Ileal transposition provides insight into the effectiveness of gastric bypass surgery

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Abstract

Despite dramatically increased research efforts to discover cures for the rising health issue of obesity, bariatric (obesity) surgery remains the most effective treatment. Obese people and especially those classified as morbidly obese often suffer from associated co-morbid conditions such as type-II diabetes. In most cases, bariatric surgery results in rapid and sustained decreases in excess body weight. Recent reports have identified significant improvements in glucose homeostasis after surgery that are coincident and often precedent to any measurable weight loss. These studies suggest an inhibition or enhancement of a “factor” within the intestinal tract that improves glycemia independent of body fat stores. These observations have sparked renewed investigation into the mechanisms underlying successful obesity surgeries such as gastric bypass. It is becoming increasingly clear that restriction and malabsorption are not the only two mechanisms important for inducing long-term weight loss or the improvements in diabetes. Investigating the hypothesis that the distal intestine (ileum) holds additional answers into a third mechanism, I used the model of ileal transposition to help identify endocrine changes in the gut following obesity surgery. This review will explore the model of ileal transposition and speculate on its usefulness as a tool to dissect out additional mechanisms underlying effective obesity surgeries. Also discussed will be the ileal-produced hormone glucagon-like peptide and its role in mediating the improvements in diabetes and weight loss after bariatric surgery.

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1. Introduction

In 2001 the Surgeon General released a Call to Action to prevent obesity as it has become a major public health issue. Obesity and the associated health problems it causes will claim over 300,000 lives this year alone, making it a nationwide epidemic. In addition, obesity rates of those classified as morbidly obese (BMI ≥ 40 kg/m²) have risen in an alarming and disparate fashion, increasing more than five times the rate of those overweight and other classifications of obesity. In a 2000 study it was determined that persons categorized as morbidly obese made up only 2.8% of the obese population yet their healthcare expenditures made up nearly 20% of the $56 billion spent on obesity-related costs that year [1]. Obesity surgery (bariatric) is by far the most effective treatment for morbid obesity, usually resulting in massive weight loss with minimal recidivism. In recent years there have been significant improvements in surgical expertise as well as affordability through health insurance for obesity surgery making it a very attractive treatment option. It was estimated that the number of people who chose surgery to treat their obesity increased five-fold within recent years, with fewer than 13,000 surgeries in 1998 to more than 72,000 in 2002 and an increase to over 100,000 in 2003 [2].

2. Obesity surgery and type-II diabetes

Weight loss resulting from obesity surgery is substantial, often achieving more than a 50% reduction of excess body weight. In addition to dramatic weight loss, obesity surgery often results in partial or complete amelioration of many co-morbid conditions such as hypertension, type-II diabetes, sleep apnea, and liver and gastrointestinal disorders [3]. Much of the improvement can be explained by the amount of weight lost after surgery, however some effects appear to be independent to weight loss. Most notable are the effects seen in obese patients that display either impaired glucose intolerance or type-II...
diabetes. Recent publications based on close observations of patients immediately following obesity surgery have identified rapid and permanent improvements in glucose control [4,5]. In most cases, diabetic patients find that bariatric surgery eliminates the need for medication to control their glucose [5]. The reason this observation is so surprising is that the improvement in glucose control occurs prior to any substantial weight loss. Prior to these observations the most parsimonious explanation for improvements in glucose control had been massive weight loss, mostly because the improvements in glycemia were noted months after surgery (for a systematic review see [6]). The beneficial effects of bariatric surgery on glycemic control also depend on the length of time with the disease. Long-term follow-up of patients that underwent gastric bypass surgery with impaired glucose tolerance revealed that they never progress to type-II diabetes and remain euglycemic. Similarly, persons with longstanding type-II diabetes prior to surgery show less likelihood of a substantial improvement. Surgeries based solely on restriction of the stomach are typically less effective in improving type-II diabetes than surgeries that involve a substantial amount of intestinal bypass or malabsorption [8–10].

