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REVIEW ARTICLE

Review of the management of diarrhea syndrome after bariatric surgery☆

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Abstract Obesity is a prevalent health problem in our population. Bariatric surgery is the indicated treatment for severe cases. It is very effective (together with an adequate lifestyle modification) but it is also associated with frequent adverse events. One of the most frequent and disturbing adverse event is diarrhea. Diarrhea after bariatric surgery may be secondary to multiple causes and the physiopathogenic mechanisms may depend on the type of surgery performed.

The most frequent diarrhea mechanisms are Dumping syndrome, vagotomy, short bowel syndrome, carbohydrate malabsorption, protein malabsorption, alterations of the microbiota, Clostridum difficile infection, bacterial overgrowth, bile salt malabsorption, pancreatic insufficiency, endocrinological disorders, addictive disorders, and other digestive disorders not necessarily related to surgery.

PALABRAS CLAVE
Cirugía bariátrica;
Diarrea;
Malabsorción;
Síndrome de dumping;
Sobrecrecimiento bacteriano;

Revisión del manejo del síndrome diarreico después de una cirugía bariátrica

Resumen La obesidad es un problema de salud frecuente en nuestra población. La cirugía bariátrica es el tratamiento de elección en los casos graves, es muy efectiva (junto con una adecuada modificación de los hábitos de vida), pero también se asocia a múltiples efectos secundarios. Uno de los más frecuentes y que puede reducir marcadamente la calidad de vida es la diarrea. La diarrea que aparece posterior a una cirugía bariátrica puede ser de distintas causas y mecanismos fisiopatogénicos que van a depender, en parte, del tipo de cirugía realizada.

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Intestino corto;
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Las causas más frecuentes son el síndrome de Dumping, la diarrea por vagotomía, el síndrome de intestino corto, la malabsorción de carbohidratos, la malabsorción proteica, las alteraciones de la microbiota, la infección por *Clostridum difficile*, el sobrecrecimiento bacteriano, la malabsorción de sales biliares, la insuficiencia pancreática, trastornos endocrinológicos, trastornos adictivos, y, otros trastornos digestivos no necesariamente relacionados con la cirugía.

Introduction

The incidence of obesity has increased worldwide in recent years. According to the World Health Organization (WHO), in 2016 approximately 13% of the world adult population (11% of all men and 15% of all women) were obese. In the period between 1975 and 2016, the worldwide prevalence of obesity tripled.[1] As a result of this increase, there has been a rise in surgical techniques to treat the disorder. Many surgical procedures are available, divided into restrictive (vertical sleeve gastrectomy, adjustable gastric banding), mixed (Roux-en-Y gastric bypass, mini-gastric bypass [bypass with a single anastomosis]) and malabsorptive techniques (biliopancreatic bypass or duodenal switch, modified duodenal switch with single anastomosis duodeno-ileal bypass and sleeve gastrectomy [SADI]).[2] Bariatric surgery has experienced an exponential growth in Europe, from 33,771 surgeries in 2008 to 112,843 in 2011, with a stabilization of the figures in recent years.[3,4]

Due to this rising number of bariatric surgeries, there has also been an increase in undesirable side-effects. Diarrhea is a common problem in obese patients, with a prevalence of up to 30% versus 17% in the non-obese population.[5] Following bariatric surgery, the prevalence increases to 75% in patients subjected to Roux-en-Y anastomosis.[6] This can result in fecal incontinence in up to 50% of all patients subjected to surgery, with a consequent strong negative impact upon quality of life.[7]

There are many causes of diarrhea after bariatric surgery. The present review enumerates and reviews the multiple causes of diarrhea in bariatric surgery patients, with a view to establishing an etiopathogenic diagnosis and adequate treatment, and thus improving patient quality of life.

Dumping syndrome

Diarrhea is one of the most common symptoms of dumping syndrome. Its prevalence is 75% after Roux-en-Y bypass surgery, and 45% after vertical sleeve gastrectomy.[8] Two types of dumping syndrome have been defined:

