Gastric bypass and glucose metabolism

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Abstract

Gastric bypass (GBP) surgery was originally developed to treat patients with severe obesity. Nevertheless, in those with type 2 diabetes, GBP also exerts a spectacular effect on glucose metabolism, leading to remission of the diabetes in many cases. In this report, the basic principles of the surgical procedure are outlined together with a summary of the potential mechanisms that might explain the remarkable effects of this type of operation on glucose metabolism.

Keyword: Gastric bypass; Bariatric surgery; Glucose metabolism; Review

1. Introduction

Gastric bypass (GBP) is the preferred operation for treating severe obesity in North America [1]. The use of the procedure is also rapidly growing in Europe, accounting for approximately 20% of all bariatric operations performed last year in France. One likely explanation for the widespread enthusiasm over the rather complex procedure is its efficacy in terms of weight loss compared with rapid exclusively restrictive procedures such as gastric banding [2]. Another appealing feature of GBP is its spectacular effect on glucose metabolism, even in patients with overt type 2 diabetes (T2D) [3]. Initially reported by Pories et al. [4], this specific and initially unexpected benefit of GBP is now well established. In a recent meta-analysis of the outcome of T2D after bariatric surgery, more than 80% of patients achieved diabetes remission following GBP [5]. Several studies also suggest that GBP can markedly reduce diabetes-related mortality [6, 7]. We outline here the basic principles of the surgical procedure, and summarize the potential mechanisms that might explain the outstanding effects of this operation on glucose metabolism.
2. The GBP operation

The basic idea of bypassing the stomach, duodenum and proximal jejunum for treating severe obesity was first suggested by Mason and Ito in 1969 [8]. This operation was later refined by Griffen et al. [9], who described the basics of the procedure that are still in use today, known as the ‘roux-en-Y gastric bypass’. As illustrated in Fig. 1, GBP can be divided into three distinct components: (1) construction of a small gastric pouch (30 ml or less) along the small curvature of the stomach that is divided from the gastric remnant, which is left in place, but disconnected from the upper alimentary tract; (2) sectioning of the jejunum approximately 50 cm from the ligament of Treitz, with reanastomosis of the distal jejunal (alimentary) limb to the gastric remnant (gastrojejunal anastomosis); and (3) reconnection of the proximal jejunal limb (excluding the biliopancreatic limb) to the alimentary limb (jejunojejunal anastomosis). Following GBP, ingested food travels directly from the gastric pouch to the alimentary limb, where it comes into contact with biliopancreatic juice after merging with the common limb, downstream of the jejunojejunal anastomosis. The vagus nerves are carefully preserved during the procedure by most surgeons, although many of the distal neural tributaries along the small curvature may be disrupted. However, with the ongoing improvements in the available technologies and surgical skills, this operation can now be performed by laparoscopy in the vast majority of patients, including many of those with massive obesity or a past history of previous abdominal surgery.

3. Effects of GBP on glucose metabolism

3.1. Calorie restriction

Even in the absence of surgery, the dramatic metabolic effect of calorie restriction alone on T2D is well documented in the short term, but also in the longer term in cases where it can be prolonged [10]. By design, GBP is a severely restrictive operation that enforces calorie restriction by at least three mechanisms that work in synergy. The first is mechanical, and related to the limited volume of the gastric pouch and its reduced outlet. This is why anatomical restriction per se (such as gastric bands) can also induce significant metabolic improvement. However, GBP can also significantly modulate satiety by perturbing neurointestinal cross-talk, and favouring the postprandial induction of satiety signals such as an increase of the anorexigen peptide YY [11] (ileal break) or of intestinal neoglucogenesis [12]. In addition—and albeit still a controversial point—GBP also appears to decrease levels of orexigen peptides such as ghrelin [13]. The final mechanism that may contribute to restricted caloric intake after GBP is the selective food eviction spontaneously adopted by patients to limit the burden of postprandial dumping syndrome [14].
3.2. Insulin sensitivity

As expected, the rapid and dramatic weight loss induced by GBP is associated with a major improvement in peripheral insulin sensitivity. This rapid restoration of insulin sensitivity is not totally explained by weight loss, and may also be related to enhanced insulin signalling in muscle [15]. Another landmark of surgical weight loss is the marked decrease in non-alcoholic fatty liver disease [16], a condition commonly seen in T2D patients [17]. As regression of liver steatosis appears to be closely related to insulin resistance [18], GBP may have specific hepatic benefits beyond weight loss.

