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The Role of Bariatric Surgery in the Resolution of Type 2 Diabetes Mellitus

Yasmin Khan

Clinical Points

- In obesity, type 2 diabetes mellitus is largely due to location of adipose tissue and the adipokines released from it. Weight management is usually the primary goal in controlling hyperglycaemia
- With the difficulties and limited achievement presented in non-surgical weight loss, bariatric surgery has become increasingly popular as it is more successful in alleviating obesity-related diseases and obtaining significant weight loss
- BPD, RYGB, VBG, and AGB are the four main bariatric procedures performed today, all of which involves a restrictive and/or malabsorportive component
- Evidence has demonstrated that the exclusion of the hormonally active foregut in BPD and RYGB is far more superior in obtaining glycaemic control than are weight loss and decreased caloric intake alone.
- Changes in the levels of gastrointestinal hormones following foregut exclusion in BPD and RYGB have led to the speculation of their involvement in the aetiology of type 2 diabetes

ABSTRACT

Obesity is a major risk factor for many diseases, most notably for type 2 diabetes. Due to this correlation, weight loss has been a primary objective in managing type 2 diabetes. Current medical weight loss therapies and programs have proved disappointing, presenting an increasingly frustrating problem for the obese and diabetic population. At present, bariatric surgery is the most effective treatment for obesity and type 2 diabetes by inducing significant, long-term weight reduction. The cornerstone for inducing weight loss in these procedures comprises elements of gastric restriction, malabsorption by means of bypassing the foregut, or a combination of both. Depending on the type of bariatric procedure, observation of euglycaemia has been found in 48% to 99% of cases following surgery, therefore proving to be far more superior in treating obesity and type 2 diabetes in comparison to nonsurgical methods. While weight loss may seem like the most reasonable explanation in the improved glycaemic control, several findings have suggested the involvement of other factors. Interestingly, the alterations of various gastrointestinal hormones imparted by the malabsorptive procedures appear to be the dominant feature in the resolution of type 2 diabetes. This article provides an overview of the various bariatric procedures and the physiological mechanisms that contribute to the weight loss and cure of type 2 diabetes after surgery.

INTRODUCTION

Type 2 diabetes, a non-insulin dependent form of diabetes, is one of the most common endocrine disorders that comprise approximately 90% of the 200 million diabetic patients worldwide[1,2]. Obesity is one of the primary factors contributing to the rise in type 2 diabetes and other life-threatening co-morbidities, all of which are growing in parallel with one another[3-5] (Table 1). Initially, this problem was only a matter in the Western world. However, the prevalence of obesity and type 2 diabetes has become much more widespread, rapidly increasing in areas where the conditions have been infrequent [6-8].

Given the association of obesity and type 2 diabetes, effective weight management is a key component in preventing and treating both of these conditions[9]. Several short-term studies have demonstrated that a 5-10% weight loss improves glycaemic control and insulin sensitivity in overweight and obese subjects with type 2 diabetes[10]. A variety of medical (nonsurgical) weight loss therapies exist and have been successful through a combination of diet, exercise, behavioural management and anti-obesity medications[11-13]. However, long-term maintenance of this weight loss has proven to be difficult, especially for individuals with type 2 diabetes as compared to non-diabetic control subjects[14]. This unfortunate outcome may be due to the altered regulation in energy balance due to the effects of hyperglycaemia, or even related to the diabetes therapy itself since most forms of anti-diabetic medications promote weight gain[14]. Furthermore, despite evidence of reduced hyperglycaemia and complications related to type 2 diabetes, the mild weight loss achieved through medical treatment is not substantial enough to return patients to euglycaemia[15].

Bariatric surgery currently serves as the most successful method in achieving significant and long-lasting weight loss. It has proven to be far superior in ameliorating obesity-related diseases in comparison to the short-term mild weight loss obtained by medical treatment[16]. This outcome appears to have a profound effect on type 2 diabetes, completely resolving the disease in 76.8% of patients, and resolving or improving type 2 diabetes in 86% of patients[17]. Weight loss may seem like the most logical explanation for this outcome; however, there is leading speculation that these improvements may be directly attributed to anatomical changes presented by the operation itself and independent of weight loss. In an attempt to unravel this phenomenon, a closer look will be taken into the obesity and type 2 diabetes relationship, current bariatric procedures, and the mechanism of improved glycaemic control that follows bariatric surgery.