1 Early dumping syndrome occurs in the immediate postprandial period (after 10—30 min), due to exposure of the small intestine to undigested carbohydrates. These produce intraluminal hyperosmolarity that causes secondary osmotic diarrhea, with the passage of interstitial and intravascular fluid into the intestinal lumen. The associated loss of endovascular volume often leads to arterial hypotension. This overall process activates vasoactive intestinal peptides (neurotensin, VIP, serotonin, substance P and catecholamines) that cause palpitations, diaphoresis and flushing.[9]
2 Late dumping syndrome in turn manifests between 2 and 4 h after intake as hypoglycemia, which may prove severe, and result in lowered consciousness, seizures, or even death. It has been found to occur in any type of bariatric surgery. In the case of Roux-en-Y bypass, a prevalence of 0.2–6.6% has been reported.[10] Although the underlying physiopathology is not well known, many hypotheses have been proposed. One of the most widely accepted explanations is rapid glucose absorption, which stimulates enteroglucagon release and generates a hyperinsulinic state that causes posterior hypoglycemia.[9] Other studies attribute hypoglycemia to pancreatic beta-cell hypotrophy and hyperplasia secondary to diabetes prior to surgery and/or insulin resistance, leading to insulin hypersecretion.[11,12] More recent studies have reported that in the event of accelerated gastric emptying, glucagon-like peptide 1 (GLP-1) hypersecretion and/or hypersensitivity occurs. This peptide stimulates insulin production, thereby causing hypoglycemia.[13,14]

Table 1 Sigstad questionnaire for the diagnosis of dumping syndrome.

Sigstad questionnaire (>7 points)			
Shock	+5	Dizziness	+2
Syncope or lipothymia	+4	Headache	+1
Wanting to sit down	+4	Flushing	+1
Dyspnea	+3	Nausea	+1
Fatigue	+3	Abdominal bloating	+1
Drowsiness	+3	Borborygmus	+1
Palpitations	+3	Belching	−1
Restlessness	+2	Vomiting	−4

The diagnosis is based on the Sigstad questionnaire (a score of >7 points establishes the diagnosis; Table 1) and/or the oral glucose test,[15] which involves the administration of a glucose overload to trigger the symptoms.

First-line treatment involves a change in diet, reducing rapidly absorbed carbohydrates and fractionating food intake. In second line treatment, pectin or galactomannan supplements may be useful, as they increase the viscosity

of the food bolus and reduce gastric emptying (between 10-15 g per meal are recommended). Their effect is limited by low tolerance, however.[15]

Octreotide can be an effective treatment. However, since this molecule is a somatostatin analogue, diarrhea may occasionally worsen. It is advisable to start treatment at doses of 50—100 μg three times daily. If tolerability is good, the patient can be switched to the LAR® (lanreotide) formulation at doses of 20 mg/month.[16]

Other treatments based on less solid scientific evidence are acarbose (at a dose of 100 mg/day), which is only useful in late dumping syndrome and is characterized by poor tolerance.[17] Diazoxide (100—150 mg before meals) and verapamil (80 mg before meals) have also been used in isolated cases.[18,19]

Reversal surgery should be considered in refractory cases,[20] whenever possible. Finally, we have total parenteral nutrition (TPN), which is reserved as a last resource in the event of difficult control despite medical treatment and/or reversal surgery.

There are future prospects for the management of dumping syndrome. Of note in this regard is the clinical trial carried out by Craig et al. Assuming the hypothesis of GLP-1 hypersecretion and/or hypersensitivity in late dumping syndrome, the authors administered treatment in the form of exendin-9—39, a GLP-1 receptor antagonist, and found hypoglycemia to be avoided in 100% of the cases (a total of 10 patients).[21] Sitagliptin (a dipeptidyl peptidase IV inhibitor) has also been described as an effective treatment for late dumping syndrome in a case report published by Kurihara et al.[22] Further prospective and randomized studies are needed to demonstrate the efficacy of these therapies, in order to include them in the treatment algorithm.

Post-vagotomy syndrome

Vagotomy may be performed intentionally to cause early satiety and thus improve dietary habits, or inadvertently as an intraoperative complication.[23] The characteristic clinical signs include early satiety and vomiting, though diarrhea may occur in up to 10% of all cases. The underlying physiopathology of this diarrhea is not fully clear, though an altered microbiota, hypomotility and gastric hypoacidity are involved.[8] Octreotide may be a good treatment option for diarrhea secondary to post-vagotomy syndrome.

Short bowel syndrome

Short bowel syndrome occurs in approximately 4% of all patients after bariatric surgery,[24] due to excessive reduction of the intestinal absorption surface area.

There is no sufficiently sensitive or specific test for the diagnosis of short bowel syndrome. It therefore should be suspected, and an adequate diagnosis of exclusion should be made.

