Importance of Ghrelin in metabolic surgery and decreasing its effect by Bypass surgery modification

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Abstract

Bariatric surgery is any surgical procedure that is directed toward losing weight. In the 1970s' cases were reported that patients, who had bariatric surgery, developed rapid postoperative remission of type 2 diabetes mellitus. In the 1960s' it was discovered that GI hormones play an important role in insulin secretion and regulation of glycemia. Changes in GI hormone secretion establish a mechanism, which determines the remarkable therapeutic effect of bariatric surgery, leads to weight loss, and controls glycemia. The most important hormone is considered to be Ghrelin. Ghrelin is a peptide of 28 amino acids, which is produced by close type cells of the fundus of the stomach, as well as by enteroendocrine cells of the small intestine, cells of the pancreatic island, neurons of different parts of the brain, including the hypothalamus. Data shows that, since most intensive expression of Ghrelin is in the fundus of the stomach, the decrease in the concentration of circulating Ghrelin in patients who had various bariatric surgery depends on to what extent is fundus disconnected during surgical procedures and how isolated are Ghrelin producing cells from food, which regulate Ghrelin concentration. Most interesting for our research is Mini-Gastric Bypass. A simplified method of gastric bypass anastomosis with a single anastomosis. The advantages of the Mini-Gastric Bypass procedure, the removal of the fundus during Bypass operations, the associated changes in ghrelin concentration, and ultimately the impact of all this on excess weight loss and glycemic homeostasis, formed the basis of our team's research on the new modification of Bypass procedure. We hope, it will allow us to develop a procedure that will ensure optimal control of weight correction and optimal control of glycemia in the future.

Methods: We used PubMed and Google Scholar as databases of information. Articles were filtered with keywords: Bariatric surgery, Type 2 diabetes mellitus, Ghrelin, Mini-Gastric Bypass.

Keywords: Bariatric surgery, Type 2 diabetes mellitus, Ghrelin, Mini-Gastric Bypass.

Introduction

Bariatric surgery is any surgical procedure that aims the reduction of excess weight (1). It dates back to the 50s' of the last century. The introduction of the laparoscopic methods played a special role in the development of bariatric surgery and triggered the rise of it in the whole world. The bariatric operations are divided as follows: 1. restrictive type-directed to decrease stomach volume 2. malabsorptive type-directed to decrease absorption of substances. 3 combination type-restrictive + malabsorptive. Restrictive surgical procedures, such as laparoscopic adjustable gastric banding (LAGB) or vertical banded gastroplasty (VBG), induce early satiety during meals by decreasing the volume of the stomach. Malabsorptive procedures, such as biliopancreatic diversion (BPD), divert bile into the terminal segment of the ileum so that bile and food are only mixed in the final 50–100 cm of the small bowel, thereby nutrient absorption is significantly reduced. Mixed procedures, such as Roux-en-Y gastric bypass (RYGB) or mini-gastric bypass, ensure restriction of the stomach and bypass of the small bowel.

Since the 1970s, there have been reports of rapid postoperative remission of type 2 diabetes mellitus (T2DM) after bariatric surgery procedures. In 1984, it was reported that bariatric surgery improves glucose tolerance in insulin-treated severely obese patients (2,3). In a 1992 article, "Is Type II Diabetes Mellitus (NIDDM) a Surgical Disease?"

Pories et al. reported reversible development of T2DM in 78% of patients who underwent gastric bypass (4). However, the group of the same authors published an article in 1995, "Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus," that triggered to start the research, identifying the mechanisms by which bariatric surgery improves glucose

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homeostasis and promotes T2DM remission (5).
Latest data has shown that bariatric surgery induces the remission of diabetes or reduces the need for medications with durable long-term results in morbidly obese patients, thereby providing a potentially rentable approach to treating T2DM.

The finding that glucose homeostasis can be achieved with bariatric procedures, especially gastric bypass, has led to the paradigm of metabolic surgery.

Nowadays widely used term "metabolic surgery" applies to those types of weight loss surgery modalities, that involve an anatomical bypass of the upper gastrointestinal tract and functional remodeling of the intestine, which is important for maintaining glucose homeostasis (6,7).