2.1. Bariatric surgery and mechanisms of action

Historically, surgical manipulations of the gastrointestinal system were developed to promote and maintain weight loss through two primary mechanisms, volume restriction (reducing stomach size) and malabsorption (bypassing the small intestine) [11]. Purely restrictive procedures such as vertical-banded gastroplasty restrict the amount of food that can enter the stomach, thus promoting weight loss through decreased intake (Fig. 1) [11]. Other procedures, such as jejunoileal bypass surgery limit the area of intestinal lumen exposed to ingested food and thus promote decreased absorption of nutrients. Although jejunoileal bypass is effective as a surgical treatment for obesity, the malabsorption results in a host of metabolic disorders and adverse nutritional consequences, prompting its eventual discontinuation [12]. The current gold standard for bariatric surgery in the United States is the Roux-en-Y Gastric Bypass (RYGB). This procedure combines both restrictive and malabsorptive mechanisms that depend on the length of the bypassed intestine. In the RYGB an extremely small stomach pouch is formed (restriction) in combination with a jejunal segment routed to the pouch. This procedure effectively bypasses the proximal small intestine and the remaining stomach (resulting in malabsorption) [13]. An interesting structural commonality of the RYGB and other highly effective bariatric surgical procedures including jejunoileal bypass and biliopancreatic diversion (Fig. 1) is the delivery of nutrient-rich chyme to the distal small intestine earlier in the post-ingestive period than would occur otherwise. Hence, the malabsorptive strategy of bypassing portions of the small intestine and delivering nutrients directly to the ileum may also promote weight loss by enhanced activation of a negative feedback mechanism known as the “ileal brake” [14]. The ileal brake refers to the stimulation of the ileal segment of the small intestine, resulting in neural and endocrine mechanisms that lead to delayed gastric emptying, gastrointestinal transit, and satiety [15].

2.2. The third mechanism: endocrine changes in the gastrointestinal tract

Restriction and malabsorption are undeniably effective in causing substantial weight loss, however past and present studies implicate surgery-induced changes in gastrointestinal hormones as an important third mechanism through which sustained weight loss can be achieved. Because many vital roles for gut hormones in the regulation of feeding and glucose control are only now being clarified, it is unlikely that their involvement was considered in the initial bariatric surgical designs and outcomes over 40 years ago [14]. However, our understanding of the intestinal regulation of body weight has experienced enormous growth in recent years [16], and it is now recognized that changes in secretion of hormones produced within the stomach, duodenum and ileum may all help promote satiety after obesity surgery. For example, activation of the ileum by nutrient-rich chyme results in reduced food intake through neural and endocrine mechanisms, a phenomenon known as the ileal brake. Recent data suggest that increased activity of the ileal brake, mediated in part by the hormones produced in the ileum, may account for much of the weight loss, reduced food intake, and improved glucose regulation seen following obesity surgery.

2.3. Ileal transposition: a “pure” model of ileal activation

Ileal transposition is a surgical manipulation designed to allow assessment of the exclusive role of ileal activation as a mediator of surgically-induced weight loss. Described as eliciting early and enhanced activity of the ileal brake, ileal transposition surgery involves the resection of a 10–20 cm portion of distal ileum, and then transposing the fully innervated and vascularly-intact ileal segment into the proximal jejunum.

![Fig. 1. Vertical banded gastroplasty (a) is a purely restrictive surgery that is distinct from the purely malabsorptive surgery jejuno-ileal bypass (b). The most commonly performed surgery in the United States is the gastric bypass (c) that involved both restrictive and malabsorptive components.](image-url)
2.3.1. Behavioral effects of ileal transposition

Although never systematically investigated in humans, ileal transposition reliably reduces food intake and body weight in rats and dogs [18–22]. In our hands we have corroborated the reports that ileal transposition promotes greater weight loss compared to sham-operated rats and that this is partly due to a reduction in post-operative food intake [18]. Importantly, as a model of pure ileal stimulation, ileal transposition results in weight loss and reduced food intake despite the absence of restriction and malabsorption. The exact mechanism underlying the reduced food intake following ileal transposition may involve more than “pure” activation of the ileum or engaging the ileal brake. In fact, comparisons between jejunoileal bypass and ileal transposition in early studies by Sclafani revealed that both procedures result in the development of a conditioned taste aversion. The feeling of visceral illness alone may be the mechanism through which rats reduce their food intake after surgery [23].

2.3.2. Physiological effects and ileal transposition

2.3.2.1. Morphology and function. Ileal transposition results in significant hyperphasia, hypertrophy, and even complete jejunalization of the transposed ileal segment [22,24–27]. Despite increased weight of the transposed segment, the gut retains its capability to absorb nutrients, in fact some report an increase in absorbance capacity [28]. Because ileal transposition causes enhanced stimulation of the ileal segment and consequently the ileal brake, it is not surprising that significant decreases in gastric emptying and gastrointestinal motility occur [29].

