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BILIARY SALT-INDUCED DIARRHEA AND THEIR ASSOCIATIONS WITH SMALL BACTERIAL OVERGROWTH SYNDROME

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Abstract: The present work explains the association of the occurrence of diarrhea induced by bile salts in patients with bacterial overgrowth of the small intestine, detailing the physiology of bacterial dehydroxylation and conjugation of these bile acids, which, increased by the greater number of bacteria, influences the reabsorption of these substances, causing episodes of diarrhea. In addition, diagnostic methods, such as biopsy and expired hydrogen test, and possible treatments are discussed. The question of changing bowel habits in post-cholecystectomy patients is also raised, associated with individual factors, one of which may be small intestine bacterial overgrowth.
Keywords: Diarrhea; bile acids and salts; intestinal microbiota; bacterial overgrowth; cholecystectomy

INTRODUCTION

Acids, or even salts, bile, are the main components of bile; among its functions is the formation of micelles with fats, due to its amphiphilic character, facilitating the action of pancreatic enzymes, such as lipase, and allowing the degradation and absorption of lipids. These salts have a defined and complex metabolism and circulation, in which bacteria of the digestive tract are involved, which are responsible for reactions, for example, dehydroxylation, of such acids. Primary bile acid, produced by the liver, is conjugated in hepatocytes. In the intestine, this conjugated bile acid has some destinations, with emphasis on the aforementioned article a) undergoes deconjugation and is reabsorbed in the colon b) undergoes dehydroxylation and becomes secondary bile acid. However, pathological conditions, such as bacterial overgrowth of the small intestine, appear to influence the imbalance of these enzymatic reactions. From this, the occurrence of diarrhea in these patients can be related, through mechanisms better elucidated below.

METHOD

The present study is an integrative review of the literature, carried out in the first half of 2022, focusing on studies related to diarrhea caused by bile acids associated with bacterial overgrowth of the small intestine, through searches in the PubMed, Medline and SciELO, in addition to Gastroenterology and Hepatology books, using the descriptors: small intestine bacterial overgrowth, diarrhea, intestinal microbiota, bile acids and salts, cholecystectomy

Articles in Portuguese and English were included, which adequately addressed the proposed topic, without restriction on the time of publication, but that were made available in full, considering among the types of study the reviews, original articles and essays on that topic. The exclusion criteria were: duplicate articles, available in the form of an abstract and that did not directly address the proposal studied.

After the selection criteria, ten documents remained, which were subjected to a thorough reading to collect information on the topic addressed. The results were presented in a descriptive way, divided into thematic categories addressing bile salt diarrhea.

RESULTS AND DISCUSSION

Bile acids, or even bile salts, are amphiphilic molecules, that is, they are related to both fat-soluble and water-soluble molecules, which gives bile acids the ability to form mixed micelles with fats in the small intestine, where they are released together with the bile, which is one of its main functions (GARRUTI et al., 2018). They are synthesized by the liver, not originating from the diet, through a chain of enzymatic reactions, whose core is the catabolism of cholesterol (LONGO; FAUCI, 2015).

Daily, there is a liver production of approximately 500 mg of bile acids; these molecules are conjugated, in hepatocytes, via coenzyme-A, with taurine or glycine, forming tauro-conjugated primary bile acids, or with glycine, forming glycoconjugated bile salts. This occurs to provide an increase in the solubility of bile salts in aqueous systems (GUYTON, 2017). In the intestine, secondary bile acids are synthesized from dehydroxylation reactions by colonic bacterial enzymes, having primary bile acids as a substrate (LONGO; FAUCI, 2015).

Such bile acids correspond to the organic majority of the bile, which is stored in the gallbladder and dumps its contents in the small intestine when it contracts, due to the stimulus that occurs during meals, and participate in the digestion and absorption of fat in the intestinal tract, creating conditions for action of the pancreatic lipase enzyme on lipid substances. There are two types of bile acids, primary and secondary.

In the terminal ileum, almost all of the conjugated bile acids are absorbed by active transport, and the deconjugates are absorbed by passive transport throughout the small intestine and colon, with the help of anaerobic enterobacteria. Through this absorption, bile salts travel through the portal circulation again to the liver, where they are taken up by hepatocytes and conjugated once again, forming part of the bile again. Thus, the enterohepatic circulation of bile acids is completed (LONGO; FAUCI, 2015).

