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*Review Article*

# The success of sleeve gastrectomy in the management of metabolic syndrome and obesity

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## Abstract

The rapid reversal of diabetes, hypertension, hyperlipidaemia and obesity by surgical means has challenged accepted doctrines regarding the management of metabolic syndrome. Sleeve gastrectomy, which developed initially as a preparatory procedure for biliopancreatic diversion with duodenal switch, has seen an exponential rise in popularity as an effective lone laparoscopic bariatric procedure. Superior excess weight loss, a low complication rate, and excellent food tolerance, combined with a short hospital stay, have made this the procedure of choice for patients and surgeons across the globe. High volume centres nurture the ongoing development of experienced and specialized teams, pathways and regimens. Optimum surgical outcomes allow minimization of metabolic syndrome, reducing cardiovascular and cerebrovascular risk.

**Keywords:** metabolic surgery, sleeve gastrectomy, diabetes mellitus, obesity

## Introduction

The most widely used definition of metabolic syndrome is that of the Third Report of the American National Cholesterol Education Program[1]. Three or more of the following risk factors, which are easily mesured, must be present for diagnosis: abdominal obesity ($>$ 102 cm/40 in men, $>$ 88 cm/35 in women), triglycerides $\geqslant$ 150 mg/dL, low high density lipoprotein (HDL) cholesterol ($<$ 40 mg/dL men, $<$ 50 mg/dL women), high blood pressure $\geqslant$ 130/$\geqslant$ 85 mmHg and raised fasting glucose $\geqslant$ 110 mg/dL. Risk of myocardial infarction is increased considerably by this cluster of variables.

Obesity alone may result in sleep apnoea, congestive cardiac failure, spine and joint degenerative conditions, and depression. In South East Asia, obesity rates are among the lowest in the world, but are increasing quickly along with unprecedented economic growth. The Asian Consensus Meeting on Metabolic Surgery has outlined guidance for metabolic surgery in individuals of Asian ethnicity. Indications include obesity with a body mass index (BMI) of $\geqslant$ 35 kg/m$^2$, or $\geqslant$ 32 kg/m$^2$ with co-morbidities, or $\geqslant$ 30 kg/m$^2$ with 2 or more of: raised triglycerides, abdominal obesity (waist $>$ 80 cm in females and $>$ 90 cm in males), reduced HDL cholesterol, hypertension, and raised fasting plasma glucose levels[2]. Between 2004 and 2009, a 449% increase in bariatric surgical procedures was noted among 11 Asian countries[3].

Weight control via dietary modifications and increased physical activity remain the primary and most cost-effective initial interventions for obesity. Lipid lowering drugs have a central role in prevention of atherogenesis, coronary artery disease and cerebrovascular disease. However, for the majority of patients with moderate to

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severe type II diabetes and obesity, intensive medical therapy including lifestyle changes does not provide sufficient reduction in the glycated haemoglobin level to effectively reverse diabetes (HbA1c $< 6.0$). Surgery has come to the fore in metabolic syndrome following the success of bariatric procedures. An improvement in type II diabetes, observed in addition to weight reduction, has been demonstrated.

The ongoing expansion from bariatric into metabolic surgery for sleeve gastrectomy reflects international recognition of its role in the correction of co-morbidities in the moderately obese, particularly insulin resistance diabetes. The inclusion of bariatric surgery in the algorithm of the International Diabetic Federation for type II diabetes[4] consolidates the evidence.

## Mechanisms

Sleeve gastrectomy, which involves laparoscopic removal of approximately 75% of the stomach, is regarded as a restrictive bariatric procedure, with a considerable calorie restriction effect on BMI. However, the metabolic effects are much greater than calorie restriction alone. Several plausible hypotheses for the metabolic effects of the surgery have been articulated. Alterations in the secretion of hormones like ghrelin, peptide-YY (PYY), leptin, glucagon-like peptide 1 (GLP-1), glucose dependent insulinotropic peptide (GIP), decrease in insulin resistance, long-term weight loss and alterations in gut microbiota together contribute to optimal glucose homeostasis after surgery[5,6].

