Effect of SGLT in Type 2 Diabetes and Gastric Bypass Surgery - A Narrative Review

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ABSTRACT

Body fat is regulated by a complex neuroendocrine system, making it difficult to maintain weight loss achieved via caloric restriction. Bariatric surgery produces greater weight loss and weight loss that is more durable than caloric restriction, and therefore is currently the most effective therapy for obesity. Sodium-glucose-co-transporter inhibitors are glucose lowering drugs that reduces plasma glucose levels by inhibiting glucose and sodium reabsorption in the kidneys, resulting in glycosuria.

Sleeve gastrectomy is one such bariatric surgical procedure that involves the creation of a reduced stomach lumen along the lesser curvature of the stomach through the removal of gastric tissues along the greater curvature from the fundus to the antrum. Stomach capacity is typically reduced 80% or more, and the intestine remains intact. This procedure produces dramatic weight loss in humans and in rodents. In fact, recent reports indicate that its efficacy is close to that of the more common Roux-en Y gastric bypass.

There are many diverse factors on which operative mortality of bariatric surgery depends such as facility related, surgeon related, followed by patient and procedure-related. To minimize operative mortality, specific factors were considered for the specific patients. As a result, to treat type 2 diabetes in association with obesity, slightly obese patients or overweight patients were treated with conventional bariatric procedures worldwide. For the management of morbidity obese diabetic patients, there is no single or standard procedure.

Keywords: SGLT, Bariatric Surgery, Type-2 Diabetes, BMI

INTRODUCTION

The most important molecule to act as basic fuel is glucose which is essential for the brain and other vital organs. There are many cells evolved for the transport of extracellular glucose during fasting. In mammalian cells, there are two types of glucose carriers: active sodium-glucose co-transporters (SGLTs) and facilitative glucose transporters (GLUTs).[1,2] The most important mediators of glucose uptake across apical cell membrane is SGLT1. Almost uptake of all sodium-dependent glucose takes place in the small intestine, while in the kidney SGLT2, and to a lesser extent SGLT1. It nearly account for more than 90% and nearly 3% respectively, of glucose reabsorption from the glomerular ultra-filtrate. It has a role in transporting apical sodium and glucose across the cell membranes. GLUTs are cell specific intrinsic membrane proteins that have an ability to respond metabolic and hormonal regulation.[3,4] The passive transfer of glucose across cell membranes down a concentration gradient is also done by them. In the human genome, there are 12 members of the SGLT family including co-transporters for sugars, anions, vitamins, and short-chain fatty acids. Some of the transporters of sugars are SGLT1, SGLT2, SGLT4 and SGLT5 except SGLT3 which works as a glucose sensor. The main components are SGLTs are SGLT1, responsible for the absorption of glucose from the small intestine whereas SGLT2 helps in reabsorption of most of the glucose filtered

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in urine.[5]

SGLT1 has very less affinity for galactose which is expressed in the trachea, kidney, heart, and brain, followed by testes, prostate and pancreatic α-cells whereas SGLT2 is expressed predominantly in the kidney, but is also expressed in the brain, liver, thyroid, muscle and heart including pancreatic α-cells. These inhibitors are relatively new classes of drugs that work by increasing urinary glucose excretion. Furthermore, SGLT1 also acts as a glucose sensor in entero-endocrine cells.[6] It has been seen from the previous research that single mutation in the SGLT1 gene is the cause for glucose galactose malabsorption disorder. In contrast to this, the growing evidence suggests that obesity and type-2 diabetes are associated with disorders of intestinal glucose absorption and SGLT1expression.[7]

Bariatric surgery was first reported to possibly prevent type-2 diabetes by Pories et al in 1992 and was revised in 1995. Patients potentially eligible for bariatric surgery included those who were well informed and motivated, had a BMI >40 kg/m^2 with acceptable risk for bariatric surgery and had failed previous attempts at non-surgical weight loss. The consensus statement also suggested that individuals over 18 years of age with a BMI >35kg/m^2 with obesity- related co-morbidities such as diabetes, sleep apnea, obesity-related cardiomyopathy, or severe joint disease are also indicated for this type of surgery.[8,9]

