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Metabolic Effects of Bariatric Surgery

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BACKGROUND: Obesity can be defined as a chronic subcortical brain disease, as there is an important neurophysiological component to its etiology based on changes in the functioning of those areas of the brain controlling food intake and reward. Extensive metabolic changes accompany bariatric surgery-based treatment of obesity. Consequently, the term "metabolic" surgery is being increasingly adopted in relation to the beneficial effects these procedures have on chronic diseases like type 2 diabetes.

CONTENT: In the present review, we focus on the key biochemical and physiological changes induced by metabolic surgery and highlight the beneficial effects accrued systemically with the use of an organ-based approach. Understanding the impact on and interactions between the gut, brain, adipose tissue, liver, muscle, pancreas, and kidney is key to understanding the sum of the metabolic effects of these operations.

SUMMARY: Further mechanistic studies are essential to assess the true potential of metabolic surgery to treat metabolic comorbidities of obesity beyond type 2 diabetes. Approaches that may mitigate the metabolic side effects of surgery also require attention. Understanding the positive impact of metabolic surgery on metabolic health may result in a wider acceptance of this intervention as treatment for metabolic, comorbid conditions.

Bariatric surgery has evolved since its inception, with the use of advanced laparoscopic techniques leading to improved outcomes and safety. The procedures used in current clinical practice are the Roux-en-Y gastric bypass (RYGB)[4], vertical sleeve gastrectomy (VSG), and laparoscopic adjustable gastric banding, as well as the less commonly performed biliopancreatic diversion with duodenal switch.

Although these operations were originally developed to treat morbid obesity, the indications for their use have expanded as a consequence of the emerging evidence of their wider metabolic benefits. The myriad metabolic effects have indeed prompted the uptake of the new terminology of metabolic surgery to describe the benefits of a range of procedures, which derive as much from metabolic and cardiovascular gain as from weight reduction. In the present review, we focus on the key biochemical and physiological changes induced by metabolic surgery and highlight the beneficial effects accrued systemically and at the end-organ level.

Dysmetabolism in Obesity and the Effects of Metabolic Surgery

Recognition that obesity is a complex and chronic subcortical brain disease helps explain susceptibility, progression, and the overwhelming rate of long-term treatment failure using conservative diet and lifestyle-based approaches *(1)* wherein the body fat set point is increased and maintained by excess food intake. The "obesogenic" environment, which provides increasing ease of access to inexpensive and highly palatable high calorie foods, has facilitated the growth of obesity as a disease. Obesity can result in further stresses including insulin resistance, local and systemic inflammation, as well as oxidative cellular injury, which drive a deranged metabolic milieu *(2)*.

Metabolic surgery breaks the vicious cycles associated with this deranged milieu and leads to secondary improvements in the comorbid conditions of obesity such as type 2 diabetes. Underlying mechanisms include acute and sustained reductions in food intake, alterations in food preferences and reward, changes in energy expenditure, optimization of the incretin effect and glycemic control, as well as improved liver function and lipid homeostasis.

Organs Impacted by Metabolic Surgery and Metabolic Repercussions

Metabolic changes after surgery occur because of the impact on the gut, brain, adipose tissue, liver, muscle, pancreas, kidney, and bone. Many secondary benefits arise through the downstream effects on organs and organ systems from the primary metabolic improvements, thus

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[4] Nonstandard abbreviations: RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy; PYY, peptide YY; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PCOS, polycystic ovarian syndrome.

