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Metabolic Surgery, Reality or Myth: Scientific Side of Obesity Pathophysiology and Management

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Introduction

Etymologically, the term 'bariatric surgery' means surgery to reduce weight, deriving from the Greek 'baros' (heavy). It is clear however that most bariatric operations have dramatic effects on type 2 diabetes mellitus and other metabolic conditions, many of which occur independently of weight loss. Weight loss may be regarded as just one of several clinical outcomes that result from the systemic changes in nutrient metabolism conferred by operations such as Roux-en-Y gastric bypass (RYGB): hence these operations can be considered examples of 'metabolic surgery'.

This chapter will outline the existing evidence that bariatric procedures have clinical outcomes independent of weight loss and may therefore be termed 'metabolic'. It will then outline current understanding of the main mechanisms by which weight loss-independent changes in metabolism are conferred: caloric restriction, gut hormones, bile acids and the gut microbiome (summarised in Fig. 36.1). Finally, it will consider potential limits to the notion that bariatric surgery is purely metabolic.

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'Bariatric' or 'Metabolic': Mere Semantics?

The concept of metabolic surgery is not new. In 1978 William Buchwald and Richard Varco published the book *Metabolic Surgery*, a practice they defined as 'the operative manipulation of a normal organ system to achieve a biological result for a potential health gain' [1]. From this broad perspective, bariatric surgery is one part of metabolic surgery, a much larger field that also includes operations as diverse as partial ileal bypass for primary hypercholesterolaemia [2], oophorectomy for hormone-sensitive breast cancers [3] and deep brain stimulation for refractory depression [4].

More recently, Professor Rubino proposed that 'gastrointestinal metabolic surgery' should be characterised by its 'intent to treat diabetes and obesity from the perspective of a metabolic illness as opposed to traditional bariatric surgery intended as mere weight-reduction' [5]. This change in emphasis from weight-reduction to treatment of metabolic disease has profound ramifications for the goals and expectations of patients and care providers regarding this branch of surgery. A striking example of this was shown in an elegant study of two otherwise identical surgical programs run from the same medical centre in the USA, one entitled 'bariatric surgery' and the other 'metabolic surgery', which attracted patients with significantly different demographics [6]. The former attracted patients with a higher BMI, whereas