Bariatric surgery is contraindicated in patients with untreated major depression, psychosis, binge eating disorders, current drug and alcohol abuse, severe cardiac disease or those who have other major anesthesia- related risks, severe coagulopathy or an inability to comply with nutritional requirements such as lifelong vitamin replacement. Bariatric surgery in children under 18 years of age remains a controversial topic.[10,11]

The laparoscopic sleeve gastrectomy was originally conceived as a first stage for achieving weight loss in superobese (BMI >60kg/m^2) patients and those with severe co-morbidities to reduce perioperative morbidity and mortality. The procedure is relatively new, initially described in 2003. It was often first step prior to duodenal switch or RYGB, or a rescue after another failed bariatric procedure, but it has become the primary choice of some surgeons, replacing gastric banding.[12] Hence, this narrative review article discusses the effect of SGLT in type 2 diabetes and gastric bypass surgery.

Sodium-Glucose Co-Transporters

Function, physiology, and clinically significant polymorphisms

SGLT1 is an extracellular amino terminus and an intracellular carboxyl terminus which is a 75-kDa membrane protein with 14 trans-membrane α-helices. It is not only responsible for the sodium-dependent, active uptake of glucose across the apical membrane of the small intestine but has a role in kidney where it helps in reabsorption of about 10% of the tubular glucose. SGLT is the primary renal glucose transporter and is a member of SLC5 family. The last steps of glucose oral absorption and renal reabsorption are performed by another transporter family which includes the SLC2A or GLUTs.[13]

Clinical significance

For the treatment of type 2 diabetes, glucose transporter inhibitors are under assessment as therapeutic agents. The anti-diabetic agent are developed to be used as selective SGLT1 inhibitor KGA 2727 that has proper ability to block the transporter function in cells overexpressing SGLT1. To tolerate gastrointestinal side effects such as diarrhoea which occurs as a common consequence of intestinal glucose retention, LX4211 was well tolerated to avoid such effects.[14] In a Phase I clinical trial, the selective SGLT1 inhibitor GSK-1614235 blocked glucose absorption but also impaired glucose-dependent insulin-tropic peptide release. When there are mutations in the coding sequence of the SGLT1, glucose-galactose malabsorption (GGM) takes place which is a rare inherited autosomal recessive disease. Symptoms such as watery and acidic diarrhoea that is commonly present in neonates occurs due to water retention in the intestinal lumen caused by the osmotic loss generated by non-absorbed glucose, galactose, and sodium in the intestine. One solution to this problem is oral rehydration therapy which is an effective treatment for GGM, where sodium and glucose are combined with water for intestinal absorption by direct co-transport and sodium/glucose-induced osmosis, the latter resulting from sodium and glucose co-transport via SGLT1 in the apical membrane of the enterocytes.[15]

Firstly, in patients with uncontrolled diabetes, SGLT1 plays an important role in the intestinal absorption and the renal reabsorption of glucose, especially those receiving SGLT2 inhibitors. As a result, there is an interesting therapeutic option in patients with diabetes which is inhibition of SGLT1 transporters. Furthermore, drugs which interfere with SGLT1-mediated transport of glucose may protect cardiac tissue by lowering glycogen accumulation and reducing the formation of reactive oxygen species. Secondly, this inhibition may result in diarrhoea, volume depletion, and interferes with the correction of hypoglycemia through the oral administration of carbohydrates and leads to the development of euglycemic diabetic ketoacidosis. Hence, inhibition of SGLT1 acts as a two-edged sword.[15]

BARIATRIC SURGERY AND OBESITY

The problem most commonly faced by physicians and surgeons on a daily basis is whether surgical intervention for all patients with severe obesity should be advised or not because of the following reasons such as fear of post-operative complications, increased cost, lack of current knowledge of the evolving literature related to bariatric surgery. The obesity-related diseases are prevalent in adolescents and severely among due to the increase in incidence of obesity-related glucose intolerance/diabetes, coronary heart disease, stroke and impaired quality of life. Studies from previous literature indicates that this surgery is safe which helps in weight loss, improved self-image and increases socialization among adults as well as in adolescents. Further research is

clearly needed to investigate for future attention.[16]

