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Surgical Treatment of Obesity

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The surgical treatment of obesity has existed for over 50 yr. Surgical options have evolved from high-risk procedures infrequently performed, to safe, effective procedures increasingly performed. The operations used today provide significant durable weight loss, resolution or marked improvement of obesity-related comorbidities, and enhanced quality of life for the majority of patients. The effect of bariatric surgery on the neurohormonal regulation of energy homeostasis is not fully understood. Despite its effectiveness, less than 1% of obese patients are treated surgically. The perception that obesity surgery is unsafe remains a deterrent to care.

Key Words: Morbid obesity; gastric bypass; adjustable gastric band; treatment outcome; gastroplasty; jejunoileal bypass.

Surgical Treatment of Obesity

Many obese patients are able to lose significant amounts of weight but most are unable to sustain their weight loss *(1–4)*. The efficacy of conservative treatments has perhaps been difficult to accurately ascertain. Trials of medical interventions are plagued by high patient dropout rates and lack of long-term data. Bariatric surgery, while invasive, does afford significant weight loss, long-term weight loss maintenance, improved quality of life, decreased incidence of disease, and decreased mortality *(5–8)*. The evidence for surgery as a superior obesity treatment is sufficiently compelling to question the value of a randomized prospective trial testing medical vs surgical intervention. Such a trial may not be ethically appropriate for patients with body mass index (BMI) >40 kg/m^2, although it may be for lower BMI ranges.

This article gives basic history with descriptions of bariatric procedures. Procedure advantages, disadvantages, short-term morbidity, and mortality are stated. Potential advantages of a particular operation for certain subsets of obese patients are presented. Effects of each procedure on the endocrine system are discussed. Diabetes, glucose intolerance, polycystic ovarian syndrome, hyperparathyroidism, osteoporosis, and satiety are highlighted. Finally, unanswered questions are summarized.

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History of Obesity Surgery

Bariatric surgery has gone from a practice endeavored by few clinicians to now common and widespread. The change has come about because of the increased prevalence of obesity and newer safer surgical procedures. High impact technical developments led to the ability of surgeons to perform minimally invasive bariatric operations. The laparoscopic approach decreased certain short- and long-term complications of surgical intervention. Postoperative pain, pulmonary complications, incidence of wound infection, and incidence of incisional hernia are significantly decreased *(9–12)*. In 2001 the FDA approved use of adjustable gastric bands. The placement of laparoscopic adjustable gastric bands (LAGB) yields lower perioperative mortality than laparoscopic gastric bypass (GB) or laparoscopic biliopancreatic diversion (BPD) without or with duodenal switch (BPD/DS). Now many general surgeons, instead of only obesity specialty surgeons, are able to treat obesity safely.

In the United States and Canada, 103,000 bariatric operations are performed annually (2002–2003 data) *(13)*. This number represents over two-thirds of bariatric operations preformed yearly worldwide. Of these procedures, GB is by far the most common, with LAGB 9%, BPD/DS 2%, and vertical banded gastroplasty (VBG) 1.4% of the total. Approximately 66% of all bariatric procedures are done laparoscopically with the remaining done by the traditional open method. A minority of patients with previous bariatric procedures have been revised to either a GB or LAGB.

The total number of procedures in the United States represents estimated treatment of as little as 0.06% of all obese patients who meet the accepted criteria for surgical treatment *(14)*. One concern that limits surgical intervention is safety. Although the immediate postoperative death rate of bariatric surgery is low, the requirement for rehospitalization is high, indicating complication rates up to 40%. Obesity surgery is perceived as a high-risk elective procedure.

Table 1
Anatomical and Physiological Characteristics of Bariatric Operations

	Type	Pouch size (cm^3)	Stoma size (diameter, cm)	Biliopancreatic limb length (cm)	Roux/alimentary limb length (cm)	Common channel length (cm)	Fat absorption
Jejunoileal bypass (JI) *(146)*	Malabsorptive	None	Pylorus intact	Duodenum and first 36 cm of jejunum are intact, in continuity		10 cm of distal ileum	15% *(147)*
Vertical banded gastroplasty (VBG)	Restrictive	15–40	1.1	Small intestine unaltered	Small intestine unaltered	Small intestine unaltered	97%
Gastric bypass (GB)	Restrictive/ malabsorptive	15–30	1–1.5	30–45	75–150	Jejunum and ileum	62% *(23)*
Adjustable gastric band (LAGB)	Restrictive	10–15	Adjustable	Small intestine unaltered	Small intestine unaltered	Small intestine unaltered	97%
Biliopancreatic diversion (BPD)	Restrictive/ malabsorptive	100–500	≥1	Duodenum, jejunum, and proximal ileum	200–300 distal ileum	50–100 ileum	19%
Biliopancreatic diversion with duodenal switch (BPD/DS)	Restrictive/ malabsorptive	100–200	Pylorus intact	Duodenum, jejunum, and proximal ileum	150–350 distal ileum	50–100 ileum	19%

The risks and complications of surgical treatment may lessen in the hands of skilled surgeons at high volume centers *(7,15)*.

Obesity Operations

Bariatric procedures are categorized into restrictive, malabsorptive, or combined restrictive/malabsorptive (Table 1, Fig. 1). History of obesity surgery dates back to the 1950s when the fated jejunoileal bypass (JI) was introduced *(16)* and subsequently abandoned because of intolerable complications including metabolic derangements *(17)*. Malabsorption of nutrients and subsequent weight loss was a direct result of ingested food bypassing 90% of the small intestine and a learned response of diminished food intake to avoid side effects *(18)*.

Postoperative pathology arose from overgrowth of bacteria in the bypassed limb or decreased nutrient absorption. Vitamin deficiencies and electrolyte imbalances were difficult to manage. Death from liver failure was unacceptably high *(19)*. Complications such as nephrolithiasis, severe diarrhea, fever, and impaired mentation were relatively common. Despite its high morbidity and mortality, JI had excellent weight loss and was performed with minor variations for 20 yr *(20)*. JI is the prototype malabsorption procedure *(21)*. The hazards of JI gave rise to the development of safer effective procedures.

