Acta Biomed 2018; Vol. 89, Supplement 9: 76-80 DOI: 10.23750/abm.v89i9-S.7908

Review

Renal lithiasis and inflammatory bowel diseases, an update on pediatric population

Laura Bianchi[1], Federica Gaiani[2], Barbara Bizzarri[2], Roberta Minelli[2], Pablo Cortegoso Valdivia[3], Gioacchino Leandro[4], Francesco Di Mario[2], Gian Luigi de'Angelis[2], Claudio Ruberto[1]

[1] Pediatric Emergency Unit, University Hospital of Parma, Maternal and Infant Department, Parma, Italy; [2] Gastroenterology and Endoscopy Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3] Gastroenterology Unit, Molinette Hospital, Torino University, Torino; [4] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. *Background and aim of the work:* Historical studies have demonstrated that the prevalence of symptomatic nephrolithiasis is higher in patients with inflammatory bowel disease (IBD), compared to general population. The aim of the review was to analyze literature data in order to identify the main risk conditions described in literature and the proposed treatment. *Methods:* A research on the databases PubMed, Medline, Embase and Google Scholar was performed by using the keywords "renal calculi/lithiasis/stones" and "inflammatory bowel diseases". A research on textbooks of reference for Pediatric Nephrology was also performed, with focus on secondary forms of nephrolithiasis. *Results:* Historical studies have demonstrated that the prevalence of symptomatic nephrolithiasis is higher in patients with inflammatory bowel disease (IBD), compared to general population, typically in patients who underwent extensive small bowel resection or in those with persistent severe small bowel inflammation. In IBD, kidney stones may arise from chronic inflammation, changes in intestinal absorption due to inflammation, surgery or intestinal malabsorption. Kidney stones are more closely associated with Crohn's Disease (CD) than Ulcerative Colitis (UC) in adult patients for multiple reasons: mainly for malabsorption, but in UC intestinal resection may be an additional risk. Nephrolithiasis is often under-diagnosed and might be a rare but noticeable extra-intestinal presentation of pediatric IBD. Secondary enteric hyperoxaluria the main risk factor of UL in IBD, this has been mainly studied in CD, whether in UC has not been completely explained. In the long course of CD recurrent urolithiasis and calcium-oxalate deposition may cause severe chronic interstitial nephritis and, as a consequence, chronic kidney disease. ESRD and systemic oxalosis often develop early, especially in those patients with multiple bowel resections. Even if we consider that many additional factors are present in IBD as hypomagnesuria, acidosis, hypocitraturia, and others, the secondary hyperoxaluria seems to finally have a central role. Some medications as parenteral vitamin D, long-term and high dose steroid treatment, sulfasalazine are reported as additional risk factors. Hydration status may also play an important role in this process. Intestinal surgery is a widely described independent risk factor. Patients with ileostomy post bowel resection may have relative dehydration from liquid stool, which, added to the acidic pH from bicarbonate loss, is responsible for this process. In this acidic pH, the urinary citrate level excretion reduces. The stones most commonly seen in these patients contain uric acid or are mixed. In addition, the risk of calcium containing stones also increases with ileostomy. The treatment of UL in IBD involves correction of the basic gastrointestinal tract inflammation, restricted dietary oxalate intake, and, at times, increased calcium intake. Citrate therapy that increases both urine pH and urinary citrate could also provide an additional therapeutic benefit. Finally, patients with IBD in a pediatric study had less urologic intervention for their calculosis compared with pediatric patients without IBD. (www.actabiomedica.it)

Key words: inflammatory bowel disease, secondary hyperoxaluria, urolithiasis

Background and aim of the work

Historical studies have demonstrated that the prevalence of symptomatic nephrolithiasis is higher in patients with inflammatory bowel disease (IBD), compared to general population. The aim of the review was to analyze literature data in order to identify the main risk conditions described in literature and the proposed treatment.

Methods

A research on the databases PubMed, Medline, Embase and Google Scholar was performed by using the keywords "renal calculi/lithiasis/stones" and "inflammatory bowel diseases". A research on textbooks of reference for Pediatric Nephrology was also performed, with focus on secondary forms of nephrolithiasis. Only full text papers in English were included.