The role of incretins in the promotion of insulin production is frequently postulated as a mechanism for the success of metabolic surgery. Two main incretins, GLP-1 and GIP, are produced from the small intestine epithelium in response to intestinal glucose concentrations. Incretins enhance glucose-dependent insulin production at the pancreatic $\beta$-cells. Additionally, GLP-1 inhibits glucagon production. In diabetic individuals, the secretion of GLP-1 and response to GIP are blunted.

A comparative analysis of gut hormones after sleeve gastrectomy and gastric bypass found that both exerted influence on GLP-1, GIP, obestatin and leptin, and bypass had an additional duodenal effect on cholecystokinin[7]. Exaggerated GLP after gastric bypass has been associated with increased pancreatic beta cell function although causality remains uncertain[8].

Insulin secretion happens in two phases, the first of which is restored considerably following sleeve gastrectomy. Basso et al. in their study reported a ''gastric hypothesis'' for this restoration of 1$^{st}$ phase insulin secretion, which improves glycaemic control. They proposed that a decrease in hydrochloric acid-stimulated, vagally-innervated, antral mucosa secretion of gastrin releasing peptide (GRP) in turn stimulated GLP-1 release[9].

Faster gastric emptying was demonstrated scintigraphically in 11 patients at 6 months from surgery, and then compared to pre-operative testing. The time from the end of meal until the beginning of emptying into the duodenum was reduced from 19.2 to 9.5 minutes. Gastric emptying half-time decreased from 94.3 to 47.6 minutes, indicating a quicker transit through the stomach. Quicker entry of food to the distal small bowel directly stimulates the L-cells for the 2$^{nd}$ phase of GLP-1 peptide release[10,11]. Another study by Tzovaras et al. supported this theory when they demonstrated symptoms suggestive of dumping syndrome after provocation in patients post-sleeve, reinforcing the notion that sleeve is not a purely restrictive procedure[12].

Ghrelin, an appetite stimulant, produces orexigenic effects via stimulation of neuropeptide Y from the hypothalamus. Ghrelin is mainly produced by the oxyntic cells of the stomach, and has been implicated in obesity and metabolic syndrome. Diet induced weight loss raises circulating ghrelin levels. Sleeve gastrectomy significantly lowers fasting ghrelin despite weight loss, with suppression of ghrelin after meals, compared with no change from baseline fasting or post-prandial ghrelin levels after gastric bypass[13]. The reduction in serum ghrelin levels persists at 5 year follow-up of sleeve gastrectomy[14]. Insulin inhibits release of ghrelin.

PYY is co-secreted with GLP 1 from the distal intestine after meals, and increases insulin sensitivity and also inhibits the hypothalamic production of neuropeptide Y. PYY levels are increased after either sleeve gastrectomy or gastric bypass[13].

Pharmacological GLP-1 agonists have been approved by the United States Food and Drug Administration (FDA), as have inhibitors of dipeptidyl peptidase 4 (DPP 4), a protease which degrades GLP-1 and GIP. While such medications may control hyperglycaemia in diabetes, and even produce slight weight loss and hypertension reduction, the effects are not comparable to metabolic surgery.

## Metabolic outcomes of sleeve gastrectomy

The Fourth International Consensus Summit on Sleeve Gastrectomy in New York, 2012 included a survey of 46,133 sleeve gastrectomy cases, among 130 surgeons, at an average of 5 years after surgery. Excess weight loss was 59% at 1 year, gradually falling to 50% at 6 years. Low complication rates were noted:

high leak 1.1%, haemorrhage 1.8% and stenosis 0.9%[15].

