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Review

Bariatric surgery and the gut-brain communication—The state of the art three years later

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ABSTRACT

Objective: This review analyzes the literature concerning gut peptides and bariatric surgery, from 2005 to July 2009. In particular, we are interested in whether, and how, gastrointestinal peptide alterations following surgery interfere with appetite/satiety, and what role they might play in the resolution of comorbidities.
Research methods and procedure: PubMed/MEDLINE and ISI Web of Knowledge were used to search for human studies concerning gut peptides profiles after any bariatric operation technique.
Results: Most of the studies reviewed had longitudinal design, short follow-up, and low statistical power. The diversity of study results may be partially explained by methodological aspects. Glucagon-like peptide-1, gastric inhibitory peptide, and peptide YY alterations may contribute to the excellent results in glycemic control of diabetics. Results do vary depending on bariatric operation technique; this is particularly evident in the case of ghrelin, which has been much studied in recent years. Ghrelin suppression has been linked to increased satiety, alterations in energy homeostasis, and better glucose metabolism.
Conclusions: There is a lack of long-term data on gastrointestinal hormone profiles after bariatric surgery and the studies have many methodological pitfalls. We still need prospective, long-term, good methodological studies in this area.

Bariatric surgery has been considered the choice treatment for morbid obesity, and its long-term results, which were superior to clinical treatment, had generated research interest in the mechanisms of such efficiency [1].

Three years ago, we reviewed the literature to look for possible implications of different bariatric operations on gastrointestinal peptides and their relationships with the neural paths involved in the central regulation of appetite and satiety. At that time, one could say that there was a lack of comparability between studies. The samples were too small, and statistical power was poor. The design approaches and study protocols were very different. Furthermore, laboratorial techniques could not be compared. As in all new research areas, human studies involving gastrointestinal peptides are limited by the number of participants and short follow-up in longitudinal studies. At the conclusion to that review, it was still not clear how gastrointestinal peptides changed after different bariatric techniques or whether abnormalities in the gut brain communication contributed to the bariatric surgery outcomes [2].

Currently, the main questions are still the following: what are the alterations of gastrointestinal peptides after bariatric surgeries? Could these alterations be related to weight loss and the resolution of comorbidities after the operations? Is appetite related to gastrointestinal peptide changes after surgery? Can we predict the long-term results of surgery by measuring changes in these peptides? Understanding the role of gastrointestinal peptide alterations after bariatric surgery may allow for a more comprehensive approach to obesity and its comorbidities.

Therefore, this article aims to critically review the recent literature and search for human studies that examine the profile of gut peptides after any bariatric surgery technique.

Methods

PubMed/MEDLINE and ISI Web of Knowledge were used to search the English- and French-language literature from March 2005 to July 2009. Search terms included "gut peptides", "gastrointestinal peptides", "gut hormones", "bariatric surgery", "morbid obesity", and each peptide individually: "cholecystokinin", "glucagon-like peptide-1" (GLP-1), "gastric inhibitory polypeptide"

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(GIP), "pancreatic polypeptide" (PP), "peptide YY" (PYY). We considered both cross-sectional and prospective studies. Subsequently, a handle search was performed in the reference lists of the selected articles. We included only human studies that enrolled any number of patients.

Results

Bariatric surgical techniques reduce food volume intake and/or absorption of nutrients [1]. Several peptides are secreted by neuroendocrine cells of the digestive tract and are also expressed in the central nervous system (CNS). Because bariatric surgery modifies the anatomy and physiology of the digestive tract, altering hormonal and neural afferent signs in the stomach and bowel, several authors have postulated that gastrointestinal peptide changes could be related to weight loss, appetite reduction and improvement in comorbidities in patients submitted to operations. Table 1 resumes the studies related to gastrointestinal peptides and its alterations after bariatric operations.

Specific peptides

Ghrelin

Ghrelin is the peptide produced mainly by A/X cells of the gastric fundus, and its bioactive form is thought to have potent orexigenic action through peripheral or central pathways [2]. Furthermore, ghrelin modulates pancreatic function and is involved in energy balance regulation and glucose homeostasis [3]. As of 2005, the answers from the published studies were controversial. In the 3-y period since then, we were able to find more than 30 studies investigating the same issue, and the controversies still exist! Concerning ghrelin levels after surgery, the operative technique seems to influence these results. In Roux-en-Y gastric bypass (RYGBP) longitudinal studies with different follow-up, fasting ghrelin was increased in four studies [4–7], decreased in two [8,9], and unaltered in six [10–15]. The postprandial or 24-h ghrelin profile was reduced in one study [16] and unchanged in four [10,12,13,17]. Cross-sectional RYGBP studies showed fasting unmodified levels in three trials [18–20], and reduced levels in another two [19,21]. Korner et al. [18] had diverse results regarding total or octanoylated ghrelin levels: unmodified total fasting ghrelin and reduced octanoylghrelin. Adjustable gastric banding (AGB) has been linked to increased fasting ghrelin in the same studies [22–25], and unmodified [18,20,26,27] or decreased levels in others [28]; four of these studies were cross-sectional [18,20,23,28]. After AGB, postprandial ghrelin was elevated [23] or suppressed [20]. On the other hand, Rodieux et al. [20] demonstrated that the maximal postprandial suppression was significantly greater in the RYGBP group than in the AGB and control groups. le Roux et al. [19] testing fasting and postprandial ghrelin levels after RYGBP and AGB failed to present the fasting results.