Results

Urolithiasis (UL) consists in the formation of urinary stones and comprises those stones formed in the kidney (nephrolithiasis), or anywhere in urinary tract as well as in the bladder. Recurrent UL may lead to end-stage renal disease (ESRD) via multiple damages in the kidney, from obstructive uropathy to tubulo-interstitial nephritis, or renal scarring, or recurrent infection. The global incidence of urolithiasis in childhood is approximately 10% of that seen in adults, it appears at all ages, with moderate preponderance in males. Urolithiasis has become more common in children over the past few decades, mainly in adolescents, as a result of rapid variations in habits such as a high salt and a high protein content diet (1-5). Nephrolithiasis results from urine supersaturation of some components. In industrialized countries calcium-oxalate (CaOx) stones are prevalent in pediatric population. Hypercalciuria is recognized worldwide as the most frequent underlying factor in calcium oxalate stones in children. Another metabolic risk factor is hyperoxaluria, although it might be underestimated, as it is less frequently described. Struvite or infection-related stones, which were very common in children until the last century, are rarely seen nowadays in industrialized countries, possibly due to the improved management of both pediatric obstructive uropathy and urinary tract infections (3).

Historical studies have demonstrated that the prevalence of symptomatic nephrolithiasis is higher in patients with inflammatory bowel disease (IBD), compared to general population, typically in patients who underwent extensive small bowel resection or in those with persistent severe small bowel inflammation (6). In IBD, kidney stones may arise from chronic inflammation, changes in intestinal physiology due to inflammation, surgery or intestinal malabsorption. UL is quite rare in pediatric IBD patients (0,37-1%) compared to the incidence in adult cases (described as 9-18%), and the main studies and reports derive from adult experience. Renal calculi are more closely associated with Crohn's Disease (CD) than Ulcerative Colitis (UC) in adult patients for multiple reasons, mainly for malabsorption, but in UC intestinal resection may be an additional risk (6, 7). Nephrolithiasis is often under-diagnosed and might be a rare but noticeable extra-intestinal presentation of pediatric IBD (3).

Various pathophysiological mechanism at the basis of nephrolithiasis in IBD-patients are considered, and additional factors as surgery or infections may aggravate the situation (9). Principal factors are:

- intestinal malfunction unabsorbed fatty acids bind intraluminal calcium; therefore, less insoluble calcium oxalate is excreted in stools, resulting in higher oxalate reabsorption and higher oxalate concentration in urine.
- decolonization of the gastrointestinal tract of the oxalate fermenting bacterium Oxalobacter fromigenes was associated with hyperoxaluria and kidney stones in IBD patients
- due to intestinal malabsorption, patients have less urinary excretion of citrate and magnesium which can act as inhibitors of oxalate stone formation
- loss of water and salt in patients with ileostomy or pronounced diarrhea will lead to the production of more concentrated urine. Moreover, in patients with ileostomies, large amounts of alkaline fluids will be lost, and the urine of those patients will be acidic.

Analyzing the main risk factors for UL in general population, focusing to a pediatric population, several factors and their relative their role in IBD were considered (9, 10).

Hypercalciuria is the most common cause of UL in children, but secondary forms are less frequent than primary or idiopathic forms. In IBD secondary hypercalciuria is a rare mechanism and it may be principally related to high-dose and/or long-term steroid treatment, and rarely to vitamin-D intoxication (1-3, 10). Oral vitamin administration rarely leads to intoxication, while in IBD patients with intestinal failure the use of vitamin C-supplemented parenteral nutrition can cause hypercalciuria (11).

Secondary hyperoxaluria is a rare but emergent cause of UL in children, as dietary intake has increased in the last decades up to 50% in industrialized countries. Secondary enteric hyperoxaluria is the main risk factor of UL in IBD. This has been mainly studied in CD, whether in UC it has not been completely explained. In the long course of CD recurrent urolithiasis and calcium-oxalate deposition may cause severe chronic interstitial nephritis and, consequently, chronic kidney disease. ESRD and systemic oxalosis often develop early, especially in those patients with multiple bowel resections (2). Malabsorption associated with ileal disease, mainly of bile-salts and fatty acids, causes increased oxalate absorption by increasing oxalate solubility in the intestinal lumen and permeability of the colonic mucosa (9-12). Kumar et al. examined the association of intestinal oxalate degrading bacteria Oxalobacter formigenes with the development of hyperoxaluria in IBD. The investigators studied stool samples of IBD patients and controls respectively for the presence of O. formigenes using polymerase chain reaction. Only 10.4% of patients with IBD had positive for O. formigenes stool samples, compared to 56% of controls (13). Patients positive for O. formigenes had higher urinary oxalate than the negative ones. A recent study suggested that oxalate is not only absorbed but can also be secreted by the small intestine. Probably chronic inflammation may impair this function (10, 14). The most the urinary output of oxalate is high, the most the risk of UL is increased, and the symptoms are severe. In patients with Crohn's disease, ileocolonic disease was associated with a greater risk of nephrolithiasis than isolated ileal or colonic disease (6). Intestinal resections, including bariatric surgery, represent an additional risk factor. In some studies, urinary saturation index for calcium-oxalate was not statistically different in Crohn's patients with and without urolithiasis, but it was significantly higher in patients after bowel resection, compared with those who did not undergo resection (10).