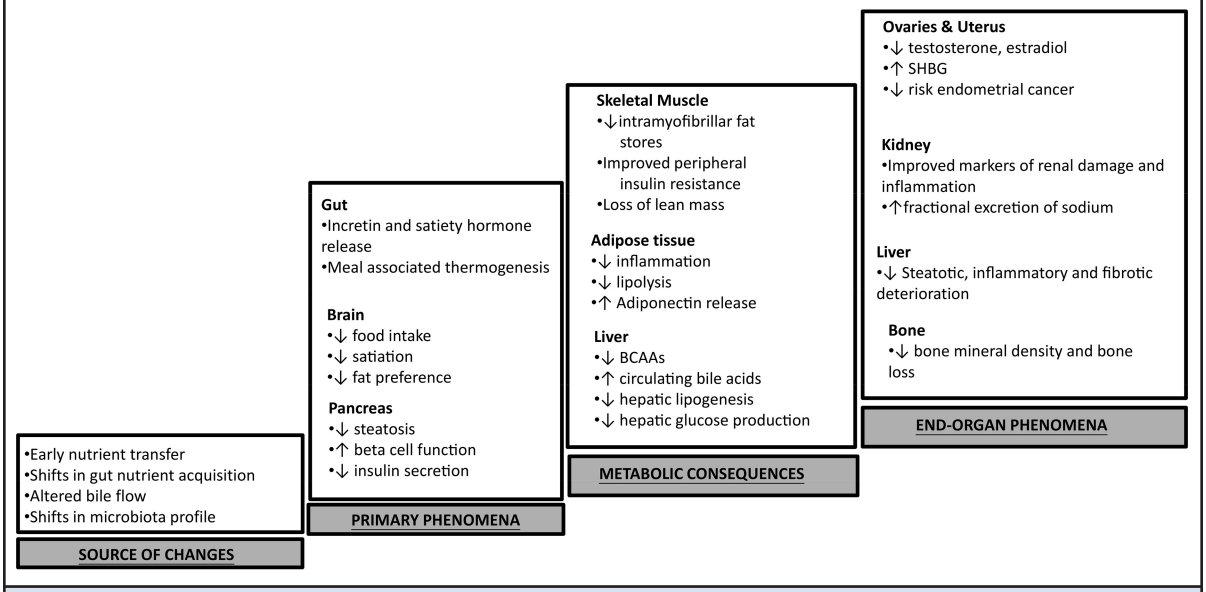

Fig. 1. Multilevel metabolic repercussions of RYGB.
BCAAs, branched-chain amino acids; SHBG, sex hormone-binding globulin.

creating an interreliant chain reaction of effects that on the whole have a positive impact on health (Fig. 1).

The Gut

Metabolic surgery involves surgical interventions on the stomach and/or small bowel. These anatomical alterations result in gut adaptation, which is responsible for many of the visceral signals that set off the chain of events observed after metabolic surgery.

The liver and skeletal muscle are considered the major players in glucose disposal. However, we now understand that the gut also has important roles in this regard. After RYGB, rats demonstrate gut remodeling with intestinal hypertrophy and crypt cell proliferation *(3)*. Saeidi et al. compared the metabolic profile of the Roux limb with the same jejunal segment in sham-operated rats and identified alterations suggesting increased glucose utilization, increased glycolysis, reduced or unchanged gluconeogenesis, and increased cholesterol uptake in the Roux limb *(4)*. Furthermore, fluorodeoxyglucose positron emission tomography studies were performed to confirm that glucose utilization was higher in the Roux limb compared to sham-operated jejunum, suggesting reprogramming of intestinal glucose metabolism to meet the increasing needs of the hypertrophic small bowel. Elsewhere, an increase in intestinal gluconeogenesis has been described in mice undergoing enterogastric anastomosis. This phenomenon has been linked to improvements in glucose homeostasis via a vagovagal glucose-sensing arc that stimulates insulin secretion *(5)*.

Although basal metabolic rate reduces after metabolic surgery in relation to the amount of weight lost, metabolic surgery has been associated with increases in meal-associated energy expenditure secondary to small bowel hypertrophy and recruitment of brown adipose tissue *(6, 7)*.

GUT HORMONES

Several enteroendocrine hormones known to increase after metabolic surgery are involved in promoting satiety and reducing food intake, including peptide YY (PYY), glucagon-like peptide-1 (GLP-1), cholecystokinin, gastrin, and gastric inhibitory peptide *(8)*. Many of these gut hormones also have satiety-independent metabolic effects.

GLP-1 and gastric inhibitory peptide are the 2 main "incretin" hormones, so named for their capacity to enhance glucose-stimulated insulin release. However, gastric inhibitory peptide has received less attention because it does not affect glucagon secretion, eating behavior, or appetite and is secreted from K cells in the proximal small intestine in response to small amounts of less-complex nutrients. This suggests that it may have a smaller contribution to glucose homeostasis than GLP-1, although it may have a greater role in lipogenesis *(8)*.