3.3. Insulin secretion

In contrast to purely restrictive operations, GBP significantly affects the secretion of insulin. Restoration of a near-normal postprandial insulin response after GBP in patients with T2D has been documented in longitudinal studies. It presents early after the operation [19], and is independent of weight loss [20]. Insulin secretion is only modestly stimulated by intravenous glucose, and the postprandial insulin response appears to be intimately related to a rise in circulating glucagon-like peptide-1 (GLP-1) levels (incretin effect). However, the precise stimulus for such an exaggerated postprandial secretion of GLP-1 remains a subject of debate. It might be provoked by direct stimulation of L cells in the distal ileum, or mediated by earlier jejunal stimuli through neurointestinal cross-talk [21]. The role of the modulation of other incretins, such as glucose-dependent insulinotropic polypeptide (GIP) [22], hyperglycaemic peptides such as glucagon or some still undiscovered anti-incretin peptides potentially increased by duodenal exclusion [23], has been suggested, but has yet to be documented in humans.

3.4. Beta-cell mass

In many cases, GBP appears to fully reverse the diabetic phenotype. Basal insulin and the proinsulin-to-insulin ratio are decreased, while beta-cell sensitivity, as estimated by homoeostatic model assessment (HOMA), increases markedly after GBP. The drastic reduction of both hyperglycaemia and dyslipidaemia, two highly toxic conditions for beta cells, must surely contribute to the long-term favourable effects of all bariatric operations on beta-cell function [24]. Alternatively, another hypothesis to explain this apparent reversal of diabetic phenotype is that GBP can truly restore the endocrine cell mass through proliferation and decreased apoptosis. The occurrence of inappropriate postprandial hyperinsulinaemia after GBP, which may eventually lead to symptomatic hypoglycaemia in some cases, supports this theory [3]. However, it is worth remembering that, despite being well established in rodent models, the trophic effects of GLP-1 and its pharmacological counterparts remain elusive in human islet cells. Thus, the potential restoration of the beta-cell mass in humans after GBP remains highly speculative.

3.5. Other intestinal changes

GBP also induces several non-hormonal changes in intestinal physiology that might contribute to the modulation of glucose metabolism. Malabsorptive procedures such as jejunoileal bypass are classically associated with a decrease in jejunal glucose absorption [25], but the picture is less clear with GBP. An early and transient rise in absorbed glucose has been directly measured after GBP in humans [26]. On the other hand, in rats, Rubino et al. [23] could find no changes in nutrient absorption after duodenojejunal bypass, and a recent study showed a decrease in the expression of the intestinal active sodium-dependent glucose transporter 1 (SGLT1) after GBP [27]. These apparently discordant observations need to be reconciled by further clinical studies. In addition, GBP might also significantly modulate energy metabolism by bringing about changes in the microbial intestinal microflora and proinflammatory lipopolysaccharides [28].

4. GBP limitations

The main limitations of GBP are related to its associated risks over both the short and long term. Laparoscopic GBP in patients with T2D and, often, other related co-morbidities, represents a major surgical procedure. The most frequent severe adverse events after GBP include anastomotic leaks, haemorrhage and thromboembolic events. Although the postoperative mortality rate remains <1% in experienced centres, the overall risk of serious complications reaches 5% [29]. GBP also carries a long-term risk of various medical hazards such as vitamin deficiencies, malnutrition, osteoporosis and psychiatric disorders. Furthermore, despite its favourable effects on overall survival, GBP may increase the risk of accidental death [7]. Eventually, partial weight regain is often observed over time, and the long-term outcome for glucose metabolism after GBP is not well known. This indicates that careful multidisciplinary evaluation and follow-up need to be organized and put in place prior to the operation, and enforced for life thereafter.

5. Conclusion

Initially proposed for severely obese patients as an effective surgery for weight loss, GBP has also brought unexpected benefits in glucose metabolism, including the apparent remission of overt diabetes in many cases. GBP can modulate various metabolic pathways such as calorie intake, insulin sensitivity and beta-cell function as well as glucose intestinal
absorption, all of which are beneficial for glucose control and potentially synergistic. It is likely that further studies will unravel additional mechanisms of actions related to such major anatomical change. Understanding these mechanisms will help in the development of alternative and potentially less-invasive interventions [30], as well as in the identification of new pharmacological targets for treating diabetes [31].

**Conflicts of interests**

The authors have reported no conflict of interests.

**References**