Initial treatment consists of supportive measures in the form of enteral nutrition. The restoration of normal anatomy though reversal surgery should be attempted, if possible. In refractory cases, treatment in the form of parenteral nutrition is recommended. Short bowel syndrome secondary to bariatric surgery accounts for 6.4% of all patients receiving home parenteral nutrition in the United States.[25,26]

Teduglutide (Gattex®, Revestive®), an analogue of glucagon-like peptide 2 (GLP-2), which acts by inhibiting dipeptidyl peptidase, has recently been placed on the market. This drug increases the half-life of GLP-2 from 20 min to 2 h, thus promoting intestinal mucosal growth. The results of the phase III study are still pending publication, though the hypothesis is that a clear decrease in the need for parenteral nutrition is obtained.[27]

Carbohydrate malabsorption

There are several types of carbohydrate malabsorption, the most relevant referring to lactose, fructose and saccharose. Lactose malabsorption is the most common type in the general population (with a prevalence of up to 80–95% in Scandinavia and Germany, versus 30–40% in Spain).[28] Our attention therefore will only focus on this form of carbohydrate malabsorption. Lactose is a carbohydrate that is absorbed following the action of the enzyme lactase. This enzyme naturally tends to decrease with age. In addition, certain intercurrent events, such as intestinal infections, may exacerbate this natural tendency and cause lactase deficiency, thereby preventing lactose absorption.

The influence of bariatric surgery as a phenomenon that exacerbates this condition is not clear,[29] though an old Scandinavian study reported a lactose intolerance rate of 30% after jejunal-ileal bypass surgery.[30]

When lactose is not absorbed, it reaches the colon intact, generating a hyperosmolar state that causes osmotic diarrhea. In addition, the saprophytic flora of the colon metabolizes lactose, producing short chain fatty acids, carbon dioxide, hydrogen and methane. This in turn results in the characteristic clinical triad of bloating, diarrhea and flatulence.

The diagnosis of lactose malabsorption is based on the patient response to a test diet. A lactose breath test can also be performed, though its reliability is limited. Treatment is based on a lactose-exclusion diet. The enzyme lactase can also be supplied exogenously in special situations where an adequate lactose-free diet is difficult to guarantee (restaurants, travel, etc.).

Protein malabsorption

Most macro- and micronutrients, including proteins, are absorbed in the middle and distal jejunum.[31] Certain bariatric surgery techniques, including the Roux-en-Y bypass procedure, exclude these segments, and malabsorption therefore may result.

Hypoalbuminemia occurs in 18% of all patients undergoing duodenal switch surgery.[32] Hypoalbuminemia in turn is associated with diarrhea and malnutrition, with a physiopathology similar to that of Kwashiorkor disease.[33]

Management is based on supportive measures. In certain situations, attempts should be made to restore the anatomy through reversal surgery. Parenteral nutrition is reserved as the last therapeutic option.

Microbiota

The microbiota is not a fixed system, but changes over time in an individual, influenced by diet, obesity, physical exercise, drugs, etc. Bariatric surgery may alter the microbiota, not only as a consequence of the anatomical changes in bowel transit, but also due to weight loss and dietary changes. Shao et al.[34] showed that Roux-en-Y bypass surgery decreases the diversity of the microbiota, increasing the presence of the family *Gammaproteobacteria* and decreasing that of *Clostridia*. It has been postulated that this alteration of the microbiota may also be a cause of diarrhea.

Clostridium difficile

Diarrhea due to *C. difficile* represents a situation different from the rest. It is characterized as acute diarrhea secondary to acute infectious colitis caused by this pathogen. Bariatric surgery, together with antibiotic treatment - either as prophylaxis or as therapy in the case of complications - is a risk factor for colitis due to *C. difficile*.[35] The condition manifests as inflammatory colitis, causing secondary diarrhea and protein-losing enteropathy.

It should be suspected when acute diarrhea occurs in the immediate postoperative period, or after surgery in the presence of prior antibiotic therapy. The diagnosis is based on the detection of the microbial toxin in a stool sample. The first line of treatment consists of oral vancomycin,[36] with oral metronidazole as a second line of treatment, due to the pharmacokinetics of metronidazole (it is almost completely absorbed in the small intestine) and the anatomical alterations following bariatric surgery. In severe cases, the combination of oral vancomycin and intravenous metronidazole is indicated. Fidaxomicin is used as a third line treatment.[37] In patients with relapsing disease, fecal transplantation (bacteriotherapy) is a treatment option.[38]

Bacterial overgrowth

Bacterial overgrowth is defined as an excessive amount of bacteria in the small intestine.[39] Its prevalence is 41% in obese patients, being secondary to alterations in small bowel motility.[40]

Following bariatric surgery there is an increased risk of bacterial overgrowth due to surgical anastomoses.[41] In effect, anastomotic zones are a point of altered motility, particularly end-to-side anastomoses, where there is a blind end that acts as a reservoir.