As weight loss plays a key role in metabolic syndrome outcomes after sleeve gastrectomy, for excess weight loss, increasing numbers of trials demonstrate its effectiveness. Himpens et al. reported the percentage excess weight loss (EWL) after sleeve gastrectomy as 77.5% and 57.3% at 3 and 6 years, respectively[16]. Among super obese patients, the reported mean EWL is 52%, 43% and 46% at 72, 84 and 96 months follow up, respectively[17].

Although widely considered safe and effective, post-operative complications do remain a feature of this surgery, though fewer and earlier in comparison to other procedure, with leak rates of 2.2% in a meta-analysis of 9,991 cases[18].

Direct comparison of medical versus bariatric surgical management of obesity and diabetes was performed in the STAMPEDE prospective randomised controlled trial at the Cleveland Clinic[19]. Gastric bypass (Roux En Y) or sleeve gastrectomy provided a mean of 29.4 kg and 25.1 kg EWL, respectively, versus 5.4 kg in the intensive medical group. Regarding diabetes, the success rate for reduction in HbA1c to 6.0% at 12 months was over 3 times greater after sleeve gastrectomy or gastric bypass surgery (42% and 37% versus 12%, respectively)[20]. As a result, lesser medications for diabetes, hypertension and hyperlipidaemia need composite improvement in all parameters of metabolic syndrome. Long-term follow up of sleeve gastrectomy patients at 6–8 years showed a 77% improvement or remission of diabetes[17].

A systematic analysis of 33 studies comprising 3,997 patients demonstrated reduction in hypertension in 75% of cases, with resolution in 58%, at an average follow up of 16.9 $\pm$ 9.8 months[21]. Cardiac remodelling following sleeve gastrectomy has been shown on echocardiography. Reduced left ventricular mass, septum and posterior wall thickness, were demonstrated in the study by Cavarretta et al.; thus, there is improvement in cardiac function[22]. Lipid profile improvement, specifically HDL and triglyceride levels, total cholesterol/HDL and triglyceride/HDL ratios at 1 year follow-up have been reported without lowering of total cholesterol and LDL levels after sleeve gastrectomy[23].

The Asian population in general is known to develop metabolic syndrome at lower BMIs in comparison to their Caucasian counterpart and hence, studies have reported outcomes from Asia in this cohort. In Asian populations with type II diabetes and non-morbid obesity (BMI, 25–35 kg/m$^2$), sleeve gastrectomy has demonstrated up to 50% resolution in diabetes at 1 year[24]. The principal mechanism is thought to be related to calorie restriction and weight loss, and C-peptide levels returning to $>$ 3 ng/mL appears to be the most reliable marker of resolution.

## Why Sleeve Gastrectomy?

In subjects with moderate obesity (36 +/- 2 kg) and uncontrolled type II diabetes, an extension of the STAMPEDE trial has shown restoration of pancreatic $\beta$-cell function, in contrast to intensive medical therapy or sleeve gastrectomy[25].

However, in Asia, where expertise regarding metabolic procedures and their long term management is limited, widespread promotion of a malabsorptive procedure without equipping the masses with the necessary knowledge may prove detrimental for this field and for patients. A procedure with risk and benefit between the gastric band and gastric bypass is appealing. Sleeve gastrectomy has been shown to have greater excess weight loss, and improvement in diabetes, than gastric band[26]. Indeed, sleeve is a successful revision procedure following failure of gastric band, with concomitant band removal at sleeve gastrectomy, and 53% excess weight loss at one year[27]. Food tolerance and gastrointestinal quality of life after sleeve gastrectomy are comparable to pre-surgery controls. The food tolerance questionnaire and the Gastrointestinal Quality of Life index (GIQLI) at 2 and 4 years found sleeve gastrectomy superior to adjustable gastric band, and Roux-En-Y gastric bypass[28]. At 6 years from sleeve gastrectomy, 95.2% report their food tolerance from acceptable to excellent[29]. Sleeve gastrectomy can be employed for obese patients with metabolic syndrome who are at high risk of developing complications after malabsorptive proce–dures, including chronic smokers and non-steroidal anti-inflammatory drug users. It is a valuable option for patients who are elderly and those with inflammatory bowel disease[30].