GB, the direct descendent of gastric resection for cancer or ulcer disease, was developed in the 1960s *(22)* and has endured. The idea of GB as a treatment for obesity was conceived by observed postoperative weight loss in gastrectomy patients. GB is a hybrid restrictive/malabsorption procedure. Restriction (of oral intake) occurs with creation of a gastric "pouch." The pouch volume is approximately 15–30 cm or 10% of the native stomach. Stretch on the pouch wall with a small volume of food leads to early satiety. Satiety is sustained because the pouch outlet to the jejunum is small enough to slow the emptying of solid foods. Malabsorption (62% ingested fats absorbed, 150 cm roux limb) also contributes to weight loss *(23)*. GB was quickly adopted as its complication rate was superior to the JI. Side effects such as the dumping syndrome, and iron, B12, or calcium deficiencies are mostly manageable with restriction of refined carbohydrates and vitamin and mineral supplementation, respectively. Laparoscopic GB is technically difficult to perform and requires advanced surgical skills to optimize perioperative morbidity and mortality *(24,25)*. Weight loss outcomes are greater than 50% excess body weight loss (EBWL) at 14 yr *(26)*. The short-term morbidity is 0.14–4% and mortality is 0.4–1.9% *(11,27)*.

VBG, a purely restrictive procedure was developed in the early 1970s *(28,29)*. Through use of a vertical pouch with a small synthetically reinforced outlet, early and sustained satiety is achieved. Advantages of the VBG are that it is relatively easy to perform and a patient's anatomy largely remains intact. Side effects of VBG were less severe than the JI bypass but still troublesome. Reoperation is required

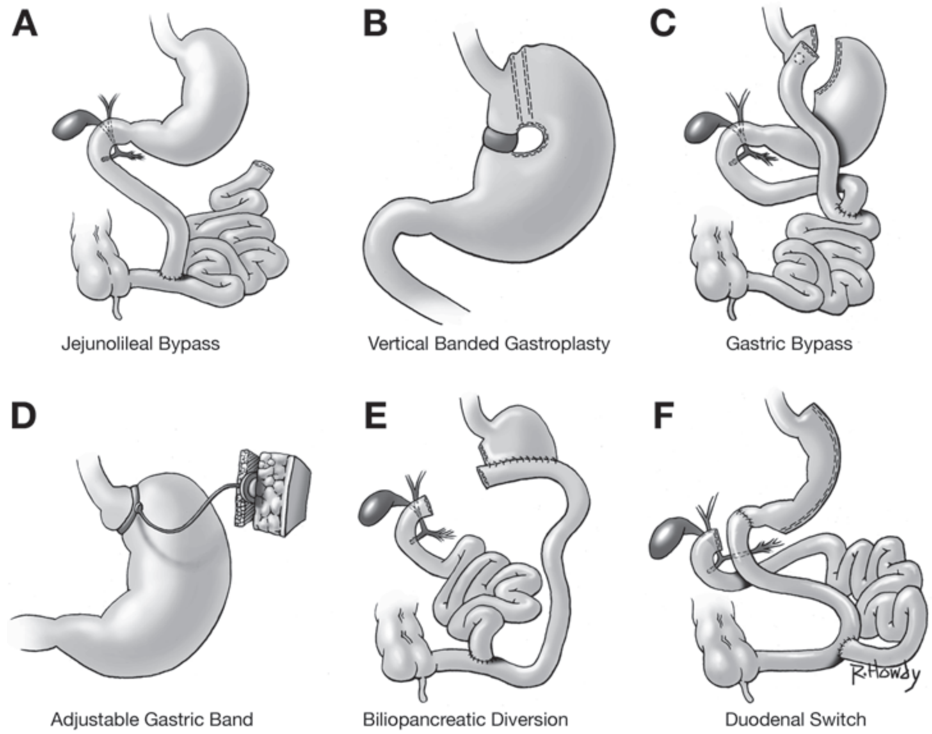

Fig. 1.

in up to 43% of patients for stenosis or break down of the gastric stapled partition *(30)*. A fistula between pouch and remnant (stapled partition breakdown) leads to weight gain or *de facto* reversal of the gastroplasty. Gastric pouches may also distend and lose their restrictive mechanism for weight loss. Although initial weight loss was acceptable, weight loss maintenance was inferior to that of the gastric bypass *(30,31)*.

A 1991 consensus statement issued by the National Institutes of Health endorsed both GB and VBG as effective weight loss operations *(32–34)*. Prospective randomized controlled trials later showed GB to have significantly greater %EBWL long term *(35)*. The vertical banded gastroplasty was then performed less often. The development of a laparoscopic approach to gastric bypass was first reported in 1994 *(36)* and became the most common bariatric procedure in the United States.

Next generation malabsorptive procedures sought to improve the jejunoileal bypass by eliminating the blind intestinal loop that gave rise to complications. BPD reported on in 1979 *(37)* and DS reported on in 1993 *(38)* accomplish weight loss predominately by restricting absorption of fat to a 50 cm common channel and absorption of protein and carbohydrates to a 250 cm common channel. Both operations minimize protein malnutrition to less that 7% *(39)*. These operations are favored by the surgeons who developed them and have not seen widespread adoption in the US. %EBWL mean at 8 yr is >70%, but side effects of diarrhea, flatulence, anemia, stomal ulcers, and bone demineralization are disadvantages *(39)*. In experienced hands the short-term mortality is 0.4%.

In the early 1990s, in Australia and Europe, LAGB was performed. The initial non-adjustable gastric band was likened to VBG and thought to have inferior weight loss to gastric bypass. Instead of creating a small volume pouch by partitioning the stomach with a stapler, the pouch is created by placing a silicone belt around the proximal stomach and cinching it. LAGB enables patients under caloric restriction to experience early and sustained satiety from a restricted gastric pouch and outlet *(40)*. The small outlet from the pouch, maintained with band fluid adjustments, sustains satiety by slowing pouch emptying. Weight loss with LAGB is more gradual than with GB.

