Each case is unique and requires its own analysis and diagnosis. One thing is universal though, sufficient hydration is essential for the prevention of kidney stones.

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