

UNIT NO. 5

METABOLIC SURGERY: A NEW APPROACH IN THE TREATMENT OF METABOLIC DISEASE OF THE 21ST CENTURY

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ABSTRACT

Metabolic surgery is “the operative manipulation of a normal organ or organ system to achieve a biological result for potential health gain”¹. More recently, it has been applied to describe the stunning reversal of metabolic disorders noted after bariatric (weight loss) surgery. Indeed, the improvement in conditions such as type 2 diabetes mellitus, hypertension, dyslipidaemia and non-alcoholic fatty liver disease have been so dramatic that national obesity surgery societies have quickly added “metabolic” to their names to capitalise on the health benefits of these procedures. These recent findings, well-documented over the past 2 decades, have added a new dimension to bariatric surgery which hitherto was focused on weight loss, giving rise to the present specialty of metabolic-bariatric surgery (MBS). This paper looks at the various types of metabolic surgical interventions and analyses the purported benefits in improving each of these obesity-related metabolic disorders. The appropriate indications for surgery and possible complications arising are also discussed.

Keywords: metabolic bariatric surgery, weight loss, diabetes, remission, mortality

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INTRODUCTION

The rise in obesity world-wide is paralleled by a steep rise in metabolic disorders such as type² diabetes mellitus (T2DM), hypertension, dyslipidaemia, stroke, sleep apnoea and non-alcoholic fatty liver disease (NAFLD)². In Singapore, a rise in the prevalence of obesity (defined as a body-mass index {BMI} $\geq 30\text{kg/m}^2$) from 6.9% in 2004 to 10.8% in 2010, saw a parallel increase in the T2DM prevalence of a similar magnitude – from 8.9% to 11.6%.

The postulate that obesity, and in particular, visceral adiposity, is correlated to metabolic diseases was conceptualised in the “Syndrome X”³, now more commonly known as the metabolic syndrome. All these conditions contribute to atherosclerosis resulting in end-organ complications such as coronary artery disease, stroke, and peripheral vascular disease. The microvascular complications of T2DM also result in retinopathy, nephropathy and neuropathy.

There is much evidence for a critical link between obesity and metabolic disease, and a rise in BMI is positively correlated with a rise in mortality⁴. Fortunately, intensive lifestyle intervention with successful weight loss can markedly improve glycaemic and lipid profiles and cardiovascular risk in diabetic patients⁵. Weight loss can even prevent or delay the development of T2DM in susceptible individuals⁶. Similar benefits are observed after weight-loss (bariatric) surgery. In Dr Pories’ landmark study in 1995, 83% of the obese diabetic patients who had a gastric bypass underwent “remission” of T2DM, without need for diabetic medication while nearly all patients with impaired glucose tolerance (IGT) never went on to develop diabetes⁷.

Further evidence from the bariatric surgery literature gave rise to the awareness in the 1990s that weight loss surgery was in fact more significant in treating metabolic disorders than obesity itself! As a result, the specialty has been renamed in many centres across the globe as metabolic-bariatric surgery (MBS). MBS is growing at an exponential rate, partly due to the widespread adoption of newer, minimally invasive (laparoscopic or key-hole) surgical techniques and the use of less aggressive interventions such as gastric banding, which avoid any cutting or stapling of the stomach.

We discuss the types of surgical interventions, the benefits of MBS as well as its risks and complications. Last but not least, the selection of the suitable patient along with the appropriate intervention is of critical consideration.

TYPES OF INTERVENTIONS

The surgical options for treating metabolic disease arise from

traditional bariatric surgical procedures⁸. They may be divided into 2 categories according to their mechanism of action: a) restrictive and b) bypass-type (malabsorptive) procedures.

Early attempts at metabolic surgery involved intestinal bypass in an attempt to interrupt the entero-hepatic circulation of cholesterol and bile acids to treat severe hypercholesterolemia⁹. However, these procedures are less commonly performed today due to the potential for severe protein-loss and nutritional deficiencies, and safe and effective lipid-lowering medications are now available.