When the gastric band was approved for use in the US in 2001, many health insurance companies would not reimburse for what they deemed an experimental procedure. There were no substantive clinical trials in the United States evaluating LAGB. Large clinical outcome studies did exist in Australia and Europe *(41,42)*. Now the use of LAGB in the US is rising exponentially. Comparative and case series studies show slower but still significant weight loss vs GB. Beyond 36 mo postoperative, weight loss may be comparable to that of GB *(43)*.

GB carries a median morbidity of 11% and mean mortality of 0.05% *(44)*. Mortality of LAGB is the lowest of the obesity surgical procedures. Although reversing any bariatric operation is advisable only under extraordinary circumstances, LAGB has the advantage of relatively easier removal. At any time fluid can be drained from the band rendering the stoma ineffective at slowed pouch emptying with subsequent loss of enhanced satiety. Reversal of any bariatric procedure leads to weight regain such that reversibility should not be considered in the decision of which operation to choose. Long-term and/or high-quality studies of LAGB relative to GB are still lacking in the US *(44)*.

Finally, two obesity treatment procedures are currently in clinic trials. The intragastric balloon, which is placed endoscopically, acts to induce early satiety and, along with calorie restriction, weight loss. Preliminary findings in 111 patients undergoing a 6-mo trial of intragastric balloon treatment showed a %EBWL of 44.9% *(45)*. Patients had an average BMI of 33 kg/m^2. The indicated length of treatment is only 6 mo, at which time the balloon is removed and the patient is subject to weight regain. This is the second appearance of the intragastric balloon as a treatment modality. A previous study in 1991 *(148)* revealed no weight loss benefit when trialed against a sham arm. (Mathus-Vliegen, E. M., et al. (1991). *Gastroenterology* **100(3),** 387–388.)

Implantable gastric stimulation induces early satiety and reduces appetite by altering electrical impulses in the muscular layer of the gastric wall. European trials have shown inconsistent weight loss results *(46)*. These trials were conducted on small numbers of patients and were not standardized. Currently, there are two US trials underway to better delineate the risks and efficacy of implantable gastric stimulation *(47)*.

Efficacy of Bariatric Surgery: Are Comorbidity Improvement Outcomes Secondary to Weight Loss or to the Operation Itself?

Medical weight loss interventions can lead to resolution of diabetes and other obesity comorbidities. Although patients often have a goal of attaining ideal body weight *(48)*, it is recognized that 5–10% weight loss, if maintained, may be adequate to resolve diabetes, dyslipidemia, and hypertension *(49–51)*. Other nonendocrine common comorbidities such as joint pain or obstructive sleep apnea require greater weight loss before improvement occurs *(52–55)*. When patients are successful at attaining adequate weight loss by lifestyle and behavioral interventions, they are unable to maintain it *(56)*. Generally, weight loss must be sustained to retain health benefits. Successful patients maintain a 5–10 kg weight loss for 2 yr but follow-up beyond 2 yr is lacking *(57,58)*. With aging, patients experience worsening insulin resistance *(59)*, and may require a greater percentage of weight loss to maintain resolution of diabetes.

Surgical intervention brings long-term weight loss to obesity treatment. Weight loss maintenance after surgery is superior to behavioral, lifestyle, and pharmacological interventions *(8,60)*. As a tool, surgery gives patients the opportunity to achieve >50% EBWL long term. Is it just caloric restriction or is it a new physiology from rearranged anatomy that fosters this phenomenon? Neuroendocrine changes of uncertain clinical importance occur after surgery and vary with procedure.

Weight loss from surgery that excludes the gastric antrum, duodenum, and proximal jejunum affords additional hormonal changes that can normalize blood glucose, and induce anorexia. Resolution of diabetes soon after GB and BPD/DS occurs even before the significant weight is lost *(61–63)*. These endocrine changes are different than those seen with LAGB. Although a proximal pouch is made, LAGB leaves the foregut intact in its native configuration. LAGB mimics the hormonal state described in prolonged low-calorie diets.

While obesity surgery leads to improvement or resolution of comorbidities, there are also potential negative endocrine consequences. Malabsorption procedures disrupt the balance of calcium and vitamin D, leading to potential stimulation of parathormone (early) and osteoporosis (late).

What Patient Should Have Which Procedure?

All presently used bariatric operations result in significant long-term weight loss in the majority of patients. Therefore, any obese patient will potentially benefit from any procedure. Comorbidities of obesity such as type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, etc., resolve or improve as weight is lost. Patients may have strong preferences for a procedure based on anecdotal information gleaned by word of mouth or the internet. Are individual procedures more efficacious in certain subsets of obese patients? In the case of patients with type 2 diabetes and hyperlipidemia, possibly. There is no agreement that one operation is preferred over another. Studies have partly addressed which procedures optimally benefit diabetics, the superobese, adolescents, or binge-eaters. Efforts are hindered by lack of technical standardization, lack of long-term follow-up, and lack of delineation of mechanism of action.

Endocrine changes brought on by these procedures differ depending on whether or not the stomach is divided and blocks food from contact with the distal stomach and proximal small intestine. Enteroglucagon, insulin-like growth factor-1 (IGF-1), and glucagon like protein-1 (GLP-1) increase, while leptin levels decrease under these anatomical conditions. The new hormone levels appear to improve insulin sensitivity and decrease its secretion. Both GB and BPD/DS have shown 67–100% cure of diabetes *(64)*. Diabetes, glucoses intolerance, and polycystic ovarian syndrome, the comorbidities that have decreased insulin sensitivity as an etiological factor may have greater improvement or resolution with GB or BPD/DS.

The degree of nutrient malabsorption specific to each operation effects lipid and calcium levels to different degrees. A patient's risk of cardiovascular disease may decrease best with the operation that affords the greatest weight loss. A patient with or at high risk for osteoporosis may be better served by a restrictive procedure that ensures normal absorption of calcium and vitamin D. Patients with eating-behavior disorders may do better when caloric restriction is not as critical to weight loss success, as occurs with the malabsorptive procedures.

In patients with high perioperative risk (elderly or high BMI), the least invasive procedure may be advantageous alone or as a bridge to a second procedure. Patients who are superobese (BMI>60) or high BMI and with multiple comorbidities can undergo sleeve gastrectomy as a first step to lose weight. Initial weight loss may then decrease their perioperative mortality risk with subsequent BPD *(65)*.