TYPES OF BARIATRIC PROCEDURES

Bariatric surgery has proved to be an effective procedure in the treatment of obesity. Vertical banded gastroplasty (VBG) was developed by Mason et al in which reported that stomach is partitioned with staples and fitted with a plastic band to restrict the passage of food through the stomach. It does not involve rerouting of food within the digestive tract as in GI bypass surgeries but this procedure is now abandoned.[17]

LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING (LAGB)

This procedure was developed in the early 1990s as original, open gastric which was modified later on to laparoscopic implanted device. It is a restrictive procedure that encircled the upper part of the stomach with a band-like, fluid-filled tube to create a small pouch. This band has a circular balloon inside that is filled with salt solution and wrapped around the upper portion of the stomach 1-2 cm distal to the gastro-oesophageal junction. If the band creates problems and is not helpful in losing the weight, the surgeon may remove it.[18]

RETROCOLIC ROUX-EN-Y GASTRIC BYPASS (RYGBP)

In 1970's this technique was developed by Mason in response to the ileojejunal intestinal bypass, a procedure which has several complications such as malabsorption, diminished food intake and weight loss. The latest technique involved the use of a surgical stapler to create a small and vertically oriented gastric pouch of approximately one ounce capacity which is located on the lesser gastric curvature.

The upper pouch is completely separated from the gastric remnant and is anastomosed to the jejunum through a narrow gastrojejunal in a Roux-en-Y fashion. The continuity of bowel can be restored by an entero anastomosis between the excluded biliopancreatic limb and the alimentary limb. After RYGBP, ingested food bypasses most of the stomach and the first part of the small intestine.[19]

RYGB improves T2D more than expected from weight loss alone. This suggests that excluding a portion of the stomach and the proximal intestine from the alimentary circuit may directly improve glucose metabolism. Among several potentially intricate mechanisms, carbohydrate malabsorption is generally not considered to significantly improve glucose homeostasis. However, the efficacy of surgical procedures progresses from the purely restrictive to mostly restrictive and then mostly malabsorptive.[20]

Clinical evidence also showed that gastric bypass variants with a shorter common limb, such as the long-limb gastric bypass, the omega loop gastric bypass, or the biliopancreatic diversion, all more effectively treat T2D. It has been found interesting that metabolic features of RYGB can be experimentally reproduced in rodents by simply diverting bile flux from the hepatic duct directly to the distal intestine. Several studies from previous literature suggested that the bile deprived alimentary limb (AL) causes changes in glucose handling. The proposed mechanisms include an increase in intestinal gluconeogenesis and portal glucose sensing and an increase in enterocyte metabolism and GLUT1-mediated uptake of circulating glucose. Other studies have identified a functional defect in SGLT1 in the AL. It was recently explored that the handling of dietary glucose by the various segments of the RYGB in a minipig model mimicking the clinical procedure. This study found that the ingested glucose was only absorbed in the common intestinal limb, where food meets bile and other gastrointestinal fluids.[21,22]

BPD

In 1979, the concept of biliopancreatic diversion (BPD) was developed by Scopinaro. The operation consists of subtotal gastrectomy which involved distal, horizontal gastrectomy that leaves behind a functional upper stomach 200–500 ml in size (according to the individual patient's characteristics). This remnant stomach is anastomosed to the distal 250 cm of small intestine (alimentary limb). The excluded small intestine (including the duodenum, the jejunum, and part of the proximal ileum) carries bile and pancreatic secretions (biliopancreatic limb), and it is connected to the alimentary channel 50 cm proximal to the ileocecal valve which is the only segment of small bowel where digestive secretions and nutrients mix. A modification called as biliopancreatic bypass (BPD/DS) with duodenal switch consists of a sleeve gastrectomy where the greater curvature of the stomach is resected creating a tubular section along the lesser curvature of the stomache.[23]

Sleeve Gastrectomy

This was proposed by Gagner et al to reduce the time of the laparoscopic BPD-DS among patients with high-risk. This is a two-stage approach in which sleeve gastrectomy is performed first, with the duodenoileostomy and ileoileostomy as a second stage a few months later. In super-obese patients with BMI of 60 kg/m2 this approach was successful in decreasing surgical morbidity and mortality compared with the traditional one-stage approach As a result, patients achieved remarkable weight loss after the first stage is now being proposed as an independent anti-obesity operation by various authors in the literature but the long-term efficacy of this procedure, however, needs to be further investigated.[24]

