Association Between Overlapping Syndromes and Renal Lithiasis in Patients with Inflammatory Bowel Disease

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Abstract

Background: Irritable bowel syndrome (IBS) is considered a motor disorder due to the absence of a specific organic disease. The diagnosis of IBS is based on clinical criteria, including the Rome III criteria. Patients with IBS can have overlapping conditions, such as lactose intolerance (generally underdiagnosed) and inflammatory bowel disease (Crohn's disease or idiopathic ulcerative colitis). All of these lead to diarrhea, which is a risk factor for renal lithiasis. The objective of this study was to evaluate the combined presence of lactase intolerance and IBS as a risk factor for renal lithiasis in patients with inflammatory bowel disease, as well as the role of diagnostic tests in preventing renal complications of lithiasis.

Methods: We analyzed the electronic medical records of 168 patients with inflammatory bowel disease treated between 2009 and 2010 (for 24 months) at the Inflammatory Bowel Disease Center of the Scope Clinic, located in the city of Campo Grande, Brazil.

Results: Ulcerative colitis was diagnosed in 75 patients, of whom 29 were diagnosed with lactose intolerance, without an increased risk for renal lithiasis, and 24 had IBS, which was found to increase the risk for the formation of renal calculi (OR = 3.7; 95% CI: 1.2–11; P = 0.03). Crohn's disease was diagnosed in 93 patients, of whom 25 had lactose intolerance and 21 had IBS. Lactose intolerance was directly related to the underlying disease (OR = 4.0; 95% CI: 1.6–9; P = 0.003). Crohn's disease correlated strongly with IBS; of the 93 Crohn's disease patients, 40 also had IBS (OR = 4.0; 95% CI: 1.6–9; P = 0.003). Ulcerative colitis, especially when active, was found to increase the risk of renal lithiasis.

Conclusions: Patients with diseases that are accompanied by diarrhea should be screened for renal lithiasis in order to prevent renal complications.

Keywords: Irritable Bowel Syndrome; Kidney Calculi; Malabsorption Syndromes; Lactose Intolerance

Introduction

Inflammatory bowel diseases (idiopathic ulcerative colitis and Crohn's disease) are complex diseases, and their etiologies have yet to be fully understood. Inflammatory bowel diseases can be present in combination with other syndromes, such as lactase intolerance and irritable bowel syndrome (IBS). In addition, extraintestinal manifestations such as renal lithiasis are not uncommon.

Chronic diarrhea or constipation with abdominal pain are indicative of IBS, which is classified as a functional gastrointestinal disorder. The syndrome is characterized by changes in bowel habits in the absence of a specific organic disease. Various criteria have been proposed for the diagnosis of IBS, and these criteria have un-

dergone changes over time; the Rome II criteria are currently the most widely used [1].

In the field of gastroenterology, IBS is quite common. It can represent a serious social problem because it compromises the quality of life of patients, being the second most common cause of work absenteeism, which occurs in 25–50% of the cases [2,3].

The pathophysiology of IBS remains unknown, although some hypotheses have been raised as to the potential causative factors [4–7]: visceral hypersensitivity; emotional stress; motor disorders; and infections. The syndrome can occur in isolation or in combination with other diseases, such as lactase intolerance and inflammatory bowel disease [8,9].

Lactose intolerance is known to cause diarrhea, and it has been estimated that 70% of the world population has lactose intolerance, albeit undiagnosed in many cases [10].

Without a doubt, IBS and lactase intolerance can contribute to renal lithiasis because both are accompanied by malabsorption, and potentially with increase of high oxalate absorption and oxaluria, decrease of citrate and hypocitraturia and periods of dehydration with high urine concentration. Very few studies have investigated this issue or the association between these conditions and the formation of renal calculi.

Renal lithiasis, which is currently one of the most serious health problems because it declines life quality and may contributes to chronic kidney disease, can be avoided if diagnosed early.

To date, there have been no studies investigating the association between the formation of renal calculi and the combined presence of IBS, lactose intolerance, and inflammatory bowel disease.