Adolescents are not adults, and while it is not valid to extrapolate from adult bariatric studies, randomized controlled trials have not been conducted in this younger age group. Current research, although limited, shows promising outcomes with GB and LAGB *(66,67)*. Obesity is rising at a greater rate in the pediatric vs the adult population, thus there is a need for scientific data to formulate treatment decisions. Adolescents may be appropriate candidates for surgery once properly screened. Compliance problems with long-term exercise (76% are not routinely active) and postoperative diet (74% eat high fat snacks between meals) may develop *(67)*. LAGB does offer a safety advantage with relatively lower morbidity and mortality. A potential compliance disadvantage with the LAGB is the need for follow-up every 6–8 wk to ensure weight loss success *(68)*. Adolescents may experience greater benefits in comorbidity resolution because of earlier surgical intervention *(69)*. The question, do obesity health risks in the teenage years justify an operation or can that decision be delayed without undo harm until an individual is an adult and able to make an informed decision, has not been clearly answered *(70)*.

Again, obesity surgery should not be thought of as reversible except when deteriorated health justifies the surgical risk. If necessary, the restriction of a LAGB can be significantly reduced or reversed without reoperation. The surgical removal of the LAGB is potentially a shorter, less risky procedure than revising a GB or BPD. The LAGB also offers the benefit of minimal morbidity and mortality. Adolescents, like adults, must be willing to comply with long-term bimonthly clinic visits to ensure good weight loss outcome.

Endocrine Consequences of Bariatric Surgery

Diabetes and Glucose Intolerance

Weight loss and physical activity improve insulin sensitivity *(71,72)* and prevent type 2 diabetes in patients with glucose intolerance *(69,73,74)*. Unfortunately, weight loss, exercise, behavior modification, oral hypoglycemic agents, or insulin, rarely return patients to euglycemia *(75)*. Bariatric surgery accomplishes euglycemia and is the only known intervention to do so. The normalization of fasting blood glucose levels and insulin sensitivity happens after GB and BPD before significant weight loss occurs. Morbidly obese patients with type 2 diabetes (n = 146) or with impaired glucose tolerance (n = 152), who underwent GB, achieved normal levels of plasma glucose, insulin, and glycosylated hemoglobin (83% diabetic patients, 99% glucose intolerant patients) *(26)*. These normalized values occurred within 4 mo. After significant weight loss and maintenance of a plateau weight, patients may still be obese and yet their diabetes does not return.

Type 2 diabetes resolves in 67–98% of patients after obesity surgery *(5,26,62,76–78)*. The resolution is superior after GB or BPD compared to VBG or LAGB *(39,79,80)*. The mechanism of diabetes resolution in the long term is thought to be caloric restriction and/or weight loss. The mechanism of immediate correction of diabetes is thought to be simple caloric restriction, or, in bypass procedures, endocrine changes brought about by changes in gut anatomy. The hormonal effect post GB and BPD is an area of active research involving, in part, changes in enteroglucagon, GLP-1, IGF-1, leptin, plasma protein YY, and ghrelin. In malabsorptive procedures the rapid presentation of undigested food to the distal ileum stimulates secretion of peptides that inhibit gastrointestinal motility, cause satiety, and are insulinotropic *(34,81)*. The L-cells in the ileum produce enteroglucagon and GLP-1 *(82,83)*. Levels of enteroglucagon and GLP-1 increase post GB and BPD *(84,85)* causing increased insulin production and improved insulin sensitivity *(86,87)*. IGF-1, similar to insulin, has a potent hypoglycemic effect *(88)*. GB increases circulating levels of IGF-1 in morbidly obese patients with diabetes *(89)*.

Leptin, a hormone produced by adipocytes, also improves insulin sensitivity and decreases insulin levels *(90)*. Obese patients suffer from leptin resistance and have elevated levels of leptin *(90)*. Leptin levels generally correlate with BMI. After GB and BPD, before weight is lost, leptin levels decrease rapidly *(77,84,91,92)*. It is thought, but not definitively known, that bypassing the foregut corrects leptin resistance, which enhances leptin-induced fatty acid oxidation and glucose uptake *(93)*. Ghrelin, produced in the gastric fundus and duodenum, is either decreased or inappropriately low after gastric bypass. Unlike leptin, ghrelin acts antagonistically in glucose metabolism by stimulating counter regulatory hormones (cortisol, epinephrine), and hindering insulin secretion *(94,95)*. The relative decrease in ghrelin levels post gastric bypass may enhance postprandial glucose metabolism.

Purely restrictive procedures such as LAGB, change the underlying levels of fasting plasma glucose and insulin sensitivity similar to the state found in low-calorie diets after weight loss. LAGB results in 40–66% resolution of diabetes at 3 yr postoperative *(5,96,97)*. The resolution of diabetes takes months to years to develop with LAGB compared to days to weeks with GB or BPD *(62,63)*.

Metabolic Syndrome

Fifty-two percent of obese patients seeking surgery meet metabolic syndrome criteria *(98)*. The syndrome is composed of hypertriglyceridemia, low high-density lipoproteins, hypertension, hyperglycemia, and central adiposity. The metabolic syndrome is a cluster of risk factors for development of coronary heart disease and type 2 diabetes mellitus *(92)*. These patients' metabolic derangements resolve 96% of the time by 1 yr post VBG or GB surgery *(98)*. High fat malabsorption leads to decreased levels of triglycerides and raises levels of high-density lipoproteins. These effects are seen even at 10 yr post BPD *(99)*. The improvement in high-density lipoproteins, low-density lipoproteins, and triglycerides may be related to increased insulin sensitivity or due to dietary changes alone *(100)*.