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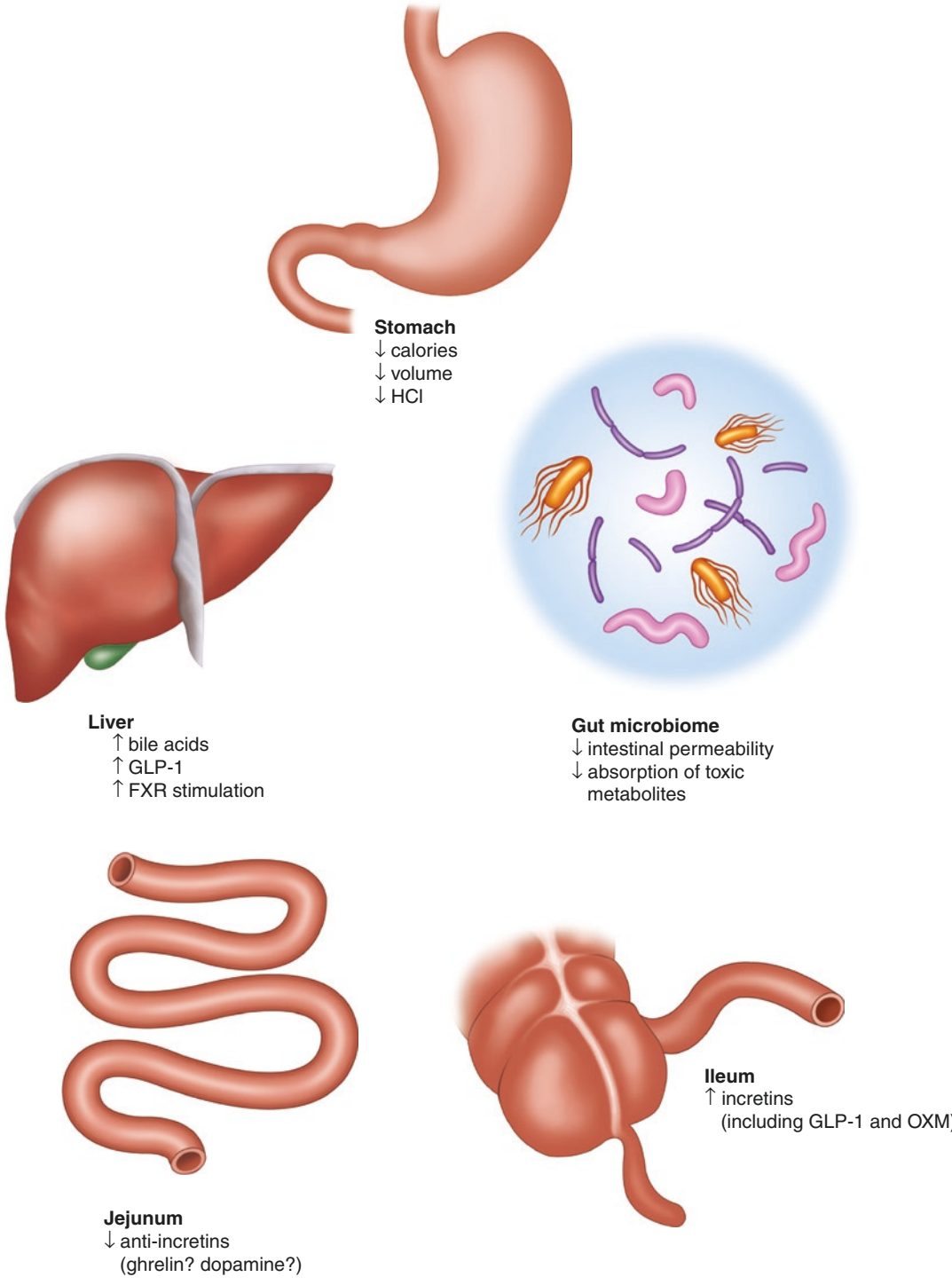

Fig. 36.1 Main mechanisms by which weight loss-independent changes in metabolism are conferred: caloric restriction, gut hormones, bile acids and the gut microbiome

the latter attracted patients with higher rates of diabetes and cardiovascular disease. A focus on metabolic health as the primary outcome of surgical intervention informs changes in eligibility criteria to reflect the value of surgery in diabetes [7] and opens the door to the potential use of surgical procedures to treat diabetes and related conditions in the nonobese [8].

Metabolic Surgery: For Better and for Worse

In the early development of bariatric surgery, the metabolic consequences of intestinal manipulation to achieve weight loss were dramatic, mostly problematic, and a significant drive for evolution of the specialism. For example, the jejunoileal bypass was developed as an alternative to the ileal bypass with jejunocolic anastomosis, due to the severe electrolyte imbalance and diarrhoea experienced with the latter procedure [9, 10]. Resulting morbidity was often so severe as to require reversal of these early bariatric procedures.

Positive metabolic sequelae of bariatric surgery were also quickly apparent, however. Buchwald and Varco's jejunoileal bypass was found not only to induce significant weight loss, but also to significantly improve hyperlipidaemia [11]. These effects on hyperlipidaemia are not explained by weight loss alone, as a less extensive ileal bypass [2] has been shown to improve long-term lipid profile without significant change in weight.

The most dramatic effect of bariatric surgery on metabolic disease, its ability to restore normal glycaemic control in type 2 diabetes, has been known for over 30 years [12]. The speed of normalisation of blood sugars – far before any significant weight loss – was noted in early reports, and at that time early diabetes resolution was proposed to occur due to reduction of caloric intake [13]. The superiority of bariatric surgery over conservative measures in improving diabetes was reported in the mid-1990s [14] and has subsequently been confirmed in several large randomised controlled trials and meta-analyses [15–18].