Table 1. *Obesity co-morbidities*

Cardiovascular • Coronary artery disease • Congestive heart failure • Hypertension • Hyperlipidemia ***Endocrine*** • Diabetes mellitus • Polycystic ovary syndrome ***Musculoskeletal*** • Arthritis • Gout ***Cancer risk*** • Colon • Prostate • Uterine • Breast	***Respiratory*** • Asthma • Sleep apnea • Obesity hypoventilation syndrome ***Neurologic and psychiatric*** • Migraine headache • Anxiety • Depression • Stroke ***Gastrointestinal and hepatobilary*** • Abdominal hernia • Gastroesophageal reflux • Nonalcoholic fatty liver diseases ***Hematopoietic*** • Deep venous thrombosis • Pulmonary embolism

Obesity and Type 2 Diabetes

Type 2 diabetes stems from a combination insulin resistance (IR), where the body fails to respond normally to insulin, and the inability of pancreatic beta cells to produce enough insulin to overcome this resistance[18]. While the direct correlation between obesity and type 2 diabetes has always been known, the exact mechanism of the association still remains indefinite.

For a long time, adipose tissue was thought to be an inert, non-active compartment. However, this view has been refuted with the recent discovery of a certain class of hormones released by adipose tissue called adipokines which play a key role in the regulation of appetite and metabolism[19]. Now known as an "endocrine organ," strong evidence exists showing that the amount of adipose tissue may directly contribute to type 2 diabetes by secreting various adipokines, which can also affect the body's sensitivity to insulin[19]. Levels of leptin, for example, are proportional to the amount of fat mass, which explains the elevated levels observed in obesity and the lower levels found upon weight reduction[20]. This adipokine acts by communicating with receptors in the hypothalamus to maintain fat stores at a certain level by means of reducing appetite and increasing energy expenditure[21]. In obesity, however, the effects of leptin are blunted due to the development of leptin resistance[21]. Suppressor of cytokine signalling 3 (SOCS3), an intracellular protein that limits leptin signalling, is likely to play a significant role in leptin resistance[22]. Interestingly, the expression of SOCS3 has been found to also dampen insulin signalling, providing a common point between obesity and type 2 diabetes[23].

The location of adipose tissue is also a large determinant of IR and type 2 diabetes. Visceral fat, as opposed to subcutaneous fat, contributes more to IR and is a prime indicator of health risk[24,25]. The relationship between visceral fat and type 2 diabetes has been demonstrated in the improvement of insulin sensitivity upon the surgical removal of visceral fat in obese Sprague-Dawley rats[26]. Moreover, Gabriely et al. observed different metabolic outcomes upon the excision of adipose tissue from different anatomical sites and found that the most dramatic improvements in insulin sensitivity came from the removal of visceral fat[27]. One of several reasons for this observation is the increased amount of free fatty acids (FFA) due to the enhanced lipolytic activity of visceral adipose tissue. FFA are directly delivered to the liver via portal circulation, acting as a toxic substance and interfering with the regulation of blood glucose levels by resisting the antilipolytic actions of insulin and inhibiting the metabolic breakdown of insulin by the liver[25,28].

Bariatric Surgery: an overview

Nowadays, increasingly more patients are turning towards bariatric surgery as a means for treating obesity. In the United States, the number of bariatric procedures performed has jumped from approximately 5,000 in 1990 to 63,000 in 2002, representing an almost 12-fold increase[29]. While the incidence is not nearly as high, Australia has also seen an estimated 7-fold rise in bariatric procedures from 399 in 1993 to 2992 in 2003[30]. The increasing trend of bariatric procedures can be attributed to the epidemic of obesity, unsatisfactory results obtained from medical treatments for obesity, and the recent advances that have made it a minimally invasive and safe procedure, particularly the application of laparoscopy[5,31].

Table 2 lists the requirements for a patient to become elected for bariatric surgery accordinf to the 1991 guidelines from the National Institutes of Health in the United States[32].

Table 2. *Criteria for Bariatric Surgery*

- Body mass index (BMI) ≥ 40 kg/m2, or BMI ≥ 35 kg/m2 with significant obesity-related disease
- Documented failure of nonsurgical attempt at weight-loss
- Clear understanding of how surgery causes weight loss
- Psychological stability
- Absence of uncontrolled psychotic or depressive disorder
- No active alcohol or substance abuse
- Pre-operative psychiatric evaluation of selected patients

The bariatric procedures performed today can be classified based on their design: intestinal malabsorption, gastric restriction, or a combination of both[3,5].

