Perioperative glycaemic control on diabetes outcome following gastric bypass surgery

Ling Ling Chuah
Metabolic Medicine
Imperial College London

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Statement of Originality

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Abstract

Bariatric surgery such as Roux-en-Y gastric bypass (RYGB) is increasingly performed in obese patients with type 2 diabetes (T2DM) due to its beneficial metabolic effect. RYGB is distinct from non-bariatric surgery as it improves glycaemic control immediately post-surgery. Most bariatric centres also use a low calorie diet preoperatively which also impacts on glycaemic control before surgery. Glycaemic management of these patients therefore needs to be reviewed perioperatively to avoid hypoglycaemia. To date, no study has assessed how best to manage this group of patients preoperatively and postoperatively. GLUCOSURG-pre and GLUCOSURG-post studies were designed to assess the effect of intensive glucose management before and after RYGB on glycaemic outcome.

Moreover, patients with difficult controlled diabetes are more at risk of complications of diabetes. Given the rapid improvement in glucose control following RYGB, its effect on microvascular complications needs to be assessed. In this thesis, I measured the changes in diabetic nephropathy, retinopathy and neuropathy; and compared the changes in nephropathy and retinopathy to a control group.

My study showed that 3 months of intensive management of glycaemia before surgery, or the first 2 weeks after surgery had not resulted in better glycaemic control at 1 year. RYGB has substantial effects on glucose control, and additional intensive glucose-lowering interventions do not confer clinical benefits compared to conservative approaches. In the case-control study, RYGB patients showed substantial reductions in albuminuria, while the rates of retinopathy progression were similar to those observed in a medically treated group. There was no change in peripheral nerve function 1 year after RYGB surgery. My study was limited by small sample size and short duration of follow up. Nonetheless, the result would reaffirm the importance of annual surveillance for diabetic retinopathy and neuropathy after RYGB.
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Introduction

1.1 Prevalence of obesity

1.1.1 The obesity epidemic

Obesity has become the major public health problem in developed and developing countries due to its rising prevalence and association with obesity related diseases. The prevalence of obesity began in 1970, and had seen a significant increase since 1999. In 2008, it was estimated that 1.4 billion adults worldwide were overweight, of which 500 million were obese. Overweight is defined as body mass index of $\geq 25\text{kg/m}^2$, and obese is defined as body mass index of $\geq 30\text{kg/m}^2$ (Organisation, 2012). In England, 26% of adult were classified as obese (The NHS Information Centre, 2012). Wang et al used a simulation model to project the health and economic consequences of obesity in UK and US at 20 years’ time (Wang et al., 2011). The projection showed prevalence of obesity would increase from 26% in 2007-8 to 41-48% in men in 2030; similarly, there is an increase from 26% to 35-43% in women, an estimate of 11 million more obese adults in the UK by 2030. (Wang et al., 2011). Alarmingly, children are also affected by this epidemic. More than 40 million children under the age of five are classified as overweight globally. (WHO, 2010). In England, 30 % of children aged 2-15 were classed as overweight or obese (The NHS Information Centre, 2012).

1.1.2 Aetiology of obesity

The development of obesity is led by chronic excess of energy intake over expenditure. Obesogenic environment, fuelled by easy accessibility of sugar-dense food, increased in mechanised work and reduction in physical work; led to inactivity and sedentary lifestyle. However, not everyone within the same environment becomes obese. Genetic predisposition to fat accumulation, or the drive to overeat, coupled by the obesogenic environmental factors exacerbate the extent of obesity. Advancement in food technology and expansion of food industry also played a part. Cultural differences such as body size preferences could also modulate the prevalence of obesity (Swinburn et al., 2011).
1.1.3 Treatment of obesity

The conventional treatment of obesity encompassed physical activity (Shaw et al., 2006), diet (Thomas et al., 2007) and pharmacotherapy (Bray, 2008). Comparing with low intensity exercise, high intensity exercise had better weight loss result. In addition, combined exercise and diet was shown to yield better weight loss than diet alone.

Pharmacotherapy was once a popular option to control weight loss. However, the availability of these medications is restricted since the beginning of year 2000 due to drug safety issues. For example, Sibutramine are now withdrawn from sales in many countries due to its associated increased risk with cardiovascular and cerebrovascular events. Rimonabant were linked to increased risks of severe depression and suicidal thoughts and hence been withdrawn from the America and European market.

Orlistat is now the only medication licensed for weight loss intervention in United Kingdom. It works by inhibiting the breakdown of ingestible fat by pancreatic lipase. It causes weight loss and had been shown to reduce incidence of diabetes in those with impaired glucose tolerance (Torgerson et al., 2004). These interventions could achieve weight loss of about 10% but the success of these interventions is limited by long term adherence (Bray, 2008).

More recently, weight loss surgery or bariatric surgery is shown to be more effective in losing weight and maintain the weight loss long term. It also has positive effect on hypertension and hyperlipidaemia; and had shown to reduce obesity related diseases such as obstructive sleep apnoea and cardiovascular event (Colquitt et al., 2009, Buchwald et al., 2004, Sjostrom et al., 2012).

1.1.4 Relationship between obesity and chronic diseases

Obesity is now the major public health problem because of its association with metabolic syndrome and chronic diseases. Obesity related conditions are projected to increase significantly. Consequently, it is estimated that by 2030 there will be an additional 544 000- 668 000 cases of diabetes, 331 000- 461 000 of coronary heart disease and strokes, and 87 000-130 000 of cancer in UK and US combined (Wang et al., 2011).
Obesity and obesity related diseases such as T2DM, hypertension and dyslipidaemia are risk factors for cardiovascular disease, and are associated with atherogenesis (Husain et al., 2015). Atherosclerosis and endothelial dysfunction are discussed at Chapter 1.2.2.1. Endothelial dysfunction, reduction in nitric oxide, activation of renin angiotensin system and inflammation are the proposed mechanisms for atherosclerosis. Similar mechanisms have also been proposed to link between obesity and chronic kidney disease (Wahba and Mak, 2007).

Animal study had shown that obesity was associated with increased abdominal pressure, and hence increased systemic blood pressure and vascular resistance, which impairs renal perfusion and activates juxtaglomerular apparatus and the renin, angiotensin system. Chronic activation of renin angiotensin system eventually leads to hypertension, glomerulopathy, and proteinuria (Heneghan et al., 2013, Currie et al., 2011).

### 1.1.4.1 Relationship between obesity and diabetes

There are two main classifications of diabetes. Type 1 diabetes is autoimmune in origin and is characterised by insulin deficiency and it is not usually associated with obesity; its treatment is insulin injection. Type 2 diabetes (T2DM) forms 90% of the population of diabetes (UK, 2012). Risk factors of T2DM include obesity, metabolic disease, and increased abdominal adiposity. Its aetiology is multifactorial, with genetic makeup, environment, and prevalence of obesity all played the key part (Kahn, 2003). ‘Diabesity’ (Zimmet et al., 2001) is a term referred to diabetes resulted from obesity. There are 346 million patients with diabetes worldwide ((WHO), 2011) and the prevalence of diabesity populations is on an increasing trend.

T2DM is a progressive disease. It is associated with impaired insulin sensitivity and beta cell dysfunction. Insulin sensitivity is influenced by genetics, lifestyle measures such as diet and exercise, medications and body fat composition. Central body fat or visceral adiposity has shown to impair insulin sensitivity.

Beta cell dysfunction including loss of beta cell mass and diminished first phase insulin response occur at an early stage of the disease (Kahn, 2003). The normal pulsatile
insulin secretion is also disrupted. Consequently, there is failure in suppression of hepatic glucose production, leading to postprandial glycaemic excursion.

1.2 The diabetes epidemic

The prevalence of T2DM for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with T2DM is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004). In UK, T2DM affects 2.61 million adults in 2011, this number is estimated to rise to 4.5 million in 2025 (UK, 2012). Following the increase in childhood obesity, a rise in T2DM in children was noted in United States, Australia, and Japan. In UK, incidence of T2DM in children was 0.53/100,000 per year(Haines et al., 2007). Incidence of diabetes is higher in ethnic minority such as blacks and South Asians. Of these, 95% of children were overweight and 83% obese (Haines et al., 2007). Onset of childhood obesity is associated with 24 times of Hba1c≥ 7% in adulthood, at age 45 (Power and Thomas, 2011).

1.2.1 Natural history of T2DM

T2DM used to be disease that affects middle-aged and elderly, increasingly it is diagnosed in younger generations. It may present as polyuria, polydipsia, and recurrent infection (Organisation, 1999). Frequently, patients may be asymptomatic. It is estimated that 850,000 people in UK have undiagnosed diabetes. At diagnosis, 25% of the patients would have diabetes retinopathy, and 8% would have developed nephropathy(Astrup and Finer, 2000). Despite treatments, T2DM is a progressive disease; with time, patients will progress to combination therapy including insulin, which often lead to weight gain, exacerbating insulin resistance.

1.2.2 Complications of diabetes

Exposure to hyperglycaemia was known to increase risk of developing macrovascular and micorvascular complications of diabetes. Management of macrovascular complications such as coronary artery disease and stroke; microvascular complications such as retinopathy, nephropathy and neuropathy have significant impact on morbidity and mortality, both at personal level and population level (Remuzzi
et al., 2002, Watkins, 2003, Young et al., 1993). Cardiovascular death was the commonest cause of mortality in T2DM population.

1.2.2.1 Macrovascular complications

**Atherosclerosis**

Atherosclerosis is the central pathological mechanism of cardiovascular disease. It results from accumulation of oxidised lipids in the endothelial wall of arteries in response to endothelial injury and inflammation. This oxidised lipids form foam cells which stimulate macrophages proliferation and attract T-lymphocytes. T-lymphocytes in turn induce smooth muscle proliferation in the arterial walls and collagen accumulation. This leads to formation of a lipid-rich atherosclerotic lesion with a fibrous cap (Brownlee, 2001, Fowler, 2008).

**Endothelial dysfunction**

Although the mechanisms of which diabetes increases the risk of atherosclerotic plaques formation are not known, endothelial dysfunction involving hyperglycaemia and pathway specific insulin resistance has been implicated in its pathogenesis (Brownlee, 2001). The reduction in endothelial production of nitric oxide, and increased proliferation of vascular smooth muscle cells lead to atheroma formation; while production of plasminogen activator inhibitor-1 (PAI-1) increased platelet adhesion and hypercoagulability, as well as impaired fibrinolysis (Fowler, 2008). This results in diffuse narrowing of arterial walls.

T2DM is a strong independent risk factor for ischaemic heart disease, stroke and death (Fowler, 2008). Being female, and presence of microvascular complications are risk factors for coronary heart disease (Fowler, 2008).

Contrary to Type 1 diabetes study which showed intensive glycaemic control is associated with preventing cardiovascular event; studies in T2DM had not conclusively shown that intensive glycaemic control is associated with statistically significant reduction in cardiovascular event. The inconsistencies might be related to the complex relationship between hyperglycaemia and cardiovascular risk in T2DM. While hyperglycaemia had implications on endothelial dysfunction and proinflammatory
state, effects of improving glycaemia maybe less profound than blood pressure (BP) and lipid management.

1.2.2.2 Microvascular complications

This is a disease of small vessel affecting eye, kidney and nervous system. They have pronounced effect on morbidities and mortality such as visual loss, amputation, renal failure and cardiovascular death. Diabetes is the leading cause for blindness and end-stage renal diseases (Brownlee, 2001). The risk of developing these complications increases with poor glycaemic control, and intensive glycaemic control had shown to reduce the risk (DCCT, 1995, 1998c) (Stratton et al., 2000).

Mechanisms of hyperglycaemia induced damage:

**Polyol Pathway**

In the polyol pathway, aldose reductase is the first enzyme that catalyses the NADPH-dependent reduction of glucose to the polyalcohol sorbitol in event of hyperglycaemia (Brownlee, 2001). Osmotic stress from sorbitol accumulation has been postulated as an underlying cause of microvascular complications (Fowler, 2008). In animal studies, sorbitol accumulation has been linked to microaneurysm formation, thickening of basement membranes, and loss of pericytes. However, treatment studies with aldose reductase inhibitors have been disappointing (Fowler, 2008). The decrease in NADPH which is also requires for glutathione reductase activity resulted in increase in oxidative stress and activates pathways that increase cellular damage (Cumbie and Hermayer, 2007).

**Formation of advanced glycation end products (AGEs)**

Hyperglycaemia promotes the nonenzymatic formation of AGEs. AGEs are a heterogeneous group of modified proteins, lipids and nucleic acids implicated in the aging process and diabetes (Cumbie and Hermayer, 2007). Hyperglycaemia may also influence production of AGEs through polyol pathway and oxidative stress (Cumbie and Hermayer, 2007). AGEs were noted in increased level in diabetes retinopathy and nephropathy (Brownlee, 2001). It has been associated with formation of microaneurysms and pericyte loss in animal studies (Fowler, 2008).
Reactive oxygen species

Hyperglycaemia can stimulate reactive oxygen species formation; oxidative stress may play a role in cellular injury. Treatment with antioxidants has yet to show any benefit in the disease progression (Fowler, 2008).

Vascular endothelial growth factor production

Vascular endothelial growth factor (VEGF) stimulates angiogenesis, enhances collateral vessel formation, and increases the permeability of the microvasculature (Ray et al., 2004). VEGF production is known to be stimulated by hyperglycaemia, advanced glycosylation end products, IGF-I, angiotensin II, and hypoxia (Ray et al., 2004).

Diabetic Retinopathy

Diabetic retinopathy is the commonest cause of blindness. It may develop as early as seven years before the diagnosis of T2DM. Duration of diabetes, hyperglycaemia and hypertension are risk factors for retinopathy (Fowler, 2008). Presence of microalbuminuria and duration of diabetes are independent variables for the presence of proliferative diabetic retinopathy (Ray et al., 2004).

Hyperglycaemia has been shown to induce apoptosis of retinal pericytes. Pericytes are essential in protecting endothelial cells of retinal capillaries, its loss is associated with microaneurysms formation, herald the initial stages of diabetic retinopathy. This is worsen by frequent fluctuation of blood glucose between high and low (Cai and Boulton, 2002). The retinal increases its vascular permeability, leading to swelling through macular oedema, or formation of new vessels (Ciulla et al., 2003). This results in reduction or loss of vision.

The early stage of retinopathy is characterised by microaneurysms, dot haemorrhages, and hard exudate which may appear due to retinal capillary dilatation, occlusions or leaks. This progresses to cotton wool spots which are microinfarctions of the nerve fibre layer. This heralds the development of new vessels, or proliferative retinopathy. It carries a high risk of blindness as a result of vitreous haemorrhage and
fibrosis (Ciulla et al., 2003). Laser photocoagulation was often used to prevent the progression of proliferative retinopathy to visual loss.

Diabetic Neuropathy

Martyn and Hughes found that diabetic neuropathy presented in 4% of diabetic population diagnosed within 5 years of diagnosis and the prevalence rose to 15% in 20 years (Martyn and Hughes, 1997). Population study showed that up to a third of patients with diabetic neuropathy were asymptomatic (Fowler, 2008). Diabetic neuropathy is associated with duration of diabetes, poor glycaemic control (Martyn and Hughes, 1997) and often co-existing with other microvascular complications.

Chronic sensorimotor distal symmetric polyneuropathy is the commonest form of neuropathy in diabetic patients. Sensory loss is most prominent bilaterally in stocking distribution. Electrophysiology studies showed a more pronounced decrease in sensory and motor compound action potential amplitude, which is suggestive of axonal degeneration as the underlying pathology (Martyn and Hughes, 1997). Pure sensory neuropathy is relatively rare. Mononeuropathy affecting femoral nerve is common, and it is often rapid onset and reversible. Compression neuropathies involving entrapment of nerves such as median and ulnar nerves are also more common in diabetes population. Autonomic neuropathy such as gastroparesis, postural hypotension, and silent myocardial ischaemia could occur in patients with long duration of poorly controlled diabetes.

Positive symptoms of neuropathy are distressing. Management include symptomatic control with medication, and improvement in glycaemic control with avoidance of glycaemic excursion. 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy (Fowler, 2008).

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of renal failure. Seven per cent of patients with T2DM had nephropathy by the time of diagnosis. The incidence of nephropathy in UKPDS was 2% per year and its prevalence at 10 years was 25% (Fowler, 2008). It is characterised by presence of persistent albuminuria, progressive decline in
glomerular filtration rate, and elevated blood pressure. Presence of albuminuria is defined in stages: microalbuminuria, albumin creatinine ratio (ACR) > 2.5 mg/mmol for men, > 3.5 mg/mmol for women; macroalbuminuria (ACR >30mg/mmol). Detection of persistent microalbuminuria is defined as the early marker of diabetes renal disease; it is also a predictor for cardiovascular morbidity and mortality (Fowler, 2008). Microalbuminuria is potentially reversible; while macroalbuminuria is progressive. With increasing albuminuria, glomerular filtration rate (GFR) elevated and eventually declined as it progressed to end stage renal failure.

Diabetic nephropathy is characterised by increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Fowler, 2008). The underlying mechanisms of diabetic nephropathy are similar to retinopathy. VEGF is implicated in the development of diabetic nephropathy. Use of anti-VEGF antibodies to neutralise effect of VEGF in experimental models has significantly reduced hyperfiltration, microalbuminuria, and glomerular hypertrophy (Ray et al., 2004).

Management of diabetes nephropathy stresses importance of glycaemic and blood pressure control. ACE inhibitor has been shown to reduce the risk of developing diabetic nephropathy and cardiovascular events in patients with T2DM (Fowler, 2008). Renin angiotensin blockade appeared to have renoprotective effect which is independent of its effect on blood pressure lowering (Fowler, 2008). Screening for diabetic nephropathy is carried out annually in United Kingdom using spot urine measurement.