GLP-1 is an anorexigenic and glucoregulatory hormone secreted by the intestinal L cells and by the nucleus tractus solitarius of the brainstem. GLP-1 has been shown to increase glucose-dependent insulin secretion, insulin synthesis, β-cell proliferation, insulin sensitivity, cardioprotection, cardiac function, neuroprotection, and

satiety, while inhibiting hepatic glucose production, β-cell apoptosis, and glucagon secretion, as well as slowing gastric emptying and therefore the rate of absorption of nutrients *(9)*.

Oxyntomodulin (OXM) is another enteroendocrine hormone released from the L cell in response to nutrient influx to the gut. OXM can signal through both the glucagon receptor and GLP-1 receptor *(10)*, although the former reduces the beneficial glycemic effects of GLP-1 receptor activation. OXM has also been implicated in weight loss by increasing energy expenditure and reducing appetite and food intake *(11)*. OXM agonism of the GLP-1 receptor may activate alternative signaling pathways to GLP-1 *(12)*, and as such coagonism with GLP-1 has been considered as a therapeutic modality.

GLP-2, secretin, and cholecystokinin are also altered after metabolic surgery and have potential roles as part of the gut adaptation seen after these operations *(8)*. Ghrelin is orexigenic and known to increase appetite and food intake. Ghrelin may also be involved in suppressing glucose-stimulated insulin secretion and worsening insulin resistance *(13)*. However, its role after metabolic surgery remains unclear, as studies vary as to whether ghrelin increases, decreases, or remains unchanged *(14)*.

GUT MICROBIOTA

The gut microbiota is radically altered by bariatric surgery and transfer of gut microbiota from mice after RYGB to germ-free mice results in weight loss *(15)*. The implicated gut microbes are involved in extracting calories from carbohydrates by fermentation, and the resulting short-chain fatty acids serve both as a substrate for gluconeogenesis and lipogenesis *(16)*, but also as signaling molecules. Gut flora can also influence nutrient sensing and gut–brain signaling by altering the absorptive and secretory capacity of the intestinal epithelial cells *(17)*. This demonstrates a potential role for gut microbiota in influencing gut hormone secretion and gut–brain signaling postmetabolic surgery. Gut microbiota also have an interdependent relationship with bile acids. Bile acids affect microbiota composition by altering bacterial membrane integrity and potentially causing DNA damage or oxidative stress, while gut microbiota can alter bile acid synthesis and function.

Some gut microbes, such as *Lactobacillus* and *Bifidobacterium* species, have been directly linked to improvement in weight, metabolic status, and energy intake in rodent studies, an effect attributed to conjugated linoleic acid production, which has been shown to reduce body fat *(18)*. However, one study revealed a reduction in both *Lactobacillus* and *Bifidobacterium* species after RYGB in rats *(19)*, which may be attributable to different strains having differing effects on energy metabolism and body weight. *Faecalibacterium prausnitzii* increase after RYGB in rats and correlate with a reduction in inflammatory markers (C-reactive protein and interleukin 6) *(19)*.

Evidence in humans to date suggests that metabolic surgery alters not only the composition but also the functionality of the gut microbiota, which may enhance regulation of host metabolism *(20)*. Gut microbiota profiles are altered in humans, with a reduction in *Firmicutes* species and an increase in *Bacteroides (21)*; the latter has been associated with a reduction in body fat mass *(19)*. The exact role of gut microbiota after metabolic surgery requires further exploration.

The Brain

After RYGB, gut satiety hormones, including PYY and GLP-1, are increased and may act centrally to affect metabolism. GLP-1's effect is more complex than purely homeostatic regulation of food intake via the hypothalamus; it also contributes to reductions in hunger-driven feeding, the hedonic value of high-fat and high-sugar foods, palatability, and food motivation via its effect on dopaminergic reward pathways in the brain *(22)* and hypothalamic GLP-1 receptors *(23)*. When octreotide is used to block the gut satiety hormone responses, behavioral and brain reward pathways are altered with increased appetitive behavior, increased food appeal, and increased reward system blood oxygen level–dependent signals in functional MRI tests, which correlate with reductions in PYY and GLP-1 release *(24)*. Some evidence disputes whether GLP-1 is required for the appetite and metabolic effects of metabolic surgery, and it is likely that 1 hormone alone is insufficient. Rather the combination of multiple hormones is required *(25)*.