The clinical manifestations of bacterial overgrowth comprise diarrhea and abdominal pain, sometimes accompanied by extraintestinal manifestations such as polyarthritis and skin lesions.[42]

The diagnosis is ideally based on culture of the jejunal aspirate ($>10^4$ colonies/mL), though the availability of this technique is low. In clinical practice, a breath test with labeled glucose/lactulose is commonly performed, exhibiting a sensitivity and specificity of 62% and 83%, respectively.[43] Treatment involves the administration of non-absorbable antibiotics one week a month on a cyclic basis, generally rifaximin (400 mg every 12 h) or metronidazole (250 mg every 12 h).

Due to the low yield of the diagnostic tests and the absence of adverse effects, a therapeutic test with rifaximin is indicated in the event of suspected bacterial overgrowth.

Malabsorption of bile salts

Bile salts are mostly absorbed in the ileum (95%), and any anatomical or functional changes at ileal level caused by bariatric surgery may result in the malabsorption of bile salts. The disorder is also related to cholecystectomy (before or concomitant to bariatric surgery) and vagotomy.[44]

Malabsorption of bile salts causes diarrhea without abdominal pain. The diagnosis is based on the 75-selenium homocholic acid taurine (SeHCAT) test, which involves the fecal quantification of ingested radiolabeled bile acids.[45] This is an expensive test that is difficult to apply in the clinical setting. A therapeutic test with cholestyramine (a bile salt chelator that affords a success rate of up to 96% at adequate doses) is therefore indicated.[46]

Exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency has been reported to occur in 19–48% of all cases after Roux-en-Y bypass surgery, and is also seen in duodenal switch and SADI techniques. This is due to the fact that the pancreatic enzymes become degraded during transit through the biliopancreatic loop, before coming into contact with ingested food.[47] In addition, the proportion of enzyme that reaches the food loop intact has a shorter duration of contact with the food.

The diagnosis is based on 72-h fecal fat quantification (the Van de Kamer test). In patients of this kind, fecal elastase is not a good marker. This is because pancreatic enzyme secretion may be preserved, but the enzymes are unable to act (they require neutralization of the acid coming from the stomach by the high concentration of duodenal bicarbonate, which is absent after bariatric surgery), resulting in a false negative result.

Treatment is based on oral pancreatic enzyme replacement therapy. However, these enzymes may not be useful, as they are administered as enteric-coated microspheres in gelatin capsules. The capsules dissolve in the stomach, freeing the microspheres, which on reaching the duodenum ($pH > 6$) disintegrate to release the active enzymes. Since these patients have anatomical alterations with gastrojejunal anastomosis, the mentioned pH is often not reached. As a result, the enzymes are not released, and the malabsorption and diarrhea persist.[48] In this case, since few therapeutic alternatives are available, reversal surgery should be considered, if possible.

Endocrine disorders

Endocrine disorders are more related to morbid obesity itself and its comorbidities than to bariatric surgery.

A range of factors are associated with diarrhea in diabetes mellitus and obesity, the most significant being the consumption of sugary foods, the association of diabetes with celiac disease, and impaired motility secondary to alterations of the enteric autonomic nervous system (which

