Neuroendocrine mechanisms of early remission of type 2 diabetes in bariatric surgery: a review article

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The earliest report of a successful treatment of obesity can be traced back to Spain in the 10th century. The treatment was performed by Hisdai Ibn Shaprut on Sancho I, the then King of Leon to help him regain the throne that he had lost as a result of obesity-related unfitness. He reportedly lost weight and his throne was restored.[1] The first bariatric surgery procedure, a jejuno-colic bypass, was however performed by Victor Henrikson in 1952.[2] Thereafter, Varco in 1953 and Kremen et al.,[3] developed and described the jejuno-ileal bypass, a procedure that excludes most of the small intestine from contact with food.[4,5] The development of these procedures were largely influenced by their years of experience with the short-bowel syndrome.[5] Since then, the field of bariatric surgery has experienced remarkable developments, with numerous procedures being described and performed successfully. The incorporation of minimally invasive techniques with the advantages of cosmetic incisions, decreased wound-related complications, and shorter convalescence over open surgery[2] has further boosted acceptance of the procedure by the public with even more operations being performed. The 2013 global survey on bariatric surgery reported that, 96% of the 468,609 procedures were performed laparoscopically.[6] Currently, bariatric surgery represents the most effective treatment modality for morbid obesity, with the advantages of substantial and long-term weight loss over pharmacological therapy and/or dietary modifications.[7,8]

Although originally devised to treat obesity,[9] it has been observed that most diabetic patients undergoing bariatric surgery experience remission of type 2 diabetes (T2DM),[10,11] defined as the normalisation of blood glucose and glycated hemoglobin levels, as well as restoration of insulin sensitivity with discontinuation of all anti-diabetic medications.[7,12] This remission is not only dramatic but also durable.[13] This has triggered numerous clinical studies that have successfully demonstrated the potential use of surgery for the treatment of diabetes. In the light of this overwhelming body of evidence, the term 'metabolic surgery' has been adopted.[13,14] The mechanisms behind resolution of T2DM following surgery however remains poorly understood. Reduced calorie intake, intestinal malabsorption and subsequent weight loss have all been offered as possible explanations for the remission.[15] Most clinical studies have however demonstrated that T2DM remission occurs prior to any significant weight loss.[9,16] Further, bariatric surgery has been demonstrated to induce T2DM remission in both obese and non-obese subjects.[7] These observations coupled with findings from experimental models[11,17] suggests the presence of weight-loss independent mechanisms of T2DM remission. These mechanisms are likely to be neuroendocrine in nature, based on post-operative neuro-hormonal changes,[18,19] as well as the close anatomical and physiological relationship between the gastro-intestinal tract and the pancreas.[20] Elucidation of these mechanisms may be important in the refining of existing procedures as well as the development of new and more efficacious ones. This review therefore aims to integrate the available knowledge on the neuroendocrine mechanisms of T2DM remission in bariatric surgery.

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Literature search

Literature was searched using the search engines Google Scholar™ and the databases Hinari™, PubMed Central™, Cochrane™ and Embase™. The MeSH headings used included: 'bariatric surgery', 'metabolic surgery', 'obesity', 'diabetes remission', 'type 2 diabetes', 'jejuno-ileal bypass', 'jejuno-colic bypass', 'sleeve gastrectomy', 'vertical banded gastrectomy', 'gastric bypass', 'Roux-en-Y gastric bypass', 'bilio-pancreatic diversion' and 'duodenal switch'. No limit was set for the year of publication. The inclusion criteria was any article describing a surgical procedure for treatment of obesity and/or type 2 diabetes. Meta-analysis, randomised and non-randomised clinical trials, cohort studies, case-control, experimental and descriptive studies were all included. Relevant articles found in the references of the selected articles were also included.

Findings

Types of bariatric surgery procedures

Description of the various procedures is essential in understanding the anatomical rearrangements of the gastrointestinal (GI) tract performed, the fundamental concept of bariatric surgery.