Malabsorptive operations involve reconstruction of the small intestine by shortening its length or by bypassing certain parts of the intestinal loop. This decreases the functional area of mucosa available for nutrient absorption, and resulting in less caloric absorption and therefore weight loss[5]. Nutrient deficiency is a large downfall of malabsorptive procedures, thus their use has been limited and modified to a great extent in order to reduce these complications[5,33]. Restrictive procedures limit the storage capacity of the stomach by creating small neogastric pouch. The effect of a smaller gastric pouch causes prompt filling by a small amount of food, thereby decreasing meal size, calorie intake, and inducing early satiety, which inevitably results in weight loss[5]. Metabolic complications are less common in purely restrictive procedures since they do not involve alterations in the nutrient absorptive component[5].

Bariatric surgery has greatly evolved from when it was first introduced in the 1950's by Mason, who performed the jejuno-ileal bypass (JIB)[34]. This was a strictly malabsorptive procedure that bypassed most of the absorptive small intestine (Figure 1A). Despite satisfactory results in terms of weight loss, the quantity and severity of the post-surgical complications have led to its abandonment[35]. Based on this experience, a number of bariatric operations have been devised to diminish postoperative complications and to provide patients with more options in achieving weight loss since each operation entails substantially different lifestyle modifications[36,37].

Biliopancreatic Diversion

The biliopancreatic diversion (BPD) was introduced by Scopinaro in the late 1970's and involves a primarily malabsorptive and small restrictive component (Figure 1B)[38]. Weight loss occurs from gastric restriction by a partial gastrectomy, and the diversion of biliopancreatic (bile and pancreatic) juice to the terminal ileum which significantly reduces nutrient absorption. BPD with a duodenal switch was later introduced in the 1990's to avoid the complication of marginal ulcer often seen in BPD alone (Figure 1C). Because this surgery has the greatest amount of anatomical restructuring, the occurrence of peri- and post-operative death is highest in this procedure[5,37].

The mean percentage of excess weight loss (%EWL) following BPD is approximately 75% and has shown to still be maintained at 8 years following the surgery. BPD with a duodenal switch also had comparable weight loss to BPD, but with fewer complications[39]. Substantial improvements in comorbidities have also been observed[40]. In comparison to other procedures, BPD allows patients to eat larger portions since they are left with a greater stomach volume, thereby obtaining weight loss primarily by malabsorption. However, additional therapy is required due to the several long-term complications that exist from its fairly considerable malabsorptive component[38,40]. This procedure is rarely performed nowadays and is mainly reserved for the severely obese (BMI $\geq$ 50 kg/m^2) [41].

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass surgery (RYGB) lacks popularity worldwide, but is the most common bariatric procedure performed in the US[41,42]. Similar to BPD, it incorporates both restrictive and malabsorptive characteristics, but is primarily restrictive. In this procedure, a surgical stapler is used to divide the stomach to form a small, proximal gastric pouch, which is anastomosed to the proximal jejunum in a Roux-en-Y fashion (Figure 2C)[33]. As with all restrictive procedures, the smaller gastric reservoir induced early satiety after a small meal[5], and the Roux-en-Y loop provides a moderate degree of malabsorption by bypassing approximately 95% of the stomach, the entire duodenum, and a small portion of the proximal jejunum[36,37].

By limiting the amount and rate of food ingestion and malabsorption, a 65-75% EWL is maintained at 2 years with a recidivism of 10-15% between 3 and 5 years postoperatively[17]. Durable weight loss has shown to last up to 14 years though[43]. Several long-term risks are associated with RYGB, and lifelong changes must be made in order to avoid complications. Due to the malabsorptive component of the operation, patients need to remain on a high protein, low fat diet, and take nutritional supplements to avoid metabolic deficiencies[37,44]. In addition to avoiding foods that may inhibit normal emptying of their gastric pouch, patients are advised to keep sweets to a minimum due to the risk of dumping syndrome. This is a common side effect that occurs with rapid emptying of the gastric pouch directly into the jejunum especially with the ingestion of carbohydrates, causing an osmotic overload which leads to nausea, palpitations, cramps and abdominal discomfort[45]. This unimpeded load can also contribute to hypoglycaemia by rapid release of insulin from the pancreas. Other complications include stenosis of the gastrojejunal anastomosis and marginal ulcers[37].