Satiety

Ghrelin, an endogenous ligand for the growth hormone receptor, stimulates the secretion of growth hormone. Ghrelin is synthesized primarily in the stomach *(101)*. When secreted, ghrelin acts on the hypothalamus to stimulate hunger and weight gain *(102,103)*. Plasma ghrelin levels increase with fasting and decrease with feeding. Ghrelin is part of the sophisticated neurohormonal system which works to maintain fat mass in the setting of short-term fluctuating energy balance *(104,105)*. Circulating ghrelin plasma levels are increased in states of cachexia or anorexia and decreased in obesity *(106,107)*. High levels of ghrelin stimulate appetite, low levels of ghrelin do not. It is postulated that the anorexia that accompanies GB is present because the stimulus for ghrelin has been removed by excluding the gastric fundus *(108)*. Evidence exists to refute this theory *(109)*. Of course, the synthesis of ghrelin may be controlled by redundant mechanisms.

Ghrelin secretion may require contact of the fundus with food. Ghrelin levels have been measured post GB with conflicting findings. Ghrelin levels have been found to both decrease *(108,110–112)* and increase *(113,114)*. These varied results may stem from surgical variables such as pouch size, roux limb length, or an intact vagus nerve *(109,115)*. Ghrelin levels may be influenced by the state of active weight loss vs stabilized weight *(114)*. Ghrelin levels either decrease overall or decrease post-meal after GB in most studies *(116, 117)*. LAGB, like dietary weight loss, stimulate increased ghrelin levels *(118)*. Despite elevated ghrelin levels patients with LAGB experience prolonged satiety evidently via a different mechanism *(119)*. BPD does retain some fundus in its pouch and, like LAGB, leads to an increase in ghrelin postoperatively.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility in women in the United States *(120)*. Although PCOS affects approx 6% of women *(121,122)* and has a high prevalence of obesity with its characteristic metabolic derangements *(123)*, few outcome analyses of have tracked its resolution post bariatric surgery.

Obese female patients with symptoms of PCOS may come to surgery without previous formal work-up or diagnosis. Because anovulation and infertility occur more frequently in obese women relative to normal weight controls *(124)*, patients may be prescribed weight loss instead of referred to specialists for infertility work-up. Improved preoperative data collection and PCOS based outcome measures in bariatric surgery are needed.

PCOS is marked by hyperandrogenemia and anovulation resulting in hirsutism, acanthus nigrans, amenorrhea, or infertility *(125)*. In obese patients with PCOS, weight loss can cure or ameliorate excess androgens and infertility. While obesity is not thought to cause PCOS *(126)*, a relationship that is not fully understood does exists between obesity and PCOS. In general, anovulation and infertility occur relatively frequently in obese women *(124)*. As a group, obese infertile women irrespective of infertility etiology, have improved reproductive outcomes with weight loss *(127,128)*.

Hyperinsulinemia and insulin resistance are key pathophysiologic factors in the development of PCOS *(120,121)*. Similar to obese patients, PCOS patients are at risk for development of the metabolic syndrome and type 2 diabetes *(123, 129)*. Also similar to obesity, insulin resistance and elevated insulin levels are not universal to PCOS *(130)*. The incidence of insulin resistance increases with increasing BMI in PCOS women *(131)*. Insulin levels bear a relationship to PCOS, which is different from that which is attributed just to BMI *(132)*.

Weight loss and very-low-calorie diets lead to the normalization of insulin levels and sensitivity; therefore, obesity surgery should lead to amelioration of PCOS. Additionally, it is possible that GB or BPD may better suit patients with PCOS. These procedures have the effect of increasing enteroglucagon/IGF-1 and GLP-1 levels, while decreasing leptin levels, leading to improved insulin sensitivity. With improved insulin sensitivity, hyperinsulinemia resolves. The normalization of insulin occurs prior to significant weight loss. Theoretical advantages of GB or BPD vs LAGB for treatment of PCOS have not been studied.

Calcium Homeostasis, Hyperparathyroidism, and Osteoporosis

Obesity has traditionally been thought to be protective against osteoporosis. Researchers have recently found, however, that obese restrained eaters are at risk for low bone mass *(133)*. Surgical weight loss candidates often have histories of chronic dieting and poor presurgical vitamin D status, and thus may be at risk for bone disorders even before surgery. Patients with a history of glucocorticoid use to treat comorbid conditions such as asthma , long term use of antiseizure medication, smokers, and those who have a history of fractures have additional risk worthy of consideration.

Postsurgically, significant weight loss coupled with calcium malabsorption or decreased dietary intake may put patients at risk for osteoporosis while disruptions in vitamin D metabolism may lead to osteomalcia. Evidence shows that weight loss can decrease bone mass and increase risk of fractures *(134)*. The mechanism of decreased calcium absorption in obesity surgery may be the result of decreased dietary intake (restrictive procedures), and decreased absorption. The duodenum and proximal jejunum are bypassed in GB and BPD and these are the sites where the bulk of calcium absorption occurs (malabsorptive procedures). Increased unabsorbed free fatty acids in the gut (malabsorptive procedures) complex with calcium and further decrease calcium available for absorption. Additionally, in malabsorptive procedures less dietary vitamin D is absorbed potentially decreasing promotion of calcium absorption *(135)*.

In GB the loss of gastric antrum acidity required for optimal calcium absorption also occurs. Supplementation with calcium requires consideration of the decreased acid environment. Calcium citrate may be more bioavailable and better absorbed in post-bypass patients than the more common calcium carbonate *(136,137)*. One study found that calcium citrate decreased markers of bone resorption in postmenopausal women *(138)* but this has not been repeated with GB subjects. Decreased body mass means decreased stimulus to the maintenance of adequate bone mineral density.

Parathormone (PTH) levels decrease with dietary weight loss in the morbidly obese *(139)*. PTH levels also correlate with BMI *(140)*. Although obese patients lose weight rapidly after GB, their PTH levels have been shown to increase. With weight loss after BPD/DS, PTH levels increase, 25-hydroxy vitamin D (25-OH D) levels decrease, and corrected calcium levels remain within normal limits *(141)*. Vitamin D supplementation in these patients did not correct either serum 25-OH D or PTH levels; however, questions have been raised regarding the amount of vitamin D supplementation required to significantly impact 25-OH D levels. PTH levels are also increased along with markers of bone resorption compared to controls in postmenopausal GB patients *(142)*. These metabolic aberrations did not correct with modest calcium and vitamin D supplementation. Bone mineral content in the femoral neck also decreased in these patients, yet findings of low bone mass after GB have been inconsistent in the literature. The use of lumbar bone mineral content may be an important consideration in defining risk *(133)*. Postmenopausal women, but not premenopausal women with primary hyperparathyroidism suffer a pattern of bone loss similarly seen pre- and postmenopausal after GB *(143–145)*.