As well as improvement in diabetes and hyperlipidaemia, bariatric surgery is associated with long-term reduction in overall mortality, due to decreased myocardial infarction, stroke and cancer death [19]. Reduction in cardiovascular events following bariatric surgery (stroke and myocardial infarction) is not associated with degree of weight loss, implying that again this benefit occurs through other mechanisms [20]. Bariatric surgery is associated with reduced overall cancer incidence in obese women; again, this effect is not correlated with weight loss [21]. The effect of bariatric surgery on cancer mortality varies according to cancer type. Colorectal cancer is the only known malignancy where the risk of being diagnosed with the disease seems to increase after obesity surgery. In fact, mortality from rectal cancer increases threefold in patients that have had bariatric surgery [22]. Again, this would suggest that effects of bariatric surgery on cancer risk are not solely due to weight loss.

The strong association between Billroth II gastrojejunostomy and late metabolic complications including bone disease and anaemia was recognised from the mid-twentieth century [23]. Although the mechanisms behind these complications were difficult to elucidate, comparison with similar procedures led researchers to deduce that certain severe nutritional deficiencies were due to duodenal bypass, for example, although Billroth I (direct anastomosis of proximal stomach to pylorus) was noted to cause milk intolerance and osteopenia, it did not cause vitamin D deficiency and osteomalacia [24]. Fracture risk increases after bariatric surgery, associated with accelerated bone turnover, a phenomenon which appears to be in part but not entirely weight loss dependent [25, 26].

The relationship of liver disease with obesity and its response to surgery is complex. Non-alcoholic fatty liver disease is extremely common in obesity and responds well to weight loss including that induced by RYGB [27, 28]. Interestingly after bariatric surgery, there is initially a transient increase in liver fat, probably due to increased circulating free fatty acids released from adipose tissue lipolysis as insulin sensitivity improves

[29]. Improvement in liver enzymes correlates reasonably well with extent of weight loss [30], although findings of the recent LEAN trial of liraglutide suggest that some of the beneficial effects of GLP-1 agonism on steatosis are weight loss independent [31]. Other conditions improved by bariatric surgery potentially through mechanisms distinct from weight loss include male and female fertility [32, 33]and obstructive sleep apnoea [34].

Caloric Restriction as a Mediator of Metabolic Surgery

The beneficial effects of bariatric surgery on glucose homeostasis in the immediate post-operative period are in part due to the customary severe caloric restriction. Patients with diabetes administered a very low calorie diet (VLCD) as inpatients experienced similar improvements in hepatic insulin secretion in response to intravenous glucose administration to those undergoing RYGB over a 3-week period [35]. In this study, although all patients lost weight, the improvement in glucose metabolism was not correlated with weight loss. Changes conferred by acute caloric restriction are largely due to decrease in liver fat, which occurs very rapidly and improves insulin sensitivity, followed by decrease in pancreatic fat, which occurs over a few weeks and improves B cell function [36, 37].

Gut Hormones as Mediators of Metabolic Surgery

Although caloric restriction improves insulin secretion and sensitivity to an intravenous glucose stimulus, augmentation of incretin gut hormones post-bariatric surgery plays an important role in attenuation of post-prandial blood sugar peaks. The incretin effect refers to the additional insulin secretion conferred by oral glucose in excess of that stimulated by an equivalent intravenous glucose load; the incretin effect accounts for around 50% of post-prandial insulin secretion [38, 39].

The best studied and most therapeutically tractable incretin hormone is glucagon-like peptide 1 (GLP-1), so-called because it derives from the same precursor as glucagon 'proglucagon' and is structurally related [40]. GLP-1 is secreted from the enteroendocrine L cells of the terminal ileum in response to the presence of luminal nutrients. The most important metabolic effect of GLP-1 is to stimulate pancreatic insulin secretion; additionally it slows gastric emptying, elicits satiety, reduces food intake and reduces weight [41]. It also inhibits glucagon release, contributing to improved glucose tolerance [42].