Basic mechanisms, which determine the efficacy of bariatric/metabolic surgeries, effect on tissue-specific insulin sensitivity, β-cell function and incretin responses, changes in bile acid composition and flow, modifications of gut microbiota, intestinal glucose metabolism and amount of brown adipose tissue, tissue metabolic activity (8).

Ghrelin

Metabolic procedures, by altering the anatomy of the intestine, affect intestinal hormones, which contribute to the modeling of the intestinal-brain axis (9). Weight loss and remission of diabetes mellitus, which occur after metabolic procedures, today is no longer explained only by restrictive or malabsorptive mechanisms. Many researchers are focused on the study of hormonal and metabolic changes.

The role of GI hormones in insulin secretion and glycemic regulation was discovered back in the 60s of the last century. By the 2000s, it was assumed that about 12 hormones of the gastrointestinal tract are involved in the nutrition process (10; 11). In 2002, Cummings et al. (12) reported that levels of the gastric hormone ghrelin, which had been shown to increase food consumption after being administered intravenously in humans, were inversely related to body adiposity in healthy-weight, obese, and skinny people, that corresponds to a tonic signaling function (13).

Subsequent data have shown that alterations in GI hormone secretion create a mechanism that mediates the remarkable therapeutic effect of bariatric surgery, especially in bypass procedures, induces weight loss, and maintains glycemic control (14-19).

Ghrelin plays a special role in metabolic surgery. Ghrelin, which is a 28 amino acid peptide, was discovered in 1990. It is secreted by cells of the closed type of the fundus of the stomach, as well as enteroendocrine cells of the small intestine, cells of the pancreatic island, and neurons of different parts of the brain, including the hypothalamus (20-23). Ghrelin is an endogenous ligand for the growth hormone secretion stimulating receptor (24). It regulates the release of growth hormone and plays an important role in the absorption of nutrients and the regulation of energy balance (25). Its effects on food consumption are mediated by protein neurons that are connected with NPY/Agouti genes in hypothalamus. The stomach is a major source of circulating ghrelin (26,27). The gastric fundus contains 10 –20 times more ghrelin per 1 g of tissue than the duodenum, which is the second biggest source of ghrelin (26,28). Lesser concentration of ghrelin is found in the jejunum and the concentration decreases as the distance of the organ from the stomach increases (18,29). Gastric ghrelin-producing cells are found in the oxyntic glands, where they are connected with the basolateral membrane, which is separated from blood-stream, and most do not have direct contact with the stomach lumen (30). The circulating concentration of ghrelin is determined by many physiologic factors. The first is body weight. Plasma ghrelin concentrations correlate negatively with body mass index (BMI) over a wide range (31,32). Ghrelin secretion is upregulated under conditions of negative energy balance and downregulated in the setting of positive energy balance (33,34). During obesity, the ghrelin concentration is low, which may be related to the high caloric intake. Obese individuals, after diet-induced weight loss, manifest significantly increased circulating ghrelin levels (35).

Ghrelin and Glucose

As it was for the discovery of the orexigenic potential of ghrelin, the human study was one of the first studies to find the effect of ghrelin on blood glucose levels. In particular, intravenous bolus injection of ghrelin caused hyperglycemia, followed by decreased plasma insulin and an increased GH levels (60). These findings are supported by the administration of ghrelin to rodents, which increases blood glucose levels, decreases insulin levels, and weakens the insulin response during glucose tolerance testing (61,62). Similar effects of ghrelin on blood glucose and insulin release have been demonstrated in isolated rodent islets, isolated pancreas, ghrelin overexpressing mice, and in other human studies (62-64).

There are several mechanisms by which ghrelin raises glucose levels or prevents glucose levels from falling. It can inhibit the secretion of insulin by glucose-stimulated pancreatic β-cells and increase the secretion of glucagon by α-cells of the pancreas by direct exposure to these cells (61,62,64,66,67). However, some studies have shown that ghrelin indirectly affects the activity of these cells - by acting on pancreatic D-cells that produce somatostatin (68,69). Ghrelin also affects blood glucose levels by acting on the brain, regulating gluconeogenesis and growth hormone.