Levels of calcium and vitamin D supplementation that are adequate to offset decreased levels in postmenopausal women after obesity surgery have not been established formally. Furthermore, the role of magnesium and other nutrients on maintaining PTH levels in bariatric patients has not been addressed. Studies that follow patients long term after their obesity surgery are necessary to assess whether secondary hyperparathyroidism leads to decreased bone density and increased fracture rates. Follow-up after 20 yr (n = approx 2000 patients) and 8 yr (n =747 patients) post BPD showed fracture rates of 2% per year, within the incidence range of the general population *(99)*. Patients who undergo surgical weight loss procedures should regularly be monitored for changes in bone mass.

Summary

The question of whether resolution of comorbidities is a result of weight loss alone or if it is a function driven by the operative changes in physiology is being explored. There is evidence for both mechanisms. Endocrine changes brought about by anatomical changes have yet to be fully described. Subsets of individuals may have better outcomes with a type-specific obesity operation. Overall the surgical benefits in weight loss, resolution of obesity induced comorbidities, decreased mortality, and enhanced quality of life are established. While bariatric surgery is not risk free, current procedures are relatively safe and subsequent benefits are unattainable by medical or lifestyle interventions.

References

1. McTigue, K. M., et al. (2003). *Ann. Intern. Med.* **139(11),** 933–949.
2. Yanovski, S. Z. and Yanovski, J. A. (2002). *N. Engl. J. Med.* **346(8),** 591–602.
3. Bray, G. A. and Tartaglia, L. A. (2000). *Nature* **404(6778),** 672–677.
4. Safer, D. J. (1991). *South Med. J.* **84(12),** 1470–1474.
5. Buchwald, H., et al. (2004). *JAMA* **292(14),** 1724–1737.
6. Christou, N. V., et al. (2004). *Ann. Surg.* **240(3),** 416–423; discussion 423–424.
7. Flum, D. R. and Dellinger, E. P. (2004). *J. Am. Coll. Surg.* **199(4),** 543–551.
8. Sjostrom, L., et al. (2004). *N. Engl. J. Med.* **351(26),** 2683–2693.
9. Nguyen, N. T., et al. (2001). *Ann. Surg.* **234(3),** 279–289; discussion 289–291.
10. Nguyen, N. T., et al. (2001). *J. Am. Coll. Surg.* **192(4),** 469–476; discussion 476–477.
11. Podnos, Y. D., et al. (2003). *Arch. Surg.* **138(9),** 957–961.
12. Puzziferri, N., et al. (2006). *Ann. Surg.* **243(2),** 181–188.
13. Buchwald, H. and Williams, S. E. (2004). *Obes. Surg.* **14(9),** 1157–1164.
14. Encinosa, W., et al. (2005). *Health Aff.* **24,** 1039–1046.
15. Liu, J. H., et al. (2003). *Am. Surg.* **69(10),** 823–828.
16. Kremen, A. J., Linner, J. H., and Nelson, C. H. (1954). *Ann. Surg.* **140(3),** 439–448.
17. Buchwald, H. and Rucker, R. D. (1987). In: *Surgery of the small intestine.* Nelson, R. L. and Nyhus, L. M. (eds.). Appleton Century Crofts: Norwalk, CT, pp. 529–541.
18. Bray, G. A., et al. (1976). *Am. J. Clin. Nutr.* **29(7),** 779–783.
19. Kroyer, J. M. and Talbert, W. M. Jr. (1980). *Am. J. Surg.* **139(6),** 855–859.
20. Halverson, J. D., et al. (1978). *Am. J. Med.* **64(3),** 461–475.
21. Payne, J. H. and DeWind, L. T. (1969). *Am. J. Surg.* **118(2),** 141–147.
22. Mason, E. E. and Ito, C. (1967). *Surg. Clin. North Am.* **47(6),** 1345–1351.