Post-prandial GLP-1 is augmented after bariatric operations that accelerate delivery of nutrients to the small bowel (e.g. RYGB), but not after gastric banding or caloric restriction [43, 44]. This elevation in post-prandial GLP-1, which occurs within days of surgery and lasts for at least 10 years [45, 46], is associated with an increase in the incretin effect in patients post-RYGB [47]. Administration of the specific GLP-1 receptor antagonist exendin (9–39) in patients post-RYGB diminishes the augmentation of insulin secretion post-prandially by 43% [39]. This evidence would strongly suggest that enhanced GLP-1 secretion is responsible for at least part of the improvement in diabetes seen after bariatric surgery.

Another gut hormone which is augmented post-prandially after bariatric surgery is oxyntomodulin (OXM), a dual glucagon and GLP-1 receptor agonist, also released from L cells in response to nutrients. OXM reduces food intake and gastric emptying in humans. As a weak agonist of the GLP-1 receptor, OXM generates a small incretin effect, [44, 48] although it is likely to be much less important than GLP-1 for weight loss-independent diabetes improvements in humans [49].

Although subcutaneously injected GLP-1 agonists are licensed for use in diabetes, their effects on glucose control are modest at approximately 1% reduction in HbA1C over 26 weeks [50]. Maximal dose is limited by side-effects of nausea and vomiting. The far more dramatic effects induced by endogenously secreted GLP-1 are likely due to the fact that GLP-1 is extensively degraded by dipeptidyl peptidase 4 (DPP4) and therefore levels in the portal

circulation are much higher than peripheral levels in the post-prandial post-RYGB patient [36].

'Foregut' and 'Hindgut' Hypotheses

RYGB and BPD are complex procedures, resulting in several anatomical and functional changes: these include reduction in stomach volume; exclusion of the 'foregut', duodenum and part of the small bowel; and accelerated delivery of poorly digested nutrients to the 'hindgut' – distal ileum. Correspondingly, an improvement in glucose control post-surgery could theoretically derive from one of three changes: firstly, a reduced caloric intake due to a smaller stomach (or exclusion of hormonal or other signalling factors usually secreted by the excluded stomach in response to nutrient stimuli); secondly, exclusion of factors usually produced by the foregut in response to nutrient stimuli (the 'foregut hypothesis'); or thirdly, augmentation of factors produced by the hindgut in response to accelerated delivery of nutrient stimuli (the 'hindgut hypothesis'). Of these latter 'hindgut hypothesis' mediators, GLP-1 and the other incretins are examples. Theoretical mediators of the 'foregut hypothesis' would worsen glucose tolerance and so they are named 'anti-incretins'.

To investigate the importance of the different components of these complex procedures, Professor Rubino performed a series of experiments on a rat model of nonobese type 2 diabetes [51, 52]. Duodenojejunal bypass (DJB), in which there is no reduction in stomach volume but bypass of the duodenum and proximal jejunum, led to significant improvements in glucose profile compared to sham operated rats [52]. Interestingly, the two groups of rats ate the same quantity and gained weight at the same rate. This experiment provides good evidence that glucose tolerance is improved post-RYGB due to mechanisms beyond reduction of stomach volume, reduced caloric consumption and weight loss. Indeed in the same experiment, a control group of rats treated with caloric restriction experienced less improvement in glucose homeostasis despite losing more weight than the DJB-treated rats.