The objectives of the present study were as follows:

- To evaluate the role of lactase intolerance and IBS as risk factors for renal lithiasis in patients with inflammatory bowel disease
- To determine whether the combination of inflammatory bowel disease and IBS can be a risk factor for renal lithiasis
- To evaluate the role of diagnostic tests in preventing the complications of renal lithiasis.

Materials and Methods

The present study evaluated 168 patients with inflammatory bowel disease over a period of 24 months (2009–2017). Of those, 93 had Crohn's disease and 75 had ulcerative colitis. The Rome III criteria were applied, and lactate levels were determined.

All of the patients were being monitored at the Inflammatory Bowel Disease Center of the Scope Clinic, located in the city of Campo Grande, Brazil, and all patient data were registered in electronic medical records.

Crohn's disease was categorized in accordance with the Vienna classification (Table 1), and ulcerative colitis was classified, by location, as proctosigmoiditis, left-sided colitis, or pancolitis.

Age at diagnosis (A)	A1: < 40 years
	A2: ≥ 40 years
Location (L)	L1: Terminal ileum
	L2: Colon
	L3: Ileocolon
	L4: Upper gastrointestinal tract
Behavior (B)	B1: Nonstricturing nonpenetrating
	B2: Structuring
	B3: Penetrating

Table 1: The Vienna Classification of Crohn’s Disease.

At the first medical appointment, a lactose tolerance test and an ultrasound of the kidneys and urinary tract were requested, the latter in order to identify renal calculi. In addition, the Rome II criteria were applied.

In patients with symptoms of lactose intolerance, the lactose tolerance test was considered positive when, after lactose ingestion, there was an increase of < 20 mg/dL in the blood glucose level (as determined by high-performance liquid chromatography).

The relative risk of developing renal calculi was calculated for patients with inflammatory bowel disease accompanied by IBS and lactose intolerance.

Results

Of the 75 patients with ulcerative colitis, 29 were diagnosed with lactose intolerance and were not found to be at an increased risk of developing renal calculi, whereas 24 were diagnosed with IBS, which was found to correlate strongly with the formation of renal calculi, principally when the disease was active (OR = 3.7; 95% CI: 1.2–11.0; P = 0.03).

Of the 93 patients with Crohn's disease, 37 were diagnosed with lactose intolerance and 40 were diagnosed with IBS. Lactose intolerance was directly correlated with the IBS (OR = 4.0; 95% CI: 1.6–9.0; P = 0.003). Likewise, there was a strong correlation between IBS and Crohn's disease. Despite this strong association, the combination of Crohn's disease and ulcerative colitis was not found to increase the risk of renal lithiasis over that associated with ulcerative colitis alone, whereas the combined presence of IBS and ulcerative colitis was directly correlated with renal lithiasis.

Discussion

The gastrointestinal disorder known as IBS is characterized by chronic abdominal pain and changes in bowel habits in the absence of an organic disease per se. Of all patients who seek a gastroenterologist, 25–50% present with IBS, which is the second most common cause of work absenteeism in the United States [2,3]. Although the etiology of IBS has yet to be fully understood, the syndrome is believed to be a multifactorial disorder in which the intestinal microflora trigger the innate immunity. Some studies have reported that IBS patients present with increased intestinal permeability, as occurs in patients with Crohn's disease. In addition, motor disorders (such as visceral hypersensitivity), physiological dysfunction, psychological abnormalities, emotional stress, and bacterial overgrowth are believed to be contributing factors to IBS [11,12].

In the United States, IBS affects 10–15% of the population and accounts for one third of all gastroenterological complaints. It is well known that patients with inflammatory bowel disease can present with symptoms that are similar to those of IBS (and vice-versa), and the combination of the two conditions is not uncommon. Although the differential diagnosis is important, it cannot

always be established through the application of clinical criteria alone [8].

It has been reported that IBS can precede or accompany inflammatory bowel disease; in some cases, the symptoms are not directly related to the underlying disease, and the identification of these differences dramatically changes the therapeutic approach to these patients [8].

