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EDITORIAL

GASTROINTESTINAL MOTILITY DISORDERS IN OBESITY

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Abstract

The gastrointestinal (GI) motility, which is important for the digestion and absorption, may be altered in obesity. The aim of this review is to present the GI motility changes occurring in obesity, as well as their underlying mechanisms. We have conducted a systematic review of the published literature concerning GI motility and obesity and have described recent published data on the changes throughout the entire GI tract. Most recent discoveries include evidence supporting the increase of gastroesophageal reflux disease in obesity and inhibition of gastric motility. Intestinal transit of the distal small bowel generally slows down, ensuring enough time for digestion and absorption. Constipation is more frequent in obese patients than in those with a normal weight. The gut-brain axis plays an important role in the pathophysiology of GI motility disorders in obesity. This bidirectional communication is achieved by way of neurons, hormones, metabolites derived from intestinal microbiota and cytokines. The molecular mechanisms of GI motility changes in obesity are complex. Current data offer a starting point for further research needed to clarify the association of obesity with GI motility disorders.

Key words: constipation, gastrointestinal motility, gastroparesis, GERD, obesity.

INTRODUCTION

The prevalence of obesity has reached epidemic proportions in recent decades, thus becoming a serious global public health challenge (1). Obesity leads to systemic low-grade chronic inflammation, which plays a role in both the beginning and the progression of cardiovascular diseases, type 2 diabetes, nonalcoholic fatty liver disease and cancer (2). Obesity is strongly associated with chronic gastrointestinal (GI) disorders, many of which overlap with functional digestive disorders, especially constipation (3).

Obesity depends on both food intake and nutrient absorption; these two processes are associated with GI motility. Changes in gastric motility can influence appetite and satiety. Furthermore, nutrient absorption within the small bowel can be affected by changes in GI motility (4). In high-fat diet-induced obesity (HFD), changes were shown to occur in the enteric nervous system (ENS) involving both the stomach and the small bowel (5,6). In the bowel of mice and rats fed an HFD, an increased permeability of the mucosa was observed along with signs of inflammation (7), which led to the hypothesis that changes involving the ENS appearing in obesity may be the result of low-grade enteric inflammation (8). GI motility disorders are one of the main factors contributing to functional gastrointestinal disorders (FGID), representing more than 40 percent of observed patients in gastroenterology clinics and affecting more than 20 percent of the general population (4). Each part of the GI tract, the esophagus, the stomach, the small bowel and the large bowel has a unique function in digestion, and each has a distinct type of motility. When the nerves or the muscles in any part of the digestive tract do not work with normal force and coordination, a person develops motility-related symptoms. Upon first contact with food, the upper GI tract offers information on the physical and chemical characteristics of a meal, leading to stomach distension and the interaction between nutrients and digestion products with receptors located on enteroendocrine cells (EC) from within the intestinal mucosa, thus releasing hormones in the intestinal lumen. These signals are then relayed to the brain, regulating hunger, satiety and GI motility. GI sensitivity in obesity is decreased and this leads to motility disorders (9). In this review, we discuss the potential pathophysiologic mechanisms involved in GI motility changes in obesity.

Obesity and esophageal motility

Several meta-analyses have shown an association between obesity and gastroesophageal reflux disease (GERD). Previous studies have shown

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that an increment in body mass index (BMI) greater than 3.5 units was associated with a three-fold increase in the risk of reflux symptoms. Obesity is associated with an increased frequency of transient relaxation of the inferior esophageal sphincter (IES). The increased intraabdominal pressure in obesity is associated with an increased risk of hiatal hernia, thus exposing the esophageal mucosa to the gastric content. However, not all obese patients are exposed to the same risks, as there are data showing that ventral fat deposition is more prone to be associated with GERD, as opposed to trunk fat disposition (10).

More than half of obese patients develop hypomotility of the esophageal body. Leptin, a hormone derived mostly from the fat tissue, plays an important role (11). In the obese population, leptin levels are high. Receptors located in the blood-brain barrier are saturated and the response of hypothalamic cells to leptin is decreased in obese patients, which leads to the inability of leptin to regulate satiety and modulate the energy balance (12). Elevated leptin levels worsen reflux esophagitis by its pro-inflammatory effect, namely by increasing the infiltration of the esophagus by CD3+ lymphocytes (13). The increased prevalence of erosive esophagitis or Barrett's esophagus in obese patients is also explained by decreased antiinflammatory adiponectin (14,15).

Elevated circulating estrogens are responsible for GERD symptoms during pregnancy. This condition was also found in obese women due to decreased sex hormone-binding globulin and increased estrogen synthesis caused by adipose tissue (16).