White Adipose Tissue

Visually, the most striking effect after surgery is weight loss and predominantly fat mass loss. White adipose tissue is metabolically active, not only storing cholesterol and triglyceride but also releasing numerous immune- and endocrine-modulating factors and immune cells (Table 1). Two main adipokines involved in the metabolic effects of surgery are adiponectin and leptin. Adiponectin is decreased in obesity, and its levels have been negatively correlated with insulin resistance, inflammation, and atherosclerosis *(26)*. Adiponectin increases after metabolic surgery, and this increase has been associated with improvements in nonalcoholic steatohepatitis, including recovery of hepatic inflammation and fibrosis *(27)*. Leptin levels decrease after RYGB, and this correlates to weight loss and caloric restriction *(28)*. However, improvements in insulin sensitivity and glucose homeostasis did not correlate with reductions in leptin after surgery *(29)*. Whether this is due to a reversal of leptin

Table 1. Analyte changes after metabolic surgery.

Adipose tissue	Adipokines	↓ leptin (→ ↓ catecholamine release)
		↑ adiponectin
		↓ IL-6
		↓ CRP
Pancreas	Hormones	↑ insulin
		↓ glucagon
Gut	Bile Acids	↑ circulating bile acids
	Hormones	↓ orexigenic ghrelin
		↑ anorexigenic GLP-1, PYY, oxyntomodulin
Cardiovascular	Lipids	↓ total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol
		↑ HDL cholesterol
Liver	Biochemical	↓ AST, ALP, ALT, and GGT
		↑ branched chain amino acids
Kidney	Urine	↓ urinary albumin creatinine ratio
		↑ sodium excretion
Musculoskeletal	Myokines	FGF21
Ovary		↑ progesterone and metabolites, luteinizing hormone
		↓ estradiol and metabolites

IL-6, interleukin-6; CRP, C-reactive protein; GLP-1, glucagon-like peptide-1; PYY, peptide YY; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma glutamyl-transferase; FGF21, fibroblast growth factor-21.

resistance after surgery or whether leptin's role in insulin resistance is secondary to weight loss remains unclear.

Increase in the fat mass associated with obesity results in adipocyte and adipose tissue dysfunction, termed adiposopathy. Metabolic surgery improves adipocyte dysfunction associated with improvements in metabolic parameters (e.g., glucose concentrations and blood pressure), dyslipidemia, and cardiovascular risk *(30)*.

Inflammation contributes to many obesity-related metabolic comorbidities by worsening dyslipidemia and insulin resistance *(2)*. Calorie restriction after surgery may improve the inflammatory influence on metabolic complications by reducing adipocyte immune factors [leptin (which may reduce atherosclerosis and catecholamine release, decreasing blood pressure), growth factors], adipose tissue immune cells, and adipose tissue release of adipocytokines (interleukin 6 affects lipolysis and insulin resistance; TNF-α affects adipose tissue lipolysis, adipogenesis, and lipogenesis to increase free fatty acids, worsening insulin resistance and dyslipidemia) *(31)*.

Liver

Bariatric surgery leads to metabolic improvement in the liver with reductions in biochemical indices of nonalcoholic fatty liver disease, which include the liver enzymes γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, as well as histological parameters such as steatosis, fibrosis, lobular inflammation, and hepatocyte ballooning *(32)*. Weight loss is a recognized treatment strategy for nonalcoholic fatty liver disease, and as such surgery-related weight loss, combined with changes in other metabolic parameters such as reduced insulin resistance and less dyslipidemia, is a major contributor to the improvements *(33)*. Various weight-independent mechanisms have also been postulated, including effects of gut hormones such as GLP-1 that increase after surgery. This has received indirect support based on the results of the LEAN trial, which demonstrates that the GLP-1 receptor agonist liraglutide can reduce fibrosis in patients with nonalcoholic steatohepatitis *(34)*.