1.3 Type 2 diabetes treatments

1.3.1 Diet and Lifestyle

Treatment of diabetes has also evolved, although at a much slower pace compared to the expansion of obesity and diabetes epidemic. T2DM is largely regarded as a lifestyle disease. Lifestyle and dietary changes was the treatment for T2DM since 1800 (K, 2009). Today, it remained the first line treatment for T2DM. Dietary input and physical activity has shown to maintain weight loss of 2.0-3.3 kg over a six year period in patients with T2DM and impaired glucose tolerance (IGT); leading to 53.8% of remission of diabetes, and 75.8% of normalisation of oral glucose tolerance tests (Eriksson and Lindgarde, 1991, Heymsfield et al., 2000). Individualised dietary
therapy and physical activities have also been supported by American Association of Clinical Endocrinologists/American College of Endocrinology/ American Diabetes Association (AACE/ ACE/ ADA) as part of treatment algorithm for T2DM. Calorie restriction such as use of low calorie diet (LCD) has also shown to improve insulin sensitivity and beta cell function (Lim et al., 2011).

1.3.2 Pharmacotherapy

T2DM is a progressive disease, hence polypharmacy is not uncommon. Patients’ compliance to medications is therefore often limited by its side effect, hypoglycaemia and weight gain.

**Biguanide**

Metformin, from the biguanide family, has been recommended as first line oral agent for T2DM due to its safety and efficacy. It is effective at decreasing both fasting plasma glucose and postprandial glucose levels (Goldman-Levine, 2011). It improves insulin sensitivity at peripheral tissues, reduces hepatic glucose production, and increases intestinal glucose uptake and utilization (Bergenstal et al., 2010). Metformin does not stimulate insulin production and therefore has a very low risk for hypoglycaemia. It is weight neutral, and may also result in weight loss. It has also been shown to lower mortality and improved heart failure (Goldman-Levine, 2011).

**Sulphonylurea**

Sulphonylureas was first discovered in 1956. It works by stimulating glucose independent release of insulin from the pancreas. The effect of sulphonylureas relies on the functioning of pancreatic islets. Primarily effective at reducing fasting plasma glucose. It could cause hypoglycaemia and weight gain (Goldman-Levine, 2011).

**Thiazolidinediones**

Pioglitazone is the only licensed thiazolidinedione available since rosiglitazone was withdrawn due to cardiovascular risks. It decreases peripheral insulin resistance by improving insulin sensitivity in adipose tissue, skeletal muscle, and the liver. This results in increase insulin-dependent glucose disposal and decreased hepatic
gluconeogenesis. It works by reducing fasting glucose. It could cause weight gain (Goldman-Levine, 2011).

**Glinides**

Glinides stimulate the release of insulin from the pancreas. They are primarily effective at decreasing postprandial glucose (Goldman-Levine, 2011).

**Alpha-Glucosidase Inhibitors**

The alpha-glucosidase inhibitors delay the digestion of polysaccharides in the proximal small intestine and decrease the rise in plasma glucose concentrations postprandial. It is effective in patients whose diet contains large amounts of complex carbohydrates. It is weight neutral (Goldman-Levine, 2011).

**Glucagon-Like Peptide-1 Receptor Agonists**

The GLP-1 receptor agonists mimic effect of gut hormone GLP-1 which is elevated post RYGB surgery. Its binding to GLP-1 receptor exerts incretin effect, leading to increased glucose-dependent insulin secretion, glucose dependent suppressed glucagon secretion, reduced hepatic glucose production, delayed gastric emptying, and greater satiety. Animal studies have shown that use of GLP-1 receptor agonist lead to an increase in β-cell mass, and β-cell preservation. It has effects on postprandial glucose or/and fasting glucose. It is also associated with weight loss of up to 5kg (Goldman-Levine, 2011).

**Dipeptidyl Peptidase-4 Inhibitors**

The DPP-4 inhibitors prevent endogenous GLP-1 and gastric inhibitory polypeptide inactivation, therefore prolong the physiologic levels of endogenous GLP-1. It is effective at decreasing postprandial glucose levels. They are weight neutral (Goldman-Levine, 2011).

**Sodium/glucose cotransporter 2 inhibitors**

SGLT-2 inhibitors are the competitive inhibitors of the renal SGLT-2 system, preventing glucose reabsorption from the glomerular filtrate in the proximal tubules. Its
effect is therefore insulin independent. It is associated with weight loss (Vasilakou et al., 2013).

**Insulin**

Development of insulin has transformed diabetes management. Insulin is the third line medications, when oral medications and GLP-1 agonist had been exhausted. It improves glycaemic control by inhibiting hepatic gluconeogenesis and glycogenolysis. Its use is limited by its mode of delivery, and its effect on weight gain and hypoglycaemia. The weight gain associated with insulin use often led to worsening of insulin resistance and β cell dysfunction (Goldman-Levine, 2011).

1.3.3 Bariatric surgery

Increasingly, bariatric surgery has been seen as a treatment for patients with T2DM and severe and complex obesity defined as a body mass index above 35 kg/m² with life or limb threatening co-morbidities (Schauer et al., 2012a). The International Diabetes Federation’s (IDF) position statement in 2011 recommend bariatric surgery to be included in future algorithms for treatment of complex obese T2DM (Dixon et al., 2011).

Obesity surgery originated as a form of gastrointestinal surgery, which was first performed in 1954. The jejuno-intestinal bypass strived for weight loss by circumventing the middle section of the small intestine (Pories, 2008). Over time, this has evolved and today the three commonest weight loss surgeries are laparoscopic Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and vertical sleeve gastrectomy (VSG) (Buchwald et al., 2009). RYGB and biliopancreatic diversion (BPD) have also been termed as metabolic or diabetes surgery due to their effects in improving glycaemic control (Schauer et al., 2003, Pories et al., 1995, Buchwald et al., 2009). They are also effective in improving BP, lipid and obstructive sleep apnoea.

Biliopancreatic diversion, with or without duodenal switch (BPD and BPD-DS), is less commonly performed but remains to be considered in extremely obese individuals. All
procedures can be performed laparoscopically with a lower rate of complications such as wound infection and incisional hernias (Neff and le Roux, 2013).

**Roux-en –Y gastric bypass**

In RYGB, the gastric pouch is created from the stomach, approximately 15–30 ml in size. The gastric pouch is anastomosed to the jejunum after it has been divided approximately 30 to 75 centimetres distal to the ligament of Treitz; this distal part is brought up as a “Roux-limb”. The excluded biliary limb including the gastric remnant is connected to the bowel approximately 75 to 150 centimetres distal to the gastrojejunostomy (Figure 1. RYGB) (Neff and le Roux, 2013). The effect of RYGB on diabetes remission and its proposed mechanisms are discussed in more details in 1.4.

**Adjustable gastric banding**

In AGB, a band with an inflatable balloon is placed around the proximal stomach just below the gastroesophageal junction. (Figure 2. AGB) The band can be adjusted by filling the band with saline solution through a subcutaneous access port (Neff and le Roux, 2013)
Sleeve gastrectomy

In SG, approximately 80% of the stomach is removed. The stomach is transected vertically over a 34 or 36F bougie creating a gastric tube and leaving a pouch of 100-200 mL (Figure 3. SG). Although many regard SG as a restrictive procedure, it is increasingly recognised as a metabolic procedure (Neff and le Roux, 2013).

Biliopancreatic diversion

The BPD involves a partial gastrectomy which results in a 400 mL gastric pouch. The small bowel is then divided 250cm proximal to the ileocaecal valve, and the alimentary limb is connected to the gastric pouch to create a Roux-en-Y gastroenterostomy. An anastomosis is performed between the excluded biliopancreatic limb and the
alimentary limb 50 cm proximal to the ileocaecal valve (see figure BPD) (Neff and le Roux, 2013).

Figure 2. Adjustable gastric band

(Karl Neff 2012)
Figure 3. Sleeve gastrectomy

(Karl Neff 2012)
Recent development

Non-surgical treatment such as Endobarrier has been developed to mimic some of the mechanism of bariatric surgery. It is a synthetic duodenojejunal bypass liner which is placed endoscopically, and lines the first 60cm of the duodenum, therefore achieving duodenal exclusion. It has positive effect on weight loss and improving glycaemic control in T2DM. The liner last for 12 months and therefore the durability of weight loss and long term data is yet to be reviewed. Other method such as insertion of intragastric balloon is developed to achieve short term weight loss in patients that were too high risk to proceed to bariatric surgery. Long term data on benefits of these methods are currently unavailable for review. (Neff and le Roux, 2013).
1.3.4 Roux-en –Y gastric bypass and proposed mechanisms

Both RYGB and BPD achieve excellent diabetes outcome. However, BPD is not commonly performed due to its higher complication rates. The impact of RYGB on diabetes remission could be influenced by weight loss and weight independent factors. Weight loss preoperatively while on liver shrinking diet; and in the long term follow up postoperatively would have contributed to the improved glucose homeostasis. However, the effect of gastric bypass on glucose control immediately postop, before significant weight loss is established suggested that mechanisms other than weight loss are at play. Despite similar weight loss, the rate of diabetes remission achieved by RYGB is disproportionately high compared to other procedures such as SG and AGB. Several weight independent mechanisms have been proposed:

i) Small stomach
Following the procedure, the stomach pouch is reduced to 15-30ml. This reduced gastric capacity limits the size of meals, as storage capacity of the stomach is reduced to 5% of its normal volume (Näslund and Kral, 2006). This leads to early satiety. The rapid reduction in calorie intake post-surgery leads to improved hepatic insulin sensitivity immediately after surgery, whereas peripheral insulin sensitivity only improves later in response to the postoperative weight loss. This was evidenced by the reduction in homeostasis model assessment of insulin resistance (HOMA-IR) (Dirksen et al., 2012).

ii) Bypass of nutrients- foregut
Ingested food bypasses 95% of the stomach, the duodenum, and a small portion (15–20 cm) of the proximal jejunum (Näslund and Kral, 2006). This is supported by the rodent study where duodenal-jejunal bypass that excludes nutrient passage through the duodenum is compared with gastrojejunotomy with intact duodenal nutrient passage. Significant improvement in glucose metabolism was observed in the group that had duodenal-jejunal bypass. There was no difference in food intake, nutrient absorption, or weight loss between both groups (Rubino et al., 2006). This effect is independent of weight loss, as further supported by RYGB on T2DM with BMI<35kg/m² who did not showed excessive weight loss , despite significant improvement in glycaemic control (Rubino et al., 2010).
iii) **Stimulation of hindgut**

Contrasting to the theory of bypassing foregut, a rapid stimulation of the hindgut by arrival of maldigested food may have affected the alterations in gastrointestinal peptide release. This activates mechanoreceptors and chemoreceptors (17) or neurohumoral mechanisms. This leads to changes in gut hormones.

iv) **Gut hormone changes**

**Incretin hormones**

Fasting level of GLP-1 has not changed, whereas GLP-1 level was several fold increase postprandial. The exaggerated response of GLP-1 to nutrients was abolished when gastrotomy catheter was inserted in the gastric remnant and the nutrients passed through the excluded pathway, suggestive that the GLP-1 changes was related to changes in gastrointestinal nutrient transit. This was further supported by study with ileal transposition which showed improved glucose homeostasis in diabetes patients with BMI 24-35kg/m² (Dirksen et al., 2012). GLP-1 increases insulin and decreases glucagon secretion. It also has trophic effects on the pancreas via anti-apoptotic and proliferative effects on β-cells (Dirksen et al., 2012).

Increased GLP-1 might reverse the impaired first phase insulin response in T2DM. After RYGB, there was an earlier and exaggerated postprandial rise in insulin concentrations that reaches a higher peak than level before surgery. There was also a more rapid return of insulin to fasting levels. The total postprandial insulin AUC was unchanged or reduced suggestive of improved insulin sensitivity (Dirksen et al., 2012).

**Appetite regulating gut hormones**

Gut hormones including GLP-1 and peptide YY (PYY), oxytomodulin are released from the intestinal L-cells postprandially. They play a role in appetite regulation. Their increased levels postprandially have been shown to reduce hunger, decreasing food intake and therefore lowering plasma glucose levels (Dirksen et al., 2012).

There was contradictory result on secretion of ghrelin post gastric bypass surgery. Ghrelin is an orexigenic hormone. Exclusion of foregut and ghrelin producing cells
had been proposed as the cause of decreased ghrelin, and therefore lack of hunger. However, subsequent studies had not been able to reproduce similar results. There were also reports on ghrelin levels return to pre-operative level or even increase, years after RYGB (Dirksen et al., 2012). These gut hormone changes were the likely contributing factors to the postoperative weight loss and indirectly improve insulin sensitivity.

v) **Changes in food preferences**
Changes in food preferences had been observed in patients having bariatric surgery. Following RYGB, there was reduction in intake of sweet and fatty meal. This has been associated with change in sense of taste. The altered food preferences coincided with functional MRI studies which showed a corresponding reduction in activation of brain reward centres to high energy food (Behary and Miras, 2015).

vi) **Bile acids**
Cholestyramine, a bile acid sequestrant was shown to lower LDL-cholesterols and improve glycaemic control in T2DM in a short term study (Garg and Grundy, 1994). Further studies had shown that it has effect on lowering glucose in prediabetes (Handelsman et al., 2010), and early T2DM (Rosenstock et al., 2010). Altered bile flow after RYGB surgery, and the increased level of total plasma bile acids post-surgery may contribute to the improvement in glycaemic control. Bile acids inhibits gluconeogenesis through Farnesoid X receptor pathway. It also promotes insulin signalling and glycogen synthase activation, which influence the hepatic glucose metabolism. The binding of bile acid to the G-protein coupled receptor, TGR5, which is expressed on L cells might explain the increased secretion of GLP-1. Combination of food and bile was shown to increase gut hormone, GLP-1 and PYY secretion, therefore enhance insulin release, and satiety. Bile acids also have an effect on fibroblast growth factor (FGF) 19, which enhanced mitochondrial activity, and improves insulin resistance (Pournaras et al., 2012b).
vii) Vagal nerve fibres transection

Gastrointestinal tract is extensively innervated by vagus nerve, which are mainly afferent sensory fibres. Vagus nerve is involved in the regulation of feeding. The presence of nutrient in the stomach or intestine activates the stretch and chemoreceptors which then transmit information through vagal signalling. Apart from mechanosensor effect, there was evidence that gastrointestinal hormones acting on vagal afferent. Ghrelin and hyperglycaemia were shown to suppress, while gastric distension and cholecystokinin (CCK) increased the firing activity of vagal afferent (Thaisetthawatkul et al., 2004). The transection of vagus nerve during RYGB might offer explanation to disruption of ghrelin secretion post-surgery. This was supported by animal study which shows vagotomy eliminates the normal response of ghrelin to weight loss. It might also influence gastric emptying.

viii) Changes in gut microflora

Recent studies had shown that composition of gut microflora altered after RYGB. In rodent study, the population of gut microorganisms changes after RYGB. The transfer of gut microflora from the RYGB mice to the non-operated germ-free mice resulted in weight loss and decreased body fat. RYGB induced significant changes to the gut microbial communities that was independent of changes in diet. The change in microflora distributions has been postulated to alter energy expenditures, and therefore weight loss (Kugelberg, 2013)
1.4 Diabetes and surgical outcome

1.4.1 Diabetes and general surgery outcome

Patients with T2DM have 2 to 4 fold increase in cardiovascular disease (Stamler et al., 1993, Dhatariya et al., 2011). Most diabetic patients planning for surgery are likely to have 1 or more cardiovascular risk factors and a significant number will have microvascular disease (retinopathy, nephropathy or neuropathy). They are at high risk of perioperative complications and even mortality (Dhatariya et al., 2011), with perioperative mortality rate reported to be up to 50% higher than that of the non-diabetic population (Dhatariya et al., 2011, Clement et al., 2004). Diabetic patients are more at risk of poor wound healing, respiratory infection, myocardial infarction, admission to intensive care, and increased length of stay in hospital (Frisch et al., 2010, Sehgal et al., 2011, Dhatariya et al., 2011). Perioperative poor glycaemic control has significant impact on postoperative infection (Clement et al., 2004). The UK national guideline recommended that all patients with diabetes undergoing elective surgery should have their glycaemic control optimised preoperatively (Dhatariya et al., 2011). This recommendation was made based on the majority of evidence on morbidity and mortality of T2DM patients undergoing surgery, which were from the setting of cardiac surgery and to a lesser extent non-cardiac surgery. There was no specific evidence for bariatric surgery (Chuah and le Roux, 2013).

Distinction between non-bariatric surgery and bariatric surgery

Bariatric surgery such as RYGB should be distinguished from general surgery because of its immediate beneficial effect on glycaemic control postoperatively. The rapid glycaemic improvement appears independent of weight loss (Pournaras et al., 2010). Moreover, these patients often followed low calorie diets preoperatively (Adrianzen Vargas et al., 2011, Van Nieuwenhove et al., 2011) which lead to improvement in glycaemia immediately before surgery. General surgery does not alter glycaemic control postoperatively; neither does it require patients to follow low calorie diet preoperatively. The question thus arises whether bariatric patients should follow a distinct pathway from the general surgical population and that their diabetes should be managed differently. There was also lack of prospective study to assess if preoperative, perioperative and postoperative glucose management would impact on improvement and remission of diabetes (Chuah and le Roux, 2013).
Management of diabetes on pre-operative low calorie diet

Low calorie diet (800-1200 kcal/day) lead to rapid weight loss and improvement in T2DM (Anderson et al., 2003). The diet is used preoperatively in many bariatric centres to induce acute weight loss before surgery. LCD has shown to reduce visceral fat, liver volume and intrahepatic fat, facilitates the use of laparoscopic approach in obesity surgery (Colles et al., 2006).