Restrictive procedures result in a smaller gastric reserve hence limiting intake and are gradually gaining traction among both patients and surgeons as they are less complex than the bypass-type procedures, and are less likely to require life-long vitamin and nutrient supplementation. Laparoscopic adjustable gastric banding (LAGB) (Figure 1) involves the placement of an inflatable balloon around the proximal circumference of the stomach resulting in a gastric pouch of 30 ml, thus increasing the sensation of satiety in patients. Laparoscopic sleeve gastrectomy (LSG) (Figure 2) involves the reduction of stomach volume to approximately 15% of its original capacity by resecting the greater curve.



Figure 1. Adjustable gastric band



Figure 2. Sleeve gastrectomy

The most commonly performed bypass-type operation today is the laparoscopic Roux-en-Y gastric bypass (LRYGB) (Figure 3). This is a combined restrictive-malabsorptive procedure which essentially works by (a) reducing the functional stomach

to approximately 30ml or less; (b) delaying gastric emptying by reducing the gastric outlet to approximately 1 cm or less; (c) bypassing the foregut with a 40-150 cm Roux-en-Y gastrojejunostomy, causing reduced nutrient absorption. Depending on the length of the bypassed intestine, there is a risk for malnutrition, in particular of vitamin B12, iron, calcium, and 25-vitamin D. Therefore, patients require lifelong vitamin and mineral supplementation. More extensive bypass-type procedures include bilio-pancreatic diversion (BPD) and BPD with duodenal switch (BPD-DS), which result in the largest amount of weight loss, but are associated with higher operative mortality and risk of nutritional deficiencies due to the longer intestine bypassed.



Figure 3. Roux-en-Y gastric bypass

Weight loss is greater with the bypasses compared with the restrictive procedures. It is greatest typically at 1-2 years and mostly sustained at 10-15 years. Unlike medical therapy, weight loss with MBS is durable. Compared with control subjects, patients with MBS had an average (absolute) weight loss of 23.4% and 16.1% from baseline at 2 and 10 years respectively while the control group had a weight gain of 0.1% and 1.6%. Typical weight losses at about 2 years in the subgroups are: gastric bypass 32% and gastric banding 20%. After 10 years, most of the weight lost is still sustained with weight losses from baseline stabilised at 25% and 14%, respectively¹⁰. In comparison to banding and bypass, LSG is a relatively new technique and performed widely as a stand-alone weight-loss procedure only in the last 5 years.¹¹ Long term data on durability of weight loss and impact on metabolic co-morbidities is not yet available for the gastric sleeve procedure.

Pure “metabolic” surgery, i.e. interventions that seek to change physiology without achieving weight loss, and therefore applicable to normal weight individuals - such as endoluminal sleeves, gastric electro-stimulation, duodeno-jejunal bypass and ileal transposition¹²⁻¹⁴ - are still considered to be at the

experimental stage and will not be discussed further in this article.

METABOLIC EFFECTS OF MBS

Metabolic surgery aims to effect physiologic changes to either improve or “reverse” the various components of the metabolic syndrome, thereby reducing the risk of cardiovascular complications long-term. With durable weight loss and permanent changes to gastrointestinal anatomy, the beneficial effects of metabolic surgery on the various cardiovascular risks are noted to be sustained as well.

EFFECT OF MBS ON TYPE 2 DIABETES MELLITUS

The greatest metabolic risk associated with obesity is T2DM, a progressive disorder characterised by insulin resistance, which is largely as a result of visceral obesity, and concomitant impaired insulin secretion.

A large body of evidence suggests that MBS results in remission of T2DM, defined as normal sugars without the use of DM medications, the degree of which is proportional to the extent of excess weight loss, with LAGB having the least (56.7%) and LRYGB and BPD/DS seeing the highest rates of remission (80.3% & 95.1% respectively) (Table I). This remission is sustained in about half of these patients up to 10 years while matched obese controls on medical weight loss treatment are at a 4-fold higher risk of developing diabetes¹⁶. The benefits of IGT reversal to normoglycaemia after MBS (~99% of subjects) are also noted to be sustained over the 14-year period of the study by Pories et al⁷.

Multiple mechanisms are responsible for this phenomenon, including restriction of caloric intake with resultant weight loss. However, early remission of DM has been reported even before significant weight loss has taken place⁷, triggering postulated mechanisms that MBS invokes altered foregut and hindgut

hormonal balances independent of weight loss. Proponents of gastric bypass are convinced that bypass of the duodenum has a positive impact on glucose metabolism by diminishing inhibitory peptides from the duodenum (“anti-incretins”) which oppose the effects of incretin hormones such as glucagon-like peptide¹ (GLP-1) this is called the “foregut hypothesis”. After bypass procedures, the increased transit time of food passage leads to rapid delivery of nutrients to the hindgut with accelerated/early and enhanced secretion of GLP-1, which is increased by 40% (the “hindgut hypothesis”¹⁷.