In order to investigate whether the mechanism responsible for improved glucose tolerance post-surgery is exclusion of the duodenum and proximal jejunum (the 'foregut hypothesis') or rapid delivery of nutrients to the terminal ileum (the 'hindgut hypothesis'), Rubino next compared DJB with gastrojejunal anastomosis (GJ) [51]. The latter procedure simply consists of anastomosis between the stomach and proximal jejunum, with the result that just as in DJB nutrients are delivered rapidly to the terminal ileum (preserving any potential increase in incretin release due to enhanced nutrient delivery to the terminal ileum, as proposed by the hindgut hypothesis), but a small amount will pass through the duodenum allowing stimulation of any potential anti-incretins (preventing any effects attributable to the foregut hypothesis). Rats undergoing DJB and GJ had similar post-operative food intake post-operatively and lost comparable amounts of weight. DJB-treated rats, however, had markedly improved glucose tolerance in comparison to both controls and GJ-treated diabetic animals. This finding would support the foregut hypothesis, as exclusion of the foregut in this experiment is necessary to improve diabetes in diabetic rats.

Further experiments in rats using anatomical variants to unpick relative contributions of the foregut and hindgut to glucose metabolism revealed that resection or bypass of jejunum, but not ileum, improves insulin sensitivity in nonobese diabetic rats, again supporting the hypothesis that anti-incretins are secreted from the foregut [53]. In this experiment, DJB and ileectomy were surprisingly not associated with increased post-prandial GLP-1, leaving the authors to conclude that the effects on glucose homeostasis must be due to putative anti-incretin factors. In contrast, GLP-1 is known to rise dramatically post-prandially after RYGB. It has therefore been proposed that manipulation of stomach anatomy is in some way important for incretin response, rather than that it occurs simply due to an increased delivery of nutrients to the distal small bowel [54]. This would help to explain why sleeve gastrectomy (where there is no small bowel bypass) and RYGB produce similar early improvements in glucose tolerance and increased secretion of post-prandial GLP-1 [55].

Additional evidence that incretins are not the whole story derives from experiments in genetically modified mice that lack the GLP-1 receptor. These mice nonetheless experience improvements in glucose homeostasis and reduced body weight following RYGB [56], which would imply that GLP-1 is dispensable for improved diabetes post-RYGB. Furthermore, in nondiabetic patients after RYGB, blockade of the GLP-1 receptor with exendin 9–39 does alter glucose and insulin profile after a standardised meal, but appears not to alter overall disposition index (composite of insulin secretion and insulin sensitivity) [39, 57], again suggesting that effective glucose control post-bypass does not solely rely on GLP-1 action.

On the other hand, GLP-1 is implicated in the pathogenesis of post-prandial hyperinsulinaemic hypoglycaemia (PHH), a condition that affects a small proportion of patients post-RYGB. These patients experience hypoglycaemia due to dramatically elevated insulin post-prandially compared to asymptomatic post-RYGB controls, which is associated with higher post-prandial GLP-1 peak and can be blocked with exendin 9–39 [58]. This would suggest that PPH is dependent on GLP-1. Proponents of the foregut hypothesis claim that PHH is in fact relatively uncommon, which suggests that there are control mechanisms in place to prevent excessive stimulation of B cells and insulin secretion in response to GLP-1 [59]. Although severe PPH requiring hospitalisation is rare, however, the incidence of mild symptomatic PPH may affect as many as one-third of patients post-RYGB or sleeve gastrectomy [60]. It appears to be less common following sleeve gastrectomy than RYGB [60], so given that the foregut is not bypassed in the former condition, this might support a role of anti-incretins in preventing the complication.

What Are 'Anti-incretins'?

In spite of the persuasive evidence that the foregut may produce substances that are 'diabetogenic', acting to suppress insulin and increase glucagon and generally counteracting the effects of the incretins, the nature of these substances has not been identified [59]. In order to positively confirm their existence, Salinari et al. examined jejunal extracts from insulin-resistant humans and diabetic mice and demonstrated that they secrete proteins which impair insulin signalling in skeletal muscle cells in vitro [61].