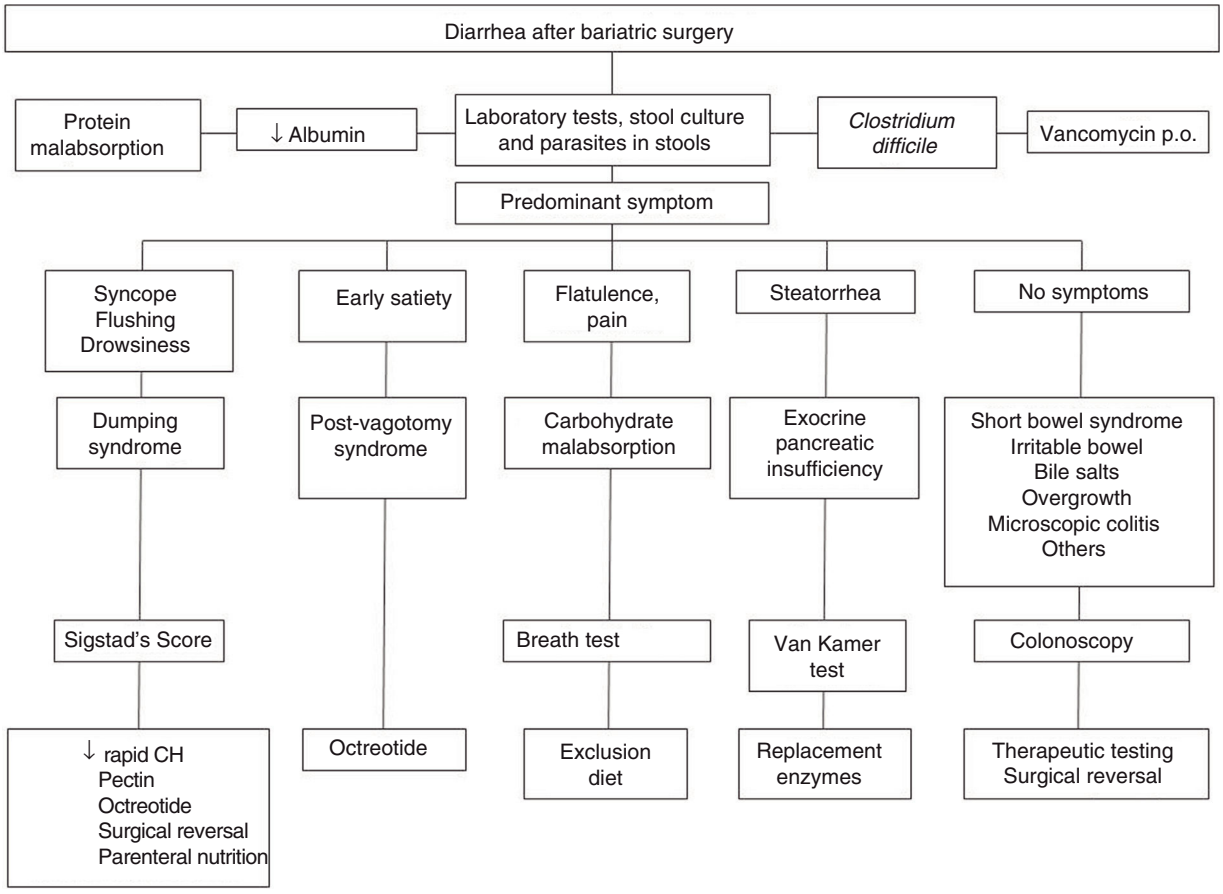

Figure 1 Algorithm for the management of diarrhea after bariatric surgery.

at the same time may promote overgrowth and exocrine pancreatic insufficiency). In cases of bariatric surgery indicated for metabolic syndrome or diabetes mellitus, resulting in cure, the postoperative relapse rate ranges from 11%[49,50] to 35.1%[51] at 5 years, according to the literature.

Another endocrine disorder that may cause diarrhea is hypothyroidism in replacement therapy. Both TSH and T4 should be closely monitored in hypothyroid patients undergoing bariatric surgery. This is because drug distribution is altered after significant weight and adipose tissue loss, and this may result in L-thyroxine overdose and consequently diarrhea due to pharmacological hyperthyroidism.[52]

Addictive disorders

Alcohol and nicotine cause diarrhea when consumed in excessive amounts. King et al.[53] reported an increased risk of alcohol abuse after bariatric surgery.

Other gastrointestinal disorders

It should be borne in mind that patients subjected to bariatric surgery can also experience diarrhea due to the same reasons as in the general population. In effect, they may suffer gastroenteritis, irritable bowel syndrome, celiac disease and microscopic colitis (both associated with diabetes), and even inflammatory bowel disease.

Discussion

As previously mentioned, diarrhea is a common problem in obese patients, but is exacerbated after bariatric surgery. There has been a very important increase in the number of patients undergoing bariatric surgery in recent years; as a result, its adverse effects - including diarrhea - have also increased.

The etiological diagnosis of diarrhea after bariatric surgery may prove challenging. The most common diagnoses that should be considered are dumping syndrome, bacterial overgrowth, the malabsorption of bile salts, carbohydrate malabsorption, and pancreatic insufficiency. The patient clinical history is the most useful tool available for establishing the diagnosis. Based on this history, the patient guiding symptom (apart from diarrhea) should be identified, and supplemental tests should be guided, based on that symptom (Fig. 1).

If an etiological diagnosis is established, the patient can be offered targeted treatment, which will prove more effective, will secure better management of the diarrhea, and will contribute to an improvement in the quality of life.

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Authorship

With regard to the contributions of the signing authors, Eduard Brunet conducted the systematic review of the study subject and drafted the manuscript. Assumpta Caixàs and Valentí Puig collaborated in drafting and reviewing the manuscript. All the authors read and approved the final manuscript.

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