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IS THERE ANY INTERPLAY BETWEEN INCRETINS AND BILE ACIDS? WHAT IS THE ROLE OF BARIATRIC SURGERY?

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Abstract

Obesity and type 2 diabetes are associated with the impairment of the incretin effect. Evidence has revealed that bile acids are involved in glucose homeostasis. Bariatric surgery, referred also as metabolic surgery, exerts beyond weight loss an important metabolic effect by inducing amelioration or remission of type 2 diabetes. Surgical procedures that involve rearrangements of the gastrointestinal tract and therefore rerouting of the food such as laparoscopic Roux en Y gastric by pass (LRYGB), induce an increase in glucagon-like peptide 1 (GLP-1) levels and of bile acids, which will both promote an early improvement of glycemic control. Emerging data have revealed that there might be an interplay between GLP-1 and bile acids regarding glycemic control, raising the question about considering bile acids as the new gut hormones.

Keywords: obesity, type 2 diabetes, incretins, bile acids, bariatric surgery

Incretins are hormones released by the gastrointestinal tract in response to nutrients intake that stimulate glucose-mediated insulin secretion [1]. The "incretin effect" refers to the increase of glucose stimulated insulin secretion and it is estimated to be between 50%–70%. The two gastrointestinal hormones that fulfill this criteria are glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [1,2].

GLP-1 is produced and released from L cells that are mainly located in the distal jejunum and ileum while GIP is synthesized by a cluster of cells from the duodenum and proximal jejunum which are called the K cells. They are both released in response to ingestion of nutrients, especially to glucose, carbohydrates, and fats [3,4]. With respect to GIP both fat and protein stimulate GIP secretion [5]. During fasting both incretins have low circulating levels that increase rapidly after nutrient ingestion and the release is directly related to the size of the meal [3,4,6]. In patients with malabsorption the release of GIP is low as it is influenced by the rate of absorption rather than the simple presence of ingested nutrients into the gut [2].

Rapid increases of GLP-1 levels occur right after the ingestion of a meal (5-15 min) even though the nutrients have not yet reached the L cells. This early response could be explained by an indirect stimulation via endocrine or neural mediators through a proximal-distal neuroendocrine loop. The early phase of GLP-1 release is followed by a 30-60 minutes of second phase due to the direct response of L cells to ingested food [7].

Incretins exert their insulinotropic effects mainly through acting on the pancreas, but other organs involved in glucose homeostasis have been discovered to express receptors for GLP-1 such as liver, stomach, small intestine, skeletal muscle, adipose tissue and brain. GIP receptors can be found in the same organs, except liver where it acts in an indirect manner but the mechanism for this route of action has not been elucidated [2,7]. In the pancreas both GLP-1 and GIP stimulate glucose-dependent insulin secretion, β-cell proliferation and inhibit β-cell apoptosis [3,4,8]. In addition, GLP-1 inhibits glucagon production, whereas GIP stimulates glucagon secretion [1,9,10]. The main action of GIP seems to be in the pancreas and in the adipose tissue where it stimulates lipoproteinlipase activity and induces incorporation of fatty acids [1]. GLP-1 is a better studied hormone regarding glucose homeostasis and in this respect studies have demonstrated that it delays gastric emptying, stimulates glycogenogenesis, glucose uptake in the muscle and adipose tissue and decreases appetite and food intake [1,3,7]. It seems that GLP-1 acts both through endocrine and neural pathways [11].

Recent studies have revealed that bile acids are important modulators of whole-body metabolism [12]. Furthermore, it seems that bile acids are involved in glucose homeostasis and the circulating levels correlate with insulin sensitivity [13]. More exactly, bile acids inhibit gluconeogenesis and act directly promoting insulin signaling and glycogen synthase activation, thus aiding insulin-dependent control of glucose metabolism in the

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liver [14,15]. Also, bile acids increase energy expenditure in brown adipose tissue, thus preventing obesity and insulin resistance [16,17].

Bile acids' involvement in glucose metabolism seems to be mediated also by incretins, i.e. by GLP-1. After being released by the gallbladder into the intestine 95% the bile acids become reabsorbed in the terminal ileum, decreasing the need for de novo synthesis [18]. Under normal conditions after meal ingestion the gallbladder contracts and the amount of bile reaching the intestine increases and in turn stimulates nutrient induced GLP-1 secretion by the L cells. Hence, bile acid stimulating GLP-1 could induce insulin release, delay gastric emptying and decrease appetite [19]. Moreover, it has been demonstrated that both food and bile acids on their own can stimulate GLP-1 release but the combination of food and bile results in a greater GLP-1 response compared with food alone [20].