In patients with proctosigmoiditis, active ulcers and the consequent scarring can, over time, lead to motor disorders, which can contribute to IBS. The same can occur in patients with extensive disease (e.g., left-sided colitis and pancolitis) or with Crohn's disease; ileal resections can also contribute to IBS [8]. Furthermore, IBS can be accompanied by lactose intolerance. The lactase enzyme is expressed on the small intestinal brush border membrane and is responsible for breaking down lactose. The lactase deficiency produces symptoms such as abdominal discomfort and diarrhea, principally after lactose ingestion, because lactose is not digested and therefore undergoes fermentation, a process that leads to diarrhea and excessive gas [9,13]. A study involving children showed that lactose intolerance is not uncommon and therefore should be included in the differential diagnosis of IBS [9]. Lomer, *et al.* estimated that 70% of the world population has lactose intolerance, albeit undiagnosed in many cases [10]. The authors demonstrated that many patients with lactose intolerance can consume milk and present no symptoms, whereas others have to restrict lactose intake. This is because some patients present total lactase deficiency whereas others present only partial lactase deficiency. Nevertheless, the authors stated the importance of including lactose intolerance in the differential diagnosis of gastrointestinal symptoms. Patients with inflammatory bowel disease, principally those with Crohn's disease, can also present with lactase deficiency [13].

Lactose intolerance, IBS, and inflammatory bowel diseases all cause diarrhea and can therefore lead to the formation of renal calculi through various mechanisms. To date, there have been no reports suggesting that the combined presence of IBS, inflammatory bowel disease, and lactase deficiency leads to renal lithiasis. The importance of collecting data regarding this issue lies in the prevention of serious complications, such as chronic kidney disease.

Among the 75 ulcerative colitis patients evaluated in the present study, lactose intolerance was observed in 29, whereas 24 had symptoms of IBS at some point during the study period. Of the 93 patients with Crohn's disease, 37 had lactose intolerance and 40 presented with symptoms of IBS at some point during the study period. In terms of the presence of IBS symptoms and lactose intolerance, no significant differences were observed between patients that had Crohn's disease with diarrhea-predominant IBS and those that had Crohn's disease with constipation-predominant IBS. However, when we correlated the combined presence of lactose intolerance

and IBS with the risk of developing renal lithiasis, we found that lactose-intolerant patients with ulcerative colitis and IBS (regardless of the clinical presentation) were at an increased risk of developing renal calculi (OR = 3.7; 95% CI: 1.2–11.0; P = 0.03).

In patients with Crohn's disease, lactose intolerance, and IBS were both strongly correlated with Crohn's disease (OR = 4.0; 95% CI: 1.6–9; P = 0.003 and OR = 4.0; 95% CI: 1.6–9; P = 0.003, respectively). However, none of the patients with Crohn's disease were at risk of developing renal lithiasis.

These data show that patients with inflammatory bowel disease should be treated with great care, since other entities present in these patients can provoke symptoms that mimic those of the underlying disease. Other diagnostic approaches, such as colonoscopy, are often required in order to establish the differential diagnosis. The study sample comprised patients with severe ulcerative colitis, which might explain why renal lithiasis was more common among the patients with ulcerative colitis than among those with Crohn's disease. The combination of ulcerative colitis and IBS would lead to more severe diarrhea, which in turn would lead to dehydration and greater changes in nutrient absorption, thus increasing the risk of developing renal lithiasis. Moreover additional metabolic alterations may contribute to the renal stone risk, as for instance hyperoxaluria, hypocitraturia and hyperuricosuria that are necessary to investigate in each patient with ulcerative colitis, lactose intolerance and IBS.

Conclusion

In conclusion, the combined presence of IBS, lactose intolerance, and Crohn's disease was not found to be a risk factor for the formation of renal calculi, although all three conditions are accompanied by diarrhea. However, the combined presence of IBS, lactose intolerance, and ulcerative colitis was found to be a major risk factor for renal lithiasis, possibly due to the underlying disease (ulcerative colitis).

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