A decrease of the gastric emptying rate and of the esogastric junction pressure along with an increase in the frequency of transient LES relaxations (through the release of cholecystokinin (CCK)) have been observed in obese patients (17). The presence of gastric acid in the proximal part of the stomach after a meal is an important determinant of GERD, however further studies are required to establish whether a correlation between obesity and the presence of gastric acid at this level exists (18).

Obesity and gastric motility

Over the past few decades, it has been discovered that the GI tract plays a role not only in nutrient digestion and absorption, but it is also a great endocrine system. Over 30 peptides are released by EC residing in the GI mucosa. These hormones are secreted in relation to the ingested nutrients. They coordinate GI functions and regulate the energetic homeostasis (19).

Ghrelin, considered a "hunger" hormone, is released especially during fasting and suppressed after meals (20,21). It is secreted especially by gastric oxyntic cells and, to a smaller degree, by the duodenum. Ghrelin secretion is regulated by multiple factors, with positive regulators being fasting, muscarinic stimulation by the vagus nerve, beta-adrenergic stimulation, glucagon, estrogen and deep sleep. The negative regulators are alpha-adrenergic stimulation, cortisol, insulin, glucose, long-chain fatty acids, obesity, somatostatin, growth hormone (GH), leptin, insulin growth factor 1 (IGF1), peptide YY (PYY), CCK, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and oxyntomodulin (22-24). Structurally, ghrelin is similar to motilin, playing a role in gastric emptying (25). In obese persons, ghrelin levels are decreased, thus gastric motility is affected (26,27).

Leptin is predominantly secreted by adipocytes, proportionally to fat stores. Leptin levels increase after a meal to suppress appetite and increase energy expenditure. During a meal, leptin levels are low, thus stimulating appetite. Developing a resistance to leptin in the hypothalamus inhibits appetite suppression after a meal, thus contributing to hyperphagia in obese patients. Hyperphagia determines hyperinsulinemia, leading to leptin resistance, with insulin being an antagonist of leptin. Studies have shown that leptin reduces gastric emptying and inhibits pyloric relaxation.

Studies show a positive correlation between stress and weight (28). Chronic stress leads to increased catecholamine production, such as noradrenalin (NA) and adrenalin (A). NA and A not only influence the blood flow, but GI motility and the microbiome as well. Thus, A determines smooth muscle relaxation in the stomach through beta-receptors, leading to delayed gastric emptying. The stress also increases corticotropin releasing factor (CRF) which in turn, by way of the adrenocorticotropic hormone (ACTH), releases cortisol that plays a role in weight gain through increased food intake. Furthermore, it inhibits gastric motor function in the antrum and corpus through CRF-2 receptors.

The pancreatic polypeptide (PP) is secreted by the PP cells located in the Langerhans islets and in smaller quantities by the L-cells in the colon and rectum. Its level increases after a meal, related to its caloric value. PP reduces gastric emptying (29). PYY is produced by the L-cells within the distal bowel and higher quantities in the colon and rectum. Previous studies have shown a decrease in PYY levels in obese

patients. However, after a meal, PYY production increases according to meal composition (30). PYY inhibits gastric acid secretion, gallbladder contraction and mouth-cecum transit time. Therefore, PYY released by short-chain fatty acids (SCFA), either exogenous or produced by the intestinal microbiota, inhibits GI motility (31). NPY is a neurotransmitter with a role in increased food uptake and fat storage. It is secreted by visceral fat tissue and leads to adipocyte proliferation. Its receptors can also be found in the stomach, inhibiting gastric motility (32).

Chronic fat intake increases GIP and GLP-1 production. GIP is a peptide secreted by the K cells in the duodenal, jejunal and proximal ileal mucosa. GLP-1 is a different peptide secreted by three tissues in humans: by EC type L in the bowel (the distal jejunum, ileum and colon), by pancreatic α cells and by the central nervous system (CNS). These hormones suppress appetite and inhibit gastric emptying (33). Glucagon-like peptide 2 (GLP-2) plays an important role through its receptors located in the gastric fundus, causing gastric relaxation as a response to food intake (34).

CCK is secreted by L cells in the duodenum and small bowel after a meal. Its role is in stimulating pancreatic hormones and bile secretion and to inhibit gastric emptying. Studies have shown that in obese subjects the CCK levels after a meal increase for a longer duration than in leaner subjects (35). Somatostatin is secreted by the hypothalamus and by other tissues. At the GI level, it inhibits GH, IGF-1 and the release of gastrin, a hormone responsible for increasing GI motility and hydrochloric acid secretion (36).

