Nephrolithiasis in Crohn’s disease patients: A review of the literature

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Abstract
Crohn’s disease is a complex chronic inflammatory disease of the digestive tract. Crohn’s disease presents with extraintestinal complications, such as nephrolithiasis. Patients with Crohn’s disease are at a higher risk of developing nephrolithiasis; however, there are preventative measures that can be taken to reduce their risk. This article provides a brief review of prevalence, risk factors, pathophysiology, presentation, and management of nephrolithiasis in Crohn’s disease patients. In addition, it explains the preventative measures that can be taken to reduce the incidence of nephrolithiasis in Crohn's disease patients.

Keywords: Crohn's Disease; Nephrolithiasis; Presentation; Risk Factors; Prevention

1. Introduction
Crohn's disease is a complex chronic disorder of the gastrointestinal system and can be further classified as a type of inflammatory bowel disease (IBD). Crohn’s disease may affect any segment of the gastrointestinal tract and presents with symptoms of fever, abdominal pain, diarrhea, and weight loss. Up to 25% of Crohn's disease patients can present with extraintestinal manifestations, such as peripheral arthropathy, erythema nodosum, osteoporosis, and nephrolithiasis. Nephrolithiasis is common in Crohn’s disease patients and should be considered in patients that present with urinary tract infection or if renal dysfunction is detected.

2. Epidemiology
Crohn’s disease incidence is 3-20 in 100,000 globally. Furthermore, it was found that developed nations have a higher prevalence of Crohn’s disease than developing nations [1]. Those who suffer from IBD are at risk of developing multiple extraintestinal complications. These include optical, dermatological, and renal complications, among others. The probability of developing one of these complications ranges between 6-46% [2]. The general population has a lifetime risk of 1-15% for developing nephrolithiasis, whereas multiple studies have reported Crohn’s disease patients' risk of developing nephrolithiasis ranges from 7-28%, with patients that have undergone abdominal surgery at an even greater risk [2, 3].

3. Risk Factors
Patients with Crohn’s disease are at a higher risk of developing kidney stones, specifically calcium oxalate and uric acid stones. One of the main symptoms of Crohn’s disease is chronic diarrhea which results in dehydration and decreased urine volume [4]. In addition, Crohn’s disease patients generally have a low urine pH (<5.5) [5, 6]. Crohn’s disease
patients are inclined to favor a high protein diet rich in oxalate and purines [7]. Calcium oxalate stones form in Crohn’s disease patients mainly due to increased urinary oxalate excretion in conjunction with decreased urinary magnesium and citrate levels [1]. In addition to diet, other factors can lead to higher urinary oxalate excretion levels. For instance, Crohn’s disease patients are more likely to have altered intestinal bacteria flora due to increased concentration of oxalate-decomposing bacteria as a result of frequent antibiotic use or bowel resection [7]. Many Crohn’s disease patients will undergo small bowel resection, leading to the development of steatorrhea, which subsequently increases colonic permeability of oxalate in the presence of fatty acids [4]. Fatty acid particles will bind to luminal calcium allowing higher levels of free oxalate in the bowel lumen [4]. Finally, bowel resection will also lead to decreased absorption of citrate and magnesium which normally act as inhibitors of calcium oxalate crystallization. [4]. On the other hand, serum uric acid levels are higher in patients with Crohn’s disease due to multiple factors, including diet. Uric acid stones are formed due to increased urine acidity. Some factors that increase urine acidity in Crohn’s disease patients include high levels of serum uric acid, colon resection and ileostomy, which lead to loss of bicarbonate absorption.

Table 1 Risk factors that increase risk of developing nephrolithiasis in Crohn’s patients

<table>
<thead>
<tr>
<th>Chronic diarrhea</th>
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<tbody>
<tr>
<td>Frequent use of antibiotics</td>
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<tr>
<td>High protein diet</td>
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<tr>
<td>Bowel resection</td>
</tr>
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</table>

4. Pathophysiology

A study published in 1968, by Dr. Gelzayd, was one of the first studies that reported the association between inflammatory bowel disease and nephrolithiasis [9]. In this study, 885 patients with IBD were included; 7.2% (64 patients) were reported to have nephrolithiasis. The primary site of organic acid secretion, such as oxalate, are the proximal tubules through which 90-95% of the circulating oxalate is eliminated, while the remaining 5% is excreted by the intestines. Normal urinary oxalate excretion is less than 45 mg/day. Patients with Crohn’s disease have a reduced amount of calcium available to bind oxalate due to the binding of calcium to unabsorbed fatty acids within the lumen, which results in higher oxalate reabsorption from the intestines. Furthermore, transmural inflammation causes distortion of the mucosal architecture in the intestines of Crohn’s disease patients, reducing the absorption of citrate and magnesium. Citrate and magnesium both inhibit the formation of calcium oxalate crystallization in kidneys, however magnesium also inhibits the absorption of dietary oxalate from intestinal lumen [11]. Additionally, the mucosal inflammation leads to less absorption of osmotic active solutes from the gut lumen resulting in osmotic diarrhea and volume contraction. This volume contraction further increases the formation of insoluble forms of calcium oxalate within the kidneys.