One contender for an anti-incretin is ghrelin, an orexigenic hormone secreted from the stomach and proximal small bowel, which has an inhibitory effect on glucose-stimulated insulin release in humans [62] and from pancreatic B cells in vitro [63]. There is evidence from some studies that ghrelin is suppressed post-RYGB for up to 2 years [64], although other researchers have detected no change [65]. Mathematical modelling indicates that ghrelin changes are unlikely to be solely responsible for the remission of diabetes post-bariatric surgery [66], although ghrelin could perhaps be one of several anti-incretins.

Recently gastrointestinal dopamine has been proposed to be a chief anti-incretin, on the basis that it is secreted by the foregut and can prevent the effect of incretins on beta cell insulin secretion in vitro [67]. This is an exciting area that merits further investigation. Positively identifying physiological anti-incretins would potentially enable their inhibition to medically treat diabetes and/or their stimulation to treat PPH.

Sleeve Gastrectomy

Sleeve gastrectomy is highly effective for weight loss and resolution of metabolic comorbidities [68]. Specific mechanisms that have been proposed for the efficacy of sleeve include the 'gastric hypothesis', which relates a reduction in gastric hydrochloric acid release to decrease in secretion of gastric releasing peptide and increased GLP-1 release [69]. Another possible mechanism is due to faster delivery of nutrients to distal small gut, leading to increased GLP-1 and PYY secretion [70].

Bile Acids as Mediators of Metabolic Surgery

Bariatric procedures disrupt physiological enterohepatic circulation of bile acids, resulting in changes in overall levels and nature of circulating bile acids [71]. In particular, RYGB increases fast-

ing and post-prandial circulating levels of bile acids and alters relative proportions of different types of bile acid in circulation and luminally [71, 72].

Bile acids stimulate GLP-1 secretion from L cells in the distal gut via their action on TGR5 receptors [73]. Infused into the jejunum with a glucose load, the potent TGR5 agonist taurocholic acid increases circulating GLP-1 and improves glucose tolerance in healthy volunteers [74]. In nondiabetics and fasting obese diabetics, rectal taurocholate is associated with increases in GLP-1 and insulin secretion and decreases in plasma glucose [75, 76].

Surgical experiments involving bile diversion support the notion that bile acids are important stimuli of improved glucose tolerance following metabolic surgery, albeit an effect largely mediated through gut hormones. In obese rats, a catheter inserted from the common bile duct to the mid-distal jejunum results in weight loss, improved glucose tolerance, higher post-prandial GLP-1 levels and less hepatic steatosis [77]. In a mouse model of obesity, comparison of bile acid diversion from the gallbladder to the duodenum (i.e. sham), jejunum or ileum reveals that only the latter procedure results in sustained weight loss and sustained improvements in glucose homeostasis [78]. In this study the observed weight loss was slightly greater than that observed in control mice treated with RYGB, which would imply that bile acid diversion is a very important contributor to the effects of RYGB. It was also higher than that observed in mice pair-fed to the ileum bile acid diversion group, confirming that bile acid diversion has metabolic effects independent of caloric restriction.

Changes in bile acids may also improve glucose metabolism independently of gut hormones. One proposed mechanism is due to their ability to act as Farnesoid X receptor (FXR) agonists. Hepatic FXR stimulation inhibits hepatic gluconeogenesis; adipose stimulation of FXR leads to improvements in insulin sensitivity; and intestinal FXR stimulation leads to release of FGF19 (FGF 15 in mice), which also inhibits hepatic gluconeogenesis [72]. Evidence that bile acid stimulation of FXR is important for effects of bariatric surgery comes from FXR knockout mice, which do not experience the sustained weight loss after sleeve gastrectomy observed in wild type controls [79]. Additionally, although FXR knock out mice have lower fasting blood glucose compared to wildtype, after SG their fasting glucose increases rather than decreases as in wildtype, and there is no improvement in their overall glucose homeostasis [79].