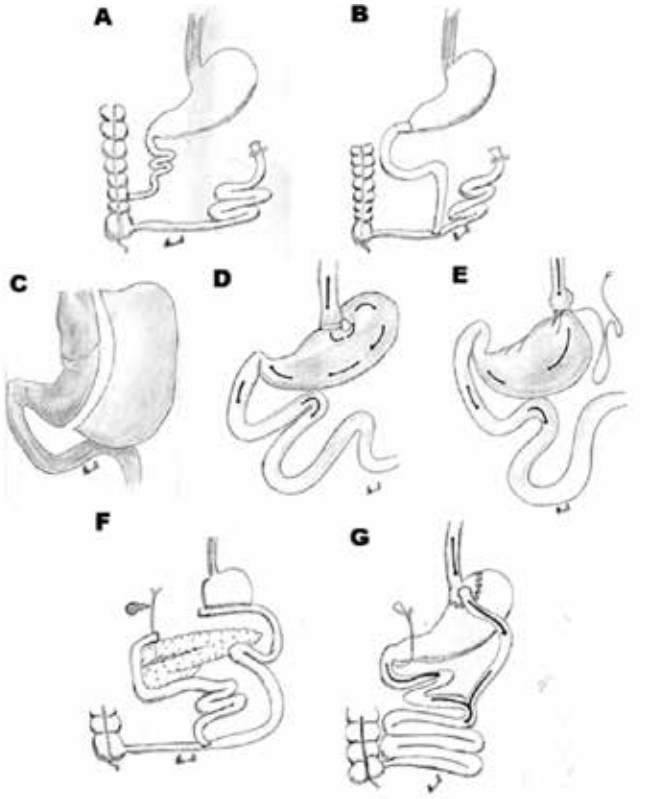
Bariatric surgical procedures are conventionally classified into malabsorptive, restrictive or mixed (hybrid) procedures.[21] The earliest to be described and performed were malabsorptive procedures. These include jejuno-colic (JCB) (Figure 1A) and jejuno-ileal bypass (JIB) (Figure 1B)[5] (Moshiri et al., 2013). They involve transection of the jejunum 30-50 cm distal to the ligament of Treitz, with the proximal end being anastomosed to the ascending colon in the JCB and to the terminal ileum, 10 cm proximal to the ileo-caecal valve in the JIB4. These procedures reduce the length and therefore absorptive surface of the small intestine. Additionally, biliopancreatic secretions mix with the food in the distal ileum, further reducing food digestion and absorption.[21,22] These procedures are however no longer performed due to their high rates of complications.

Restrictive bariatric surgery procedures such as sleeve gastrectomy (SG) (Figure 1C), vertical banded gastrectomy (VBG) (Figure 1D) and adjustable gastric banding (AGB) (Figure 1E) act by reducing the gastric volume, therefore inducing early satiety with subsequent weight loss.[21,23] In addition to gastric restriction, SG also acts by reducing levels of ghrelin. This is an orexigenic hormone mainly produced by 'A' cells in the gastric fundus, part of the stomach that is normally resected in SG. Further, SG also reduces the duodenal food transit time, minimising the duration of contact between food and the duodenal mucosa.[24] Unlike malabsorptive procedures, continuity of the GI anatomy is maintained. In VBG, a window (via perforation of both walls) is made close to the lesser curvature. A stapler is then inserted into this window up to the angle of His. This creates a small vertical pouch, with its outlet into the rest of the stomach being banded using a polypropylene collar.[5,25] AGB is the least invasive and involves placement of an adjustable silicon band in the upper part of the stomach, therefore creating a small upper and larger lower pouch, with the reduced size of the channel between the two gastric pouches.[25] Both AGB and VBG have lost favour due to a myriad of complications including, but not limited to, pouch enlargement, band slip and erosion, pouch ulcer and reflux esophagitis.[26,27] SG involves resection of the majority portion of the greater curvature of the stomach, leaving behind a narrow tube of about 60 to 80 ml in volume. This procedure was used in morbidly obese patients prior to a definitive bariatric surgery procedure due to its rapid and substantial weight loss.[5] Currently, it is performed as a definitive procedure.