Evidence suggests that the 'incretin effect' is impaired in obese patients even with normal glucose tolerance [3]. The same impairment is to be seen in patients with type 2 diabetes [21,22]. It seems that the reduced incretin effect in obesity might be due to the dysregulation of hormones and/or a reduction in their insulinotropic potency. Some studies have reported reduced postprandial GLP-1 levels in obese compared with lean subjects [21-23]. GLP-1 secretion may be reduced because L-cell responsiveness to carbohydrates is impaired in obesity [3]. However, other authors suggested that the impairment of the incretin effect in obesity is rather the result of the β-cells lack of response to incretins than the reduced GLP-1 levels [21]. In type 2 diabetes the intravenous administration of supra-physiological GLP-1 dose can overcome the decreased responsiveness of β-cells, while synthetic human GIP does not have the same effect. Hence, the findings from the literature suggest that the mechanisms of incretin impairment in obesity and type 2 diabetes are different. Basal and stimulated GIP levels are higher in obesity and glucose intolerant individuals and are associated with GIP resistance caused by a down-regulation of the receptors, explaining why GIP cannot be used as a therapeutic agent [1,3].

Could incretins be a link between obesity and type 2 diabetes? The sequence of cause and effect remain uncertain. We could presume that as the 'incretin effect' is impaired in obesity and that obesity often precedes type 2 diabetes, the impairment could lead to the onset of type 2 diabetes [3]. However, some authors have suggested that decreased 'incretin effect' is not a primary defect in type 2 diabetes but rather a consequence of the diabetic state [24]

In type 2 diabetes, the gallbladder motility is impaired leading to a reduced flow of bile acids into the intestine and furthermore to a lower secretion of GLP-1 and poor glucose homeostasis with decreased insulin secretion [25]. However, although the role of bile acids on increasing GLP-1 release is intensely discussed, a paradox should be explained. Bile acid sequestrants that prevent their reabsorption and promote fecal excretion have been used for control of hyperlipidemia for decades and have shown to be effective in improving glycemic control in patients with type 2 diabetes [7]. An explanation for this paradox was proposed by Hofmann and would consist in the fact that passage of fatty acids into the ileum may lead to increased GLP-1 release from the ileal L cells [26]. In patients with type 2 diabetes the addition of bile sequestrants to oral medication such as sulfonylurea and/or metformin was associated with improvements in glycemic control together with increased plasma levels of GLP-1 and GIP, compared with placebo [27].

Bariatric surgery also termed as metabolic surgery, has been widely accepted as the best treatment for obese patients with a body mass index over 40 kg/m² or over 35 kg/m² with associated diseases. Several procedures have been developed from pure restrictive ones to those that combine restriction with malabsorption. Beyond weight loss, it seems that surgery involving rearrangements of the gastrointestinal tract associated with rerouting of the food bring about an important early metabolic benefit regarding glycemic control.

Restrictive procedures limit the luminal diameter of the stomach, but do not involve exclusion of intestinal segments. Such procedures include laparoscopic adjustable gastric band (LAGB) which uses a synthetic band that is placed just below the gastroesophageal junction, creating a gastric pouch approximately 20 to 30 ml in size or vertical-banded gastroplasty (VBG) which resizes the stomach with a stapler to create a small gastric pouch. Laparoscopic sleeve gastrectomy (LSG) is a partial gastrectomy consisting in resection of the greater curvature of the stomach creating a "sleeve" [28,29].

Laparoscopic Roux en Y gastric bypass (LRYGB) is a primarily restrictive procedure with some malabsorption and involves creating a gastric pouch of 30 ml, and by-passing the entire duodenum and a portion of the jejunum. The small intestine is sectioned at 30–40 cm from the ligament of Trietz and restoration of continuity is realized by connecting the distal end of the divided bowel to the pouch, creating a gastro-jejunostomy, and anastomosing the proximal end about 100–150 cm distal to the gastro-jejunostomy [28,29].