Following vertical banded gastroplasty, fasting ghrelin was increased in three studies [8,29,30], and postprandial ghrelin was suppressed in one study [29]. Fasting ghrelin was reduced after biliopancreatic diversion (BPD) in three studies [8,30,31], elevated in one [32], and unaltered in two [5,33]. On the other hand, ghrelin was elevated after growth hormone-releasing hormone/arginine test in one study [33], and at postprandial period in another study [34]. However the ultradian pulsatility of ghrelin was diminished at the latter study [34].

Sleeve gastrectomy was linked to reduced fasting ghrelin levels in three studies [13,22,35], and reduced postprandial levels in one [13]. An elegant prospective randomized trial that analyzed the results of 13 RYGBP and 14 sleeve gastrectomy demonstrated substantially decreased fasting and postprandial ghrelin levels after both operations [36]. Glucose metabolism improved quickly after RYGBP and sleeve gastrectomy (SG) and was associated with increased levels of GLP-1 and PYY. The strength of this study is its good methodological quality: randomized, adequate laboratorial methods. Concerning ghrelin and satiety, Christou et al. [37] demonstrated that excess weight loss and satiety were not related to postprandial ghrelin levels after RYGBP. Dixon et al. [23] also found that satiety after AGB was not related to fasting and postprandial ghrelin. In contrast, satiety was significantly better in the study by Borg et al. [10], who showed unmodified fasting and postprandial ghrelin levels but increased GLP-1, PYY, and enteroglucagon levels. Korner et al. [18] found satiety to be better among RYGBP patients than among AGB ones, who had higher octanoylated ghrelin and lower PYY postprandial levels. Recently, suppression of ghrelin has been postulated as a mechanism of glucose metabolism improvement after RYGBP [38]. However, further long-term trials are necessary to define the relevance of ghrelin alterations for weight loss, satiety, energy, and glucose metabolism after bariatric surgery.

Glucagon-like peptide-1 (GLP-1)

GLP-1 is a product of the preproglucagon gene secreted by the L cells of the ileum, colon, and pancreas in response to nutrients and the neurohumoral stimulus of the proximal regions of the small intestine [39]. It contributes to satiety and has "incretin" properties: raises food-stimulated insulin secretion and increases the expression of genes that control β-cell function, inducing proliferation and reducing cell apoptosis. GLP-1 suppresses alpha cell secretion, inhibiting glucagon secretion. Furthermore, central effects of GLP-1 may play a role in the control of feeding and glucose homeostasis.

Since 2005, we found 21 studies involving GLP-1, five with cross-sectional design [19,20,40–42]. Fasting GLP-1 levels were elevated after BPD [43], SG [35,36], RYGBP [36], and AGB [25]. On the contrary, in a 2-y follow-up study, Reinehr et al. [44] found decreased fasting levels of GLP-1 after RYGBP and AGB. Finally, some authors found no change in fasting GLP-1 concentrations after RYGBP [20,42,45,46] and AGB [20,27]. In contrast to divergent fasting GLP-1 results, many authors observed increased postprandial GLP-1 levels, either after RYGBP [10,15,17,19,20,36,40–42,45,46,49,51], BPD [43,50], or SG [35,36]. The increase of GLP-1 has been associated with the substantial improvement of diabetes after bariatric surgery, which is precocious and persistent. Whitson et al. [16] could not demonstrate elevated postprandial GLP-1 levels in five diabetics patients submitted to RYGBP, as opposed to Laferrère et al. [51], who analyzed nine diabetics and could. Of note, early after RYGBP, Morínigo et al. [45] failed to find a significant correlation between the changes in insulin secretion and the GLP-1 response to a standardized meal. Six weeks postoperatively, subjects with type 2 diabetes had significant improvements in postprandial glucose tolerance and insulin secretion, despite no increase in active GLP-1 plasma concentrations. However, 1 y later, postprandial GLP-1 tended to correlate significantly with HbA1c in subjects with type 2 diabetes. Circadian rhythms of GLP-1 and GIP were analyzed before and 2 wk after BPD in five diabetics, and five normal glucose tolerance patients. The impaired GLP-1 secretion observed before the operation was reversed only in normal tolerance patients. On the other hand, GIP secretion was blunted only in diabetics. Insulin sensitivity improved in both groups. These are promising results to understand the