Bile acid circulation is a crucial component of overall lipid metabolism [80]. Bile acids excreted in faeces are replaced by synthesis from cholesterol in the liver, which can be a significant source of cholesterol elimination. Total circulating cholesterol improves after bariatric surgery; however, this does not appear to be associated with an increase in faecal bile acids [81, 82]. It may therefore be a result of weight loss or caloric restriction rather than bile acid diversion. Similarly, bile acids regulate hepatic fatty acid and triglyceride synthesis, but at present there is limited evidence that the beneficial effects of metabolic surgery on hepatic steatosis are directly related to changes in bile acid circulation [71].

Gut Microbiome as a Mediator of Metabolic Surgery

After RYGB, the gut microbiome changes towards higher levels of proteobacteria and lower levels of firmicutes [82, 83]. Microbiome changes are associated with changes in bile acid circulation bidirectionally, as bile acids are transformed by intestinal bacteria, and changes in bile acid composition will alter conditions affecting relative species of bacterial growth [84]. It is likely that changes in the gut microbiome in obesity and following bariatric surgery are secondary to changes in dietary intake, bile acid circulation and/or gut hormone milieu rather than direct consequences of surgery. Nonetheless, faecal transplant experiments demonstrate that transfer of gut microbiota from humans or mice that have undergone RYGB to unoperated mice reduces recipients' fat mass [83, 85]. This is associated with a lower respiratory quotient, indicating more energy production from fat rather than carbohydrate [83].

Other mechanisms via which a change in gut microbiome might improve metabolic health

include a decrease in absorption of toxic metabolites such as choline and ethanol metabolites [86]. These are not only produced in greater quantities by dysregulated gut microbiota, but an unhealthy gut microbiome is also associated with increased intestinal permeability, which facilitates their absorption [87]. These factors contribute to the development of obesity-associated steatohepatitis [88]. Further research is required to determine whether changes in the gut microbiome following bariatric surgery independently account for substantial metabolic effects.

Is There a Limit to 'Metabolic' Surgery?

In this chapter we have outlined evidence that bariatric procedures such as gastric bypass work through mechanisms independent to weight loss, to cause resolution of diabetes and other metabolic disorders. For these operations to be considered 'truly' metabolic, rather than bariatric, it has been argued that they should cause resolution of metabolic disorder even in nonobese patients [89]. Although evidence from nonobese cohorts is to date very limited, the metabolic effects of bariatric surgery in the nonobese appear to be modest [90], with some indication that they are inferior to results seen in the morbidly obese [91]. A recent meta-analysis of bariatric procedures in 290 patients with a BMI of under 30 (mean 26 kg/m^2), all of which were either bypass-type operations or SG, demonstrated an overall HbA1C reduction of 1.88% with a major complication rate of 6.2% [8]. Although further research is required to confirm the value of bariatric surgery as a treatment for metabolic disorder in the nonobese, it is highly likely that maximal effect of such operations is achieved through a combination of weight loss-dependent and weight loss-independent means. Perhaps, then, these procedures are best termed 'bariatric/metabolic' surgery.

Conclusion

The ability of bariatric surgery to alter metabolism via mechanisms independent of weight loss is certainly a reality and has been demonstrated for many obesity-related conditions. The mechanisms by which bariatric surgery produces these effects include reduced caloric intake, alteration of gut hormones and other signalling molecules, bile acid circulation and the gut microbiome. These factors are interlinked and depend on operation type, which presents some challenges to achieving a complete understanding.

Better understanding of the metabolic effects of surgery and the mechanisms through which they occur will enable the development of new surgical strategies, and potentially the tailoring of surgical strategies to each individual's unique profile of metabolic disorder. Ways of predicting response to bariatric surgery are still very crude: better understanding of mechanism may well lead to more physiological and accurate methods [92]. Furthermore, understanding of the mechanisms by which metabolic effects occur will enable us to develop non-surgical alternatives, for example, gut hormone analogues [93], with consequent risk reduction for a relatively high-risk cohort of patients. It may also lead to the use of medications as targeted adjuncts for non-responders [94]. Metabolic surgery, medicine and science are closely intertwined in this fast-evolving and exciting field.

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