Oxalobacter form genes is anaerobic bacterium which colonizes the large intestines as part of the normal gut flora and is responsible for degrading oxalate within the colon by its enzyme, oxalyl-CoA decarboxylase. Patients with Crohn’s disease may be predisposed to decolonization of oxalobacter due to transmural inflammation. In a study recently published in 2018, the annual incidence of intestinal infection has risen from 26.2 to 70.6 infections per 1000 IBD hospitalizations [12]. The use of increased antibiotics in patients with Crohn’s disease also further reduces the amount of oxalobacter form genes leading to increased oxalate absorption from the gut lumen.

5. Presentation and Diagnosis

On average, it will take around 10 years from the diagnosis of Crohn’s disease for patients to develop a stone and present with nephrolithiasis [9]. Of Crohn’s disease patients that present with nephrolithiasis, it was found that most had ileocolonic disease, in contrast to solely ileal disease. The extent of disease impacting Crohn’s disease patients could lead to the need for surgical bowel procedures, which may include intestinal bypasses or colonic resections. Following these surgical procedures patients may experience more severe malabsorption and diarrhea; therefore, predisposing patients to an increased chance of developing nephrolithiasis and presenting earlier on than other patients without surgical history [3]. Due to the increased intestinal absorption of oxalate in Crohn’s disease patients, calcium oxalate stones are the most common type of nephrolithiasis that patients will present with, followed by urate stones forming because of bicarbonate losses secondary to diarrhea which increases urine urate concentration [13]. The diagnosis of nephrolithiasis should be suspected in Crohn’s disease patients presenting with complaints of sudden-onset nausea, vomiting, flank pain, or urine that is pink, red, or cola-colored, which could represent hematuria and is seen in 90% of
cases [14]. Nephrolithiasis should also be considered and ruled-out in Crohn’s disease patients with recurrent urinary tract infections or patients with unexplained abdominal pain or renal dysfunction [3].

Diagnosing nephrolithiasis differs depending on the setting of presentation. Screening for nephrolithiasis in asymptomatic patients is done preferably with ultrasound, which can identify large stones (>5 mm) [3]. In an acute setting, low-dose unenhanced computed tomography scan is considered the gold-standard imaging modality [15]. While those with Crohn’s disease are at a higher risk for nephrolithiasis to present, the stones from Crohn’s disease patients and common stone formers are indistinguishable [16]. The importance of nephrolithiasis prevention is of great importance as it has been shown that recurrent nephrolithiasis can lead to chronic kidney disease and even end-stage kidney disease [17].

6. Prevention

6.1. Water intake

Diuresis of < 1 liter per day is associated with high supersaturation levels prompting spontaneous crystallization of the lithogenic salts, where as if water intake is increased to maintain urine volume > 2.5 liters per day, the urine is diluted therefore making calcium phosphate and uric acid less saturated which subsequently reduces spontaneous crystallization [18,19]. A dose-response meta-analysis study was published in 2015, which selected 15 relevant studies (10 cohort and 5 case–control studies) with 9601 cases and 351,081 total participants. The meta-analysis found that each 500 milliliter increase in water intake is associated with a significantly reduced risk of nephrolithiasis formation (RR of 0.93, 95 % CI: 0.87-0.98; P<0.01). Interestingly, the risk of kidney stones was not significantly related to intake of juice (RR=1.02, 95% CI: 0.95, 1.10; P=0.64), soda (RR=1.03; 95% CI: 0.90, 1.17; P=0.65), or milk (RR=0.96; 95% CI: 0.88, 1.03; P=0.21). However, more data and studies are needed to quantify the role of soft drinks in the setting of nephrolithiasis formation and prevention.

6.2. Sodium Intake

High sodium intake was associated with an 11 to 61 % increase in risk of developing nephrolithiasis [20]. This effect was most pronounced in women with high daily sodium intake > 3,249 mg. This finding has been confirmed with a report from the Nurses’ Health Study, which demonstrated that high sodium intake in women increased risk for nephrolithiasis by 30%, RR = 1.30, 95% CI 1.05-1.62. Possible explanations include increasing sodium intake reduces the sodium reabsorption from the proximal tubules due to over saturation of the transporters; therefore, more sodium is presented to and absorbed by the distal tubules, making reabsorption of calcium less effective. This leads to more calcium remaining in the tubules available for spontaneous crystallization of the lithogenic salts, such as calcium oxalate and calcium uric acid stones.