BRANCHED-CHAIN AMINO ACIDS (BCAAs)

Branched-chain amino acids (BCAAs) have been shown to increase in obese patients and correlate with insulin resistance *(35)*. The combination of over nutrition and relative insulin-like growth factor-1 deficiency may stimulate entry of the BCAAs into the gluconeogenic program instead of protein synthesis in skeletal muscle *(35)*. Several studies have shown that BCAAs and their metabolites (such as C3 and C5 acylcarnitine) decrease after

Box 1. Changes in lipids after metabolic surgery.

- ↓ Total cholesterol
- ↓ Triglycerides
- ↓ LDL cholesterol
- ↓ VLDL cholesterol
- ↓ Use and need for lipid-lowering medications
- ↑ HDL cholesterol
- Larger HDL particle size
- Improved HDL functionality

metabolic procedures including VSG and RYGB *(36)*. This has been correlated with improvements in insulin resistance after surgery independent of ethnicity *(36)*.

BILE

Higher turnover and increased plasma concentrations of bile acids, in particular cholic acid, are seen after RYGB and are linked to reductions in VLDL secretion and hepatic triglyceride accumulation *(37)*. The increase in total plasma bile acids after RYGB likely results from reduced hepatic extraction of bile acids from the portal circulation. After VSG, acceleration of nutrient transfer past the duodenum is likely operative in observed changes in bile acid profiles *(38, 39)*. Bile acids also influence gut hormone secretion (via the G-protein-coupled Cbile acid receptor), control of energy expenditure, and changes in gut microbiota *(40)*. Studies in mice with genetic deletion of the farnesoid X receptor, (the nuclear bile acid receptor) demonstrate that weight loss and glycemic improvements after VSG are reliant on postoperative shifts in bile acid profiles *(41)*.

LIPOPROTEINS

The extent of reversal of the atherogenic dyslipidemic profile seen in obesity (Box 1) is greatest with RYGB compared to other metabolic surgical interventions *(30)*. Weight loss and alterations in food preferences, with a reduction in appetitive behavior, have a significant effect on this improvement. However, there are also weight-independent mechanisms that influence lipid profiles. RYGB in a rat model normalized the endothelium-protective properties of HDL and improved HDL functionality, which was associated with the increases in GLP-1 and bile acids *(42)*. HDL-mediated nitric oxide (NO) production as well as endothelial antioxidant, antiinflammatory, and antiapoptotic properties improved independent of GLP-1 receptor activation after RYGB *(42)*. The same effect was seen in humans after RYGB, with improved endothelial NO release due to improved NO synthetase dimerization, improved NO bioavailability, and HDL-stimulated cholesterol efflux capacity *(42)*. Bariatric surgery leads to changes in HDL subpopulation profiles, functionality, and results in HDL remodeling *(43)*. These changes were at least in part attributed to reductions in cholesterol ester transfer protein (which transports cholesterol ester from HDL to VLDL in exchange for TG) and increases in lethicin-cholesterol acetyltransferase (which esterifies free cholesterol into cholesterol ester, which forms HDL) *(43)*.

INSULIN RESISTANCE

Immediately after surgery there is an acute reduction in calorie intake to approximately 600 kcal/day, both due to the effect of surgery on hunger and the postoperative feeding regimen. A hypocaloric, very low-fat diet (which mimics the postoperative state) can normalize plasma glucose levels within a week. These effects are possible partly through reduced hepatic triglyceride levels and hepatic glucose production *(44)*.

Hyperinsulinemia in humans is associated with hepatic lipogenesis resulting in fatty acid synthesis *(45)*, subsequent oxidation, or anabolic production of triglyceride. The resulting high levels of diacylglycerol can interfere with the insulin signaling pathway, allowing hepatic glucose production to occur unchecked by insulin *(46)*. Surgery, by reducing hyperinsulinemia, serves to counter anabolic lipid storage in the liver.