A part of these acids that is not reabsorbed ends up being excreted with the feces, corresponding to about 1-4% of the total that is drained in the intestine through the bile. This fecal loss is equated with the hepatic synthesis of bile acids. (LONGO; FAUCI, 2015)

Therefore, it can be identified that defects in any of the steps of the enterohepatic circulation of bile acids can result in a decrease in the duodenal concentration of conjugated bile acids and, as a result, in a deficiency in the absorption of fats, manifesting clinically or subclinically, including absorption of fat-soluble vitamins. (LONGO; FAUCI, 2015)

GUT MICROBIOTA AND BILE SALTS

Precisely when this integrity of the enterohepatic circulation of bile acids, necessary for correct functioning, is broken, certain dysfunctions occur; among the factors that cause imbalance in the physiology of this circulation, we can mention the small intestine bacterial overgrowth syndrome (CRUZ, 1997).

Bacteria of the genera Staphylococcus, Streptococcus, Lactobacillus and yeasts are found in the small intestine of healthy individuals and form a transient and balanced flora, which collaborates with several factors in the absorption of nutrients, but limited to an amount below 103 CFU, colony forming units. (ANVISA, 2013). Motility and acidity are the main factors that maintain the number of bacteria in this part of the intestine (GOLDMAN; SCHAFER, 2018). However, there are many reasons that can cause the imbalance of this microbiological integrity, a factor that can be responsible for an abnormal bacterial proliferation, that is, the usual bacteria, or even unusual bacteria of the colonic flora, from the food and that were not destroyed. in the process of gastric acidity, they proliferate excessively in the duodenum and jejunum. Another source of imbalance would be the migration of bacteria from the right colon to the ileum and then to the jejunum, characterizing an ascending contamination (CRUZ, 1997).

Among these enterobacteria, we can mention the anaerobes of the genera Bacteroides, Veillonella, Clostridium, Bifidobacterium, or facultative aerobic bacteria, such as E. coli, Enterobacter sp,

Proteus sp, Klebsiella sp, Pseudomonas sp and S. faecalis. Many situations, not only clinical and surgical, but also social, such as sanitation and hygiene habits, are predisposing to the occurrence of bacterial proliferation in the small intestine (KING & TOSKES, 1979).

In this context of imbalance and differentiated bacterial colonization, important changes occur in digestive-absorptive functions, which characterize the small intestine bacterial overgrowth syndrome, or contaminated small intestine syndrome (GOLDMAN; SCHAFER, 2018).

SMALL BACTERIAL OVERGROWTH SYNDROME

The increase in the bacterial population in the small intestine, its consequences and manifestations make up this syndrome. Some important occurrences and characteristics to be mentioned are: occurrence of malabsorption of vitamin B12, fats, carbohydrates and secretion of water and electrolytes. The very variable clinical manifestations include bloating, abdominal pain, malnutrition, anemia, vitamin deficiencies, steatorrhea and secretory diarrhea.

The etiologies of this syndrome are related to the provision, for example, by intestinal stasis, of ideal conditions in the place for accentuated bacterial proliferation. Among the etiologies, the most prominent are: diabetes, scleroderma, intestinal diverticulosis, afferent loop subsequent to a Billroth II gastrojejunostomy, and intestinal obstruction due to strictures, adhesions, or cancer. Between the symptomatological development of bacterial overgrowth syndrome and the aforementioned conditions, several years may elapse (MANSBACH, 2009).

An emphasis on etiology must be given to the appearance of symptoms in an apparently stable patient, as a result of the administration of a proton pump inhibitor (PPI). This is because the decrease in gastric acidity offered by this drug allows the migration of a greater number of bacteria to the small intestine during meals, which was previously controlled by gastric acidity (MANSBACH, 2009).

The symptoms and manifestations are a direct consequence of the presence of greater amounts of bacteria and the exacerbation of their natural functions, escaping the state of balance. For example, most bacteria require cobalamin for growth and thus bacterial overgrowth depletes the supply of cobalamin. Thus, macrocytic anemia, in this case, is caused precisely by this deficiency of cobalamin, not folate (MANSBACH, 2009).

MECHANISMS OF BILE ACID-INDUCED DIARRHEA

In 1960, it was suggested, for the first time, by DAWSON & ISSELBACHER, that bacteria of the intestinal microbiota could metabolize conjugated bile acids and, thus, compromise the correct absorption of fats. Without this correct absorption, the fat would end up being eliminated along with the feces. Thus, it was raised that steatorrhea could occur by two mechanisms, which are a) there is a toxicity to the intestinal mucosa of these bile acids that are deconjugated by intestinal bacteria, or b) it would reduce the concentration in the lumen of conjugated bile acids necessary for the correct digestion and absorption of fats.