Biliopancreatic diversion (BPD) is primarily a malabsorptive procedure with some restriction and consists in a partial gastrectomy, resulting in a 200–500 ml proximal gastric pouch and creation of a distal Roux and proximal biliary limb by division of the small bowel 250 cm proximal to the terminal ileum. To restore the continuity of the bowel the gastric pouch is anastomosed to the end of the Roux limb, while the biliar limb is attached at 50 cm from the iliocecal valve, thereby creating a very short common channel [28,29].

Patients who undergo surgical rerouting of the food through exclusion of some segments of the gastrointestinal tract experience early improvements in glycemic control due to some extent to the significantly increased postprandial

GLP-1 and insulin secretion, compared with obese and lean controls, and patients who had lost an equivalent amount of weight by gastric banding. This could be explained by the arrival of mainly fats and carbohydrates into the ileum that cause an increase in GLP-1 release from L cells [30]. However, an interesting finding is that of Peterli et al. who demonstrated that even after LSG which does not imply rerouting of the food GLP-1 levels increased significantly [31].

Regarding bile acids it is reasonable to mention that any manipulation of the gut, thereby rerouting of the bile will not remain without consequence. A study from Japan showed that bile acids levels are elevated after LRYGB and after LSG with duodenojejunal bypass but also after restrictive procedures (LAGB). Furthermore, a rise in GLP-1 levels and a positive correlation with the changes of serum concentrations of primary bile acids could be observed [32]. Patti et al. revealed that after LRYGB fasting serum bile acids increased two-fold when compared to overweight or morbidly obese control participants and that total serum bile acids were inversely correlated with 2-hour postprandial glucose levels and positively correlated with GLP-1 levels [33]. From these data it can be suggested that one mechanism by which a gastric bypass leads to beneficial elevations of GLP-1 may be through the undiluted flow of bile and the altered delivery to the terminal ileum. However, we have to point out that between bile acids, food and L cells there are important interferences. To be more specific, in the presence of nutrients bile acids interfere with the intestinal digestion of fats as they would be more bound up in micelles and therefore less likely to stimulate L cells for GLP-1 secretion. On the other hand, when conjugated with food, bile acids facilitates better digestion of complex ingested fats by intestinal lipases into smaller lipid subunits, leading to a more effective stimulation of L cells. Hence, the effect of bile acids on digestion of ingested fats cannot explain the increased gut hormone response, suggesting that bile acids may play a role as signaling molecules [18]. However, a link between bile acids and gut hormones has been demonstrated. The secretion of GLP-1 by the L cells is induced by bile acids in a dose dependent manner [34].

In a recent study Steinert et al. demonstrated that before surgery (gastric bypass or sleeve gastrectomy) basal bile acids concentrations were significantly lower in bariatric patients than in healthy controls. However, whereas in both patient groups, marked increases in GLP-1 and improved glycemic control was seen already 1 week and 3 months after surgery, changes in plasma bile acid followed a different pattern: basal and postprandial plasma concentrations increased much slower, suggesting that bile acids do not appear to be key mediators of the early increase in GLP-1 response in post bariatric patients [35].

The mechanism by which bile acids in the enterohepatic circulation increase after gastric bypass is not fully understood. One explanation proposed by Patti et al. is that it occurs via increased uptake of bile acids in the gut and this increment could mediate its effects on GLP-1 enhancement [33]. On the other hand, Peterli et al. suggested that the increase after malabsorptive procedures is a consequence of the change in enterohepatic circulation with 'malreabsorption' which would lead to an enhanced synthesis of bile acids by the liver and increased consumption of cholesterol [31]. On the other hand, in an attempt to explain the same changes after restrictive procedures, Nakatani proposed the hypothesis that the decreased ingestion of cholesterol due to restriction will lead to an upregulation of cholesterol and consecutive bile acids biosynthesis [32].

In conclusion, recent findings have shown that there is interplay between bile acids and GLP-1 with an important impact on glucose homeostasis, raising the question whether bile acids could be considered as the new gut hormones. Surgical procedures such as LRYGB which involves rerouting of the food due to manipulation of the gastrointestinal tract lead to increase of GLP-1 and changes of bile flow associated with increased total plasma bile acids. The changed route of bile acids exerts an increase of gut hormone response which can be further enhanced by the delivery of food. Hence, the beneficial metabolic effect of LRYGB on glycemic control might be attributed to changes in bile acids, but still, the mechanisms need further investigation.

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