In patients with obesity and insulin resistance, cells are unable to utilize insulin effectively, resulting in hyperglycemia. The β cells of the pancreatic islets respond to prolonged elevation of plasma glucose by increasing insulin secretion. Consequently, obesity paradoxically drives the negative consequences of both hyperinsulinemia and hyperglycemia. It is plausible that many of the complications of obesity occur on the backdrop of insulin resistance, as they have all been associated with insulin resistance or hyperinsulinemia (Box 2). Metabolic surgery improves insulin resistance by both weight loss dependent and weight loss independent mechanisms.

Muscle

Abnormal fat deposition within skeletal muscle has been linked to the abnormal metabolic phenotype, with intramyofibrillar lipid metabolite accumulation associated with disrupted insulin signaling and insulin resistance *(47)*. Induction of a normal metabolic state with reversal of insulin resistance, improvement in whole-body glucose disposal, and intracellular insulin signaling 6 months post bariatric surgery can be predicted by the selective depletion of intramyofibrillar fat stores secondary to lipid deprivation *(48)*. Peripheral insulin resistance was completely reversed after biliopancreatic diversion, in excess of what could be predicted by weight loss *(48)*. Improvements after RYGB were significant but could be predicted by weight loss *(48)*. Importantly, however, loss

Box 2: Comorbidities of obesity associated with hyperinsulinemia.

Classical metabolic syndrome
• Type 2 diabetes mellitus
• Dyslipidemia
• Hypertension
• Nonalcoholic fatty liver disease
• Polycystic ovarian syndrome symptoms
• Reduced fertility or erectile dysfunction
Other comorbidities associated with hyperinsulinemia and/or insulin resistance:
• Obstructive sleep apnea
• Musculoskeletal pain and function
• Gastroesophageal reflux disease
• Urinary incontinence
• Cancer
• Psychosocial functioning

of skeletal muscle mass after surgical weight loss also occurs and could be counterproductive in relation to metabolic control. Thus, efforts should be directed on how best to preserve lean mass after surgery.

The Pancreas

A subanalysis of the STAMPEDE trial provided evidence of how bariatric surgery improves pancreatic damage, with reduced hemoglobin A1c, improved insulin sensitivity on the Matsuda Index, and improved pancreatic β-cell function all noted after RYGB *(49)*. Substantial reductions in calorie intake in the perioperative period have been linked to metabolic improvements arising from lowered intraorgan fat content, as fat is mobilized from the liver and potentially the pancreas to meet energy requirements *(50)*. Reductions in intrapancreatic fat over the 8 weeks after calorie restriction is associated with improvements in insulin secretion *(51)*.

After metabolic surgery, including VSG and RYGB, the postprandial increase in GLP-1 from the enteroendocrine cells of the small bowel acts as an incretin signal on the pancreas, increasing insulin secretion from the pancreatic β-islet cells *(9)* and allowing the first phase insulin response to be restored. Approximately 40% of patients with obesity and type 2 diabetes go into remission within days or weeks after RYGB, coincident with improvements in insulin resistance and insulin production. Notably however, the effects of GLP-1 on insulin synthesis and secretion have also been linked to symptomatic postbariatric surgery hypoglycemia *(52)*. Table 2 describes the outcomes from 4 randomized, controlled trials assessing the effect of metabolic surgery on diabetes remission. Two further trials, DiaSurg and Triabetes, have yet to report their complete outcome data.

Kidneys

More than 40% of patients with obesity and type 2 diabetes develop renal impairment as a microvascular complication, and 30% go on to develop end-stage renal disease *(59)*. Bariatric surgery improves markers of kidney damage, such as albumin creatinine ratio, urinary albumin creatinine ratio, albuminuria, and renal inflammation *(60)*. Urinary sodium excretion and renal fractional excretion of sodium increase 2-fold after RYGB *(61)*, suggesting gut–kidney–heart signaling involving GLP-1. Natriuretic peptide may influence the improvements in blood pressure and renal inflammation, including improvements in urinary cytokines that are seen after RYGB. The improvements in blood pressure are sustained at 10 years follow-up, with increased levels of urinary diuresis, increased salt intake, unchanged potassium excretion, but increased serum sodium concentrations *(62)*. The exact mechanisms underlying the diuresis and improvements in blood pressure given these findings remain unclear.