LRYGB and LSG have been used in clinical studies for the treatment of T2DM in non-obese patients and early results show that while it is effective in some, the benefit is lower than that observed in obese patients^{18,19}.

EFFECT OF MBS ON HYPERTENSION

Similarly, hypertension is noted to improve or resolve in about 79% of patients after MBS. In 66% of patients, normal blood pressures are attained without need for medications²⁰. These effects are greatest at 1-2 years and somewhat sustained at 10 years though with a drift back to baseline in the long-term¹⁶. Potential mechanisms of MBS on hypertension include a reduction in visceral adiposity which in turn reduces the inflammatory cytokines like tumour necrosis factor and the interleukins. A reduction in peri-renal fat may also play a part in reducing intravascular volume via renin²¹.

Table I: T2DM resolution after various metabolic surgery procedures

	Total	Gastric Banding	Gastroplasty	Gastric Bypass	BPD/DS
% EBWL	55.9	46.2	55.5	59.7	63.6
% Resolved overall	78.1	56.7	79.7	80.3	95.1
% Resolved <2 y	80.3	55.0	81.4	81.6	94.0
% Resolved ≥2 y	74.6	58.3	77.5	70.9	95.9

Adapted from Buchwald H et al.¹⁵

Excess weight is the weight difference between one’s current weight and one’s weight based on the population-designated ideal BMI. In this series, the mean excess weight loss (EWL) is 61.2 per cent, with greater weight loss with the bypass procedures (63.6% for BPD/DS) than with the restrictive procedures (47.5% for gastric banding).

EFFECT OF MBS ON LIPIDS

Obesity and insulin resistance is associated with dyslipidaemia in the form of lower high density lipoprotein (HDL)-cholesterol, hypertriglyceridemia (TG), and low density lipoprotein (LDL) particles that are small and dense²². Individuals with such dyslipidaemia have much higher cardiovascular risk than those without²³. Metabolic and bariatric surgery (MBS) reverses this dyslipidaemia by increasing the HDL-c and lowering the TG^{24,25}, as well as reduction of the small-dense LDL particle²⁶. MBS has been shown to reduce cardiovascular mortality in prospective studies²⁷ and the favourable lipid changes have certainly contributed to it²⁸. Interestingly, this improvement is correlated more with the decrease of insulin resistance rather than the extent of weight loss alone²⁴, suggesting that the beneficial effects of MBS on lipids work through tackling insulin resistance.

EFFECT OF MBS ON NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD encompasses a spectrum of liver disorders starting with simple steatosis, then progressing to non-alcoholic steatohepatitis (NASH) and finally cirrhosis. It has become the most common chronic liver disorder in the general population affecting up to 35% of urbanised Asians²⁹. The prevalence of NAFLD is high in the overweight (67%) and obese (91%), with insulin resistance as one of the key elements in its pathogenesis³⁰. Simple steatosis is rather benign, but NASH is associated with much higher risk of progression to cirrhosis³¹. The dramatic weight loss and reduction of insulin resistance also ameliorate the early stages of NAFLD, improving simple steatosis in 92%, NASH 81% and fibrosis 69.5%, with 70% chance of complete resolution of NASH³². The complication rate of MBS in patients with compensated cirrhosis is 2.2 times that of patients without, but patients with decompensated cirrhosis had a complication rate 21.2 times³³. Long time data is not yet available for patients with cirrhosis, but it is clear that MBS should be performed before patients with cirrhosis become decompensated.

EFFECT OF MBS ON OBSTRUCTIVE SLEEP APNOEA (OSA)

OSA is estimated to affect 25% of the general population but as high as 45% in the obese and 70% in patients going for MBS³⁴ and implicated in the aetiology of hypertension and the progression of diabetes, pulmonary hypertension, atrial fibrillation and congestive heart failure³⁵. It may worsen weight gain through reduced activity and increased appetite³⁶. Bariatric surgery reduces apnoea hypopnoea index (AHI) from 55 to 16 events per hour with an average reduction of body mass index (BMI) of 15 kg/m²³⁴.