Currently, it is known that part of the primary bile acids, which are not conjugated in hepatocytes, when released with the bile, are converted into secondary bile acids by the bacterial flora through an enzyme called 7 alpha hydroxylase. That is, secondary bile acid was an unconjugated primary bile acid that underwent a certain bacterial action. (LONGO; FAUCI, 2015)

Such a bacterial enzyme promotes dehydroxylation at position 7 of cholic acid,

giving rise to deoxycholic acid or lithocholic acid. The physicochemical properties of bile acids change dramatically when they are hydrolyzed and 7-dehydroxylated. There is a loss of polarity on the hydrophilic face of the molecule, with a consequent loss of its detergency power. Therefore, the increase in the percentage of deconjugated bile acids and secondary bile acids in the lumen, associated with the decrease in the concentration of conjugated primary bile acids, below the critical micellar concentration. Even if the critical micelle concentration (CMC) of unconjugated bile acids increases, they are less effective in forming micelles. Such an event can cause diarrhea with steatorrhea, the first being a consequence of the second. This situation is often called fatty acid-induced diarrhea. However, as long as compensatory hepatic synthesis is sufficient to maintain the level of lipid absorption in the intestinal tract, steatorrhea will not be present. (FARRUGIA et al., 2021; GARRUTI et al., 2018)

The increase in deconjugation and dehydroxylation of bile salts by bacterial enzymes limits their reabsorption. Unabsorbed bile salts, in turn, perform active chlorine stimulation, culminating in the secretion of water in the colon, causing diarrhea without steatorrhea, which is called diarrhea induced by bile acids (choleretic enteropathy), and which does not respond to cholestyramine. In these cases, it is assumed that the colonic type bacteria in question produce one or more bacterial enterotoxins that are responsible for fluid secretion and diarrhea.

Another mechanism through which deconjugated and 7-dehydroxylated bile acids can induce diarrhea is the harmful potential that these molecules exert on the mucosa. LOW-BEER et al. (1970) demonstrated, through perfusion of deconjugated bile acids in the small intestine of animals, the occurrence of morphological lesions in the intestinal mucosa at its various levels, which did not occur with the perfusion of conjugated bile acids. (LONGO; FAUCI, 2015).

DIAGNOSIS

The combination of low serum cobalamin level and high serum folate level may suggest better investigation of this syndrome, as enteric bacteria often produce folate compounds that will be absorbed in the duodenum as well as consume cobalamin (LONGO; FAUCI, 2015).

The diagnosis of bacterial overgrowth must be considered in elderly patients and in individuals predisposed to underlying disorders. Identification of amounts greater than 105 CFU/mL in a quantitative culture of small bowel aspirate (secretory) is the "gold standard" in diagnosis but is not readily available. This test requires special anaerobic sample collection, rapid sample placement on anaerobic and aerobic plates, and avoidance of oropharyngeal contamination. However, false-negative results may occur, for example, in cases of jejunal diverticula and when the overgrowth is distal to the aspirated site. (GOLDMAN; SCHAFER, 2018)

Hydrogen breath tests are non-invasive tests with sensitivity and specificity comparable to intestinal culture. The test for 50g of glucose has a sensitivity of 90% for growth of 105 bacteria in the small intestine, and administration of lactulose (an indigestible disaccharide) has also been used to detect bacterial overgrowth. If bacterial overgrowth is present, there will be an increase in exhaled H2 in the breath, due to the greater production of this gas by the bacteria. A hydrogen level (before 90 minutes) greater than 20 ppm suggests bacterial overgrowth. However, false-negative results occur if the overpopulation organisms are non-hydrogen producers.

Concomitant measurement of expired methane increases the sensitivity of the test (GOLDMAN; SCHAFER, 2018). There is often clinical suspicion of the diagnosis, which is confirmed by the patient's response to treatment. (LONGO; FAUCI, 2015).

PATIENTS UNDERGOING CHOLECYSTECTOMY

Post-cholecystectomy, there is a prevalence of around 35% of diarrhea, with compromised quality of life, according to Grande et al. (2017).

This symptom represents the period of adaptation of the biliary tree to the lack of reservoir, the gallbladder, and may show gradual improvement over time (GRANDE; LEME; MARQUES; RAMOS; RAMOS; SOUZA, 2017).

The pathophysiology of changing bowel habits occurs due to bile acid imbalance. Without the gallbladder reservoir, the flow of bile to the intestine between meals increases, consequently increasing the time of contact with the intestinal mucosa. The gallbladder also has the function of concentrating bile, with the reabsorption of water. Without the gallbladder, this does not occur, increasing the flow of liquids to the intestine, which are less concentrated. This ends up allowing greater action of bacteria on bile salts, increasing dehydroxylations (GRANDE; LEME; MARQUES; RAMOS; RAMOS; SOUZA, 2017). As a result, the intestinal absorption of bile acids is difficult, which arrive in larger amounts in the large intestine, altering the enterohepatic cycle. (MARTINS; BRATI, 2022).