Bypass

The major difference between bariatric procedures relies on their mechanisms of action and comprises purely restrictive, malabsorptive, or combination techniques. The most studied metabolic procedure to date is gastric bypass surgery. Since the beginning of the laparoscopic era, laparoscopic R-Y gastric bypass (LRYGB) has become the gold standard for bariatric -metabolic procedures and has accelerated the development of both bariatric and metabolic surgery

(36,37). The postoperative antidiabetic effect of RYGB is explained by reduced caloric intake within the first few days after surgery, induced cell membrane insulin receptors and duodenal exclusion, which results in neuro-hormonal signals and anti-incretin effects (38–42).

Improved glucose tolerance is achieved by the rapid entry of ingested nutrients into the distal small bowel, where L cells in the mucosa secrete incretin GLP-1 into the bloodstream. This effect leads to pancreatic beta-cell hypertrophy and secretion of insulin. In long-term follow-ups, glycemic control is also associated with surgically induced weight loss (42–44).

Fundus

As mentioned, the most intense ghrelin expression is in the fundus of the stomach. Numerous data show, that the rate of reduction of circulating ghrelin concentration in patients undergoing various bariatric surgeries depends on the degree to which the fundus is removed during surgical procedure and on how the ghrelin-producing cells are isolated from food that regulates ghrelin. In this case, special attention is paid to bypass surgery.

In patients undergoing RYGB, a decrease in ghrelin concentration begins 24 hours after surgery, says Gema Fruhbeck et al. (45). Their studies are further supported by dramatically lower ghrelin concentrations in patients who have undergone gastric resection (46,47).

Geloneze et al. say, that inhibition of ghrelin is a crucial factor in the complex mechanism of weight loss after bypass anastomosis procedures. According to the authors, the location of the resection line, it excludes larger or smaller part of the gastric fundus, determines the postoperative decrease in total ghrelin level, with further suppression of appetite (48). Chronaiou et al. evaluated the effect of fundus resection on patients who underwent standard LRYGB. On an empty stomach ghrelin had been decreased for 3 months after LRYGB but after 12 months it was increased compared to the initial level. When patients were treated with LRYGB fundus resection, ghrelin levels dropped dramatically and persistently. The postprandial response to insulin increased, and the postprandial glucose level in the case of fundus resection was lower than during standard LRYGB. Body mass and BMI decreased significantly after both procedures. Interestingly, fundus resection increases the effectiveness of the procedure in terms of body mass, glucose level, and hormonal secretion. The authors concluded that fundus resection in patients undergoing LRYGB was associated with lower ghrelin levels on an empty stomach, increased postprandial insulin responses, and lower glucose levels postprandially compared to standard LRYGB (49). These data allow us to assume that fundus resection together with ghrelin suppression may be considered an effective supplement in the treatment of pathological obesity and type 2 diabetes (50).

MGB

Interesting for our study is the simplified method of gastric bypass anastomosis with a single anastomosis, also known as Mini-Gastric Bypass (MGB). This method was first described by Rutledge in 2001 as an effective alternative to RYGB in the treatment of pathological obesity and type 2 diabetes mellitus (51–55). Although there was some controversy surrounding this procedure, randomized research has shown that it is a simpler and safer procedure than RYGB. Numerous serial reports have revealed the safety and long-lasting effectiveness of MGB (56–59). Significant glycemic control after MGB is explained by its physiological similarity to RYGB, reflected by an immediate decrease in caloric intake in the postoperative period, solid weight loss, and duodenal bypass. MGB is technically simpler than RYGB and is formed by only one gastrojejunal anastomosis with omega-loop (54,60). Many experts have reported encouraging metabolic results from MGB, with significant rates of diabetes remission in both the short and long term (58,61–64).

In 2001, the International Diabetes Federation stated that in the treatment of diabetes the "simplicity" and "reversibility" of metabolic procedures should be considered. These two technical features are fully protected in the MGB procedure (44).

Conclusion

The advantages of the MGB procedure, the removal of the fundus during Bypass operations, the associated changes in ghrelin concentration, and ultimately the impact of all this on excess weight loss and glycemic homeostasis, formed the basis of our team's research on the new modification of Bypass procedure. We hope, it will allow us to develop a procedure that will ensure optimal control of weight correction and optimal control of glycemia in the future.

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