6.3. Protein, sodium, fruits vegetables intake

Citrate binds with normal urinary calcium, thereby reducing supersaturation of urine, and also binds to calcium oxalate crystals preventing crystallization. One study was published which demonstrated high protein intake greater than 2g/kg/day significantly decreased urinary citrate, while significantly increasing urinary calcium and urinary uric acid [18]. These changes were more pronounced when a diet with high animal protein intake was combined with high sodium intake. Fruits and vegetables have low sodium and protein content, while having high water, potassium, magnesium, and citrate content. Magnesium and citrate both inhibit the formation of calcium oxalate crystallization in the kidneys, additionally magnesium inhibits the absorption of dietary oxalate from the intestinal lumen [11].

6.4. Calcium intake

Table 2 Factors that reduce risk of developing nephrolithiasis in Crohn’s patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>High Fluid Intake</td>
<td>target &gt;2L urine per day</td>
</tr>
<tr>
<td>Restricted Sodium intake</td>
<td>100Meq/day</td>
</tr>
<tr>
<td>Restricted animal protein intake</td>
<td></td>
</tr>
<tr>
<td>High fruits and vegetables intake</td>
<td></td>
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</table>

Calcium binds to oxalate within the intestines and is excreted via feces, reducing the absorption of oxalate into blood and urine, therefore low dietary calcium intake may increase oxalate absorption from the intestinal tract [10]. A follow up study by Curhan et al. in 1993 collected data from more than 45,000 men, and was the first study to demonstrate
that low dietary calcium intake potentially increased the risk of stones by more than 51%, compared to men with higher dietary calcium intake [21].

7. Management
Management of nephrolithiasis in Crohn’s disease patients is similar to the management of nephrolithiasis in the general population [22]. Oral hydration and pain management are part of the acute treatment once a patient presents to the hospital. Next is to determine whether the stone is causing an acute obstruction or not. If the stone is not causing an acute obstruction, determining the size of the stone indicates the next step in management. For stones <10 mm, adding alpha blockers, such as Tamsulosin, Alfuzosin, or Silodosin, can promote distal ureteral stone passage [23]. These agents are usually given for 4-6 weeks or until the stone has passed. If conservative therapy fails and the patient continues to have symptoms, surgical removal of the stone is recommended, such as extracorporeal shock wave lithotripsy (ESWL) or ureteroscopy. Percutaneous antegrade ureteroscopy is usually considered in select cases in which very large stones (>15mm) are impacted in the upper ureter. Percutaneous nephrolithotomy (PCNL) is usually reserved for renal or proximal ureteral stones that are larger than 20mm and have failed therapy with ESWL and ureteroscopy [24]. If ESWL, ureteroscopy and percutaneous ureteroscopy have failed, laparoscopic or open surgical removal of a stone is then considered.

Figure 1 Management of nephrolithiasis

Alternatively, the presence of kidney stones with an acute obstruction warrants closer attention. If there are no signs of infection, conservative management can be considered, but if conservative management fails, then decompression is recommended. If infection is suspected with an obstruction, decompression and antibiotics are essential to minimize the risk for sepsis which can be life-threatening [24]. Decompression is achieved with the placement of a percutaneous nephrostomy tube by an interventional radiologist, or placement of ureteral stent past the obstructing stone. Generally, patients that present to the hospital with urinary calculi that are found to be febrile or have other symptoms of infection would need to be started on broad spectrum intravenous antibiotics in order to cover both gram positive and negative bacteria and a urologic consultation must be made for emergent drainage [25].
8. Conclusion

Crohn's disease is a chronic disorder of the digestive tract that typically presents with abdominal distention and pain, diarrhea, weight loss, and fever. Nephrolithiasis are small, hard deposits that are made up of varying amounts of crystalloid and organic matrix and are found within the urinary system. Patients with Crohn's disease are more prone to develop nephrolithiasis. Crohn's disease can lead to lower urine pH, high urinary oxalate excretion, as well as decreased urinary magnesium and citrate levels, all of which lead to a higher risk of developing nephrolithiasis. Increasing fluid intake in order to produce over 2L of urine daily, reducing sodium intake to <100 mEq/day, restricting animal protein intake, increasing fruits and vegetables intake to supplement citrate, and normal dietary calcium intake are recommendations to prevent the occurrence of nephrolithiasis. Inpatient management of nephrolithiasis in Crohn's disease patients is similar to the management of nephrolithiasis in the general population.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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