However, not all post-cholecystectomy patients have diarrhea, suggesting individual factors. Alteration of the bacterial flora of the small intestine can be the factor for the appearance of diarrhea, due, for example, to an associated bacterial overgrowth of the small intestine. This relationship deserves further studies, since the treatment approach and the central etiology of the intestinal disorder change.

TREATMENT

Among the goals of treatment, it is mentioned a) correction of the structural or motility defect, which caused the stasis, if possible; for example, if secondary to strictures, diverticula or proximal afferent loop, surgical correction can be obtained, but in the case of functional stasis of scleroderma and others, there is no possibility of correction by this route b) eradication of bacteria involved in the overpopulation c) nutritional support, taking into account possible vitamin and nutritional deficiencies due to absorption problems. In this case, medium-chain triglycerides must be given, as they do not depend on the formation of micelles for their absorption. Monthly treatment with vitamin B12 must be considered, along with supplementation of vitamins A, D, E, and K, in addition to calcium. If possible, the use of acid-reducing agents must be discontinued, remembering that gastric acidity is one of the limiting factors of bacterial growth due to its low pH with consequent bactericidal action (GOLDMAN; SCHAFER, 2018).

In the case of antibiotic treatment, even though the natural history of these conditions is chronic, antibiotics must not be administered continuously. Symptoms usually resolve 2 to 3 weeks after initial antibiotic therapy. Therapy does not need to be repeated until symptoms recur. When possible, antibiotic therapy must be based on culture results; otherwise, empirical treatment is prescribed. The antibiotic rifaximin (550 mg orally two to three times daily) is also effective, but to a lesser extent in individuals with an excluded (blind) bowel loop. Tetracycline (250 to 500 mg orally, four

times daily) or a broad-spectrum antibiotic against enteric aerobics and anaerobes (ciprofloxacin, 500 mg orally twice daily; amoxicillin/clavulanic acid, 250 to 500 mg orally three times daily; cephalexin (250 mg orally four times daily) with metronidazole (250 mg orally three times daily). 4 times a day) or erythromycin (250 to 500 mg orally four times a day) for the treatment of small bowel motility disorders; however, these medications are often not effective.

As a secondary component of other chronic diseases, such as Crohn's disease, actinic enteritis or short bowel syndrome, bacterial overgrowth has treatment linked to these conditions. In that case, therapy will not cure the underlying problem, but it could be very important in combating a subset of clinical problems that are related to bacterial overgrowth. (LONGO; FAUCI, 2015)

Furthermore, regarding the toxicity of bile acids, the so-called bile acid sequestrants are used, the main ones being Colestyramine (most used), Colestipol and Coleveselam. The mechanism of action of these drugs is based on their binding to negatively charged bile acids in the small intestine, thus limiting their absorption and increasing their fecal elimination by up to 3 times the normal value, possibly through specific signaling pathways. In terms of dosage, a dose was not specified exclusively for malabsorption of bile salts, so the standard dose used for the treatment of hyperlipidemia will be followed (JARAMILLO et al., 2017).

CONCLUSION

Based on the readings and data collected, it was concluded that bacterial overgrowth of the small intestine, associated with the metabolism and circulation of bile acids, has different mechanisms for inducing diarrhea, which must be considered in the case of patients with acute and recurrent diarrhea, and attention factor in the existence of previous predisposing pathologies. Watery diarrhea occurs because of the osmotic load of unabsorbed carbohydrates, stimulation of colonic secretion by unabsorbed fatty acids, and damage to the intestinal mucosa caused by increased concentration of secondary bile acids and increased tissue exposure.

This tissue exposure, as it is inflammatory, must be avoided by the aforementioned treatments, such as bile acid sequestrants, in addition to advice on adherence to a low-fat diet, taking into account the decrease in the concentration of efficient acids in the formation of fatty acids. micelles. Supplementation with certain vitamins and nutrients must be considered, due to the possible deficiencies that such conditions can cause.

In short, the adequate understanding regarding the relationship between bacterial overgrowth of the small intestine and diarrhea induced by bile salts allows a differential diagnosis and that must be considered, together with the identification more quickly, which allows the beginning of the treatment as soon as possible, aiming to reduce the occurrence of adverse effects of the pathology and, thus, providing a better quality of life for the patient.

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