EFFECT OF MBS ON CANCER

Overweight and obesity is estimated to account for 20% of all

cancers³⁷. Obesity leads to insulin resistance, hyperleptinaemia, increased plasminogen activator inhibitor-1, increased endogenous sex hormones, chronic inflammation and decreased adiponectin levels are all thought to contribute to the increased risk³⁸. Indeed, MBS decreases cancer mortality by 60%²⁷ and cancer incidence by 33%³⁹ probably by reversing a lot of the effects of obesity.

MORTALITY OUTCOMES

Despite the higher risks morbidly obese patients pose during surgery, the mortality rates related to MBS are reportedly low at 0.1% to 2.0%, with greater risks with the more drastic bypass procedures. Common causes of death are pulmonary embolism and anastomotic leaks^{8,40}. In the long-term, MBS has been shown to reduce mortality. In the landmark Swedish Obese Subjects (SOS) study, a well-matched, prospective study which followed 2010 obese subjects who have undergone MBS and their 2037 matched controls treated medically over 16 years, there was an overall relative reduction in mortality of 34% in MBS subjects, with most of the reduction in cardiovascular and cancer-related deaths¹⁰.

INDICATIONS FOR METABOLIC SURGERY

There is no doubt that MBS benefits morbidly obese patients with multiple features of the metabolic syndrome in the long-term with mortality reductions^{10,27}. For patients suffering from T2DM, the sustained effect of MBS on glycaemic control is so dramatic that the American Diabetes Association and the International Diabetes Federation have recommended that MBS may be considered a treatment option in carefully selected patients with a BMI ≥ 30 kg/m² and in whom glycaemic control is suboptimal despite currently available pharmacotherapy^{41, 42}. The Singapore Ministry of Health's 2004 Clinical Practice Guidelines on obesity allows for MBS at a BMI of ≥ 32.5 kg/m² in people with obesity-related conditions like T2DM, dyslipidaemia, OSA and hypertension.

Bariatric surgery is a life-changing procedure associated with known risks and complications. Patients should be well informed about the restriction on eating ability and must be prepared to commit to life-long follow-up to treat and prevent potential complications such as nutrient deficiencies. Generally, there are relatively few contraindications for MBS (e.g. unstable coronary artery disease, active cancer with limited life expectancy). However, often overlooked are psychosocial factors such as low socioeconomic status, limited social support, unrealistic expectations and disordered eating habits (e.g. binge eating), which are associated with a suboptimal outcome and should be carefully screened for and dealt with along with the medical and surgical aspects of MBS. Hence for best long-term outcomes, the patient should be cared for by a trained multi-disciplinary team and patients must realistically understand this.

CONCLUSIONS

- 1) MBS is an effective, durable and safe treatment modality for metabolic diseases, in particular T2DM.
- 2) Furthermore, reduced mortality particularly related to T2DM, CVD and cancer, has been observed in the long-term.
- 3) However, careful patient selection with long-term management and close monitoring by an experienced and trained multi-disciplinary team should be considered mandatory to minimise the risks and maximise the benefits of MBS in these appropriately selected patients.

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LEARNING POINTS

- **Metabolic bariatric surgery (MBS) is effective, durable and safe treatment modality for metabolic diseases in the morbidly obese, in particular T2DM.**
 - **In the long term metabolic bariatric surgery results in reduced mortality particularly related to T2DM, CVD and cancer.**
 - **The surgical procedures for treating metabolic disease are divided into: (a) restrictive and (b) bypass-type (malabsorptive) procedures.**
 - **Restrictive procedures are gradually gaining acceptance among both patients and surgeons as they are less complex than the bypass-type procedures and are less likely to require life-long vitamin and nutrient supplements.**
 - **According to the Singapore Ministry of Health's 2004 Clinical Practice Guidelines on obesity, MBS is indicated for patients with BMI $\geq 32.5\text{kg/m}^2$ with T2DM and /or other obesity related co-morbidities.**
 - **The International Diabetes Federation (IDF) recommends that MBS may be considered a treatment option in carefully selected patients with a BMI $\geq 30\text{kg/m}^2$ (Asian BMI $\geq 27.5\text{kg/m}^2$) in whom glycemic control is suboptimal despite currently available pharmacotherapy.**
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