Obesity increases endocannabinoid production in both hypertrophic adipose tissue and the brain. Their action on CB1 receptors stimulates appetite and maintains a vicious circle. Thus, the orexigenic effect outweighs the anorexigenic effect of leptin. Activation of CB1 receptors delays gastric emptying and increases gastric acid secretion (37).

Knowing the roles of the stomach and of the different hormones played in GI motility disorders in obese subjects is an important aspect that could lead to a better understanding of the pathogenesis of obesityrelated endocrine disorders.

Obesity and small bowel motility

Small bowel transit time plays a very important role in obesity, namely that the longer the time, the greater the nutrient absorption is, thus leading to weight gain. Recent evidence suggests that the three major macronutrients (protein, fat and carbohydrates) are each capable of activating intestinal functions in a different manner and through different mechanisms of action. Transit time has been observed to be higher in obese patients compared to lean subjects (38).

Ghrelin receptors have been found in the small bowel myenteric plexus in rodents and humans. By way of cholinergic neurons, ghrelin has a prokinetic effect. Consequently, its effect in obese patients on GI motility is diminished because of its decreased levels (39,40). Shortly after a meal ingestion, the transit of the small bowel is accelerated as a response to fat ingestion. Food is spread throughout the small bowel in order to optimize digestion and absorption (41). Eventually, lipids trigger an inhibitory reaction, slowing intestinal transit, thus ensuring sufficient time for digestion and absorption (42). EC can activate the ENS and can stimulate motor, secretory and vasodilatory activity in the GI tract. There are studies that have shown the influence of fat on GI motility by changes in the ENS, leading to myenteric neuropathy (6, 42). Myenteric neurons that use nitric oxide as a transmitter have been grown in the small bowel in mice fed an HFD. They are mainly inhibitors of motor neurons (43). Aside from affecting myenteric neurons, an HFD also determines changes in nitric oxide and intestinal vasoactive peptide (IVP) secretion. Nitric oxide induces a greater release of IVP in the myenteric plexus, with a role in smooth muscle relaxation.

The greater quantity of fat and/or nutrients arriving in the terminal ileum induces the release of PYY, GLP-1, GLP-2 by L cells (44). PYY reduces small bowel motility and increases ileal absorption. After a meal, PYY levels remain high for several hours, having a prolonged effect, unlike GLP-1 and CCK, which have a short-lived endocrine effect (45,46). GLP-1 has an important inhibitory activity on intestinal motility and secretion (47). CCK receptors in the small bowel play a role in slowing transit in order to regulate cholesterol absorption .

GLP-2 has an important role in maintaining intestinal epithelial morphology and function, namely by increasing absorptive surface, expression and activity of nutrient transporters within the brush border, intestinal blood flow, digestive enzymes release, postprandial chylomicrons secretion, and by inhibiting GI motility (48). PP has a high affinity for the Y4 receptor, which can be found in the small bowel and colon and has a role in stimulating motility by activation of enteric excitatory neurons. However, in obese patients the postprandial release of PP is

decreased (49,50).

Elevated serotonin levels have been found in the intestine of rats fed an HFD. Serotonin or 5-hydroxytriptamine (5-HT) is synthesized by EC in the GI mucosa. Although not required for initiating the propagation of contraction, 5-HT is a potential activator of intestinal motility and gastric emptying by activating 5-HT3 and 5-HT4 receptors. Intestinal absorption of fat is mediated by the release of bile salts, synthesized in the liver, and bile acids from the gallbladder, by way of 5-HT3 receptor stimulation (5, 51).

CCK sensitivity changes in obesity due to leptin resistance, thus leading to slower transit in the distal part of the small bowel (52,53). The involvement of peptides in GI motility may also be by central nervous mechanisms, not only by ENS involvement. Sensitivity to intestinal hormones is altered in patients on an HFD, but further studies are needed to precisely identify the functions of these peptides in food intake regulation and GI motility in obese patients.

Obesity and colonic motility

In obese adults, compared to leaner subjects, constipation is more frequent. The "intestinal brake" concept has been demonstrated in humans after the entry of nutrients into the small bowel. The "ileal brake" slows down motility in the stomach, duodenum and jejunum, in order to allow nutrients more time for digestion. "Ileal brake" is activated mainly by fat. Food stagnation in the small intestine causes small intestinal bacterial overgrowth (SIBO). These bacteria produce SCFA and deconjugate bile acids that may contribute to diarrhea. Bacterial fermentation produces gases, such as methane gas, that may contribute to the development of constipation. SCFA produced by intestinal flora causes the release of PYY, neurotensin, GLP-1 that inhibits proximal gut motility, as well as the release of serotonin, motilin and somatostatin which are important mediators of intestinal motility. Therefore, this negative feedback mechanism so-called the "intestinal brake" does not necessarily lead to constipation (54).