Despite the wide use of preoperative diet, studies has reported no differences in mean operating time, estimated blood loss and intraoperative complications when compared to the groups received LCD and those without preoperatively, except the 30 days postop complications was lower in the LCD group (Adrianzen Vargas et al., 2011, Van Nieuwenhove et al., 2011). The use of LCD in patients with T2DM improves glycaemic control, and increased the risk of hypoglycaemia. There is no data on management of glucose during the perioperative period whilst on LCD.

Management of diabetes post-surgery

Although remission of diabetes after gastric bypass surgery is well recognised, there is a paucity of data on management of diabetes postoperatively. Study reported that giving a low dose of long acting insulin analogue therapy for the first few weeks after BPD improves the number of patients achieving remission (Scopinaro et al., 2011). Another cohort study in patients with type 2 diabetes requiring insulin suggested that tight glycaemic control (fasting blood glucose <6.5 mmol/L for 1-2 week after surgery) after RYGB improves the remission rate of T2DM after one year (Fenske et al., 2012). It is possible that the pancreas undergoes a period of regeneration within the early postoperative period, and a healthy glucose environment is beneficial for β cell function not only in the short, but in the long term. This may be analogous to islet cell ‘rest’ immediately post islet transplant in type 1 diabetes, where exogenous insulin is given to avoid glucotoxicity (Bretzel et al., 1999, Chuah and le Roux, 2013).
1.4.2 Diabetes and bariatric surgery outcome

**Mortality**

The Swedish Obesity Subject (SOS) Study, a prospective, controlled cohort study comparing bariatric surgery to medical treatment for long-term mortality found that the adjusted hazard ratio was 0.71 in the surgery group (p=0.01) as compared with the control group (Sjostrom et al., 2007). McDonald et al had also reported that mortality in patients with T2DM who underwent gastric bypass surgery was 9% compared to 28% of diabetes control group at 9 years follow up (MacDonald et al., 1997). The most common cause of death was myocardial infarction. SOS study had also reported that surgery was associated with a reduced number of cardiovascular death compared to the control group (28 vs 49 events, adjusted HR 0.47, p=0.02) (Sjostrom et al., 2012). The benefit of surgical treatment was significantly associated with a raised baseline plasma insulin above the median of 17 IU/L, with greater relative treatment benefit in subjects with higher insulin (p for interaction <0.001).

These are also supported by Adams et al. which showed that patients with T2DM who undergo bariatric surgery have a 92% relative risk reduction compared to the matched control group at a mean follow up of 7.1 years (Adams et al., 2007). The acute improvement in glycaemic control and other metabolic co-morbidities together with the significant weight loss after gastric bypass may play a significant role in the decreased mortality after bariatric surgery (Chuah et al., 2013).

**Morbidity**

**Perioperative complications**

A prospective study of diabetic patients under RYGB reported overall major complication rate was 13.6% and minor complication rate of 24.9%. Early major complications included pneumonia, gastrojejunal leaks, small bowel obstruction and deep vein thrombosis; minor complications included wound infections, prolonged emesis and marginal ulcers (Schauer et al., 2003). The longitudinal assessment of bariatric surgery reported that of the 2975 subjects who undertook LRYGB, the composite end point of death, venous thromboembolism, reintervention, or failure to be discharged by 30 days after surgery was 4.8%. History of pulmonary embolic event,
obstructive sleep apnoea, extreme body mass index were associated with increased risk of the composite end point (2009, Chuah et al., 2013).

Impact of pre and postoperative glycaemic control on outcome of bariatric surgery

Elevated HbA1c preoperatively has been associated with increased hospital LOS and worsen postoperative outcome in non-bariatric surgery patients (Perna et al., 2011). However, there is no data on whether preoperative glycaemic control could influence the outcome of bariatric surgery and remission of diabetes, especially as many units use a 2 week pre-operative very low calorie diet which will improve glycaemic control substantially. A retrospective study reviewed 468 patients scheduled for bariatric surgery and grouped them into three categories based on HbA1c preoperatively. Poor preoperative glycaemic control was associated with worse glucose control postoperatively, as well as less weight loss and fewer cases of complete remissions of their T2DM at 18 months. An elevated postoperative glucose was independently associated with wound infection (p= 0.008), and acute renal impairment (p= 0.04) (Perna et al., 2011). A cohort study in patients with type 2 diabetes requiring insulin suggested that after gastric bypass surgery tight glycaemic control (fasting blood glucose < 6.5 mmol/L for 1-2 week after surgery) can improve the remission rate of T2DM after 1 year (Chuah et al., 2013, Fenske et al., 2012).

Bariatric surgery and diabetes remission

T2DM is a progressive disease, and the aim of treatment is to prevent macrovascular and microvascular complications, as this had significant impact on morbidity and mortality of patients. Reversal of diabetes has not been possible with pharmacotherapy in the past, the emergence of bariatric surgery has now offered a new dimension to diabetes management as it offers the opportunity of diabetes remission. RYGB and BPD were shown to achieve 75% and 95% of diabetes remission respectively when compared to best medical therapy (Mingrone et al., 2012b). A meta-analysis showed that diabetes resolution was achieved in 80.3% of those undergoing RYGB (Buchwald et al., 2009). It is important to note that the definitions used for remission of T2DM in all the above studies varied significantly. Pournaras et al. reported 34.4 % of surgery cohort achieved complete remission of
diabetes when the American Diabetes Association guideline was used (Pournaras et al., 2012a). While longer term data on remission of diabetes is awaited, the evidence of its effect on complications of diabetes is less well known.

1.4.3 Bariatric surgery and macrovascular complications

Macrovascular complications such as cardiovascular disease were reduced following bariatric surgery (MacDonald et al., 1997) with improvements in coronary heart disease (CHD) (Iaconelli et al., 2011, Adams et al., 2007). Bariatric surgery was also associated with a reduced number of cardiovascular death compared to the control group (28 vs 49 events, adjusted HR 0.47, p=0.02) (Sjostrom et al., 2012). Metabolic complications such as hypertension, hyperlipidaemia, and obstructive sleep apnoea were all improved following bariatric surgery (Buchwald et al., 2004).

1.4.4 Bariatric surgery and microvascular complications

A case-controlled study with 10-years' follow-up had shown that microalbuminuria and glomerular filtration rate (GFR) improved in diabetic patients having BPD; whereas microalbuminuria progressed in non-operated subjects (Iaconelli et al., 2011). Some more studies had recently reported improvement in diabetic nephropathy as evidenced by reduction in microalbuminuria at 1 to 5 years post bariatric surgery (Heneghan et al., 2013, Miras et al., 2011, Brethauer et al., 2013). Most studies on diabetic retinopathy changes post bariatric surgery were retrospective except 1, all reported no significant change in retinopathy. Risk of progression of retinopathy was higher in those with pre-existing moderate to severe background retinopathy (Singh et al., 2015, Murphy et al., 2015, Miras et al., 2012, Thomas et al., 2014). There is no prospective study reporting objective changes in diabetic neuropathy post bariatric surgery so far. One study reported neuropathy symptom score and neuropathy deficit score which improved 6 month post-surgery (Muller-Stich et al., 2013).
1.5 Relationship between glycaemic control and complications

1.5.1 Glycaemic control and macrovascular complications

Despite UKPDS showing beneficial long term protective effect on macrovascular complications following early intensive management of type 2 diabetes; recent studies on patients with established diabetes had found no effect on major cardiovascular events (Patel et al., 2008, Duckworth et al., 2009). One study had shown increased risk of death in intensively treated group (Gerstein et al., 2008). Meta-analysis that included large, randomised controlled trials (Gerstein et al., 2008, Duckworth et al., 2009, Patel et al., 2008, 1998c, 1998b) observed overall 16% reduction in risk of non-fatal myocardial infarction associated with intensive glucose control after pooling the relative risk across all trials(Kelly et al., 2009). In contrast, no association was observed between intensive glucose control, fatal myocardial infarction, nonfatal stroke, fatal stroke, or peripheral artery disease(Kelly et al., 2009).

The differences in results between UKPDS 33 and 34, as compared to recent studies could partly be explained by the different study cohorts, as the UKPDS studies included only newly diagnosed T2DM, whereas recent studies recruited patients with longer duration of diabetes, some with known cardiovascular risk factors. The rate of reduction in HbA1c may also played a part, with 1 trial reported a reduction of 1.4% over 4 months (Gerstein et al., 2008). The post intervention median HbA1c in intensive treatment group in UKPDS studies were also higher than the recent studies. The recent trials also reported increased risk of hypoglycaemia in intensively treated group. Overall, the intensive glucose control showed evidence for a beneficial effect on cardiovascular disease, particularly on nonfatal myocardial infarction, but not on cardiovascular death and all-cause mortality(Kelly et al., 2009).

1.5.2 Glycaemic control and microvascular complications

United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that early intensive glycaemic control reduced the risk of developing microvascular complications in patients with T2DM (1998c, Pitale et al., 2005). The UKPDS follow up study further demonstrated that early intensive glycaemic control has long term beneficial effects on both micro and macrovascular complications (Holman et al., 2008). However, there is concern of the risk of rapid intensive glycaemic management on progression of retinopathy and neuropathy. Diabetes Control and Complications
Trial (DCCT) reported an early deterioration in retinopathy in the intensively treated T1DM cohort at 6 and or 12 months which resolved by 18 months (DCCT, 1995). Rapid improvement in glycaemic control during pregnancy is known to cause deterioration in diabetic retinopathy (Rasmussen et al., 2010). There was also a case report of worsening retinopathy 1 month after RYGB (Silva et al., 2013). There were reports of worsening neuropathy after rapid glucose lowering in diabetes (Leow and Wyckoff, 2005), and bariatric surgery (Miras et al., 2011). It is therefore important to ascertain the effect of rapid improvement in glycaemic control observed in bariatric surgery such as RYGB on the progression of diabetes complications.

Effect of glycaemic control on reversibility of retinopathy

In T2DM, UKPDS showed that the intensive treated group has a significant 25% reduction of risk in developing microvascular complications, most of which was due to reduction on photocoagulation (1998c). The Kumomata study on non-obese T2DM patients had also demonstrated that intensive treatment with insulin in the cohort with no diabetes retinopathy and the cohort with simple retinopathy reduced the cumulative percentages of the development and progression of diabetes retinopathy after 6 years (Ohkubo et al., 1995). Study in T1DM had shown that in the group that already had retinopathy at baseline, the cumulative incidence of sustained progression of retinopathy worsened at 1 year in the intensive treatment group; but the incidence reduced after third year. Intensive therapy had shown to reduce the average risk of progression of retinopathy by 54%. The deterioration of retinopathy in intensive treatment group within the first 18 months was transient (1998a).

Effect of glycaemic control on reversibility of neuropathy

Four out of 5 studies on intensive glycaemic control in T2DM had not shown significant improvement in neuropathy (Gaede et al., 2008, Azad et al., 1999, Duckworth et al., 2009, Ismail-Beigi et al., 2010, 1998c). UKPDS study only showed statistically significant effect of glycaemic control on progression of neuropathy at 15 years follow up. This is in contrast with studies in Type 1 diabetes patients, where both DCCT and Stockholm Diabetes intervention study reported a reduction in rate of progression of diabetes neuropathy at 5 to 7 years of follow up in intensive glycaemic control compared to standard treatment group (Reichard et al., 1993). It is therefore
suggestive that glycaemia may not be as critical in progression of neuropathy in T2DM as compared to T1DM, and that factors other than glycaemic is at play.

**Effect of glycaemic control on reversibility of nephropathy**

Effect of intensive glycaemic control on diabetic nephropathy in T2DM are consistently shown in all studies (1998c, Ohkubo et al., 1995, Patel et al., 2008, Duckworth et al., 2009). The reversibility of diabetic nephropathy was also observed in DCCT of T1DM, where intensive glucose control reduced the incidence of microalbuminuria by 39% (1993). It also reported a long-lasting reduction in the risk for development of microalbuminuria and hypertension 7-8 years after the end of the trial (2003).

In a small study of T1DM with known diabetic nephropathy after pancreas transplant, microalbuminuria improved after 5 years of normalisation of glycaemic control; while basement membrane thickness and mesangial volume improved at 10 years (Fioretto et al., 1998). Glycaemic control therefore had a role in reversal of diabetes nephropathy.
1.6 Relationship between weight loss and complications

Effect of weight loss on retinopathy

Some studies had demonstrated relationship between high BMI and retinopathy, although the results were inconsistent. Studies on type 1 diabetes showed that higher BMI was associated with earlier development of retinopathy (Henricsson et al., 2003). Underweight (BMI<20kg/m\(^2\)) was also shown to be a risk factor for retinopathy (Cheung and Wong, 2007). There is no report on effect of weight loss on retinopathy.

Effect of weight loss on neuropathy

There was evidence that obesity was associated with subclinical neuropathy as shown in the study of 21 obese non-diabetic subjects underwent bariatric surgery (Singleton et al., 2014). The validated neuropathy scale and skin biopsy showed that there was presence of asymptomatic neuropathy compared to lean subjects. A study on cohort with impaired glucose tolerance demonstrated reversibility of intraepidermal nerve fibre density on skin biopsy 1 year following lifestyle and diet intervention (Smith et al., 2006). There was a retrospective study compared subjects who had bariatric surgery to the group who had cholecystectomy which reported increased peripheral neuropathy post bariatric surgery, nutritional deficiency was shown to be the main cause (Thaisetthawatkul et al., 2004). Similar findings were also reported in the case series (Maryniak, 1984, Feit et al., 1982).

Effect of weight loss on nephropathy

Obesity is known to be independent risk factor for chronic kidney disease (Wahba and Mak, 2007). Renal dysfunction associated with obesity included hyperfiltration, proteinuria, followed by hypofiltration eventually. Obesity related glomerulomegaly is increasing in prevalence. It presents with proteinuria without nephrotic syndrome(Darouich et al., 2011), and is characterised by presence of glomerulomegaly and glomerulosclerosis on renal biopsy. Study compared obese non-diabetic subject underwent bariatric surgery to healthy weight control showed significant reduction in BMI, BP, 24 hour proteinuria and albuminuria at 1 year; and continue reduction in BMI and 24 hour albuminuria at second year (Navarro-Diaz et al., 2006). A systematic review of weight loss interventions in chronic kidney disease
reported that non-surgical weight loss interventions reduce proteinuria and blood pressure; whereas bariatric surgery normalise glomerular hyperfiltration, reduced BP, and microalbuminuria (Navaneethan et al., 2009).

Objectives

RYGB surgery is distinct from other gastrointestinal surgery because of its effect on improving glucose control and maintaining weight loss post-surgery. Glycaemic management of this group of patient therefore should not be generalised with other gastrointestinal surgery. There is no prospective study that assesses management of this challenging group of complex obese diabetes patients pre-operatively and post-operatively. There is also lack of data to support whether intensive glucose control pre-operatively and postoperatively (which was the common practice in most cardiothoracic and gastrointestinal surgeries), would have any added benefit on the surgical complications and glycaemic outcome postoperatively. Diabetes microvascular complications, such as retinopathy is known to deteriorate with rapid improvement in glucose. Given the rapid improvement in glucose control following RYGB, it is therefore important to study its effect on all microvascular complications.

There is no prospective study assessing all microvascular complications of T2DM using objective measurement. My study therefore aims:

1. to determine the impact of preoperative glycaemic control on remission of T2DM and progression of microvascular complications (retinopathy, nephropathy and neuropathy) 1 year after RYGB.

2. to determine the impact of postoperative glycaemic control on remission of T2DM and progression of microvascular complications (retinopathy, nephropathy and neuropathy) 1 year after RYGB.

3. to determine the impact of RYGB on progression of diabetic nephropathy, retinopathy and neuropathy 1 year after surgery
Hypotheses

1. Intensive glucose control before gastric bypass surgery results in better medium term glycaemic control and is beneficial for the microvascular complications of T2DM.

2. Intensive glucose control post gastric bypass surgery results in better medium term glycaemic control and is beneficial for the microvascular complications of T2DM.

3. Gastric bypass surgery is beneficial for the microvascular complications of T2DM.
Chapter 2. Clinical Methodology

2.1. Study 1: GLUCOSURG-pre
Participants and informed ethical consent

This was a single-centre, non-blinded, randomised, controlled trial studying obese patients with T2DM undergoing RYGB. Forty-one suitable subjects were recruited between July 2011 and August 2012 from the obesity clinic at Charing Cross Hospital, London. All subjects gave written informed consent. The study was conducted according to the principles of the Helsinki declaration. Ethics was granted from the West London 2 Research Ethics Committee, (Ref11/H0711/1). The trial was registered on the ClinicalTrials.gov NCT01353118.

Randomisation

Using a computer generated block-randomization method with a 1:1 ratio; subjects were randomised to intensive glucose management or conservative management preoperatively.

Inclusion criteria:

1. Informed consent obtained before any trial related activities.
2. T2DM according to clinical judgement.
3. BMI $\geq$ 35 kg/m$^2$
4. Age between 18 and 70 years.
5. HbA1c of greater or equal to 69mmol/mol (8.5%).
6. Able and willing to complete the trial.

Exclusion criteria:

1. Type 1 diabetes mellitus
2. Pregnancy
3. Failure to proceed to surgery
4. Proliferative retinopathy that has required acute treatment within last three months.
5. Inability to participate in capillary glucose testing
6. Inability to titrate glucose lowering pharmacotherapy
2.1.1 Study preparation

Forty-one subjects were screened for inclusion and participation in the study. The screening, randomisation, and allocation process are shown in figure 5. Three did not meet inclusion criteria. 38 subjects gave written informed consent and were randomised. Four subjects dropped out. Thirty-four subjects had completed one year follow up. The study was analysed by intention to treat and as per protocol analysis.