Hybrid bariatric surgery procedures include biliopancreatic diversion (BPD) (Figure 1F) and Roux-en-Y gastric bypass (RYGB) (Figure 1G). They incorporate both aspects of gastric volume restriction and intestinal malabsorption. In RYGB, a small gastric pouch (10% of total gastric volume) is created. The jejunum is transected approximately 50 to 75 cm from the ligament of Treitz, with the distal portion being anastomosed to the gastric pouch via a gastro-jejunostomy (GJ). The proximal part is then anastomosed to the jejunum (via a jejuno-jejunostomy, JJ), 75 to 100 cm from the GJ. This re-arrangement of GI results in the formation of an alimentary limb (portion of the small intestine from the GJ to the JJ), a bilio-pancreatic limb (from the pylorus to the JJ) and a common channel (from the JJ to ileo-cecal valve) in a Y-shaped fashion, hence the term RYGB.[7,28] BPD is a modification of the JIB. In addition to the JIB described above, a subtotal gastrectomy with a GJ and closure of the duodenal stump is performed.[25] The larger gastric pouch, removal of the pylorus, longer bilio-pancreatic limb and a shorter common channel distinguishes BPD from RYBP.[4,25]

The four most commonly performed bariatric surgery procedures however are SG, RYGB, AGB and BPD in descending order.[29] Remission of T2DM in restrictive procedures (SG and AGB) have been demonstrated to

Figure 1: Illustration of the various bariatric surgical procedures.



Legend: A- Jejuno-colic bypass (JCB), B- Jejuno-ileal bypass (JIB), C- Sleeve gastrectomy (SG), D- Vertical banded gastroplasty (VBG), E- Adjustable gastric banding (AGB), F- Biliopancreatic diversion (BPD), G- Roux-en-Y gastric bypass (RYGB).

be slow and essentially weight loss-dependent9. Hence, the mechanisms for early T2DM remission in this paper are discussed on the basis of anatomical rearrangements of the GI performed in RYGB and BPD.

Evidence for type 2 diabetes remission

A large body on evidence of T2DM remission following bariatric surgery exists. In his meta-analysis of 136 studies including 22,094 patients, Buchwald et al. reported a 76.8% overall T2DM remission rate of with BPD and RYGB having 98.9% and 83.7% remission rates respectively12. Chang et al., in a meta-analysis of 164 articles including 161,756 patients reported T2DM remission rates of 92% and 86% for randomised clinical trials and observational studies respectively.[30] Several randomised clinical trials have also demonstrated the superiority of T2DM remission over pharmacological therapy.[31,32] Durability of the remission has also been demonstrated in several studies. For instance, Pories et al.,[33] in a 14-year follow-up of 608 patients who had undergone gastric bypass surgery reported a remission rate of 83%. Similarly, Scopinaro et al.,[34] reported a 97% remission rate in a 10-year follow up of 312 patients who had undergone RYGB. The rapidity of the remission is well demonstrated by Pories et al.,[35] who reported a 100% T2DM remission rate 10 days post-RYGB in his study of 141 patients. Similarly, Rubino et al.,[7] and Laferrère et al.,[36] reported 100% remission rates each 3 weeks and 1 month after the surgery respectively.

Mechanisms of T2DM remission

The anatomical re-arrangements of the GI performed in RYGB and BPD excludes food from passing through the proximal gut (duodenum and proximal jejunum), while expediting food delivery to the distal gut11. Further, in SG, there is a decrease in the duodeno-jejunal food transit time.[24] Based on these alterations, two hypotheses for T2DM remission have been postulated: the foregut and the hindgut hypothesis.[9,27]

The foregut hypothesis: This hypothesis holds that T2DM remission is as a result of the exclusion of the proximal small intestine (duodenum and proximal jejunum) from transit of ingested food. This in turn prevents production of factors that are responsible for insulin resistance and T2DM10.