Vertical Band Gastroplasty

Vertical band gastroplasty (VBG) is one of two purely restrictive operations currently performed for weight loss. VBG consists of vertically partitioning the stomach by a surgical stapler to create a small proximal pouch, and placing a synthetic ring around the stoma for reinforcement (Figure 2A). This procedure is much easier to perform that BPD and RYGB, and post-surgical complications are less since digestion and absorption remain normal, thereby lacking nutritional deficiencies[37]. However, vomiting, band erosion, and increased severity of gastroesophageal reflux can occur[45].

In VBG, weight loss results from restricting the capacity of the stomach and thereby limiting food intake. Studies show a 30-50% EWL within the first 1-2 years, which is much lower than BPD and RYGB[39]. Due to instances of patient non-compliance, long-term results are also disappointing. Patients are often able to accommodate gastric restriction by eating more frequent small meals and calorie-dense foods[45]. It is to no surprise that an 80% failure rate is observed 10 years following VBG[46]. At this time point, only 20% of patients maintain a durable weight loss of at least 50%[46]. For this reason, VBG has become increasing unfavourable.

Adjustable Gastric Banding

Adjustable gastric banding (AGB) is a purely restrictive bariatric procedure and is one of the most frequent procedures performed in the bariatric realm, particularly in Europe and Australia[30,37]. Its popularity is most likely due to its minimal invasiveness, absence of anastomoses, adjustability and reversibility[31]. This approach involves placing a hollow silicone band around the upper part of the stomach, resulting in a small proximal gastric pouch that fills quickly and empties slowly (Figure 2B). The process of weight loss is similar to that of VBG, but has a further advantage of being able to modify gastric restriction by a simple, non-invasive office procedure that involves injecting or withdrawing saline solution from the hollow core of the band that is accessed via a subcutaneous access point (Figure 3). No other operation has this flexibility of tuning gastric restriction to meet the patient's needs[31]. Risks associated with the surgery are significantly less than all other bariatric procedures (30) and are mainly related to the band itself, specifically band slippage, band erosion into the stomach, and movement or leakage of the subcutaneous port[5,36].

With a good follow-up program, patients have been reported to lose up to 50-60 %EWL[17,47]. However, there is considerable variation of this result. Both Europe and Australia have reported excellent outcomes, which is contrary to the inadequate weight loss results in the US. Some studies in the US have reported a %EWL of 18% 3 to 18 months following surgery, prompting, in several cases, band-removal due to insufficient weight loss[48]. In a study by Chevallier et al., an observed %EWL of 50% at 2 years among French subjects has been documented[49]. Furthermore, Fielding et al. reported a 62% EWL in Australia[50]. The difference in the US results may be due to experience since it was only recently approved in 2001, whereas AGB has been an accepted and commonly practiced procedure in Europe and Australia since the 1980's[30,37,51]. Moreover, it is unclear if the poor results are due to differences in diet, lifestyle, or compliance with patients in the US[37]. AGB is slowly increasing in the US though, and their results have been getting increasingly similar to those achieved in Europe and Australia[52,53].

Mechanism of Diabetes Resolution Following Bariatric Surgery

Bariatric surgery not only induces significant and durable weight loss, but several cases have shown the improvement and complete resolution of type 2 diabetes. The degree of improvement of type 2 diabetes varies with operative procedure. According to a meta-analysis by Buchwald, diabetes was completely resolved in 99% of patients who underwent BPD and duodenal switch, 84% of RYGB patients, 72% of VBG patients, and 48% of AGB patients[17]. While the precise mechanism for this dramatic effect still remains unknown, hypotheses include decreased weight and food intake, and in the case of BPD and RYGB, bypass of the foregut[54].