![Figure 5: Recruitment, randomisation and follow up for GLUCOSURG-pre subjects.](image-url)
Preoperative care

Following randomisation, subjects in the intensive management group were assessed in a clinic by chief investigator. Their glucose-lowering therapy was optimised based on the American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) guidelines 3 months prior to surgery (Murphy et al., 2015). Intensive management was defined as an absolute reduction in HbA1c≥1% after 3 months and or before surgery. Subjects were asked to check their capillary glucose (CG) levels pre-meals every day. Adjustments were made every 2-3 days apart to reduce the incidence of hypoglycaemia. Subjects randomised to the conservative group did not undergo any glycaemic optimisation pre-surgery. Preoperative investigations included 2 urine albumin creatinine ratio (ACR), nerve conduction study and thermal threshold testing were organised. Subjects were reminded to attend their retinal screening or ophthalmology appointment before surgery.

Perioperative care

All subjects underwent a standard low-calorie diet of 800kCal for 2 weeks before admission for surgery in order to decrease their liver size. All glucose-lowering medications were discontinued on admission. Subcutaneous short-acting insulin was given as necessary according to capillary glucose monitoring using an insulin sliding scale (Table 1), as per standard operating procedure at Charing Cross Hospital bariatric unit. The target capillary glucose (CG) during the admission was 5.0-8.0mmol/L. RYGB was performed laparoscopically as described on Chapter 1.3.4.1 RYGB (Figure1). Subjects were allowed oral fluids the day after surgery, and were discharged 2 days after surgery, unless they developed a post-operative complication. Metformin 1g bd was routinely started on day 3 unless subjects had a known intolerance or evidence of kidney impairment. In addition, patients were prescribed a once daily long-acting insulin analogue at a dose equivalent to their total insulin requirements during the 24 hour prior to discharge.
Table 1. Standard bariatric insulin sliding scale.

Bariatric 4 Hourly s.c. Sliding Scale Prescription

Check BM 4 hourly. Give Actrapid 4 hourly s.c.

<table>
<thead>
<tr>
<th>BM Stix Range</th>
<th>Sub.Cut Actrapid Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&lt; 4.0</td>
<td>Call Doctor</td>
</tr>
<tr>
<td>4.1 - 8.0</td>
<td>Perfect</td>
</tr>
<tr>
<td>8.1 - 11.0</td>
<td></td>
</tr>
<tr>
<td>11.1 - 14.0</td>
<td></td>
</tr>
<tr>
<td>14.1 - 17.0</td>
<td>Call Doctor and ask to consider changing scales</td>
</tr>
<tr>
<td>17.1 - 20.0</td>
<td>Call Doctor, a senior review is needed.</td>
</tr>
</tbody>
</table>

Signature of Doctor
Bleep Number
Date Signed

Postoperative care

Following discharge, subjects emailed or texted (via short messages service) the chief investigator to report their morning fasting CG levels obtained using Accu-Chek Advantage® (Roche Diagnostics Ltd, Hertfordshire, England, UK). Insulin dosages were adjusted based on a titration schedule (Table 2), aiming for fasting CG levels between 5.5 and 7.5 mmol/L. The daily contact was discontinued once fasting CG values were documented between 5.0 and 7.5 mmol/L for at least 3 consecutive days. Subjects were advised to contact their physician if their fasting CG levels were <4.5 or >7.5 mmol/L. Glycaemic control and the use of glucose-lowering medication were assessed at 10 days, 3 months, 6 months and 1 year after surgery. Metformin was reviewed and discontinued if fasting glucose levels were ≤5.6 mmol/L.

Follow up

All subjects were reviewed at one year in bariatric clinic. Weight, medication usage and glycaemic control were assessed. Follow up investigations including 2 urine ACR, nerve conduction study and thermal threshold testing were arranged. Subjects were reminded to attend retinal screening or ophthalmology follow up.
Table 2. Daily insulin titration schedule in insulin-requiring type 2 diabetes after gastric bypass surgery.

<table>
<thead>
<tr>
<th>Self-monitored fasting glucose values</th>
<th>Adjustment of insulin dosage (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12 mmol/L (220 mg/dL)</td>
<td>6 ↑</td>
</tr>
<tr>
<td>&gt;10 mmol/L (180 mg/dL)</td>
<td>4 ↑</td>
</tr>
<tr>
<td>&gt;8 mmol/L (144 mg/dL)</td>
<td>2 ↑</td>
</tr>
<tr>
<td>≥7 mmol/L (120 mg/dL)</td>
<td>1 ↑</td>
</tr>
<tr>
<td>5.5–6.9 mmol/L (100–120 mg/dL)</td>
<td>No change in insulin dosage</td>
</tr>
<tr>
<td>&lt;5.5 mmol/L (100 mg/dL)</td>
<td>2 ↓</td>
</tr>
<tr>
<td>&lt;4.5 mmol/L (81 mg/dL)</td>
<td>4 ↓</td>
</tr>
<tr>
<td>&lt;4.0 mmol/L (72 mg/dL)</td>
<td>6 ↓</td>
</tr>
</tbody>
</table>

Start with dose equivalent to the insulin required in the previous 24 h prior to discharge and adjust it daily.
2.2 Study 2: GLUCOSURG-post

Participants and informed ethical consent

This was a single- centre, non-blinded, randomised, controlled trial studying obese subjects with T2DM undergoing RYGB. Forty-two suitable subjects were recruited between December 2010 and October 2012 from the obesity clinic at Charing Cross Hospital, London. All subjects gave written informed consent. The study was conducted according to the principles of the Helsinki declaration. Ethics was granted from the West London 2 Research Ethics Committee, (Ref10/H0711/69). The trial was registered on the ClinicalTrials.gov NCT01257087.

Randomisation

Using a computer generated block-randomisation method with a 1:1 ratio; subjects were randomised to intensive glucose management or conservative management for 2 weeks following RYGB.

Inclusion criteria:

1. Informed consent obtained before any trial related activities.
2. T2DM according to clinical judgement.
3. BMI ≥35 kg/m²
4. Age between 18 and 70 years.
5. Insulin treated T2DM.
6. Able and willing to complete the trial.

Exclusion criteria:

The same exclusion criteria as outlined in study 1.

2.2.1 Study preparation

Forty-two subjects were screened for inclusion and participation in the study. The screening, randomisation, and allocation process are shown in figure 6. One did not meet inclusion criteria. 41 subjects gave written informed consent and were
randomised. Six subjects dropped out. Thirty-five subjects had completed one year follow up. The study was analysed by intention to treat and as per protocol analysis.

Figure 6: Recruitment, randomisation and follow up for GLUCOSURG-post subjects.
Preoperative care/ Perioperative care

All subjects were seen in a specialist medical clinic prior to surgery. They shared the similar preoperative, perioperative, inpatient and postoperative care pathway as described in study 1, with exception to their target fasting CG readings. Postoperatively, intensive glucose management aimed for a fasting CG of 5.5 - 6.5mmol/L, and conservative glucose management aimed for fasting CG of 6.5-7.5mmol/L.

Postoperative care

Following discharge, subjects contacted the chief investigator with their daily fasting CG up to post-operative day 15, in the same way as GLUCOSURG-pre. The dose of the long-acting insulin analogue and metformin was adjusted to achieve target fasting CGs of 5.5-6.5mmol/L in the intensively treated group and 6.5-7.5mmol/L in the conservative treated group. Thereafter, subjects were advised to contact their physician if their fasting CG levels were <4.5 or >7.5 mmol/L. Glycaemic control and the use of glucose-lowering medication were assessed at 10 days, 3 months, 6 months and 1 year after surgery. Metformin was reviewed at follow up and discontinued if fasting glucose levels were ≤5.6 mmol/L.

Follow up

Follow up care as discussed in study 1.
2.3 Study 3: GLUCOSURG-combine

Surgical and Medical groups

Subjects from GLUCOSURG -pre and GLUCOSURG -post were collated into surgical group. The surgical subjects were matched with 25 diabetic patients with BMI ≥35 kg/m2 receiving best medical care. These patients were matched for gender, age, HbA1c and duration of diabetes. They were under the care of tertiary centre diabetes specialist clinic. The patients were seen by diabetes physicians who provided the routine diabetes care including optimisation of glycaemia, cardiovascular risk and weight. The patients were also reviewed within a year.

2.4. Data collection and analysis

Data Collection (GLUCOSURG-pre and GLUCOSURG-post)

Demographic information, duration of diabetes, body weight, height, blood pressure, HbA1c, fasting plasma glucose were collected at baseline and 12 months. Data on diabetes microvascular complications (urine ACR, retinal photography, nerve conduction study, thermal threshold testing) were collected before and a year after surgery. Data on capillary glucose readings and insulin requirement were collected up to 14 days post- surgery. Data on glucose and blood pressure lowering medications were collected before and a year after surgery. Length of stay, 30 days surgical complications, and postoperative hypoglycaemic episodes were also collected.
2.4.1 Analysis (GLUCOSURG-pre and GLUCOSURG-post)

Analysis were carried out comparing the outcomes between the conservative and intensive groups. Data were analysed with intention to treat analysis, and as per protocol analysis.

As per protocol analysis (GLUCOSURG -pre)

Subjects who were randomised to intensive group but did not achieve at least 1% reduction in HbA1c before surgery were reassigned to conservative group and vice versa.

As per protocol analysis (GLUCOSURG -post)

Subjects who were randomised to intensive group but did not achieve fasting CG of 5.5-6.5mmol/L within two weeks post- surgery were reassigned to conservative group, and vice versa.

2.4.2 Data collection and analysis (GLUCOSURG-combine)

Demographic information and data on surgical group as collated previously. Data collected on medical comparative group include demographic information and duration of diabetes. BMI, HbA1c, blood pressure, medication usage and microvascular complications were also collected within the 6 months before and at 12-18 months after intervention.

2.5 Glycaemic control

Glycated haemoglobin (HbA1c) was measured at 1 month before, and 12 months after surgery or inclusion in the trial. Remission of diabetes was based on the ADA criteria. Partial remission is defined as HbA1c of less than 6.5% for at least 1 year without active pharmacologic therapy. Complete remission is defined as HbA1c level of less than 6% of at least 1 year’s duration without active pharmacologic therapy (Buse et al., 2009).

Further analysis included collating all surgical patients in GLUCOSURG -pre and GLUCOSURG -post together as surgical group, and compared the change in HbA1c to the comparative group who received best medical treatment only.
2.6 Renal function

Albuminuria was assessed using 2 early morning ACR collected within the 6 months preceding surgery and 10 - 14 months after surgery. Albuminuria was defined as an ACR value of ≥ 2.5 mg/mmol in males or ≥ 3.5 mg/mmol in females. Improvement or deterioration after surgery was defined as a decrease or increase in the ACR value respectively. Normalisation was defined in those patients with pre-existing albuminuria who subsequently had a reduction in their urine ACR result to below the aforementioned cut off. The changes in albuminuria before and within 1 year of surgery were assessed between the intensive and conservative treated groups.

Further analysis included collating all surgical patients in GLUCOSURG -pre and GLUCOSURG -post together as surgical group, and compared the change in urine ACR to the comparative group who received best medical treatment only.

2.7 Retina

Retinal photographs within 6 months preceding surgery and within 9 to 15 month post-surgery were obtained from the national retinal screening centre or ophthalmology department. Retinal images were graded according to the English National Screening Programme for Diabetic Retinopathy and the results confirmed by an independent ophthalmologist who was blinded to the patient clinical information. The final decision on scoring was taken from the ophthalmologist’s score.

The retinal photographs were graded and given a retinal score according to features described at each stage of retinal disease (Table 3). In cases where score was different in both eyes, the higher score was taken for the purpose of analysis.
Table 3. Retinal grading and score (Adapted from International clinical disease severity scale for diabetic retinopathy)(Wilkinson et al.)

<table>
<thead>
<tr>
<th>Proposed disease severity level</th>
<th>Description</th>
<th>Retinal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>No abnormalities</td>
<td>0</td>
</tr>
<tr>
<td>Mild non-proliferative diabetic retinopathy</td>
<td>Microaneurysms only</td>
<td>1</td>
</tr>
<tr>
<td>Moderate non-proliferative diabetic retinopathy</td>
<td>More than just microaneurysms but less than severe nonproliferative diabetic retinopathy</td>
<td>2</td>
</tr>
<tr>
<td>Severe nonproliferative diabetic retinopathy</td>
<td>Any of the following:</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>More than 20 intraretinal haemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; prominent intraretinal microvascular abnormalities in 1+ quadrant and no signs of proliferative retinopathy</td>
<td></td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>One or more of the following:</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Neovascularization, vitreous/preretinal haemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

Improvement or worsening was defined as a decrease or an increase of at least two steps in the same grading system respectively (i.e. at least two steps in one eye or one step in each eye). Normalisation was defined in the patients with pre-existing diabetic retinopathy, who showed no signs of diabetic retinopathy after surgery or best medical care.
The changes in retinal images before and after surgery were compared between the intensively treated group and conservative treated group.

Further analysis included collating all surgical patients in Glucosurg-pre and Glucosurg-post together as surgical group, and compared the change in retinal images to the comparative group who received best medical treatment only.

**2.8 Peripheral nervous system function**

Nerve Conduction studies (NCS) and thermal threshold testing (TTT) were only performed on subjects who had bariatric surgery due to cost limitation. The studies were performed within 3 months preceding and 12-15 months after surgery.

**Nerve conduction study**

Nerve conduction study is the gold standard for evaluation of myelinated large nerve fibres. The study of motor and sensory nerves was performed with standard techniques of stimulation and recording using Dantec EMG machine. This test was conducted by a single operator on the right upper and lower limb. The motor nerves tested include median, ulnar, common peroneal and tibial nerves. The sensory nerves include median, ulnar, superficial radial and sural. Upper limb assessment included superficial radial sensory nerve action potential (SNAP), superficial radial conduction velocity (CV); and lower limb assessment included sural SNAP and sural CV, common peroneal CV, tibial compound muscle action potential (CMAP), minimal latency tibial F-response. Nerve conduction study was analysed quantitatively. P value was adjusted with Bonferroni correction to correct for multiple comparisons.

The data was also analysed qualitatively by a neurophysiologist. Table 5 showed normal values for motor nerve (standard operating procedure for Charing Cross Hospital neurophysiology department). Table 6 showed normal values for sensory nerve (standard operating procedure for Charing Cross Hospital neurophysiology department). Reference range for minimal latency tibial F response is height dependent, medium stature 54-58ms.
Table 4 Normal range for motor nerve values

<table>
<thead>
<tr>
<th>Nerve</th>
<th>DL (ms)</th>
<th>Amp. (mV)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>4.2</td>
<td>4.5-17.5</td>
<td>49</td>
</tr>
<tr>
<td>Ulnar</td>
<td>4.0</td>
<td>5.0-17.5</td>
<td>47</td>
</tr>
<tr>
<td>Radial</td>
<td>5.2</td>
<td>4.0-9.0</td>
<td>50</td>
</tr>
<tr>
<td>Peroneal</td>
<td>6.5</td>
<td>2.5-11.0</td>
<td>39</td>
</tr>
<tr>
<td>Tibial</td>
<td>7.0</td>
<td>2.5-14.0</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 5. Normal range for sensory nerve values

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Amp. (µV)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (index)</td>
<td>6-26</td>
<td>44-66</td>
</tr>
<tr>
<td>Ulnar (little finger)</td>
<td>4-24</td>
<td>45-71</td>
</tr>
<tr>
<td>Radial (1st webspace)</td>
<td>4-20</td>
<td>50-64</td>
</tr>
<tr>
<td>Sural</td>
<td>4-26</td>
<td>39-54</td>
</tr>
</tbody>
</table>

2.9.2 Thermal threshold testing

Thermal threshold testing is used to evaluate small sensory nerve fibres. The test was conducted on upper limb (dorsum of hand) and lower limb (dorsum of foot). This was carried out by a single operator in an ambient temperature controlled (24 ± 1 °C) room to ensure consistency. P value was adjusted with Bonferroni correction to correct for multiple comparison.
The data was also analysed qualitatively by a neurophysiologist. Patients thermal threshold values were compared to healthy controls reference ranges (Table 7 (Nicotra A, 2012)).

Table 6. Thermal thresholds values in the upper and lower limbs in healthy controls subjects. (mean ± standard error of mean)

<table>
<thead>
<tr>
<th></th>
<th>Controls ( n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hand</strong></td>
<td></td>
</tr>
<tr>
<td>Cool perception threshold(°C)</td>
<td>30.0 ± 0.7</td>
</tr>
<tr>
<td>Warm perception threshold (°C)</td>
<td>34.2 ± 1.0</td>
</tr>
<tr>
<td><strong>Feet</strong></td>
<td></td>
</tr>
<tr>
<td>Cool perception threshold(°C)</td>
<td>29.3 ± 1.3</td>
</tr>
<tr>
<td>Warm perception threshold (°C)</td>
<td>36.1 ± 1.9</td>
</tr>
</tbody>
</table>

2.9. Surgical complications

Surgical complications included any surgical related complications within 30 days of surgery. This was obtained from patient case notes, and confirmed with patients at 1 year review.

2.10 Hypoglycaemic episodes

Hypoglycaemia is defined as capillary glucose readings of < 4.0mmol/L. This was assessed between day 3 to day 15 post-surgery.