This hypothesis was elegantly demonstrated by Rubino et al.,11 in his classic experimental study using the rat model. In the study, diabetic Goto-Kakizaki (GK) rats underwent either duodenal-jejunal bypass (DJB) surgery or gastro-jejunostomy (GJ), with sham-operated and non-operated rats serving as controls. DJB closely resembles RYGB, save for the preservation of the gastric volume and anastomosis of the distal jejunum to the pylorus while GJ involves anastomosis of the pre-pyloric area of the stomach to the jejunum 10 cm distal to the ligament of Treitz.[11] Both procedures (DJB and GJ) therefore cause expedited delivery of food to the distal gut, with exclusion of the proximal gut from transit of food occurring in the DJB. Compared to all other groups, DJB-treated GK rats demonstrated significant improvement in glucose tolerance (GT) as assessed by an oral glucose tolerance test (OGTT) performed 10 days after the surgery. GJ however did not result the improvement of GT compared to sham/non-operated animals. Interestingly, conversion of GJ to DJB by excluding the duodenum and jejunum resulted in significant improvement in GT. Conversely, restoration of duodenal food passage in DJB-treated rats resulted in worsening of GT. Other than DJB, introduction of a duodenal-jejunal endoluminal sleeve also prevents contact between the ingested food and the mucosa. In their study, Aguirre et al.,[38] demonstrated that the endoluminal sleeve-treated rats experience higher weight loss and normalisation of blood glucose levels compared to sham operated animals.

These findings by Rubino et al.,[11] and Aguirre et al.,[38] are supported by clinical studies involving patients undergoing Bilroth GI reconstruction following subtotal gastrectomy for gastric cancer or intractable ulcers. Similar to RYGB and BPD, Bilroth II (BII) reconstruction involves diversion of food away from the proximal small intestine, while Bilroth I (BI) restores the anatomical continuity of the GI tract.[39,40] Kwon et al.,[41] in a meta-analysis involving 8 studies and 972 patients reported that patients undergoing BII experienced significant greater amelioration rates compared to those undergoing BI reconstruction. Similarly, Cohen et al.,[39] reported a case of a patient whose glycaemic control worsened after a BI reconstruction for drug-refractory peptic ulcer disease. Significant improvement in glycaemic control was observed when the BI was converted to a RYGB.

The above findings demonstrate that the exclusion of the proximal gut plays a crucial role in T2DM resolution. These findings may be explained on the basis of the close physiological relationship between the GI and the pancreas via the entero-insular axis, a concept first described by Unger and Eisentraut in 1969.[42] Contact between food (mainly carbohydrates and fat) and intestinal mucosa normally triggers production of incretins such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP).[20] These molecules act on their receptors located on pancreatic beta cells to stimulate post-prandial insulin production.[43,44] This phenomenon is referred to as the 'incretin effect' and accounts for the 50 to 60% more insulin produced by oral compared to intravenous administration of glucose.[45] This effect is however absent or reduced in all T2DM patients.[46] The candidate molecule in the foregut hypothesis is GIP, produced by K cells mainly in the duodenum and proximal jejunum.[17,47] Various authors have tried to explain the aberrations in the GIP pathway in T2DM. According to Rubino et al.,[7] chronic stimulation of the proximal gut leads to production of factors that impair the entero-insular axis. Accordingly, duodeno-jejunal (DJ) exclusion prevents production of the anti-incretin