At first, the level of type 2 diabetes resolution was thought to be attributed solely to the weight loss imparted by the bariatric operations. This may be true, given the relationship between adipokines and type 2 diabetes. However, several observations suggest that factors other than weight loss are likely involved. This is especially evident in BPD and RYGB which involve bypass of the hormonally active foregut. In the case of these two procedures, multiple studies have demonstrated an impressive observation of euglycaemia and normal insulin within days after surgery, long before any major weight loss has occurred[43,55]. Furthermore, the remission of their type 2 diabetes was far superior than that observed in those who had lost weight through diet alone[56]. Similar observations have also been made in a study by Hickey et al. where a group of obese women who underwent RYGB were compared to a control group of obese women. Both groups were matched for weight, age, percentage of fat, and BMI; and had maintained that weight for at least six months, thereby excluding weight loss as a variable. Despite similar characteristics, the surgical group ended up having lower fasting plasma glucose and higher insulin sensitivity compared to the control[55]. This suggests that in the case of BPD and RYGB, which both involve bypass of the foregut, there may be other factors that work alone or in conjunction with weight loss that contribute to the full remission of type 2 diabetes.

Decreased food intake has also been postulated to play a role in the remission of type 2 diabetes. If this were true, then VBG and AGB would be just as effective as BPD and RYGB because their surgeries also result in significantly reduced food intake. However, in comparison to RYGB, their effect in reducing hyperglycaemia is far inferior and evidence is lacking in the long-term cure of type 2 diabetes[57]. Furthermore, the eating capacity of BPD patients is much larger in comparison to all other bariatric procedures, yet glucose levels still remain under control[58]. Therefore, despite significant weight loss and decreased food intake imparted by VBG and AGB, the absence of foregut exclusion in these procedures suggests that this may be the very underlying feature that contributes to the superior control of glucose and insulin levels observed in BPD and RYGB[59].

One of the most convincing experiments that led to the discovery of the direct effect of gut exclusion on type 2 diabetes remission was a bypass surgery performed on Goto-Kakizaki rats by Rubino and Marescaux. With no significant change in food intake or weight loss, full remission of diabetes was observed[60]. Sugerman et al. also observed more profound changes in gut hormone profiles and greater resolution of type 2 diabetes following RYGB in comparison with VBG, which does not involve bypass whatsoever[61]. Furthermore, in a comparison between surgical and non-surgical subjects who were matched for BMI, surgical patients were found to have a noticeable decrease in both leptin and fasting glucose levels. Increased insulin sensitivity and decreased food intake were also observed[55]. These results suggest that the improved control of type 2 diabetes may not be secondary to weight loss or decreased caloric intake, but rather to the anatomical reconstruction from BPD and RYGB, specifically bypass of the hormonally active foregut.

Role of Gastrointestinal Hormones

Gastrointestinal hormones are responsible for controlling appetite and have a profound effect on insulin action and secretion upon the ingestion of food. The anatomical changes in the gut as a result of BPD and RYGB, in particular bypass of the foregut, may be a dominant factor in the beneficial effect on type 2 diabetes and weight loss by direct modification in the levels of these hormones.

Based on this observation, gastrointestinal hormones have been a new focus in elucidating the mechanism of type 2 diabetes resolution following bariatric surgery. Pories et al. hypothesized the possibility of a hormone in the foregut that causes type 2 diabetes by producing an abnormal signal from the gut to the pancreas that results in hyperinsulinaemia, inevitably leading to IR[56]. If type 2 diabetes is a disease of the foregut, then bypassing this region afforded by BPD and RYGB might explain the improvement and cure of type 2 diabetes following surgery in both of these cases.

Exclusion of the foregut may also induce the production of pro-insular hormones by expediting the delivery of nutrients to the hindgut[55,56]. Glucagon-like-peptide 1 (GLP-1), for example, is one of the most classic gut hormones known to have a potent effect on insulin secretion. GLP-1 is secreted in the ileum after food ingestion to facilitate nutrient absorption by inhibiting gastric emptying, food intake and insulin secretion. All of these characteristics have been observed upon the intravenous or subcutaneous administration of GLP-1 in subjects with type 2 diabetes[62]. The low levels found in patients with type 2 diabetes may possibly be attributed to this gut hormone[62]. Several studies have observed the rise in levels of GLP-1 after BPD and RYGB along with the improvement and resolution of type 2 diabetes[63], which dramatically increase GLP-1 levels and insulin secretion as a result, leading to the improvement of type 2 diabetes[64,65].

In review, the characteristic bypass involved in BPD and RYGB appears to be a key factor in euglycaemia in bariatric patients with type 2 diabetes. While this effect is known to be attributed to the changes in gastrointestinal hormones, their exact mechanism of action still remains in a grey area. Consequently, further investigation needs to be carried out to elucidate their function and possibly identify any other gastrointestinal hormones that may be involved in glucose metabolism, along with how physically excluding the foregut affects these hormones.