2.11. Study Endpoints

The primary end point was the proportion of patients achieving remission of diabetes as defined by ADA criteria at 12 months after surgery (Buse et al., 2009). Secondary endpoints included microvascular complications such as nephropathy, retinopathy, and neuropathy. Other secondary end points included length of stay, 30 days surgical complications, hypoglycaemic episodes, and medication usage.
2.11 Statistical analysis

Presentation of data

Descriptive statistics were expressed as mean ± standard error of the mean or median (interquartile range) depending on normality distribution or as percentages. Within group comparisons were made using the paired sample student t-test or the Wilcoxon matched pairs test, and between group comparisons using the unpaired Student t-test or the Mann Whitney U test depending on the normality distribution. Categorical data were compared using the chi square test (Graphpad PRISM software version 5.01, GraphPad Software Incorporation, USA). Bonferroni correction for multiple comparisons was applied to the neurophysiological measurements. The Pearson methodology was used to test correlations between two variables at a time. Statistical significance was accepted as p<0.05.

2.12 Power calculation

Study 1: GLUCOSURG -pre

The criteria variable selected to determine statistical power are HbA1c. There are no data on the effects of pre-operative glycemic optimisation on average glycaemia at 1 year after bariatric surgery and as such the GLUCOSURG -pre trial was a pilot.

Study 2 GLUCOSURG -post

Based on our data, with an absolute reduction in HbA1c of -3.0% in the group whose glucose control was optimised for 2 weeks after surgery and -1.2% in the group that underwent no optimisation, with a standard deviation of 1.7 around the mean, a sample size of 16 patients in each group was needed for a proposed RCT in order to have 80% power to show significant differences between the groups at α=0.05(Chuah et al., 2015).

Study 3: GLUCOSURG -combine

The criteria variable selected to determine statistical power are HbA1c. At the design of the study, there were no data on the effects of RYGB on diabetic nephropathy,
retinopathy and neuropathy at 1 year after bariatric surgery and as such the GLUCOSURG -combine trial was a pilot.
Chapter 3. Methods/ Techniques

3.1. Glycaemic measurement

Point of care measurement of blood glucose

Point of care measurement of glucose was obtained using Accu-Chek Advantage® (Roche Diagnostics Ltd, Hertfordshire, England, UK). This is the most common glucose monitoring available at home. It allows measurement of glucose throughout the day. It involves placing a blood sample on a chemically coated test strip, which is then placed in a glucose meter. The glucose in the blood reacts with the chemicals on the test strip, producing a small electrical current. This current is measured, and a result displayed on the screen. The size of the current depends on the amount of glucose in the blood sample. This could be affected by temperature. Quality control solution is used to ensure quality control.

Assessment of accuracy demonstrates excellent correlation with a value of 0.994 with 1.000 as the optimum value. The linear regression shows a slope of 1.025 with a 95% confidence interval of (1.009, 1.040). The intercept is 3.6 mg/dL (0.2 mmol/L). The data presented 97% of the individual glucose results shall fall within ± 0.83 mmol/L of the results of the manufacturer’s measurement procedure at glucose concentrations less than 4.2 mmol/L and all individual glucose results were within ± 20% at glucose concentrations greater than or equal 4.2 mmol/L.

Plasma glucose

ADVIA® 2400 Chemistry systems are used for in vitro diagnostic quantitative determination of glucose in human serum, plasma, urine and cerebrospinal fluid. It works by enzymatic method based on the method by Slein utilizing hexokinase and glucose-6-phosphate dehydrogenase enzymes. The Glucose Hexokinase II method is a two-component reagent. Sample is added to Reagent 1, which contains the buffer, ATP, and NAD. Absorbance readings of the sample in Reagent 1 are taken and are used to correct for interfering substances in the sample. Reagent 2 is added, which initiates the conversion of glucose and the development of absorbance at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration.
Glucose is phosphorylated by adenosine triphosphate (ATP) in the presence of hexokinase. The glucose-6-phosphate that forms is oxidized in the presence of glucose-6-phosphate dehydrogenase causing the reduction of NAD to NADH. The absorbance of NADH is measured as an endpoint reaction at 340 nm.

The imprecision for glucose has an inter-assay coefficient variation of <2.9%.

**HbA1c**

The principal haemoglobin (Hb) consists of two alpha chains and two beta chains. These chains can be glycated. Glycated haemoglobins consist of HbA1a (fructose-1, 6-diphosphate), HbA1b (glucose-6-phosphate) and HbA1c (glucose). HbA1c consists of a labile and a stable form. The formation of stable glycated Hb is irreversible and the blood level depends both on the blood glucose concentration and the life span of the red blood cells. Thus the level of HbA1c represents the integrated values for glucose over the preceding 6-8 weeks.

HbA1c is measured using the Menarini HA-8160. The HA 8160 differentiates stable HbA1c from HbA1a, HbA1b, and labile HbA1c and stable Hba1c as well as from the non-glycated ‘parent’ haemoglobin A0. Reversed phase partition chromatography is used to elute HbA1a, HbA1b, HbF, labile HbA1c and stable HbA1c by Eluant A. Ion exchange chromatography is then used to elute HbA by Eluant B and HbA2, HbS and HbC by Eluants C and D. Detection relies upon dual-wave length spectrophotometry.

The International Federation for Clinical Chemistry (IFCC) has produced an international reference standard. It has been agreed that the new IFCC standardised HbA1c will be reported as mmol per mol of unglycated haemoglobin.

The imprecision for HbA1c has an inter-assay coefficient variation of <2.4%.

**3.2 Retinal assessment**

**Retinal photography**

Diabetic eye disease was assessed using two field (nasal view and macular view) digital retinal images taken at the same time points. Patients received 1% tropicamide
eye drop for mydriasis, prior to retinal photograph. Photographs were obtained though fundus camera. This is part of national screening programme for diabetic retinopathy; hence the minimum accepted standards for the quality of images, the maximum accepted technical failure rate of the screening system were as specified by the national programme. The retinal grader also attended monthly online test and training session as part of quality assurance.

3.3 Renal assessment

Urine albumin creatinine ratio

ADVIA® 2400 Chemistry systems are used for in vitro diagnostic quantitative determination of human albumin in urine. This microalbumin method is based on the work of Fielding and Hellsing, and it measures very small levels of albumin in urine samples. Albumin is a plasma protein that is responsible for much of the osmotic force of the blood. In healthy population, only a small amount of albumin (up to 20 mg/L) is excreted in the urine. Elevated levels of urinary albumin indicate a high probability of damage of the glomerular filtration capacity of the kidney. During the progression of renal disease in type I diabetes mellitus, stage III or incipient nephropathy is characterized by the elevation in urinary albumin. Elevated results in urinary albumin may also be associated with hypertension, some lipid abnormalities, and several immune disorders as well as other conditions such as vigorous exercise, blood in the urine, urinary tract infection, dehydration, and some drugs.

The microalbumin method is a PEG enhanced immunoturbidimetric assay. Sample containing human albumin is suitably diluted and then reacted with specific antiserum to form a precipitate that can be measured turbidimetrically at 340 nm. By constructing a standard curve from the absorbances of standards, the albumin concentration of the sample can be determined. The imprecision for urine ACR has inter-assay coefficient variation of <5.3%.

3.4 Peripheral nervous system assessment

Nerve Conduction studies and thermal threshold testing (TTT) were performed before and 12 months after surgery or inclusion in the trial respectively.
Nerve conduction studies

Nerve conduction studies (motor and sensory) were performed with standard techniques of stimulation and recording using Dantec EMG system (Copenhagen, Denmark). Motor conduction is performed by stimulating the nerve at two points and recording form one of the distal muscles supplied by the nerve. Sensory conduction is performed either orthodromically (stimulating the nerve distally and recording proximally along the course) or antidromically (stimulating the nerve proximally and recording distally). The median and sensory nerves were tested orthodromically by stimulating the index (median) and little (ulnar) fingers distally and recording proximally at the wrists. The superficial radial and sural nerves were tested antidromically; the radial nerve by stimulating the forearm and recording distally at the first web space and the sural by stimulating the lower leg and recording behind the lateral malleolus. The motor measurements include distal motor latency (ms), conduction velocity (m/s), amplitude of the compound muscle action potential (mV) and the minimal latency of the F-responses. The sensory measurements include amplitude (uV) and conduction velocity (m/s). The imprecision for NCS has a coefficient variation of <5.0%.

Thermal threshold testing

Thermal threshold testing to cool sensation and warm sensation was carried out with a SENSELab-THERMOTEST Modular Sensory Analyser (Sweden). A thermode (25 x 50 mm) was applied to the skin of the dorsum of hands and feet. Cool and warm perception thresholds were measured using the method of limits: subjects received five successive thermal stimuli, decreasing or increasing from a starting temperature of 32°C at a rate of 1°C/second, and were required to arrest the changing stimulus by pressing a button as soon as the specific modality (cool or warmth) being tested was perceived. The cut-off temperature limit for cool perception threshold was 10 °C and for warm perception threshold was 50 °C; if those limits are reached, the machine would automatically revert to the baseline temperature of 32 °C. Thresholds were taken as the average of five successive readings for each thermal modality. (Nicotra A, 2012, Chuah et al., 2015) Threshold from left and right limb were averaged, and taken for analysis. The test
combined objective physical sensory stimuli and subject’s response to stimuli, it is therefore a psychophysical testing, which has greater inherent variability. There is interoperator variability and its reproducibility is yet to be established.
Chapter 4. Results for GLUCOSURG -pre study

4.1 Participants characteristics

Thirty-four subjects had completed one year follow up. The subject baseline characteristics are shown in Table 7.

There were 11 males, 7 females in the conservative group. The group had mean age of 48.9± 1.8, duration of diabetes 9.2± 1.5 years, and BMI of 42.1(39.4-50.8) kg/m². HbA1c was 10.3 (9.5-11.0) % [89.1 (80.3-96.7)] mmol/mol at randomisation.

There were 9 males, 7 females in the intensive group. The mean age was 49.3± 2.1, duration of diabetes 10.5± 1.9 years, and BMI of 46.2 (38.4-55.3) kg/m². HbA1c was 9.9 (8.9-10.4) % [84.7 (73.8-90.2) mmol/mol] at randomisation. HbA1c was reduced to 8.4 (7.1-9.3) % [68.3 (54.1-78.1)]mmol/mol following intensive treatment prior to RYGB. The number of glucose lowering medications was similar in both groups, 2.0 (2.0-2.0).

Following randomisation, the age, gender distribution, BMI, HbA1c, duration of T2DM and number of glucose lowering medications were similar between the groups.

Body mass index

BMI at 1 year following surgery showed significant reduction from 42.1 (39.4-50.8) to 32.1 (29.9-34.4) kg/m² in the conservative group (p<0.0001); and from 46.2 (38.4-55.3) to 36.2 (28.8-38.3) kg/m² in the intensive group (p=0.008). There was no significant difference between the 2 groups (p=0.62).

Blood pressure

There was significant reduction in systolic blood pressure (SBP) from 149(139-157) mmHg to 125 (116-142) mmHg in the conservative group (p<0.05). No significant reduction in SBP was observed in the intensive group, 146 (136-157) mmHg to 129 (122-145) mmHg (p=0.21). The change in SBP between the two groups was not significant (p=0.21).
There was no significant change in diastolic blood pressure (DBP) in conservative and intensive groups at follow up, 83 (80-91) mmHg to 82 (74-89) mmHg (p=0.16); 86 (80-93) mmHg to 80 (77-91) mmHg (p=0.57) respectively.

**Effectiveness of the intervention on pre-operative glycaemic control**

In the intensive group HbA1c was reduced significantly in the three months pre-surgery from 9.9% (85mmol/mol) to 8.4% (68.3mmol/mol) (p=0.003), whilst the HbA1c of the conservative group did not change significantly, 10.3% (89.1mmol/mol) to 9.7% (82.5mmol/mol) (p=0.25). HbA1c of the intensive group on the day of surgery was significantly lower than the conservative group (p<0.005).

**4.2 Glycaemic control at 1 year**

Both groups achieved significant reductions in HbA1c 1 year after surgery. The conservative group achieved HbA1c of 6.3 (5.9-6.8) % [45.4 (41.0-50.8)] mmol/mol, (p=0.0002) and the intensive group achieved 6.9 (5.9-7.8) % [51.9 (41.0-61.7)] mmol/mol (P=0.0001). The difference in reductions in HbA1c between both groups was not significant (p=0.07).

**Remission of diabetes**

Five (27.8%) subjects from the conservative group achieved HbA1c<6.0%, 2 subjects were not on any glucose lowering medication, and 3 were on metformin. Four (25%) subjects from the intensive group achieved HbA1c<6.0%, 1 subject was not on any glucose lowering medication, 3 were on Metformin. Overall 3 subjects achieved complete remission of diabetes at 1 year post surgery, as defined by ADA criteria.

**Medication usage**

**Glucose lowering medications**

Glucose lowering medications was reduced from 2.0 (2.0-2.3) to 1.0 (1.0-1.0) (p=0.0001), and 2.0 (2.0-2.0) to 1.0 (1.0-2.0) (p=0.004) in conservative and intensive group respectively.
**BP lowering medications**

BP lowering medications was reduced from 1 (1-2) to 1 (0-1), (p=0.007); and 2 (1-2) to 1 (0-2) (p=0.007) in conservative and intensive group respectively.

**Incidence of hypoglycaemia**

Two subjects in the intensive group had CG readings <4.0 mmol/L but did not have symptoms of severe hypoglycaemia during the two weeks monitoring post-surgery. No hypoglycaemia was noted in the conservative group.

**Length of stay**

The median length of stay was 3 days for both groups (p=0.73).

**Surgical complications**

There was no significant difference in the incidence of surgical complications between the 2 groups. One subject from the intensive group had a post-operative stroke on day 1 and made a full recovery. One patient developed abdominal pain post-surgery which resolved spontaneously. One subject from the conservative group vomited post-surgery, but settled after a prolonged inpatient stay.

**4.3 Microvascular complications**

**4.3.1 Albuminuria**

Thirteen subjects from conservative group and 11 subjects from intensive groups had complete urine ACR datasets. Median urinary albumin creatinine ratio reduced from 6.9 (1.3-14.3) to 1.8 (0.7-5.6) mg/mmol at one year in conservatively managed group (p<0.05). The change in urine ACR was not significant in the intensive treatment group, 6.1 (1.9-14.0) to 1.7 (0.8-6.8) mg/mmol, (p=0.58). There was no significant difference in the change in albuminuria between the conservative and intensive group.

Subgroup analysis of the overall cohort showed 9 subjects had normal ACR, 15 had pre-existing albuminuria at baseline. At 1 year after surgery, 13 subjects improved, 3 deteriorated, 8 had no change.
Of the 15 subjects with pre-existing albuminuria, 13 improved of which 8 normalised, 2 had deteriorated. Of the 9 normal albuminuria subjects, 8 had no change, and 1 had deteriorated.

4.3.2 Retinopathy

Fifteen subjects from conservative group and twelve subjects from intensive group had complete retinal datasets. The conservative group had a median retinal score of 1.0 (0.0-1.0) before surgery, and 1.0 (0.0-2.0) at one year follow up (p=0.46). The retinal score was 1.0 (0.0-3.0) before surgery and 0.5 (0.0-1.8) at one year follow up (p=0.55) for intensive group. There was no significant different changes in retinal score between both groups (p=0.45).

Subgroup analysis of overall cohort showed 11 subjects had no retinopathy, 12 had mild to moderate non-proliferative retinopathy, and 4 had severe non proliferative retinopathy. At 1 year after surgery, 20 (74.1%) patients had no change, 5 (18.5%) patients improved by at least two steps, and 2 (7.4%) deteriorated by at least two steps in retinopathy severity grading.

Of the 16 subjects with pre-existing retinopathy, 5 improved, 1 deteriorated, 10 were stable. Of the 11 subjects with normal retinal, 1 deteriorated, 10 remained stable.

4.3.3 Peripheral neuropathy

Nerve conduction study

Thirteen subjects from the conservative group and 14 subjects from the intensive group underwent nerve conduction studies (Table 8). There were no statistically significant changes in any of the nerve conduction parameters at 1 year. There was no significant difference between the intensive and conservative treated group.

Qualitative analysis showed 11 of the overall cohort had pre-existing peripheral neuropathy, 16 had normal NCS at baseline. At 1 year after surgery, 2 who had pre-existing neuropathy showed deterioration, 25 subjects had no change.
Thermal threshold testing

Thirteen subjects completed thermal threshold testing in the intensive and conservative groups (Table 9). There was worsening of cool perception threshold on lower limbs in conservative group after surgery, from 30.1 (29.2-30.6) to 28.6(26.8-30.3) °C (P= 0.008). There were no statistically significant changes in other perception threshold after surgery. There was no difference in changes between both groups.