factors, leading to T2DM resolution. These anti-incretin factors are however yet to be identified. Patriti et al.,[20] on the other hand hypothesised that chronic stimulation of the K cells by food in susceptible individuals leads to excess GIP production with chronic desensitisation and downregulation of GIP receptors (GIPR) in the pancreatic beta cells, hence loss of the incretin effect and glycaemic control as a consequence. Exclusion of food from DJ passage, an area with the highest concentration of K cells therefore leads to a reduction of GIP levels with upregulation of GIPR and restoration of the incretin effect. This hypothesis is supported by animal and clinical studies that have demonstrated supra-physiological levels of GIP in diabetics, which are rapidly restored to normal following DJ exclusion.[7,10,17] Further, DJ exclusion in non-diabetic individuals result in hyperglycaemia secondary to decreased GIP and therefore low insulin production.[48] The failure of exogenous GIP analogues to improve glycaemic control in diabetic patients[49] may be as a result of desensitisation and/or downregulation of GIP receptors on pancreatic beta cells.

The hindgut hypothesis: In this hypothesis, it is thought that T2DM resolution is a result of expedited delivery of nutrients to the distal small intestine (ileum) causing increased production of molecules such as GLP-1 and oxyntomodulin.[9,11] GLP-1 is an incretin produced by the 'L' cells in the distal ileum and colon.[50] Its levels are markedly decreased in diabetic patients, with a resultant loss of the incretin effect and derangements in glucose metabolism. By enhancing rapid delivery of nutrients to the distal small intestine, surgery results in increased post-prandial levels of GLP-1[10,19,51] This increase occurs as early as one week after the surgery.[19] This molecule not only stimulates insulin production in response to glucose[43,44] but also enhances insulin sensitivity,[52] decreases the rate of gastric emptying[53] and inhibits production of glucagon.[50] All these mechanisms are thought to contribute to T2DM remission. Increased post-operative levels of incretin such as GLP-1 are also supported by observations that some RYGB patients experience nesidioblastosis, a condition characterised by episodes of hypoglycemia due to inappropriate insulin production secondary to hypertrophy and hyperplasia of pancreatic beta cells.[54] These effects of GLP-1 on glucose homeostasis have largely influenced the development of GLP-1 analogues such as exanitide and liraglutide which are currently in use as anti-diabetic medications.[55] Oxyntomodulin is a molecule also produced by L cells and acts as an agonist at GLP-1 receptors, exerting similar effects as described above.

Observations that post-operative levels of GLP-1 are also increased in patients undergoing SG,[23] a purely restrictive procedure, however suggests presence of additional mechanisms of increased GLP-1 other than enhanced delivery of nutrients to the distal gut. Further, this hypothesis was not supported by the experimental study by Rubino et al.,[11] as GJ, a procedure that enhances rapid delivery of nutrients to the distal gut did not result in the improvement in glucose tolerance. He noted that bypass of the proximal gut alone was necessary, and sufficient to improve glucose tolerance in the rats.[11] More research into the hindgut hypothesis is therefore warranted.

Conclusions

The gradation of T2DM resolution rates with different bariatric surgical procedures appears to be a function of the anatomical re-arrangements of the gastro-intestinal tract involved.[7] For instance, higher resolution rates have been reported in BPD (99%) and RYGB (84%) compared to restrictive procedures such as SG (47%),[12,56,57] depicting the crucial role of the surgical manipulations of the intestine. A proper understanding of the anatomical distribution of neuro-endocrine cells of the GI tract such as K and L cells in relation to key surgical landmarks such as the ligament of Treitz is important in enhancing the efficacy of the various surgical procedures for the treatment of T2DM.

In conclusion the key anatomical re-arrangements necessary for the resolution of T2DM include duodeno-jejunal exclusion (BPD, RYGB), decreased duodeno-jejunal food transit time (as in SG) and/or expedited delivery of nutrients to the distal ileum (BPD, RYGB). These modifications of the gastro-intestinal anatomy alter the secretion and function of the putative incretins GLP and GIP, therefore restoring the normal physiology of the entero-insular axis.

Author declaration

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