Ovaries

Polycystic ovarian syndrome (PCOS) is a well-recognized and common endocrinopathy that affects 5%–10% of women of reproductive age. PCOS is associated with obesity and metabolic dysfunction, and PCOS symptoms are very sensitive to weight loss. In a recent metaanalysis of the impact of metabolic surgery on PCOS (13 studies, 2130 patients) a reduction in incidence from 45.6% to 6.8% was seen at 1 year postsurgery *(63)*. A number of small cohort studies have shown normalization of metabolic dysfunction (dyslipidemia, fasting glucose, hemoglobin A1c) within 6 months of surgery, with an associated increase in progesterone, as well as normalization of testosterone, sex hormone-binding globulin, and ovulatory cycles *(64)*. A recent position statement from the European Society of Endocrinology recommended including metabolic surgery as a treatment for PCOS in morbidly obese women, particularly if metabolic syndrome is present *(65)*.

There are few studies assessing female hormones after metabolic surgery in obese women who do not have PCOS. However, from the limited evidence available it appears that after RYGB there is little effect on the menstrual cycle other than a shorter follicular phase *(66)*. By 1 year postoperatively, testosterone and estradiol levels decreased, accompanied by an immediate increase in serum sex hormone–binding globulin *(66)*.

Table 2. Description of trials assessing the outcome of metabolic surgery on type 2 diabetes mellitus.

Trial	Citation	Participants	Follow-up	Interventions	Primary end points	Outcome
STAMPEDE	Schauer et al. *(53)*	N = 134	5 years	RYGB (*n* = 49) VSG (*n* = 47) Intensive medical therapy (*n* = 38)	HbA1c ≤ 6.0% at 5 years with or without diabetes medication	29% (*n* = 14) 23% (*n* = 11) 5% (*n* = 2)
DIBASY	Mingrone et al. *(54)*	N = 60	2 years	RYGB (*n* = 20) BPD (*n* = 20) Medical therapy (*n* = 20)	Diabetes remission (fasting glucose < 101 mg/dL and HbA1c ≤ 6.5% in the absence of diabetes medication	75% (*n* = 15) 95% (*n* = 19) 0% (*n* = 0)
CROSSROADS	Cummings et al. *(55)*	N = 32	1 year	RYGB (*n* = 15) Medical therapy (*n* = 17)	HbA1c < 6.0% in absence of diabetes medication	60% (*n* = 9) 5.9% (*n* = 1)
Diabetes surgery study	Ikramuddin et al. *(56)*	N = 180	1 year	RYGB (*n* = 60) Intensive medical therapy (*n* = 120)	HbA1c < 7.0%	49% (*n* = 28) 19% (*n* = 11)
Prospective, randomized trials of gastric bypass surgery in patients with type 2 diabetes mellitus	Lee et al. *(57)*	N = 60	1 year	RYGB (*n* = 30) VSG (*n* = 30)	Diabetes remission (fasting glucose < 126 mg/dl and HbA1c ≤ 6.5% without glycemic therapy	93% (*n* = 28) 47% (*n* = 14)
	Lee et al. *(58)*	N = 32	2 years	RYGB (*n* = 16) VSG (*n* = 16)	Complete diabetes remission (fasting glucose < 110 mg/dL and HbA1c ≤ 6.0% and without glycemic therapy	56% (*n* = 9) 6% (*n* = 1)
				RYGB (*n* = 16) VSG (*n* = 16)	Partial diabetes remission (fasting glucose <126 mg/dl and HbA1c ≤ 6.5%)	81% (*n* = 13) 19% (*n* = 3)

RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy; BPD, biliopancreatic diversion with duodenal switch; HbA1c, hemoglobin A1c.
To convert mg/dL to mmol/L, multiply glucose by 0.05551.