Citrate is the main inhibitor of calcium and oxalate crystallization. Hypocitraturia is not always adequately recognized as a risk factor. It usually derives from low dietary intake and it has been demonstrated in patient with chronic acidosis or in case of intestinal malabsorption. A reduced citrate excretion is associated to mild acidosis due to the loss of bicarbonate in liquid stools. Hypocitraturia is commonly seen in patients with gastrointestinal malabsorption, both from small bowel disease and after small bowel resection. The levels of citrate excreted in the urine of patients with CD may be half or less of that in urine of healthy subjects (15-17).

Hypomagnesuria is also typical in patients with chronic diarrhea and malabsorption and may occasionally be accompanied by hypomagnesemia. In patients with small bowel resection, the degree of hypomagnesuria correlates with the length of resected bowel. Magnesium is also thought to confer some protection against CaOx crystal formation, by chelating oxalate and possibly by an effect on crystal growth (15-17).

Even if we consider that many additional factors are present in IBD as hypomagnesuria, acidosis, hypocitraturia, and others, the secondary hyperoxaluria seems to finally have a central role. A study comparing patients with UL, either affected by CD or otherwise healthy, did not demonstrate significant differences in the urinary excretion of other lithogenic or stone inhibitory parameters (9).

Uric acid stones are more common in adult patients, depending from high protein dietary intake. In UC, especially if an ileostomy is present, urine is scanty and concentrated, and urine pH falls, leading to uric acid or mixed stones formation. Patients with intestinal resections have a tendency to form uric acid stones, particularly in patients with colon resection (10, 15-17).

A single case of pediatric patient with UC had lithiasis of ammonium acid-urate is reported in a Japa-

nese patient, secondary to diarrhea and dehydration (18).

Struvite stones are commonly founded in patients with recurrent urinary infections. Patients with IBD are a risk of urinary tract infections, especially those who have fistulas (colon-bladder fistula) or in case of anal CD. Immunosuppressive treatments should also be considered possible infectious risks (1-3).

Dehydration intended as chronic or acute loss of fluid, is at high risk of UL. In IBD both might be observed. Furthermore, all patients with colon resection share a tendency to chronic volume contraction due to loss of water and salt in liquid stools, which leads to a decreased urine volume (15).

Medications should also be considered, also if they are responsible for only 1% of UL. Drug-induced stones may form by two mechanisms: the drug or its metabolites form the main stone component when they precipitate in urine or the drug induces metabolic alterations in urine that lead to the formation of calcium or less commonly uric acid stones (1-3). Corticosteroids and vitamin D parenteral administration have already been discussed as they can lead to hypercalciuria. Many antibiotics, such as Ceftriaxone, are included in lithogenic substances with the first mechanism, as well as other immunosuppressive or immunomodulating agents as sulfasalazine or cyclosporine. Sulfasalazine is converted by gut bacteria into sulfapyridine and the clinically active metabolite 5-aminosalicylic acid (5-ASA), and its efficacy is proportional to the 5-ASA concentration within the intestinal lumen. Renal complications are commonly reported for the chemically similar 5-ASA derivative mesalamine but are not well-known side effects of sulfasalazine therapy. In a case report in an adult patient, renal ultrasound revealed multiple stones, which, once excreted and analyzed, were composed of sulfasalazine metabolites. The patient recovered after fluid administration. The author conclude that hydration status may play an important role in this process (19).

Intestinal surgery is and independent risk factor for stones formation. Patients with ileostomy post bowel resection may have relative dehydration from liquid stool, which, added to the acidic pH from bicarbonate loss, is responsible for this process. In this acidic pH, the urinary citrate level excretion reduces. The stones most commonly seen in these patients contain uric acid or are of mixed composition. In addition, the risk of calcium containing stones also increases with ileostomy (9, 10, 15). Among patients with CD, UL increases in patients with ileal resection, whereas a study evidenced that UL risk is not increased in patients with total colectomy. In UC, the risk of UL is higher in case of colectomy with J-pouch or ileostomy, but J-pouch reduce the risk of calcium-stone formation (10).