It has been shown that an HFD induces constipation in rats due to a smaller amount of serotonin in the colon (5). In mice fed an HFD, it has been shown that GI motility is slower due to inhibition of neuromuscular transmission by reducing the number of nitric oxide-releasing neurons and by affecting cytoskeletal microfilaments in the myenteric plexus (55-57).

It has also been shown in mice that ghrelin has stimulating properties on colonic secretion and motility (57). It is known that ghrelin concentration in obesity is low, thus its effects on the colon may be diminished. The ENS regulates the majority of intestinal activity through several neuropeptides under both physiologic and pathologic circumstances. One of the most important neuropeptides is IVP. It is an inhibitory neuropeptide acting on colon secretion and motility, along with NPY and nitric oxide. IVP concentration in obese patients is increased, leading to constipation (44). SCFA, especially butyric acid, stimulate PYY release. In mice, through the Y2 receptors, PYY inhibits colonic transit (58). The greater amount of fat ending up in the intestine influences the release of hormones such as PYY, GLP-1 and GLP-2. GLP-1 and GLP-2 cause colonic smooth muscle relaxation (59). Leptin stimulates GLP-1 secretion, the mechanism by which it occurs remains unclear. In mice, PP causes colonic contraction via the Y4 receptor, but, as stated before, PP levels are decreased in obesity (49,50). Furthermore, CCK suppresses contractions, thus preventing the propulsion of intestinal contents.

Beta-adrenergic stimulation participates in colonic transit inhibition. ACTH stimulates NA and A release from the adrenal gland, thus slowing GI transit during stress. The accumulation of visceral fat contributes to cortisol synthesis, which in turn will increase plasma zinc concentration. In a study on rats, the effect of zinc on CCK secretion in STC-1 (an enteroendocrine cell line found in the duodenum) cells was investigated and it was shown that zinc increases CCK secretion, which in turn inhibits colonic contractions (60). Calcitonin plays a role in obesity by decreasing adiponectin secretion in adipocytes. Recently, it has been shown that CGRP (calcitonin gene-related peptide) is a strong relaxant of GI smooth musculature in patients with diverticular disease. Thus, calcitonin may have an important role in GI motility disorders in obese patients (61). Endocannabinoids regulate GI motility and secretion. Cannabinoid agonists can inhibit colonic motility. Thus, more selective and more restrictive peripheral modulators of CB1 receptors might be effective in the treatment of obesity (37).

In obesity, the motility of the GI tract is diminished, being influenced by multiple hormones, but also by the intestinal microbiota.

The involvement of the intestinal microbiota in intestinal motility

Until recently, the main factors playing

a role in the pathophysiology of obesity were genetic, hormonal, and those concerning feeding habits and lifestyle. The intestinal microbiota also has an important role in the etiology of obesity. In the intestine, the microbiome has several important functions, such as maintaining intestinal wall integrity, preventing overpopulation of harmful microorganisms, and nutrient absorption. Weight gain determines changes of the intestinal microbiome and is associated with GI motility disorders through neuromuscular dysfunction, intestinal wall alteration, microbial metabolites, and alterations in hormone secretion (62,63).

Bacteria belonging to the Clostridia genus and the Bacteroides phylum are increased in patients with a high fat intake, leading to higher amounts of secondary bile acids, such as deoxycholic acid, which in turn increase 5-HT concentrations through EC stimulation, thus contributing to changes in GI motility and fat absorption (64-68).

Recent studies have shown connections between intestinal microbiota and GI motility disorders. Intestinal dysbiosis and constipation have been associated with an HFD (69). Butyric acid (a SCFA) levels were decreased in obese mice suffering from constipation, determining intestinal dysbiosis. Administering butyric acid may diminish dysmotility symptoms. It has been shown that an HFD reduces butyric acid levels by decreasing Lactobacillus (70, 71). Regarding the link between obesity, intestinal dysmotility and intestinal microbiota, several theories exist. Each theory analyses different aspects of dysmotility and metabolism, namely alteration of intestinal wall integrity, neuromuscular dysfunction, microbial metabolites, and intestinal hormones (72). SCFA also induce the release of intestinal hormones