Postoperative glucose management

Both conservative and intensive groups of patients were monitored and managed with the aim of maintaining blood glucose within the range of 5.5 – 7.5 mmol/L. Figure 7 showed glucose trend postoperatively in both optimised and non-optimised groups. Postoperative glucose trend was not significantly different between both groups (p=0.13).
Table 7. GLUCOSURG-pre. Baseline and 1 year follow-up results of the conservative and intensive group. (Intention to treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=18)</th>
<th>P value (within group)</th>
<th>Intensive (n=16)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
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<tr>
<td><strong>Baseline variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>48.9± 1.8</td>
<td>N/A</td>
<td>49.3± 2.1</td>
<td>N/A</td>
<td>0.93</td>
<td>N/A</td>
</tr>
<tr>
<td>Male (%;n)</td>
<td>61.1, 11</td>
<td>N/A</td>
<td>56.3, 9</td>
<td>N/A</td>
<td>1.00</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>9.2± 1.5</td>
<td>N/A</td>
<td>10.5± 1.9</td>
<td>N/A</td>
<td>0.55</td>
<td>N/A</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.1 (39.4-50.8)</td>
<td>32.1 (29.9-34.4)</td>
<td>46.2 (38.4-55.3)</td>
<td>36.2 (28.8-38.3)</td>
<td>0.008</td>
<td>0.78</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>149 (139-157)</td>
<td>125 (116-142)</td>
<td>146 (136-157)</td>
<td>129 (122-145)</td>
<td>0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 (80-91)</td>
<td>82 (74-89)</td>
<td>86 (80-93)</td>
<td>80 (77-91)</td>
<td>0.37</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Outcome variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.3 (9.5-11.0)</td>
<td>6.3 (5.9-6.8)</td>
<td>9.9 (8.9-10.4)</td>
<td>6.9 (5.9-7.8)</td>
<td>0.0001</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>a9.7 ( 8.8-10.9)</td>
<td></td>
<td>b8.4 (7.1-9.3)</td>
<td></td>
<td></td>
<td>c&lt;0.005</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>89.1 (80.3-96.7)</td>
<td>45.4 (41.0-50.8)</td>
<td>84.7 (73.8-90.2)</td>
<td>51.9 (41.0-61.7)</td>
<td>0.0001</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>a82.5 (72.7-95.6)</td>
<td></td>
<td>b68.3 (54.1-78.1)</td>
<td></td>
<td></td>
<td>c&lt;0.005</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol)</td>
<td>6.9 (1.3-14.3)</td>
<td>1.8 (0.7-5.6)</td>
<td>6.1 (1.9-14.0)</td>
<td>1.7 (0.8-6.8)</td>
<td>0.58</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>1.0 (0.0-1.0)</td>
<td>1.0 (0.0-2.0)</td>
<td>0.46</td>
<td>1.0 (0.0-3.0)</td>
<td>0.5 (0.0-1.8)</td>
<td>0.55</td>
</tr>
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<td>--------------------------------</td>
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<tr>
<td><strong>Retinal score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of stay (days)</strong></td>
<td>N/A</td>
<td>3.0 (3.0-4.3)</td>
<td>N/A</td>
<td></td>
<td>3.0 (3.0-4.5)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>30 days surgical complications (%;n)</strong></td>
<td>N/A</td>
<td>11.1, 2</td>
<td>N/A</td>
<td></td>
<td>6.3, 1</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hypoglycaemic episodes (n)</strong></td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
<td></td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>glucose-lowering medications</strong></td>
<td>2.0 (2.0-2.3)</td>
<td>1.0 (1.0-1.0)</td>
<td>0.0001</td>
<td>2.0 (2.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>BP lowering medications</strong></td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.0-1.0)</td>
<td>0.007</td>
<td>2.0 (1.0-2.0)</td>
<td>1.0 (0.0-2.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

BMI body mass index, HbA1c glycated haemoglobin, a HbA1c post-randomisation, b HbA1c post-optimisation, c p value post-optimisation, N/A not applicable, SBP systolic blood pressure, DBP diastolic blood pressure.
Table 8. Result of nerve conduction study before and one year post RYGB surgery (Intention to treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=13)</th>
<th>P value (within group)</th>
<th>Intensive (n=14)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
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<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup radial SNAP(mV)*</td>
<td>21.6 (16.1-29.5)</td>
<td>21.0 (14.7-27.8)</td>
<td>1.00</td>
<td>14.6 (10.4-18.8)</td>
<td>16.5 (10.4-21.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sup radial CV(m/s)</td>
<td>63.2 ± 1.1</td>
<td>61.7 ± 1.3</td>
<td>0.21</td>
<td>59.9 ± 2.3</td>
<td>60.1 ± 2.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Sural SNAP (mV)</td>
<td>9.8 (4.8-14.6)</td>
<td>11.1 (8.2-17.2)</td>
<td>0.98</td>
<td>7.8 (4.8-14.3)</td>
<td>9.4 (6.3-21.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sural CV (m/s)</td>
<td>50.4 ± 1.6</td>
<td>50.1 ± 1.6</td>
<td>1.00</td>
<td>49.0 ± 2.0</td>
<td>48.7 ± 2.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Common Peroneal CV (m/s)</td>
<td>46.0 ± 1.4</td>
<td>45.9 ± 1.0</td>
<td>1.00</td>
<td>43.3 ± 1.3</td>
<td>44.5 ± 1.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Tibial CMAP (mV)</td>
<td>5.2 ± 0.5</td>
<td>5.5 ± 0.6</td>
<td>1.00</td>
<td>4.0 ± 0.7</td>
<td>4.5 ± 0.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimal latency tibial F-response (ms)</td>
<td>53.8 ± 1.5</td>
<td>55.2 ± 1.6</td>
<td>0.21</td>
<td>57.5 ± 2.0</td>
<td>57.6 ± 2.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SNAP sensory nerve action potential, CV conduction velocity, CMAP compound muscle action potential
Table 9. Result of thermal threshold testing before and one year post RYGB surgery (Intention to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=13)</th>
<th>P value (within group)</th>
<th>Intensive (n=13)</th>
<th>P value (within group)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
</tr>
<tr>
<td>UL-WPT (°C)</td>
<td>35.2 (34.6-37.1)</td>
<td>34.7 (33.7-36.8)</td>
<td>0.88</td>
<td>36.5 (35.2-37.9)</td>
<td>35.8(34.2-37.7)</td>
</tr>
<tr>
<td>UL-CPT (°C)</td>
<td>30.4 (29.0-31.0)</td>
<td>30.4 (29.3-30.8)</td>
<td>1.00</td>
<td>30.0 (29.5-30.8)</td>
<td>30.2 (30.0-30.8)</td>
</tr>
<tr>
<td>LL-WPT (°C)</td>
<td>37.8 (35.0-42.0)</td>
<td>38.8 (36.1-40.8)</td>
<td>1.00</td>
<td>41.3 (36.2-44.0)</td>
<td>40.5 (37.4-44.7)</td>
</tr>
<tr>
<td>LL-CPT (°C)</td>
<td>30.1 (29.2-30.6)</td>
<td>28.6(26.8-30.3)</td>
<td>0.008</td>
<td>29.4 (26.6-30.5)</td>
<td>26.9 (23.7-30.1)</td>
</tr>
</tbody>
</table>

UL upper limb, LL lower limb, WPT, warm perception threshold, CPT cool perception threshold
Figure 7. Postoperative glucose trend of both optimised (intensive) and non-optimised (conservative) groups (Intention to treat).

The effect of optimisation was not statistically significant $F (1, 268) = 2.34, p = 0.13$. 
Chapter 5. Results of GLUCOSURG -pre (As per protocol analysis)

5.1 Participants characteristics

Criteria for as per protocol analysis was discussed previously. Of the 18 subjects randomised to conservative group, 2 met the criteria for intensive group; of the 16 randomised to intensive group, 6 met the criteria for conservative group. With the reassignment, 22 subjects were in conservative group, and 12 subject in the intensive group. The subject baseline characteristics are shown in Table 10.

There were 12 males, 10 females in the conservative group. The group had mean age of 47.7± 1.6, duration of diabetes 10.2± 1.4 years, and BMI of 42.5(39.4-47.8) kg/m^2. HbA1c was 9.9± 0.2% (83.0± 2.6 mmol/mol) at randomisation.

There were 8 males, 4 females in the intensive group. The mean age was 51.1± 2.4, duration of diabetes 8.4± 2.0 years, and BMI of 46.2 (41.0-55.8) kg/m^2. HbA1c was 10.3± 0.5 % (88.8± 5.2 mmol/mol) at randomisation. HbA1c improved to 8.4± 0.5 (73.8± 5.1 mmol/mol) following intensive treatment, prior to bariatric surgery. The number of glucose lowering medications at baseline was 2.0 (2.0-2.3) in conservative group, and 2.0 (1.0-2.0) in intensive group.

Following randomisation, the age, and gender distribution, duration of T2DM, BMI, HbA1c, and number of glucose lowering medications were similar between the groups.

Body mass index

BMI at 1 year following surgery showed significant reduction from 42.5 (39.4-47.8) kg/m^2 to 32.5 (28.9-37.1) kg/m^2 in the conservative group (p<0.0001); and from 46.2 (41.0-55.8) to 33.5 (30.1-36.8) kg/m^2 in the intensive group (p<0.0001). There was no significant difference between the two groups (p=0.79).
Blood pressure

There was significant reduction in SBP from 148 (139-157) mmHg to 132 (118-143) mmHg in the conservative group (p=0.01). No significant reduction in SBP was observed in intensive group, 146 (132-152) mmHg to 124 (119-141) mmHg (p=0.29). The changes in SBP between the two groups was not significant (p=0.84). There was no significant change in DBP in conservative group and intensive groups at follow up, 85 (80-92) mmHg to 82 (75-89) mmHg (p=0.09); 84 (79-94) mmHg to 80 (72-91) mmHg (p=0.39) respectively.

Effectiveness of the intervention on pre-operative glycaemic control

In the intensive group HbA1c was reduced significantly in the 3 months pre-surgery from 10.3± 0.5% (88.8± 5.2 mmol/mol) to 8.4±0.5% (73.8± 5.1 mmol/mol) (p<0.0001), whilst the HbA1c of the conservative group did not change significantly, 9.9± 0.2% (83.0± 2.6 mmol/mol) to 9.1 ± 0.4% (76.3± 3.8 mmol/mol) (p=0.72).

5.2 Glycaemic control at 1 year
Both groups achieved significant reductions in HbA1c at 1 year. The conservative group achieved HbA1c of 6.8± 0.2% (50.9± 2.3 mmol/mol), and the intensive group achieved 6.7 ± 0.4% (49.6 ± 4.3 mmol/mol).

Remission of diabetes

Four (18.2%) subjects from the conservative group achieved HbA1c<6.0%, 2 were not on any glucose lowering medication, 2 were on metformin. Five (41.7%) subjects from the intensive group achieved HbA1c<6.0%, 1 was not on any glucose lowering medication 4 were on metformin. Overall 3 subjects achieved complete remission of diabetes at 1 year post-surgery, as defined by ADA criteria.
Medication usage

Glucose lowering medication
Glucose lowering medication was reduced from 2.0 (2.0-2.25) to 1.0 (1.0-2.0) (p<0.0001), and 2.0 (1.0-2.0) to 1.0 (1.0-2.0), (p<0.05) in conservative and intensive group respectively.

BP lowering medication
BP lowering medications was reduced from 1 (1-2) to 1 (0-1), (p=0.004); and 2 (1-3) to 1 (0-2) (p=0.01) in conservative and intensive group respectively.

Incidence of hypoglycaemia
Two subjects in the conservative group had CG readings <4.0 mmol/L but did not have symptoms of severe hypoglycaemia during the two weeks monitoring post-surgery. No hypoglycaemia was noted in the intensive group.

Length of stay
The median length of stay was 3 days for both groups (p=1.00, Table 9).

Surgical complications
Within the conservative group, 1 subject had a post-operative stroke on day 1 and made a full recovery. One subject developed abdominal pain post-surgery which resolved spontaneously, and 1 subject vomited post-surgery, but settled after a prolonged inpatient stay. There was no surgical complication in the intensive group.

5.3 Microvascular complications
5.3.1 Albuminuria
Seventeen subjects from conservative group and 7 subjects from intensive group had complete urine ACR datasets. Median urine ACR reduced from 6.4 (1.5-12.9) to 1.6 (0.8-4.5)mg/mmol in conservative group (p<0.05) at 1 year. No significant change in urine ACR was observed in intensive group, 7.6 (2.9-16.4) to 2.6 (0.7-93.5)mg/mmol, (p=0.34). There was no significant difference in the change of albuminuria between both groups.
5.3.2 Retinopathy

Eighteen subjects from conservative group and 9 subjects from intensive group had complete retinal dataset. The conservative group had a median retinal score of 1.0 (0.0-1.3) at baseline, and 1.0 (0.0-1.3) at follow up (p=0.80). The retinal score was 0.0 (0.0-3.0) before surgery and 1.0 (0.0-3.0) at follow up for the intensive group (p=0.56). There was no significant changes in retinal score between both groups (p=0.45).

5.3.3 Peripheral neuropathy

Nerve conduction study

Twenty subjects from the conservative group and 7 subjects from the intensive group completed nerve conduction study (Table 11). There were no statistically significant changes in the nerve conduction parameters at 1 year.

Thermal threshold testing

Seventeen subjects in the conservative and nine subjects in the intensive groups completed thermal threshold testing (Table 12). There was reduction of lower limb cool perception threshold in conservative group from 29.9 (27.0-30.6) ºC to 28.5(24.4-30.0) ºC at follow up (p<0.05), but no significant changes in other perception thresholds were observed. There was no difference in changes between the groups.

Postoperative glucose management

Both conservative and intensive groups of patients were monitored and managed with the aim of maintaining blood glucose within the range of 5.5 – 7.5 mmol/L. Figure 8 showed glycaemic control in the group that had achieved preoperative optimisation of glucose, reduction of HbA1c by 1% before RYGB (As per protocol analysis).
Table 10. GLUCOSURG-pre. Baseline and 1 year follow-up results (As per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=22)</th>
<th>P value (within group)</th>
<th>Intensive (n=12)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>47.7± 1.6</td>
<td>N/A</td>
<td>51.5± 2.4</td>
<td>N/A</td>
<td>0.17</td>
<td>N/A</td>
</tr>
<tr>
<td>Male (%),n</td>
<td>54.5, 12</td>
<td>N/A</td>
<td>66.7, 8</td>
<td>N/A</td>
<td>0.72</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>10.2± 1.4</td>
<td>N/A</td>
<td>8.4± 2.0</td>
<td>N/A</td>
<td>0.46</td>
<td>N/A</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.5(39.4-47.8)</td>
<td>32.5 (28.9-37.1)</td>
<td>46.2 (41.0-55.8)</td>
<td>33.5 (30.1-36.8)</td>
<td>0.31</td>
<td>0.79</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>148(139-157)</td>
<td>132 (118-143)</td>
<td>146 (132-152)</td>
<td>124 (119-141)</td>
<td>0.29</td>
<td>0.81</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85( 80-92)</td>
<td>82( 75-89)</td>
<td>84( 79-94)</td>
<td>80( 72-91)</td>
<td>0.39</td>
<td>0.72</td>
</tr>
<tr>
<td>Outcome variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.9± 0.2</td>
<td>&lt;0.0001</td>
<td>10.3± 0.5</td>
<td>&lt;0.0001</td>
<td>0.36</td>
<td>0.21</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>83.0±2.6</td>
<td>&lt;0.0001</td>
<td>88.8± 5.2</td>
<td>&lt;0.0001</td>
<td>0.36</td>
<td>0.21</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol)</td>
<td>6.4 (1.5-12.9)</td>
<td>0.008</td>
<td>7.6 ( 2.9-16.4)</td>
<td>2.6 (0.7-93.5)</td>
<td>0.34</td>
<td>0.26</td>
</tr>
<tr>
<td>Retinal score</td>
<td>1.0 (0.0-1.3)</td>
<td>0.80</td>
<td>0.0 (0.0-3.0)</td>
<td>1.0 ( 0.0-3.0)</td>
<td>0.56</td>
<td>0.45</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>N/A</td>
<td>3.0 (3.0-4.3)</td>
<td>N/A</td>
<td>3.0 (3.0-4.5)</td>
<td>N/A</td>
<td>1.00</td>
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<td>-----------------------</td>
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<td>--------------</td>
<td>-----</td>
<td>--------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>30 days surgical complications (%,n)</td>
<td>N/A</td>
<td>13.6, 3</td>
<td>N/A</td>
<td>0, 0</td>
<td>N/A</td>
<td>0.54</td>
</tr>
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<td>Hypoglycaemic episodes (n)</td>
<td>N/A</td>
<td>2</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>0.53</td>
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<tr>
<td>glucose-lowering medications</td>
<td>2.0 (2.0-2.3)</td>
<td>1.0 (1.0-2.0)</td>
<td>&lt;0.0001</td>
<td>2.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BP lowering medications</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.0-1.0)</td>
<td>0.004</td>
<td>2.0 (1.0-3.0)</td>
<td>1.0 (0.0-2.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

BMI body mass index, HbA1c glycated haemoglobin, a HbA1c post-randomisation, b HbA1c post-optimisation, c p value post-optimisation.
Table 11. Result of nerve conduction study before and one year post RYGB surgery (As per protocol analysis)

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=20)</th>
<th></th>
<th>Intensive (n=7)</th>
<th></th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup radial SNAP (mV)*</td>
<td>18.7 (11.0-28.0)</td>
<td>21.0 (11.2-27.2)</td>
<td>1.00</td>
<td>14.1 (13.0-15.1)</td>
<td>16.5 (11.9-17.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sup radial CV (m/s)</td>
<td>62.5 (60.0-67.7)</td>
<td>61.4 (59.5-65.8)</td>
<td>1.00</td>
<td>60.9 (57.4-66.0)</td>
<td>61.3 (49.7-66.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sural SNAP (mV)</td>
<td>9.4 (4.9-15.5)</td>
<td>10.6 (7.4-17.8)</td>
<td>0.49</td>
<td>7.6 (4.5-12.1)</td>
<td>9.7 (6.1-20.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sural CV (m/s)</td>
<td>50.5 (46.1-55.0)</td>
<td>49.9 (45.0-53.6)</td>
<td>1.00</td>
<td>48.0 (43.7-53.8)</td>
<td>48.3 (43.5-57.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Common Peroneal CV (m/s)</td>
<td>44.2 (42.1-48.8)</td>
<td>45.3 (42.0-48.7)</td>
<td>1.00</td>
<td>42.1 (39.7-49.7)</td>
<td>47.1 (40.5-50.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Tibial CMAP (mV)</td>
<td>4.8 (2.8-5.8)</td>
<td>4.7 (3.1-6.9)</td>
<td>1.00</td>
<td>4.5 (3.2-6.7)</td>
<td>6.0 (2.5-6.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimal latency tibial F-response (ms)</td>
<td>55.9 (49.0-59.9)</td>
<td>55.4 (50.6-60.9)</td>
<td>0.07</td>
<td>54.3 (51.0-66.9)</td>
<td>55.6 (51.4-65.1)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SNAP sensory nerve action potential, CV conduction velocity, CMAP compound muscle action potential
Table 12. Results of thermal threshold testing before and one year post RYGB surgery (As per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=16)</th>
<th>P value (within group)</th>
<th>Intensive (n=9)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL-WPT(°C)</td>
<td>35.3 (34.7-36.3)</td>
<td>34.4 (33.6-37.1)</td>
<td>36.7 (36.0-39.6)</td>
<td>35.8 (35.0-39.2)</td>
<td>0.28</td>
<td>0.04</td>
</tr>
<tr>
<td>UL-CPT(°C)</td>
<td>30.4 (29.7-31.1)</td>
<td>30.5 (29.5-31.1)</td>
<td>30.0 (29.0-30.6)</td>
<td>30.2 (29.5-30.4)</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>LL-WPT(°C)</td>
<td>37.8 (35.0-41.8)</td>
<td>38.2 (36.0-41.9)</td>
<td>42.6 (36.2-44.4)</td>
<td>39.9 (38.6-45.8)</td>
<td>1.00</td>
<td>0.08</td>
</tr>
<tr>
<td>LL-CPT(°C)</td>
<td>29.9 (27.0-30.6)</td>
<td>28.5 (24.4-30.0)</td>
<td>29.8 (26.5-30.3)</td>
<td>26.9 (25.9-30.3)</td>
<td>0.24</td>
<td>0.72</td>
</tr>
</tbody>
</table>

UL upper limb, LL lower limb, WPT, warm perception threshold, CPT cool perception threshold
Figure 8. Postoperative glucose trend of optimised (intensive) and non-optimised (conservative) groups (as per protocol).