The treatment of UL in IBD consists in the correction of the basic gastrointestinal tract inflammation, the restriction of dietary oxalate intake, and, sometimes, in the increase of calcium intake (1-3, 20). No study directly assessing the in vivo effect of a treatment to reduce urolithiasis in IBD patients was identified. In a study using computerized models, simulated urine compositions based on reported composition values of IBD patients were compared with those from normal individuals. The authors suggested that calcium supplements can help reducing stone formation in those patients, but initial efforts should be directed towards the reduction of urinary oxalate by reducing dietary oxalate. Citrate therapy that increases both urine pH and urinary citrate could also provide an additional therapeutic benefit (21). In UC patients who underwent total proctocolectomy with ileal pouch-anal anastomosis, close monitoring for renal stone formation and administration of prophylactic oral bicarbonate has been suggested. Urinary alkalinization along with increased hydration is also advocated in IBD patients receiving aminosalicylates (1-3, 19). Finally, a study conducted among pediatric patients showed that IBD patients had less urologic interventions for calculosis compared with non-IBD ones (17).

Conclusions

Urinary lithiasis in IBD patients is increased. The pathogenesis is multifactorial including inflammation, malabsorption and consequent alterations in the hydration status and electrolytes balance. In these patients, it is necessary to be aware of this increased risk, in order to set up an accurate follow up and prompt diagnosis, and avoid complications.

References

1. Avner ED, Harmon WE, Niaudet P et al. Pediatric Nephrology 7th edition. Springer Heidelberg New York, 2016.
2. Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. MOSBY Elsevier Philadelphia, 2008.
3. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol 2010; 25: 49.
4. Dwyer ME, Krambeck AE, et al. Temporal trends in incidence of kidney stones among children: a 25-years population based study. J Urol 2012; 188: 247-52.
5. Alfandary H, Haskin O, et al. Increasing prevalence of Nephrolithiasis in Association with Increased Body Mass Index in Children: A Population Based Study. J Urol 2018; 199(4): 1044-49.
6. Cury DB, Moss Ac, Schor N. Nephrolithiasis in patients with inflammatory bowel disease in the community. Int J Nephrol Renovasc Dis 2013; 6: 139-42.
7. Fagagnini S, Heinrich H·Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. Plos One 2017;12(10).
8. Torio M, Ishimura M, Ohga S. Nephrolithiasis as an extraintestinal presentation of pediatric inflammatory bowel disease unclassified. J Crohns Colitis 2010; 4 (6): 674-8.
9. Trinchieri A, Lizzano R, et al. Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease. Arch Ital Urol Androl 2002; 74: 61-64.
10. Gkentzis A, Kimuli M. Urolithiasis in inflammatory bowel disease and bariatric surgery. World J Nephrol 2016; 5(6): 538-546.
11. Peña de la Vega L, Lieske JC, et al. Urinary oxalate excretion increases in home parenteral nutrition patients on a higher intravenous ascorbic acid dose. J Parenter Enteral Nutr 2004; 28 (6): 435-8.
12. Hueppelshaeuser R, von Unruh GE. Enteric hyperoxaluria, recurrent urolithiasis, and systemic oxalosis in patients with Crohn's disease. Pediatr Nephrol 2012; 27: 1103-9.
13. Kumar R, Ghoshal UC, et al. Infrequency of colonization with Oxalobacter formigenes in inflammatory bowel disease: possible role in renal stone formation. J Gastroenterol Hepatol 2004; 19: 1403-1409.
14. Reddy TG, Knight J, et al. Oxalate Concentrations in Human Gastrointestinal Fluid. J Endourol 2016; suppl 1: S8-11.
15. Worcester EM. Stones from bowel disease. Endocrinol Metab Clin North Am 2002; 31(4): 979-99.
16. Mc Connel N, Campbell S, et al. Risk factors for developing renal stones in inflammatory bowel disease. BJU Int 2002; 89 (9): 835-41.
17. Stark CM, Gorman GH, Nylund CM. Association of Inflammatory Bowel Disease in Hospitalized Pediatric Patients. Inflamm Bowel Dis 2017; 23 (10): 1777-82.
18. Yamamoto Y, Kurokawa Y, et al. A pediatric case of ammonium acid urate lithiasis with ulcerative colitis. Nihon Hinyokika Gakkai Zasshi 2002; 93 (5): 652-5.
19. Durando M, Tiu H, Kim JS. Sulfasalazine-Induced Crystalluria Causing Severe Kidney Injury. Am J Kidney Dis 2017; 70 (6): 869-73.
20. Alon Us. Medical treatment of pediatric urolithiasis. Pediatr Nephrol 2009; 24: 2129-35.
21. Rodgers AL, Allie-Hamdulay S, et al. Enteric hyperoxaluria secondary to small bowel resection: use of computer simulation to characterize urinary risk factors for stone formation and assess potential treatment protocols. J Endourol 2014; 28 (8): 985-94.

Correspondence:
Laura Bianchi,
Pediatric Emergency Unit, University Hospital of Parma,
Maternal and Infant Department,
Via Gramsci 14 - 43126 Parma, Italy
Tel. +39 521 702225
E-mail: lbianchi@ao.pr.it