Table 1. Hormonal profile in obesity

Hormones	Serum level in obese patients	Effects in obese patients
Leptin	Increased (resistance of hypothalamic centers to leptin)	Inability of leptin to regulate satiety and modulate the energy balance Worsens reflux esophagitis through its pro-inflammatory effect
Adiponectin	Decreased	Increase of erosive esophagitis or Barrett's esophagus
CCK	Increased	Stimulates appetite and induces body weight gain Increase in the frequency of transient IES relaxations Delays gastric emptying Inhibits intestinal motility
Ghrelin	Decreased	Delays gastric emptying Inhibits pyloric relaxation Inhibits intestinal motility Inhibits colonic secretion and motility
Adrenalin	Increased	Delays gastric emptying Inhibits intestinal motility
CRF	Increased	Inhibits gastric motor function in the antrum and corpus
PP	Increased after a meal Decreased	Reduces gastric emptying Inhibits intestinal motility Inhibits GI motility
PYY	Increased after a meal	Reduces small bowel motility and increases ileal absorption Inhibits colonic motility
NPY	Increased	Stimulates appetite and induces body weight gain Delays gastric emptying Inhibits colonic secretion and motility
GIP	Increased	Inhibits appetite Delays gastric emptying
GLP-1	Increased	Inhibits appetite Delays gastric emptying Inhibits intestinal motility and secretion
GLP-2	Increased	Inhibits gastric and intestinal motility
Somatostatin	Increased	Inhibits the release of gastrin and inhibits gastric motility
IVP	Increased	Relaxes the smooth muscles of the intestine Inhibits colonic secretion and motility
Serotonin	Increased Decreased in the colon	Activates intestinal motility and gastric emptying Stimulates release of bile salts and intestinal absorption of fat Inhibits colonic motility
Cortisol	Increased	Inhibits colonic motility by increased CCK secretion

from EC, such as GIP, PYY, GLP-1, GLP-2 with roles in regulating intestinal motility, satiety and glucose metabolism. Administering butyric acid increases plasma concentrations of GLP-1, GIP and PYY, and propionic acid (a SCFA) induces the increase of GIP (62, 73, 74). It has been shown that mice fed an HFD had higher amounts of Bacteroides, Firmicutes, Escherichia coli and Bifidobacteria, along with a reduction of enteric neurons (69). The association of dysbiosis with neuronal lesions is unclear; perhaps an important role is being played by the intestinal microbiota triggering an inflammatory response.

In recent years, an increasing number of medications have been studied on intestinal microbiota. Studies on animals and humans have shown that inulin supplements determine changes in the intestinal microbiota, leading to decreased adiposity (62,74-76). Dietary fibers, such as inulin, raise SCFA levels that in turn will lead to increased levels of hormones with roles in appetite regulation and glucose metabolism (77). Administering a probiotic, Bifidobacterium animalis, combined with fiber, has led to decreased central adiposity and waist circumference. Regarding constipation, it has been shown that kiwi intake determines increases in Faecalibacterium prausnitzii, which produces butyric acid with antiinflammatory properties (78). Administering kefir in constipation increases Firmicutes, Bacteroides, Lactobacillus and Prevotella, and reduces Proteobacteria, Enterobacteriaceae and Clostridium (79). Thus, altering the intestinal microbiota can alleviate dysmotility symptoms; however, the involved mechanisms need to be better studied. In mice fed an HFD, an increase in Firmicutes and a reduction in Bacteroides and Actinobacteria were observed. Furthermore, it has been shown that an HFD led to an increase in Allobaculum accompanied by a reduction in Lactobacillus, Bifidobacterium and Clostridium (79). While there are several mechanisms orchestrating the interaction between obesity, GI motility and dysbiosis, the most important microbial metabolites are represented by SCFA.

The endocrinological changes encountered in obesity are displayed in the Table 1.

In conclusion, obesity is associated with GI motility disorders. This relationship is bidirectional and can involve any segment of the GI tract. Most common clinical conditions caused by GI motility disorders in obesity are GERD, gastroparesis and constipation. Pathogenic mechanisms include gut-brain axis disorders and the effect of gut microbiota.

Changes in GI motility can be considered as potential factors contributing to the development and maintenance of obesity. Therapies aiming to regulate the associated changes observed in GI motility could play a crucial role in the management of obese patients. Thus, understanding the molecular mechanisms underlying these changes could guide researchers to new therapies, such as CCK1 agonists, CB1 antagonists and electrical stimulation of the stomach. Interactions between obesity, diet and intestinal microbiota alteration may offer new insights related to GI motility changes in obesity.

Conflict of interest

The authors declare that they have no conflict of interest.

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