23. Gagner, M., et al. (2005). *Surg. Obes. Related Dis.* **1(3),** 240–241.
24. Nguyen, N. T., Rivers, R., and Wolfe, B. M. (2003). *J. Am. Coll. Surg.* **197(4),** 548–555; discussion 555–557.
25. Schauer, P., et al. (2003). *Surg. Endosc.* **17(2),** 212–215.
26. Pories, W. J., et al. (1995). *Ann. Surg.* **222(3),** 339–350; discussion 350–352.
27. Biertho, L., et al. (2003). *J. Am. Coll. Surg.* **197(4),** 536–544; discussion 544–545.
28. Printen, K. J. and Mason, E. E. (1973). *Arch. Surg.* **106(4),** 428–431.
29. Mason, E. E. (1982). *Arch. Surg.* **117(5),** 701–706.
30. MacLean, L. D., et al. (1993). *Am. J. Surg.* **165(1),** 155–160; discussion 160–162.
31. Lee, W. J., et al. (2004). *Obes. Surg.* **14(5),** 626–634.
32. Brolin, R. E. (1996). *Nutrition* **12(6),** 403–404.
33. NIH Conference (1991). *Ann. Intern. Med.* **115,** 956–961.
34. NIH (1992). *Am. J. Clin. Nutr.* **55(Suppl. 2),** 615s–619s.
35. Sugerman, H. J., Starkey, J. V., and Birkenhauer, R. (1987). *Ann. Surg.* **205(6),** 613–624.
36. Wittgrove, A. C., Clark, G. W., and Tremblay, L. J. (1994). *Obes. Surg.* **4(4),** 353–357.
37. Scopinaro, N., et al. (1979). *Br. J. Surg.* **66(9),** 618–620.
38. Marceau, P., et al. (1993). *Obes. Surg.* **3(1),** 29–35.
39. Scopinaro, N., et al. (1996). *Surgery* **119(3),** 261–268.
40. Thomusch, O., et al. (2005). *Am. J. Surg.* **189(2),** 214–218.
41. O'Brien, P. E., et al. (2002). *Obes. Surg.* **12(5),** 652–660.
42. Angrisani, L., et al. (2004). *Surg. Endosc.* **18(10),** 1524–1527.
43. Jan, J. C., et al. (2005). *J. Gastrointest. Surg.* **9(1),** 30–39; discussion 40–41.
44. Chapman, A. E., et al. (2004). *Surgery* **135(3),** 326–351.
45. Berry, M. A. and Urrutia, L. A. (2005). *Surg. Obes. Related Dis.* **1(3),** 255.
46. Cigaina, V. (2002). *Obes. Surg.* **12(Suppl. 1),** 12S–16S.
47. Shikora, S. A. and Storch, K. (2005). *Surg. Obes. Related Dis.* **1(5),** 334–347.
48. Foster, G. D., et al. (1997). *J. Consult. Clin. Psychol.* **65(1),** 79–85.
49. Blackburn, G. (1995). *Obes. Res.* **3(Suppl. 2),** 211s–216s.
50. Goldstein, D. J. (1992). *Int. J. Obes. Relat. Metab. Disord.* **16(6),** 397–415.
51. Pi-Sunyer, F. X. (1993). *Ann. Intern. Med.* **119(7 Pt 2),** 722–726.
52. Kopelman, P. G. (2000). *Nature* **404(6778),** 635–643.
53. Willims, R. A. and Foulsham, B. M. (1981). *Practitioner* **225 (1352),** 231–232.
54. Sugerman, H. J., et al. (1992). *Am. J. Clin. Nutr.* **55(2 Suppl.),** 597S–601S.
55. Charuzi, I., et al. (1985). *Surgery* **97(5),** 535–538.
56. Wadden, T. A. and Foster, G. D. (2000). *Med. Clin. North Am.* **84(2),** 441–461, vii.
57. Douketis, J. D., et al. (2005). *Int. J. Obes. (Lond.)* **29(10),** 1153–1167.
58. Beliard, D., Kirschenbaum, D. S., and Fitzgibbon, M. L. (1992). *Int. J. Obes. Relat. Metab. Disord.* **16(7),** 505–517.
59. Chang, A. M. and Halter, J. B. (2003). *Am. J. Physiol. Endocrinol. Metab.* **284(1),** E7–12.
60. Maggard, M. A., et al. (2005). *Ann. Intern. Med.* **142(7),** 547–559.
61. Pories, W. J. (2004). *Ann. Surg.* **239(1),** 12–13.
62. Schauer, P. R., et al. (2003). *Ann. Surg.* **238(4),** 467–484; discussion 84–85.
63. Scopinaro, N., et al. (1998). *World J. Surg.* **22(9),** 936–946.
64. Hess, D. S. and Hess, D. W. (1998). *Obes. Surg.* **8(3),** 267–282.
65. Milone, L., Strong, V., and Gagner, M. (2005). *Obes. Surg.* **15(5),** 612–617.
66. Sugerman, H. J., et al. (2003). *J. Gastrointest. Surg.* **7(1),** 102–107; discussion 107–108.
67. Rand, C. S. and Macgregor, A. M. (1994). *South Med. J.* **87 (12),** 1208–1213.
68. Shen, R., et al. (2004). *Obes. Surg.* **14(4),** 514–519.
69. Long, S. D., et al. (1994). *Diabetes Care* **17(5),** 372–375.
70. Inge, T. H., et al. (2005). *J. Pediatr.* **147(1),** 10–19.
71. Bogardus, C., et al. (1985). *Am. J. Physiol.* **248(3 Pt 1),** E286–291.
72. Olefsky, J., Reaven, G. M., and Farquhar, J. W. (1974). *J. Clin. Invest.* **53(1),** 64–76.
73. Eriksson, K. F. and Lindgarde, F. (1991). *Diabetologia* **34(12),** 891–898.
74. Tuomilehto, J., et al. (2001). *N. Engl. J. Med.* **344(18),** 1343–1350.
75. Detournay, B., et al. (2000). *Diabetes Metab.* **26(5),** 363–369.
76. MacDonald, K. G. Jr., et al. (1997). *J. Gastrointest. Surg.* **1(3),** 213–220.
77. Hickey, M. S., et al. (1998). *Ann. Surg.* **227(5),** 637–643; discussion 643–644.
78. Sugerman, H. J., et al. (2003). *Ann. Surg.* **237(6),** 751–756; discussion 757–758.
79. Greenway, S. E., Greenway, F. L. 3rd, and Klein, S. (2002). *Arch. Surg.* **137(10),** 1109–1117.
80. Rubino, F. and Gagner, M. (2002). *Ann. Surg.* **236(5),** 554–559.
81. Mingrone, G., et al. (1997). *Diabetologia* **40(5),** 599–605.
82. Orskov, C. (1992). *Diabetologia* **35(8),** 701–711.
83. Naslund, E., et al. (1999). *Am. J. Physiol.* **277,** R910–R916.
84. Sarson, D. L., Scopinaro, N., and Bloom, S. R. (1981). *Int. J. Obes.* **5(5),** 471–480.
85. Meryn, S., Stein, D., and Straus, E. W. (1986). *Int. J. Obes.* **10(1),** 37–42.
86. Mason, E. E. (1999). *Obes. Surg.* **9(3),** 223–228.
87. Muscelli, E., et al. (2005). *Am. J. Med.* **118(1),** 51–57.
88. Le Roith, D. (1997). *N. Engl. J. Med.* **336(9),** 633–640.
89. Poulos, J. E., et al. (1994). *Horm. Metab. Res.* **26(10),** 478–480.
90. Mantzoros, C. S. (1999). *Ann. Intern. Med.* **130(8),** 671–680.
91. de Marinis, L., et al. (1999). *J. Clin. Endocrinol. Metab.* **84(7),** 2386–2389.
92. Expert Panel. (2001). *JAMA* **285,** 2486–2497.
93. Muoio, D. M., et al. (1997). *Diabetes* **46(8),** 1360–1363.
94. Cummings, D. E. and Shannon, M. H. (2003). *Arch. Surg.* **138(4),** 389–396.
95. Broglio, F., et al. (2001). *J. Clin. Endocrinol. Metab.* **86(10),** 5083–5086.
96. Spivak, H., et al. (2004). *Surg. Endosc.* **18(2),** 198–202.
97. DeMaria, E. J., et al. (2001). *Ann. Surg.* **233(6),** 809–818.
98. Lee, W. J., et al. (2004). *Arch. Surg.* **139(10),** 1088–1092.
99. Marceau, P., et al. (2001). *Surg. Clin. North Am.* **81(5),** 1113–1127.
100. Yu-Poth, S., et al. (1999). *Am. J. Clin. Nutr.* **69(4),** 632–646.
101. Jeon, T. Y., et al. (2004). *J. Clin. Endocrinol. Metab.* **89(11),** 5392–5396.
102. Nakazato, M., et al. (2001). *Nature* **409(6817),** 194–198.
103. Shintani, M., et al. (2001). *Diabetes* **50(2),** 227–232.
104. Schwartz, M. W., et al. (2000). *Nature* **404(6778),** 661–671.
105. Woods, S. C., et al. (1998). *Science* **280(5368),** 1378–1383.
106. Tschop, M., et al. (2001). *Diabetes* **50(4),** 707–709.
107. Ariyasu, H., et al. (2001). *J. Clin. Endocrinol. Metab.* **86(10),** 4753–4758.
108. Fruhbeck, G., et al. (2004). *Obes. Surg.* **14(9),** 1208–1215.
109. Williams, D. L., et al. (2003). *Endocrinology* **144(7),** 2765–2767.
110. Cummings, D. E., et al. (2002). *N. Engl. J. Med.* **346(21),** 1623–1630.
111. Geloneze, B., et al. (2003). *Obes. Surg.* **13(1),** 17–22.