The burden of taking medications daily and regularly is not easy to handle. The simple thought of taking less medications or being free from taking them is a joy. A retrospective study of sleeve gastrectomy in morbidly obese individuals reported a mean excessive BMI loss of 79.9% after 2 years. After surgery, 83.3% of patients with type II diabetes discontinued their hypoglycaemic medication after 1 month. Antihypertensive drugs were discontinued by 6 months, and medications for hypertriglyceridemia after 3 months. A significant reduction in glucose, triglyceride levels, triglyceride/HDL ratio and increased HDL levels were noted and these changes were maintained under normal ranges for at least 2 years[31].

## The future of laparoscopic sleeve gastrectomy

Alternative procedures including gastric band, laparoscopic Roux-En-Y gastric bypass and gastric balloon insertion may be performed. The relative technical simplicity of sleeve gastrectomy, low morbidity, endoscopic access to the gastrointestinal tract, absence of anastomoses, minimal nutritional deficiencies, excellent weight loss with control of associated comorbidities, and the possibility to convert to other procedures, place sleeve gastrectomy at an advantage over other bariatric procedures.

Gastric bypass has a long history and long-term results support its efficacy in treating obese patients with metabolic disorders. It is an established fact that there are mechanisms beyond weight loss that are responsible for the excellent metabolic outcomes of gastric bypass and that these are related to bypassing the foregut. To maximize the scope of sleeve gastrectomy as a metabolic procedure, innovative procedures with the benefits of both sleeve gastrectomy and gastric bypass are being employed. The sleeve duodenojejunal bypass surgery (LSG/DJB), single-anastomosis duodenojejunal bypass with sleeve gastrectomy (SADJB-SG), sleeve gastrectomy with loop bipartition, and loop duodenojejunal bypass with sleeve gastrectomy, are all largely based on manipulation of foregut. The short term outcomes have been promising; however, they are still considered experimental as both intermediate and long term data are awaited. Loop duodenal bypass in combination with sleeve gastrectomy for type II diabetes in individuals with BMI 21–38 kg/m$^2$ has shown promising early results, with 91% achieving HbA1c of 7.0 g/dL at 6 months from surgery[32].

Laparoscopic Roux-En-Y gastric bypass prohibits visualisation of the excluded stomach. For populations with a high risk of gastric cancer, including Japan, endoscopic visualisation is paramount. In obese individuals with risk factors such as *Helicobacter pylori* infection, atrophic gastric mucosa including intestinal metaplasia, or a family history of gastric cancer, Kasama et al. published a series of laparoscopic sleeve gastrectomy with duodenojejunal bypass[33]. The procedure was found to be feasible, and safe, with similar EWL to Roux-En-Y gastric bypass. Additional EWL versus sleeve gastrectomy was attributed to the added malabsorptive effects of the duodenojejunal bypass.

Sleeve with ideal interposition is an example of sleeve with hindgut manipulation. Patients undergoing this procedure have demonstrated restoration of insulin sensitivity, with increased insulin output, and doubling of $\beta$-cell glucose sensitivity[34]. The mechanism is postulated to be intestinal over-stimulation, with increased GLP 1 and incretin secretion.

## Conclusion

Sleeve gastrectomy is a valuable weapon in the fight against metabolic syndrome and obesity. Excess weight loss, resolution of diabetes, hypertension, sleep apnoea and cardiac remodelling with reduction in cardiac risk profile, provide compelling arguments for expansion of metabolic surgery. The biomedical research potential from distinct anatomical changes in the gut, occurring in a controlled manner during surgery, is inspiring. The collaboration between surgical and laboratory teams sheds new light on pathogenesis of metabolic syndrome and diabetes, through the effectiveness of gastrointestinal surgery, and heralds in a new era spurred by the necessity to curb the epidemic.

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