The effect of optimisation was not statistically significant $F (1, 256) = 0.79$ $p=0.37$
Chapter 6. Result for GLUCOSURG - post study

6.1 Participants characteristics

Thirty-five subjects had completed one year follow up. The subject baseline characteristics are shown in Table 13.

There were 10 males, 7 females in the conservative group. The group had a mean age of 50.1± 2.3, duration of diabetes was 9.2± 1.3 years. The median BMI was 44.6(41.2-51.1) kg/m², HbA1c was 8.5 (7.6-10.1) % [69.4 (59.6-86.9)] mmol/mol.

There were 5 males, 13 females in the intensive group. Their mean age was 53.9± 1.7, duration of diabetes 14.2± 1.5 years. Their median BMI was 43.7 (40.0-48.2) kg/m², HbA1c was 8.6 (7.3-10.3) % [70.5 (56.3-89.1) mmol/mol].

Following randomisation, the age, gender distribution, BMI and HbA1c were not significantly different between the groups. Subjects in the intensive group had T2DM for 5 years longer than the conservative group (p= 0.02). The conservative group was on one more glucose lowering medications 3.0 (2.0-3.0) than the conservative group 2.0 (1.0-2.0).

Body mass index

BMI at one year following surgery showed significant reduction from 44.6 (41.2-51.1) kg/m² to 32.7 (28.5-40.3) kg/m² in the conservative group (p=0.0003); and from 43.7 (40.0-48.2) kg/m² to 31.8 (27.7-37.7) kg/m² in the intensive group (p<0.0001). There was no significant difference between the two groups (p=0.98).

Blood pressure

No significant reduction in SBP was observed in the conservative group, 140± 3 mmHg to 133± 5 mmHg (p=0.36). There was significant reduction in SBP from 138 ± 23 mmHg to 124± 5 mmHg in the intensive group (p<0.05). The change in SBP between the two groups was not significant (p=0.19).
There was no significant change in DBP in conservative group, 78± 3 mmHg to 82± 2 mmHg (p=0.26). Significant reduction of DBP was observed in intensive group, 84± 3 mmHg to 76± 2 mmHg (p=0.02).

**Effectiveness of the intervention on early post-operative glycaemic control**
Following surgery, both groups of patients were monitored and managed with the aim of achieving intensive (5.5-6.5mmol/L) or conservative (6.5-7.5 mmol/L) glucose control within first 2 weeks. Figure 9 showed postoperative glucose trend of both intensive and conservative managed group (intention to treat analysis). The effect of optimisation was not statistically significant (p=0.94).

**6.2 Glycaemic control at 1 year**
Both groups achieved significant reductions in HbA1c 1 year after surgery. The conservative group achieved HbA1c of 6.2 (5.8-6.8) % [44.3 (39.9-50.8)] mmol/mol, and the intensive group achieved 6.2 (5.7-7.1) % [44.3 (38.8-54.1)] mmol/mol. There was no significant difference between both groups (p =0.73).

**Remission of diabetes**
Five (29.4%) conservatively treated subjects achieved HbA1c<6.0%, 3 subjects were not on any glucose lowering medication, and 2 were on metformin. Six (33.3%) of the intensively treated group achieved HbA1c<6.0%, 1 was not on any medication, 3 subjects were on metformin, 2 were on insulin. Overall 4 (11.4%) subjects achieved complete remission of diabetes at one year post surgery.

**Medication usage**

**Glucose lowering medications**

There were significant reductions in glucose lowering medications from 3.0(2.0 -3.0) to 1.0 (0.0-1.0) (p=0.0002) and 2.0(1.0-2.0) to 1.0(0.0-1.0) (p=0.002) in conservative and intensive groups respectively.
**Blood pressure lowering medications**

There were significant reductions in BP lowering medications from 1.0 (0.5-2.5) to 0.0 (0.0-1.0) (p=0.008), and 1.0 (0.0-2.0) to 0.0 (0.0-1.0) (p=0.04) in conservative and intensive groups respectively.

**Incidence of hypoglycaemia**

One subject in the intensive group had CG readings <4.0 mmol/L but did not have symptoms of severe hypoglycaemia during the two weeks monitoring post-surgery. No hypoglycaemia was noted in the conservative group.

**Length of stay**

The median length of stay was 3 days for both groups (p=0.91).

**Surgical complications**

There was no significant difference in the incidence of surgical complication between the two groups (p=1.00). One subject from the intensive group had diarrhoea post-surgery. No complication was observed in the conservative group.

**6.3 Microvascular complications**

**6.3.1 Albuminuria**

Fifteen subjects from conservative group and 14 subjects from intensive group had complete urine ACR datasets. The changes in urine ACR post-surgery were not significant in both groups. Urine ACR reduced from 2.8 (1.8-4.8) mg/mmol to 1.7 (1.0-6.3) mg/mmol in conservative group (p=0.69); and from 2.3 (1.4-7.5) mg/mmol to 1.6 (1.0-3.9) mg/mmol in intensive group (p=0.09). There was no significant difference in the change in albuminuria between the conservative and intensive group (p=0.84).

Subgroup analysis of the overall cohort showed 17 subjects had normal ACR, 12 had pre-existing albuminuria at baseline. At 1 year after surgery, 9 subjects improved (8 normalised), 16 no change, 4 deteriorated.
Of the 12 subjects with pre-exiting albuminuria, 9 improved (8 normalised), 2 had deteriorated, 1 had no change. Of the 17 subjects with normal ACR, 4 had deteriorated, 13 had no change.

6.3.2 Retinopathy

Thirteen subjects from conservative group and 16 subjects from intensive group had complete retinal photograph datasets. The conservative group had a median retinal score of 1.0(1.0-2.0) before surgery, and 1.5(1.0-2.0) at one year follow up (p=0.43). The retinal score was 1.0 (0.5-2.0) before surgery and 1.0 (0.5-2.0) at one year follow up (p=0.34) for intensive group. There was no significant difference in the change of retinal score between both groups (p=0.98).

Subgroup analysis of the overall cohort showed 6 subjects had no retinopathy, 20 had mild to moderate non-proliferative retinopathy, 1 had severe non-proliferative retinopathy, and 1 had proliferative retinopathy. At 1 year after surgery, 4 had deteriorated, 24 had no change, 1 improved.

Of the 23 subject with abnormal pre-existing retinopathy, 3 deteriorated, 1 improved, 19 had no change at follow up. Of the 6 subjects with normal retinal, 1 deteriorated, 5 had no change at 1 year.

6.3.3 Peripheral neuropathy

Nerve conduction study

Twelve subjects from the conservative group and 15 subjects from the intensive group completed nerve conduction study (Table 14). No significant change in the neuropathy parameters were observed in conservative group. In the intensive group, superficial radial conduction velocity reduced from 62.5 (57.4- 69.1) m/s to 60.1 (54.4- 63.6) m/s (p= 0.04). This change was also significant when compared to the conservative group (p=0.04).

Qualitative analysis showed 10 of the overall cohort had pre-existing neuropathy, 17 subjects had no neuropathy at baseline. At 1 year after surgery, 5 who had pre-existing neuropathy showed deterioration, the other 22 subjects had no change.
Thermal threshold testing

Seven subjects in the conservative group and 8 subjects in the intensive group completed thermal threshold testing (Table 15). No significant changes in perception threshold parameters were observed in both groups.

Postoperative glucose management

Conservative and intensive groups of patients were monitored and managed with the aim of achieving conservative (6.5-7.5 mmol/L), and intensive (5.5-6.5 mmol/L) glucose control post-surgery. Figure 5 showed postoperative glucose trend of both intensive and conservative managed group (intention to treat analysis).
Table 13. GLUCOSURG-post. Baseline and 1 year follow-up results of the conservative and intensive group (Intention to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=17)</th>
<th>P value (within group)</th>
<th>Intensive (n=18)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>50.1± 2.3</td>
<td>N/A</td>
<td>53.9± 1.7</td>
<td>N/A</td>
<td>N/A</td>
<td>0.20</td>
</tr>
<tr>
<td>Male (%),n</td>
<td>58.8, 10</td>
<td>N/A</td>
<td>27.8, 5</td>
<td>N/A</td>
<td>N/A</td>
<td>0.09</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>9.2± 1.3</td>
<td>N/A</td>
<td>14.2± 1.5</td>
<td>N/A</td>
<td>N/A</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.6 (41.2-51.1)</td>
<td>32.7 (28.5-40.3)</td>
<td>0.0003</td>
<td>43.7 (40.0-48.2)</td>
<td>31.8 (27.7-37.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Outcome variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 (7.6-10.1)</td>
<td>6.2 (5.8-6.8)</td>
<td>0.001</td>
<td>8.6 (7.3-10.3)</td>
<td>6.2 (5.7-7.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>69.4 (59.6-86.9)</td>
<td>44.3 (39.9-50.8)</td>
<td>0.001</td>
<td>70.5 (56.3-89.1)</td>
<td>44.3 (38.8-54.1)</td>
<td>&lt;0.0001</td>
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<td></td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140± 3</td>
<td>133± 5</td>
<td>0.36</td>
<td>138± 3</td>
<td>124±5</td>
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<td></td>
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<td>0.71</td>
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<tr>
<td>DBP (mmHg)</td>
<td>78± 3</td>
<td>82± 2</td>
<td>0.26</td>
<td>84± 3</td>
<td>72± 2</td>
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<td></td>
<td></td>
<td>0.16</td>
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<td>Urine ACR (mg/mmol)</td>
<td>2.8 (1.8-4.8)</td>
<td>1.7 (1.0-6.3)</td>
<td>0.69</td>
<td>2.3 (1.4-7.5)</td>
<td>1.6 (1.0-3.9)</td>
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91
<table>
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<tr>
<th></th>
<th>Retinal score</th>
<th>Length of stay (days)</th>
<th>30 days surgical complications (%.n)</th>
<th>Hypoglycaemic episodes (n)</th>
<th>glucose-lowering medications</th>
<th>BP lowering medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 (1.0-2.0)</td>
<td>3.0 (3.0-4.0)</td>
<td>N/A</td>
<td>N/A</td>
<td>3.0 (2.0-3.0)</td>
<td>1.0 (0.5-2.5)</td>
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<td>N/A</td>
<td>N/A</td>
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<tr>
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<td>0.43</td>
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<td>N/A</td>
<td>N/A</td>
<td>0.002</td>
<td>0.008</td>
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<td>3.0 (3.0-4.0)</td>
<td>N/A</td>
<td>N/A</td>
<td>2.0 (1.0-2.0)</td>
<td>1.0 (0.0-1.0)</td>
</tr>
<tr>
<td></td>
<td>0.34</td>
<td>N/A</td>
<td>5.6, 1</td>
<td>N/A</td>
<td>1.0( 0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
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<tr>
<td></td>
<td>0.56</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.002</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>0.91</td>
<td>1.00</td>
<td>N/A</td>
<td>0.01</td>
<td>0.80</td>
</tr>
</tbody>
</table>

BMI body mass index, HbA1c glycated haemoglobin, N/A not applicable.
Table 14. GLUCOSURG-post. Result of nerve conduction study before and one year post RYGB surgery (Intention to treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>Conservative (N=12)</th>
<th>P value (within group)</th>
<th>Intensive (N=15)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup radial SNAP (mV)*</td>
<td>13.5 (11.0-23.9)</td>
<td>15.2 (12.0-22.5)</td>
<td>1.00</td>
<td>17.0 (10.8-22.0)</td>
<td>18.3 (12.2-25.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sup radial CV (m/s)</td>
<td>60.6 (53.8-65.6)</td>
<td>62.0 (54.0-66.8)</td>
<td>1.00</td>
<td>62.5 (57.4-69.1)</td>
<td>60.1 (54.4-63.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sural SNAP (mV)</td>
<td>8.6 ± 2.0</td>
<td>8.7 ± 2.2</td>
<td>1.00</td>
<td>10.1 ± 1.0</td>
<td>11.9 ± 2.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Sural CV (m/s)</td>
<td>48.5 (40.8-52.9)</td>
<td>49.5 (44.1-51.7)</td>
<td>1.00</td>
<td>47.1 (45.7-49.5)</td>
<td>47.6 (46.9-49.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Common Peroneal CV (m/s)</td>
<td>45.4 ± 1.9</td>
<td>46.5 ± 1.1</td>
<td>1.00</td>
<td>44.0 ± 1.4</td>
<td>45.3 ± 2.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Tibial CMAP (mV)</td>
<td>6.8 ± 1.1</td>
<td>6.4 ± 1.2</td>
<td>1.00</td>
<td>4.6 ± 0.7</td>
<td>4.9 ± 0.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimal latency tibial  F-response (ms)</td>
<td>51.6 ± 1.6</td>
<td>55.8 ± 1.9</td>
<td>0.28</td>
<td>55.4 ± 2.0</td>
<td>57.4 ± 2.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

SNAP sensory nerve action potential, CV conduction velocity, CMAP compound muscle action potential
Table 15. GLUCOSURG-post. Results of thermal threshold testing before and one year post RYGB surgery (Intention to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (N=7)</th>
<th>P value (within group)</th>
<th>Intensive (N=8)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL-WPT(ºC)</td>
<td>35.0 (34.0-38.2)</td>
<td>35.1 (34.0-35.5)</td>
<td>0.72</td>
<td>37.5 (34.4-42.7)</td>
<td>34.2 (33.6-35.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>UL-CPT(ºC)</td>
<td>30.6 (30.2-31.1)</td>
<td>30.6 (29.9-31.2)</td>
<td>1.00</td>
<td>30.6 (28.6-31.1)</td>
<td>30.5 (29.5-31.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>LL-WPT(ºC)</td>
<td>37.0 (35.1-44.9)</td>
<td>38.7 (35.1-43.1)</td>
<td>1.00</td>
<td>43.7 (37.9-45.9)</td>
<td>42.2 (36.1-45.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>LL-CPT(ºC)</td>
<td>29.5 (28.0-30.6)</td>
<td>25.4 (20.7-30.6)</td>
<td>0.32</td>
<td>29.5 (23.7-30.4)</td>
<td>25.3 (22.5-30.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

UL upper limb, LL lower limb, WPT, warm perception threshold, CPT cool perception threshold
Figure 9. Postoperative glucose trend of intensive and conservative managed groups (intention to treat analysis)

The effect of optimisation was not statistically significant, $F(1,290)=0.005 \ p = 0.94$
Chapter 7. Result for GLUCOSURG -post study (As per protocol analysis)

7.1 Participants characteristics

Criteria for as per protocol analysis was discussed previously. Of the 17 subjects randomised to conservative group, 10 met the criteria for intensive group; of the 18 randomised to intensive group, 3 met the criteria for conservative group. With the reassignment, 10 subjects were in conservative group, and 25 subjects were in intensive group. The subject baseline characteristics are shown in Table 16.

There were 4 male, 6 female in the conservative group. The group had a mean age of 50.6± 3.7, duration of diabetes 10.6± 2.0 years. The median BMI was 44.0(40.9-50.9) kg/m², HbA1c was 8.5 (7.4-10.3) % [69.4 (57.4-89.1)] mmol/mol.

There were 11 male, 14 female in the intensive group. Their mean age was 52.5± 1.5 and duration of diabetes was 12.3± 1.3 years. Their BMI was 43.7 (40.9-49.0) kg/m², HbA1c was 8.5 (7.3-10.1) % [69.4 (56.3-86.9) mmol/mol].

There were no significant different between both groups in age, gender distribution, BMI, duration of diabetes and HbA1c at baseline. Subjects in the intensive group had lower SBP than the conservative group (p= 0.008).