2.3.2.2. Endocrinology: GLP-1 and PYY. When ingested food enters the ileum (and other regions of the small intestine), discrete enteroendocrine cells in the mucosa release hormones that contribute to the ileal brake; noteworthy among these are glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) [30]. GLP-1 is secreted primarily from the L-cells of the ileum and colon and is derived from a larger precursor molecule, pre-proglucagon [31]. GLP-1 is also synthesized in the central nervous system, specifically in the nucleus of the solitary tract (NTS) and the area postrema (AP) [32]. Turton et al. reported that centrally-administered GLP-1 suppressed food intake and body weight of rats, and that the effect was abolished in the presence of the GLP-1 receptor antagonist, exendin-(9–39) [33]. Peptide YY is also produced in the L-cells within the ileum of the small intestine and is also implicated in satiety (PYY 3–36) in rodents and humans [34–36]. PYY is considered to be an important component of the ileal brake and is released following the ingestion of lipid rich substances. Because there is less evidence in support of a role for PYY in the improvements in glycemia following surgery the remainder of this review will concentrate on GLP-1.

Human studies administering GLP-1 and GLP-1 derivatives have provided substantial promise for GLP-1 as a potential therapy for obesity and diabetes [37–39]. GLP-1 is a powerful incretin, meaning that it facilitates insulin secretion in the presence of glucose [40]. In regards to glucose control, many studies in humans and rodents have determined that administration of a GLP-1, a GLP-1 receptor agonist, and an inhibitor of the enzyme (DPP-IV) that degrades GLP-1 will all improve diabetes [37,41–44]. Despite the encouraging findings these studies provide, a major obstacle exists in the practical use of GLP-1 as a cure-all for diabetes. The physiological half-life of native GLP-1 is between 60 and 90 s, making chronic delivery nearly impossible [45].

The endocrine consequences of obesity surgery may provide a solution to the problem of prolonged GLP-1 delivery. Given the current knowledge of GLP-1 in food intake regulation and glucose regulation and based on its site of synthesis, it seems likely that enhanced GLP-1 activity (as a consequence of ileal stimulation) is at least partly responsible for many of the effects of the various bariatric surgery models [14]. Bariatric surgical procedures such as ileal transposition, jejunoileal bypass, gastric bypass, and biliopancreatic diversion all result in elevated basal and meal-stimulated enteroglucagon levels, a precursor for GLP-1 [46–48]. All of the above procedures involve reorganization of the intestinal tract resulting in concentrated chyme being delivered to the lower intestine. Although increased GLP-1 after ileal transposition was only recently demonstrated, the connection and possible involvement of this important hormone with improvements in post-surgical glycermia were made 5 years earlier in a paper by Edward Mason. In his paper Mason (the “father of bariatric surgery” and inventor of the gastric bypass) states that “ileal transposition may be an ideal surgical treatment for obese patients (and diabetics) since the surgery would be expected to significantly enhance endogenous levels of GLP-1 without the malabsorptive consequences of the other surgical methods” [49]. In fact in a recent report we demonstrated that ileal transposition results in a dramatic (3-fold) increase in
circulating GLP-1 (and PYY) following an intragastric infusion of nutrients (Fig. 3) [18]. More recently, Patriti et al. also recognized the GLP-1-secreting benefit of ileal transposition and demonstrated that glucose tolerance is much improved in the Goto-Kakizaki diabetic rat following this procedure [50]. The hypothesis that increased ileal hormones are important mediators of obesity surgery is further supported by a study by Naslund et al. who demonstrated that patients who received jejuno-ileal bypass surgery over 20 years ago continue to secrete significantly elevated basal and meal-stimulated plasma GLP-1 (as well as PYY, CCK, and Neurotensin) [8].

2.3.3. Ileal transposition and glycemic control

Some of the ways improvements in glucose control can be achieved include: behavioral modification, through reduced food intake and subsequent weight loss, mechanical changes, through delayed gastric emptying and a prolongation of luminal contact and absorption time, and endocrine changes, through enhanced GLP-1 secretion (Fig. 4). Because ileal transposition results in weight loss, reduced food intake, delayed gastric emptying and enhanced ileal secretion of GLP-1 it makes sense that improvements in glycemic control should follow. In our recent study and in past studies, significant improvements in fasting glucose and insulin were noted after ileal transposition. Rats with ileal transposition surgery were determined to be more insulin sensitive compared to rats with a sham operation (as measured with an insulin tolerance test) [18]. However the interpretation of these data suffer from the confounding influence of reduced food intake and body weight in all cases. Until recently a direct effect of ileal stimulation, independent of food intake and body weight could not be made. As mentioned above, using a non-obese type-II diabetic rat model, the Goto-Kakizaki rat, Patriti et al. demonstrated that ileal transposition significantly increased plasma GLP-1 and improved fasting plasma glucose, insulin and glucose tolerance compared to sham-operated controls. The rats in this study were non-obese and showed no post-operative changes in food intake or body weight. The results of this study are