112. Tritos, N. A., et al. (2003). *Obes. Res.* **11(8),** 919–924.
113. Holdstock, C., et al. (2003). *J. Clin. Endocrinol. Metab.* **88(7),** 3177–3183.
114. Faraj, M., et al. (2003). *J. Clin. Endocrinol. Metab.* **88(4),** 1594–1602.
115. Cummings, D. E. and Shannon, M. H. (2003). *J. Clin. Endocrinol. Metab.* **88(7),** 2999–3002.
116. Lin, E., et al. (2004). *Arch. Surg.* **139(7),** 780–784.
117. Williams, D. L. and Cummings, D. E. (2005). *J. Nutr.* **135(5),** 1320–1325.
118. Stoeckli, R., et al. (2004). *Obes. Res.* **12(2),** 346–350.
119. Dixon, A. F., Dixon, J. B., and O'Brien, P. E. (2005). *J. Clin. Endocrinol. Metab.* **90(2),** 813–819.
120. Nestler, J. E., et al. (1998). *N. Engl. J. Med.* **338(26),** 1876–1880.
121. Nestler, J. E. and Jakubowicz, D. J. (1996). *N. Engl. J. Med.* **335(9),** 617–623.
122. Azziz, R., et al. (2004). *J. Clin. Endocrinol. Metab.* **89(6),** 2745–2749.
123. Ehrmann, D. A., et al. (1999). *Diabetes Care* **22(1),** 141–146.
124. Bolumar, F., et al. (2000). *Am. J. Epidemiol.* **151(11),** 1072–1079.
125. Franks, S. (1995). *N. Engl. J. Med.* **333(13),** 853–861.
126. Ehrmann, D. A. (2005). *N. Engl. J. Med.* **352(12),** 1223–1236.
127. Moran, L. J. and Norman, R. J. (2002). *Nutr. Clin. Care* **5(6),** 290–297.
128. Clark, A. M., et al. (1998). *Hum. Reprod.* **13(6),** 1502–1505.
129. Glueck, C. J., et al. (2003). *Metabolism* **52(7),** 908–915.
130. Ovalle, F. and Azziz, R. (2002). *Fertil. Steril.* **77(6),** 1095–1105.
131. Mor, E., et al. (2004). *Am. J. Obstet. Gynecol.* **190(6),** 1654–1660.
132. Dunaif, A., et al. (1989). *Diabetes* **38(9),** 1165–1174.
133. Bacon, L., et al. (2004). *Eur. J. Clin. Nutr.* **58(6),** 966–971.
134. Shapses, S. A. (2001). In: Nutritional aspects of osteoporosis. Burckhardt, P., Heaney, R., and Sawson-Hughs, B. (eds.). Springer-Verlag: New York, pp. 311–354.
135. Avioli, L. V. (1972). *Arch. Intern. Med.* **129(2),** 345–355.
136. Sakhaee, K., et al. (1999). *Am. J. Ther.* **6(6),** 313–321.
137. Heller, H. J., Poindexter, J. R., and Adams-Huet, B. (2002). *J. Clin. Pharmacol.* **42(11),** 1251–1256.
138. Kenny, A. M., et al. (2004). *Osteoporos. Int.* **15(4),** 290–294.
139. Compston, J. E., et al. (1984). *Gastroenterology* **87(2),** 350–356.
140. Bell, N. H., et al. (1985). *J. Clin. Invest.* **76(1),** 370–373.
141. Hamoui, N., et al. (2003). *Arch. Surg.* **138(8),** 891–897.
142. Goode, L. R., et al. (2004). *Obes. Res.* **12(1),** 40–47.
143. Silverberg, S. J., et al. (1989). *N. Engl. J. Med.* **320(5),** 277–281.
144. Dempster, D. W., et al. (1999). *J. Clin. Endocrinol. Metab.* **84(5),** 1562–1566.
145. Vogel, M., Hahn, M., and Delling, G. (1995). *Virchows Arch.* **426(2),** 127–134.
146. Buchwald, H., et al. (1975). *Curr. Probl. Surg.* 1–51.
147. Shibata, H. R., MacKenzie, J. R., and Long, R. C. (1967). *Arch. Surg.* **95(3),** 413–428.
148. Mathus-Vliegen, E. M., et al. (1991). *Gastroenterology* **100(3),** 387–388.