Uterus

Obesity increases cancer risk, whereas weight loss significantly decreases cancer risk *(67)*. The risk of developing endometrial cancer returned to the normal range in female obese patients who lost weight and maintained weight loss *(68)*. Metabolic surgery results in a 40% reduction in endometrial cancer incidence, as well as a significant reduction in all cancer mortality in females *(69)*. This appears to be a gender- and organ-specific effect, which has been reinforced by recent publication of the long-term outcome data of the Swedish Obese Subjects Study, wherein metabolic surgery was associated with fewer female-specific cancers (breast and gynecological cancers) *(70)*. Further analysis revealed that only reduction in endometrial cancer risk in patients with preexisting insulin resistance reached statistical significance. This is coherent with findings in large population studies, such as the Metabolic Syndrome and Cancer Project, demonstrating increased cancer risk in patients with insulin resistance *(71)*.

Up to 90% of women with type 1 endometrial cancer may be overweight or obese *(72)*. Metabolic surgery may reverse histological changes of endometrial hyperplasia *(73)*, and patients with endometrial hyperplasia had a different sex hormone receptor profile, which normalized after bariatric surgery *(74)*. Reduced estrogenic drive after metabolic surgery may limit dysplastic potential in the endometrium *(75)*. Progestogens protect the endometrium from the tumorigenic effects of estrogen, and from limited studies after bariatric surgery it appears that as estrogen levels decrease, progesterone levels increase *(64, 66)*.

Low adiponectin levels have also been associated with endometrial cancer *(76)*. Leptin is another adipokine linked to oxidative stress and cancer cell proliferation, and in animal studies a reduction in leptin levels (as occurs after bariatric surgery) is associated with endometrial cancer risk reduction *(77)*. White adipose tissue also produces inflammatory cytokines (such as TNF α, C-reactive protein, interleukin 1 beta/interleukin 6) that stimulate oxidative stress and carcinogenesis *(78)*. Many inflammatory markers are consistently reduced after metabolic surgery, as well as markers of oxidative stress *(79)*. Alterations in immune cells within adipose tissue after metabolic surgery, such as increased natural killer cell toxicity after RYGB, may also affect cancer risk *(80)*.

The hormone GLP-1 may reduce the risk of cancer-related mortality via its effects on insulin resistance *(81)*. However, initial studies investigating commercial GLP-1 receptor agonists demonstrated an increased incidence of breast cancer although subsequent large studies demonstrated no true increase in incidence *(82)*. Furthermore, both in vitro and in vivo studies using liraglutide have suggested that GLP-1 may have anticancer properties in breast and pancreatic cancer cell lines *(83, 84)*. Whether this holds true for endometrial cancer needs further investigation.

Clearly metabolic surgery impacts several pathways. These complex interactions need to be dissected and analyzed in the context of cancer with use of prospective studies before metabolic surgery can be recommended as a treatment for endometrial cancer. However, the clear risk reduction and mechanistic explanation is promising.

Bone

Decreased bone mineral density after metabolic surgery is an undesirable side effect of RYGB, biliopancreatic diversion with duodenal switch, and potentially VSG. Osteoporosis is more common in postmenopausal women after bariatric surgery *(85)*, and loss of bone density continues after metabolic surgery. Both bone loss and increased markers of bone remodeling (such as increased PTH, osteocalcin, and urinary deoxypyridinoline, as well as decreased vitamin D3) have been documented after metabolic surgery and are likely implicated in the increased risk of osteoporosis or fracture risk *(86)*.

Studies have shown that bone loss can occur in the absence of vitamin D deficiency and in the presence of raised PTH levels *(87)*, suggesting a vitamin D resistance syndrome. Several humoral factors that are altered after bariatric surgery have been associated with bone homeostasis and thus bone loss. Although there is not yet a proven causative link, factors including adipokines secreted from adipose tissue (estradiol, leptin, adiponectin), factors from the pancreas (e.g., insulin, amylin), or the gut (ghrelin, glucagon-like peptide-2, glucose-dependent insulinotropic peptide, PYY) have been implicated as potentially contributing to bone loss *(88)*.

Conclusion

Metabolic surgery achieves and sustains improvements in metabolic dysfunction secondary to obesity. Further mechanistic studies are essential to assess the true potential of metabolic surgery to treat the myriad other disorders of metabolism and their consequences in terms of cardiovascular disease and cancer. Approaches that may mitigate the metabolic side effects of surgery also require attention. Understanding the positive impact of metabolic surgery on metabolic health may result in a wider acceptance of this intervention.

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