Diabetes and Bariatric Surgery

Although diabetes is traditionally viewed as a chronic, relentless disease in which delay of end-organ complications is the major treatment goal, bariatric surgery offers a novel end point: major improvement or even complete disease remission. In a study done by Schauer et al., it was found that in-depth evaluation of the clinical outcome among 240 diabetic morbidly obese bariatric patients with a follow-up rate of 80%. The results revealed that after surgery, weight and BMI decreased from 308 lbs and 50.1 kg/m2 to 211 lbs and 34 kg/m2 for a mean weight loss of 97 lbs and mean excess weight loss of 60%.[25]

There was improved fasting plasma glucose and HbA1c

concentrations which returned to normal levels among all the patients. A significant reduction in use of oral anti-diabetic agents and insulin followed surgical treatment. Patients with the shortest duration (5 years), the mildest form of type 2 diabetes (diet controlled), and the greatest weight loss after surgery were most likely to achieve complete resolution of type 2 diabetes.

Based on recent data on the existent clinical results of bariatric operations in type 2 diabetic patients with BMI, 35 kg/m2 Most of the procedures were conventional bariatric operations, but there were also two experimental procedures—ileal interposition with SG or diverted SG. Patients lost a clinically meaningful but not excessive amount of weight (from BMI 29.4 to 24.2 kg/m2; decrease of 5.1 kg/m2), moving from the overweight into the normal weight category.[26]

Of the patients, 85.3% were off type 2 diabetes medications with fasting plasma glucose approaching normal (105.2 mg/dl; decrease of 93.3), and normal HbA1c, (6%; decrease of 2.7). Operative mortality was at 0.29%. The improvement was better in the malabsorptive operations than the restrictive ones, and interestingly, the higher BMI subgroup (obesity range: 30–35 kg/m2) resolved their type 2 diabetes at a significantly higher rate than the lower BMI subgroup (overweight range: 25–29.9 kg/m2).[27]

SUGGESTED POSSIBLE MECHANISMS

These are given by Rubino et al where putative weight-independent anti-diabetes mechanisms of GI surgery have been reviewed thoroughly that includes:

1) Due to enhanced distal-intestinal nutrient delivery there is increased postprandial secretion of L cell peptides such as glucagon-like peptide 1.
2) There is removal of the proximal small intestine from nutrient flow, possibly down-regulating unidentified anti-incretin factor(s)
3) Impaired ghrelin secretion;
4) Insulin sensitivity is regulated by change in intestinal mechanism of nutrient-sensing.
5) Perturbations of bile acid
6) Alterations in undiscovered gut factors, especially in the duodenum.

Although the precise mechanisms mediating type 2 diabetes remission after certain GI procedures are still not clear, it is apparent that rearrangements of GI-tract anatomy can exert several discrete anti-diabetic effects beyond those related to reduced food intake and body weight. Various GI manipulations engage these mechanisms to differing degrees, and it is likely that operations with dramatic anti-diabetes impact, such as RYGBP, activate several of them in complementary ways. Beyond the few hormones whose changes after GI surgery have been studied, the gut produces known bioactive peptides and possibly other undiscovered relevant factors. Clarifying the molecules responsible for the benefits of GI surgery on glucose homeostasis is a compelling research objective that promises to inform the design of novel pharmaceutical therapies.[28]

CONCLUSION

Over the last three decades, scientists have become aware of the key role of SGLT transport in diabetes and obesity, as evidenced by a tremendous increase in the number of yearly publications. These have contributed to the first step into the clinical era of the usage of SGLT inhibitors. In parallel, there was an unknown effect of bile diversion in gastric bypass on sodium glucose transport and homeostasis but the mechanism that underlie this effect are unknown. Hence, with available clinical evidence, it can be concluded that metabolic surgery will open new vistas for research. So, studies with more sample size are required for improved understanding of both beneficial and adverse effects of the clinical application of SGLT2-specific inhibitors after bariatric surgery.

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