CONCLUSION

Type 2 diabetes is one of the most prevalent co-morbidities associated with obesity. With the number of cases of both increasing worldwide, much of today's focus remains on finding an effective prevention and treatment for these two conditions. Weight loss has been the mainstay of medical therapies for type 2 diabetes, but results have shown to be inadequate in achieving significant and long-term weight loss. Many have turned towards bariatric surgery as a result, which has proven to be a much more successful method in providing consistent and durable weight loss. Furthermore, a large proportion of bariatric patients with type 2 diabetes have been cured as a result of the operation. Even though all bariatric procedures result in improved weight loss and diabetes control in comparison with conservative methods, BPD and RYGB offer superior weight loss and resolution of diabetes. With weight loss aside, bypass of the foregut involved in both of these procedures seems to be the main characteristic in inducing this dramatic effect, resulting in a change in the level of gastrointestinal hormones that may have a vital component in the aetiology for type 2 diabetes. More studies are needed to fully elucidate the mechanism to gain a further understanding of the pathophysiology of type 2 diabetes and as their potential as drug targets for anti-diabetic medications.

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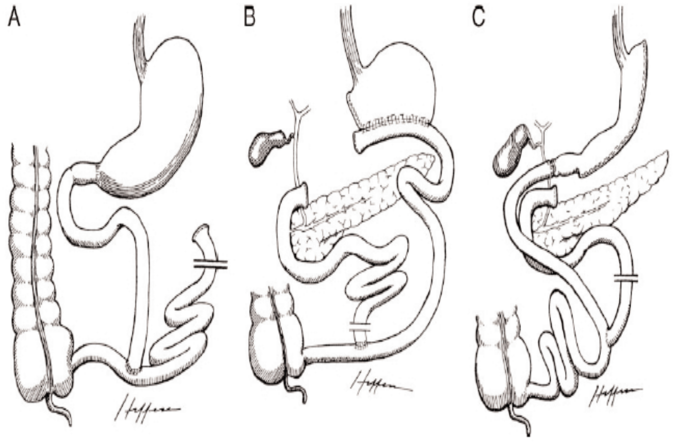

Figure 1. A - Jejunoileal bypass; B - Biliopancreatic diversion; C - Biliopancreatic diversion with duodenal switch. (32)

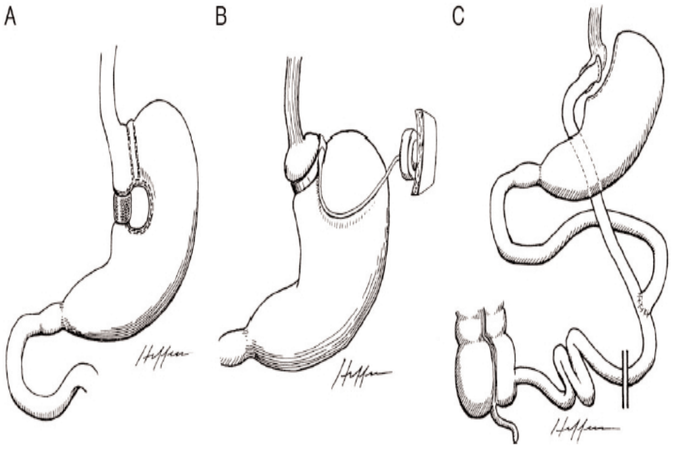

Figure 2. A - Vertical banded gastroplasty; B - Adjustable gastric banding; C. Roux-en-Y gastric bypass. (32)

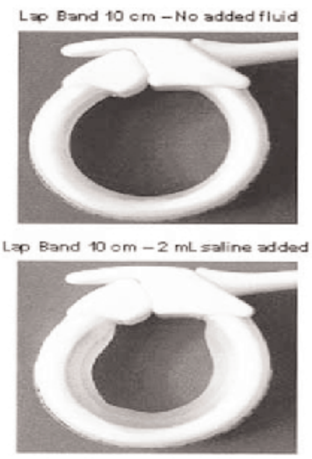

Figure 3. One common type of band used in adjustable gastric banding, with and without added saline. Note the decreased area within the band (30).

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