![Diagram](image)

Fig. 4. Improvements in glucose control as a result of bariatric surgery may involve all or some of the parts of this illustration. Ingested nutrients will enter the intestinal lumen (1), stimulate enteroendocrine cells and cause early and prolonged GLP-1 release (2) which will subsequently affect gastrointestinal motility and gastric emptying (3). GLP-1 may also directly cause feelings of visceral illness and satiety through the interaction with the central nervous system (4). GLP-1 is a well known incretin and mediates glucose-stimulated insulin secretion in addition to protection of the endocrine pancreas (5).
encouraging since they support the hypothesis that ileal stimulation, and perhaps GLP-1, may underlie the euglycemia that occurs after human obesity surgical procedures. Whether the improvements in glucose control after ileal transposition are due primarily to direct effects of GLP-1 on the pancreas, liver, muscle, or adipose tissue remains to be determined. It is possible that the effects of ileal transposition on glycemia result simply due to the delay in gastric emptying and gastrointestinal motility.

3. Alternative hypotheses and future considerations

Because the structural result of gastric bypass involves the exclusion of the foregut or duodenum, the role of its elimination from nutrient stimulation must be considered as a potential factor in mediating both weight loss and glycemic improvement after surgery [51]. A series of convincing studies by Francesco Rubino using a model of duodenal exclusion (in the absence of gastric restriction) make valid arguments for the elimination of the foregut as the critical mediator in improved glucose control [52,53]. In these studies only the duodenum is eliminated from the normal flow of nutrients entering the digestive tract. Rubino and colleagues performed the duodenal exclusion surgery in the non-obese diabetic Goto-Kakizaki rat and found that this procedure also improved glucose tolerance in the absence of weight loss or a reduction in food intake. The argument made following these findings is that some harmful “diabetogenic factor” within the duodenum is eliminated from the digestive flow and by eliminating this region with the exclusion surgery an improvement in glucose tolerance is therefore achieved. However as a consequence of the duodenal exclusion surgery a portion of foregut is eliminated which is likely to also enhance the stimulation of hind gut or ileum.

Despite all of the positive effects it appears increased plasma GLP-1 may be having on glucose metabolism and weight loss after obesity surgery, one must consider potential complications. For example in a recent clinical report in the New England Journal of Medicine cases of nesidioblastosis were hyperinsulinemic and hypoglycemic perhaps due to the delay in gastric emptying and gastrointestinal motility. Rubino and colleagues performed the duodenal exclusion surgery in the non-obese diabetic Goto-Kakizaki rat and found that this procedure also improved glucose tolerance in the absence of weight loss or a reduction in food intake. The argument made following these findings is that some harmful “diabetogenic factor” within the duodenum is eliminated from the digestive flow and by eliminating this region with the exclusion surgery an improvement in glucose tolerance is therefore achieved. However as a consequence of the duodenal exclusion surgery a portion of foregut is eliminated which is likely to also enhance the stimulation of hind gut or ileum.

There are now more than 30 hormones identified and produced within the gastrointestinal tract known to regulate metabolic improvements after obesity surgery. Whether the improvements in glucose control after ileal transposition are due primarily to direct effects of GLP-1 on the pancreas, liver, muscle, or adipose tissue remains to be determined. It is possible that the effects of ileal transposition on glycemia result simply due to the delay in gastric emptying and gastrointestinal motility.

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There are now more than 30 hormones identified and produced within the gastrointestinal tract known to regulate food intake and body weight. Interestingly, the original design of gastric bypass has stood the test of time (almost 40 years) despite the fact that at the time it was designed only CCK was a widely accepted satiety factor [16]. The identification of the only gut-derived orexigenic hormone ghrelin and the subsequent study illustrating the dramatic changes in circulating concentrations after gastric bypass surgery have significantly helped fuel research interests in this area of bariatric research [56]. In the future, and only with the coordination of the research efforts of basic scientists and bariatric surgeons, substantial progress will be made into the understanding of the contribution endocrine changes in the gut provide towards metabolic improvements after obesity surgery.

References