Body mass index

BMI at one year showed significant reduction from 44.0 (40.9-50.9) kg/m² to 31.8 (28.2-40.3) kg/m² (p=0.007) in the conservative group; and from 43.7 (40.9-49.0) kg/m² to 32.7 (28.3-37.8) kg/m² (p<0.0001) in the intensive group. There was no significant difference between the two groups (p=0.97).

Blood pressure

There was significant reduction in SBP from 150(145-159) mmHg to 131(117-144) mmHg in the conservative group (p=0.007). No significant reduction in SBP was observed in the intensive group, 140 (126-144) mmHg to 124(109-147) mmHg (p=0.10). The change in SBP between the two groups was not significant (p=0.45).
There were no significant changes in DBP in both groups, 81±4 mmHg to 81±3 mmHg (p=0.93), 81±2 to 79±2 mmHg (p=0.27) in conservative and intensive groups respectively.

**Effectiveness of the intervention on early post-operative glycaemic control**

Following surgery, both groups of patients were monitored and managed with the aim of achieving intensive (5.5-6.5mmol/L) or conservative (6.5-7.5 mmol/L) glucose control within first 2 weeks. Figure 10 showed postoperative capillary glucose trend of both intensive and conservative groups (as per protocol analysis). The effect of optimisation was statistically significant (p<0.0001). Of the 17 subjects randomised to conservative group, 10 achieved fasting capillary glucose of 5.5-6.5mmol/L, and hence were assigned to intensive group. Of the 18 subjects randomised to intensive group, 3 achieved fasting capillary glucose of 6.5-7.5mmol/L, and were assigned to conservative group for the purpose of as per protocol analysis.

**7.2 Glycaemic control at 1 year**

Both groups achieved significant reductions in HbA1c 1 year after surgery. The conservative group achieved HbA1c of 6.5 (5.8-6.9) % [46.0 (40.0-50.3)] mmol/mol (p=0.0004), and the intensive group achieved 6.2 (5.8-7.0) % [43.5 (40.3-52.5)] mmol/mol (p<0.0001). There was no significant difference between both groups.

**Remission of diabetes**

Three (30.0%) subjects from conservative group achieved HbA1c<6.0%, 1 was not on any glucose lowering medication, 1 was on metformin, and 1 was on insulin. Eight (32.0%) subjects from the intensive group achieved HbA1c<6.0%, 3 subjects were not on any medication, 4 were on metformin, and 1 was on metformin and insulin. Overall 4 subjects achieved complete remission of diabetes at one year.
Medication usage

Glucose lowering medications

There were significant reductions in glucose lowering medications, from 2.5 (1.0-3.0) to 1.0 (1.0-2.0) (P=0.009), and 2.0 (2.0-3.0) to 1.0 (0.0-1.0) (P<0.0001) in conservative and intensive groups respectively.

Blood pressure lowering medication

There was no significant change in BP lowering medications in conservative group, from 1.0 (0.0-1.3) to 0.0 (0.0-1.0) (p=0.34). Significant reduction in BP medications was seen in intensive group, from 1.5 (0.3-2.8) to 0.0 (0.0-1.0) (p=0.001). There was no difference between both groups (p=0.77).

Incidence of hypoglycaemia

One subject in the intensive group had CG readings <4.0 mmol/L but did not have symptoms of severe hypoglycaemia during the 2 weeks monitoring post-surgery. No hypoglycaemia was noted in the conservative group.

Length of stay

The median length of stay was 3 days for both groups (p=0.75).

Surgical complications

There was no significant difference in the incidence of surgical complications between the 2 groups (p=1.00). One subject from the intensive group had diarrhoea post-surgery. No complication was observed in the conservative group.

7.3 Microvascular complications

7.3.1 Albuminuria

Six subjects from conservative group and 23 subjects from intensive group had complete urine ACR datasets. The changes in urine ACR were not significant in both groups. Urine ACR reduced from 1.7 (1.2-3.2) mg/mmol to 1.6 (0.8-2.1) mg/mmol in conservative group (p=0.84); and from 3.3 (1.7-6.2) mg/mmol to 1.8 (1.0-5.5) in
intensive group (p=0.31). There was no significant difference in the change in albuminuria between both groups (p=0.59).

7.3.2 Retinopathy

Seven subjects from conservative group and 22 subjects from intensive group had complete retinal datasets. The retinal score was 2.0 (0.0-2.0) before surgery, and 2.0 (0.0-3.0) at one year (p=0.62) in conservative group. Intensive group had retinal score of 1.0 (0.0-3.0) before surgery and 2.0 (2.0-2.8) at one year (p=0.12). There was no difference in the change of retinal score between both groups (p=0.55).

7.3.3 Peripheral neuropathy

Nerve conduction study

Seven subjects from the conservative group and 20 subjects from the intensive group completed nerve conduction study (Table 17). There was no significant change in the sensory and motor nerves in both groups.

Thermal threshold testing

Four subjects in the conservative group and 11 subjects in the intensive group completed thermal threshold testing (Table 18). There were no significant changes in all perception thresholds. No difference in changes between both groups was observed.
Table 16. GLUCOSURG-post. Baseline and 1 year follow-up results of the conservative and intensive group (As per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=10)</th>
<th>P value (within group)</th>
<th>Intensive (n=25)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>50.6 ± 3.7</td>
<td>N/A</td>
<td>52.5 ± 1.5</td>
<td>N/A</td>
<td>N/A</td>
<td>0.83</td>
</tr>
<tr>
<td>Male (%,n)</td>
<td>40, 4</td>
<td>N/A</td>
<td>44, 11</td>
<td>N/A</td>
<td>N/A</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>10.6 ± 2.0</td>
<td>N/A</td>
<td>12.3 ± 1.3</td>
<td>N/A</td>
<td>N/A</td>
<td>0.47</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.0 (40.9-50.9)</td>
<td>31.8 (28.2-40.3)</td>
<td>43.7 (40.9-49.0)</td>
<td>32.7 (28.3-37.8)</td>
<td>&lt;0.0001</td>
<td>0.76</td>
</tr>
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<td><strong>Outcome variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 (7.4-10.3)</td>
<td>6.5 (5.8-6.9)</td>
<td>8.5 (7.3-10.1)</td>
<td>6.2 (5.8-7.0)</td>
<td>&lt;0.0001</td>
<td>0.94</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>69.4 (57.4-89.1)</td>
<td>46.0 (40.0-50.3)</td>
<td>69.4 (56.3-86.9)</td>
<td>43.5 (40.3-52.5)</td>
<td>&lt;0.0001</td>
<td>0.97</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150 (145-159)</td>
<td>131 (117-144)</td>
<td>140 (126-144)</td>
<td>124 (109-147)</td>
<td>0.10</td>
<td>0.008</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.4 ± 3.8</td>
<td>80.9 ± 2.6</td>
<td>81.1 ± 2.4</td>
<td>78.5 ± 2.1</td>
<td>0.27</td>
<td>0.95</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol)</td>
<td>1.7 (1.2-3.2)</td>
<td>1.6 (0.8-2.1)</td>
<td>3.3 (1.7-6.2)</td>
<td>1.8 (1.0-5.5)</td>
<td>0.31</td>
<td>0.13</td>
</tr>
<tr>
<td>Retinal score</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-3.0)</td>
<td>1.0(0.8-2.0)</td>
<td>1.0(0.8-2.0)</td>
<td>0.27</td>
<td>0.52</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>N/A</td>
<td>3.0 (3.0-4.0)</td>
<td>N/A</td>
<td>3.0 (3.0-4.0)</td>
<td>N/A</td>
<td>0.75</td>
</tr>
<tr>
<td>30 days surgical complications (%n)</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>4.0 , 1</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypoglycaemic episodes (n)</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>glucose lowering medications</td>
<td>2.5(1.0-3.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>2.0( 2.0-3.0)</td>
<td>1.0( 0.0-1.0)</td>
<td>&lt;0.0001</td>
<td>0.91</td>
</tr>
<tr>
<td>BP lowering medications</td>
<td>1.0 (0.0-1.3)</td>
<td>0.0 (0.0-1.0)</td>
<td>1.5 (0.3-2.8)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.001</td>
<td>0.16</td>
</tr>
</tbody>
</table>

BMI body mass index, HbA1c glycated haemoglobin, N/A not applicable.
Table 17. GLUCOSURG-post. Result of nerve conduction study before and one year post RYGB surgery (As per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=7)</th>
<th>P value (within group)</th>
<th>Intensive (n=20)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup radial SNAP (mV)*</td>
<td>19.0 (10.0-33.0)</td>
<td>18.5 (4.7-44.9)</td>
<td>15.5 (11.3-21.8)</td>
<td>17.0 (12.5-23.4)</td>
<td>0.35</td>
<td>0.72</td>
</tr>
<tr>
<td>Sup radial CV (m/s)</td>
<td>61.7 (50.0-65.8)</td>
<td>58.5 (38.3-68.5)</td>
<td>61.9 (57.4-67.7)</td>
<td>60.9 (56.7-63.7)</td>
<td>0.21</td>
<td>0.52</td>
</tr>
<tr>
<td>Sural SNAP (mV)</td>
<td>14.0 (8.5-18.7)</td>
<td>13.0 (6.3-18.1)</td>
<td>8.7 (5.0-11.0)</td>
<td>8.5 (6.6-14.6)</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>Sural CV (m/s)</td>
<td>52.4 (42.3-55.2)</td>
<td>50.3 (42.8-53.0)</td>
<td>47.6 (44.4-50.0)</td>
<td>48.1 (46.2-49.6)</td>
<td>1.00</td>
<td>0.35</td>
</tr>
<tr>
<td>Common Peroneal CV (m/s)</td>
<td>47.0 (43.4-51.4)</td>
<td>47.1 (44.1-56.5)</td>
<td>43.8 (41.6-47.5)</td>
<td>44.9 (40.7-48.8)</td>
<td>1.00</td>
<td>0.35</td>
</tr>
<tr>
<td>Tibial CMAP (mV)</td>
<td>6.4 (4.1-9.9)</td>
<td>5.0 (2.8-10.5)</td>
<td>5.0 (3.3-6.9)</td>
<td>5.2 (2.8-7.6)</td>
<td>1.00</td>
<td>0.54</td>
</tr>
<tr>
<td>Minimal latency tibial F-response (ms)</td>
<td>48.7 (46.6-55.6)</td>
<td>53.0 (47.7-57.4)</td>
<td>53.2 (48.8-56.8)</td>
<td>55.8 (50.5-64.1)</td>
<td>0.07</td>
<td>0.35</td>
</tr>
</tbody>
</table>

SNAP sensory nerve action potential, CV conduction velocity, CMAP compound muscle action potential
Table 18. GLUCOSURG-post. Results of thermal threshold testing before and one year post RYGB (As per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Conservative (n=4)</th>
<th>P value (within group)</th>
<th>Intensive (n=11)</th>
<th>P value (within group)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td>Pre-operatively</td>
<td>Post-operatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL-WPT(°C)</td>
<td>35.0 (33.6-38.7)</td>
<td>33.9 (33.4-35.0)</td>
<td>1.00</td>
<td>35.3 (34.5-42.5)</td>
<td>35.1 (33.8-35.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>UL-CPT(°C)</td>
<td>30.7 (28.7-31.2)</td>
<td>31.0 (30.5-31.3)</td>
<td>1.00</td>
<td>30.6 (28.9-31.1)</td>
<td>30.1 (29.3-31.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>LL-WPT(°C)</td>
<td>36.6 (35.3-43.2)</td>
<td>39.7 (34.7-43.7)</td>
<td>1.00</td>
<td>43.1 (36.2-45.6)</td>
<td>42.0 (35.6-43.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>LL-CPT(°C)</td>
<td>30.1 (21.3-30.8)</td>
<td>28.9 (23.9-30.8)</td>
<td>1.00</td>
<td>29.3 (27.3-30.4)</td>
<td>25.3 (21.8-30.6)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

UL upper limb, LL lower limb, WPT, warm perception threshold, CPT cool perception threshold
Figure 10. Postoperative glucose trend of both postop intensive and conservative managed groups (as per protocol analysis)

The effect of optimisation was statistically significant $F(1, 302)=36.28$, $p<0.0001$
Chapter 8. Results of GLUCOSURG-combine (surgical and medical groups)

8.1 Participants characteristics

In the surgical group, 69 subjects had completed 1 year follow up. The subject baseline characteristics are shown in Table 19. There were 35 males, 34 females in the surgical group. The group had mean age of 50.7± 1.0, median duration of diabetes 10.0 (5.0-16.0) years, BMI of 43.6 (40.6-49.7) kg/m^2. HbA1c was 9.6 (8.0-10.4) % [81 (64-90)] mmol/mol before surgery.

There were 25 subjects in the medical group, of which 11 were males. Their mean age was 52.6± 1.9, median duration of diabetes 13.0 (8.5-17.0), BMI of 42.0 (37.8-47.3) kg/m^2. HbA1c was 7.8 (7.0-10.9) % [62 (53-96) mmol/mol] at baseline. There were no significant baseline differences in gender, age, HbA1c and duration of diabetes between the surgical and medical groups.

Body mass index

BMI reduced to 32.9 (28.6-37.9) kg/m^2 in the surgical group at 1 year follow up (p<0.0001). This has not changed significantly in medical group, 41.9 (38.7-46.6) (p=0.39). There was significant difference in the change of BMI between both groups (p<0.0001).

Blood pressure

There was significant reduction in SBP from 143± 2 mmHg to 130± 3 mmHg in the surgical group (p<0.0001), whereas no significant reduction in SBP was observed in the medical group, 139± 4 mmHg to 134± 3 mmHg (p=0.34). The changes in SBP between the medical and surgical group was significant (p=0.04).

There was no significant change in DBP in both groups, 83 (79-90) mmHg to 80 (75-88) mmHg (p=0.08); 80 (76-88) mmHg to 77 (71-86) mmHg (p=0.16) respectively.
8.2 Glycaemic control at 1 year

Surgical group achieved significant reduction in HbA1c, from 9.6 (8.0-10.4) % [81 (64-90)] mmol/mol to 6.3 (5.9-7.0) % [45(41-53) mmol/mol] at one year (p=0.03). No significant change was observed in medical group, HbA1c was 7.8 (7.0-10.9) % [62 (53-96) mmol/mol] before and 8.5 (7.6-9.9) % [69 (60-85) mmol/mol] at 1 year (p=0.22). The difference in HbA1c changes between both groups was significant (p<0.0001).

Remission of diabetes

Twenty (29%) of the surgical group achieved HbA1c <6%. Of this, 7 (10.1%) were in remission of diabetes. No subject in medical group achieved HbA1c of <6%.

Medication usage

Glucose lowering medication

The use of glucose lowering medication was reduced in surgical group, from 2 (2-3) per patient to 1 (1-1), (P<0.0001). There was no significant change in medical group, 3 (2-3) to 3 (2-3) at one year (p=0.85).

Blood pressure lowering medication

Surgical group had significant reduction in use of blood pressure lowering medication, from 1 (1-2) to 0(0-1) at 1 year (P<0.0001) as compared to medical group which has not changed (p=1.00).

Table 20 showed the changes in glucose lowering medication classes and blood pressure lowering medication classes before and 1 year after intervention in surgical and medical groups.
8.3 Microvascular complications

8.3.1 Albuminuria

Fifty-three subjects of the surgical group had complete urine ACR datasets. Urine ACR decreased from 3.6 (1.7-9.3) mg/mmol to 1.7 (1.0-4.9) mg/mmol in the surgical group (p=0.02).

Subgroup analysis of the 27 surgical subjects who had pre-existing albuminuria at baseline showed a significant improvement from 8.5 (5.7-17.4) mg/mmol to 1.7 (1.0-6.1) mg/mmol at 1 year (p=0.009). Twenty-two subjects showed improvement, of which 16 normalised their ACR at 1 year. Four subjects had deterioration in ACR, and 1 had no change. Of the 26 subjects who had normal baseline ACR, 5 developed albuminuria at 1 year post-surgery.

Nineteen subjects from the medical group had complete urine ACR datasets. Urine ACR increased from 1.7 (1.1-4.9) mg/mmol to 4.8 (2.6-10.9) mg/mmol in the medical group at 1 year (p=0.03). Six subjects had pre-existing albuminuria, all of them still had albuminuria post intervention, from 17.8 (4.6-43.7) mg/mmol to 20.9 (9.5-47.0) mg/mmol (p=0.84). Of the 13 subjects with normal albuminuria at baseline, 5 developed albuminuria post-intervention. There was a significant difference between the surgical and medical group for the remission of albuminuria (p<0.005), but not for the deterioration of albuminuria (p=0.50), or the new incidence of albuminuria (p=0.25) at 1 year (see Figure 11).
8.3.2 Retinopathy

In the group of 56 surgical patients with complete retinal photograph datasets, there was no significant change in retinal score between both surgical and medical groups. Surgical group had no change in retinal score, from 1 (0-2) to 1 (0-2) at 1 year (p=0.40). There were 17 subjects who had no diabetic retinopathy, 32 had mild to moderate non-proliferative diabetic retinopathy, 6 had severe non proliferative diabetic retinopathy, and 1 had proliferative diabetic retinopathy. At 1 year after surgery, 44 (78%) subjects had no change, 6 (11%) improved, and 6 (11%) deteriorated. Of the 6 subjects who deteriorated, 4 had pre-existing diabetic retinopathy.

In the medical group, 21 subjects had complete retinal datasets. Medical group had retinal score of 2 (1-4) at baseline, and 3 (1-4) at follow up (p=0.38). Ten subjects had no retinopathy, 8 had mild to moderate non-proliferative diabetic retinopathy, 2 had severe non-proliferative diabetic retinopathy, and 1 had proliferative diabetic retinopathy. After intervention, 17 subjects (81%) had no change; 1 (5%) improved; and 3 (14%) deteriorated. One patient required photocoagulation at follow up. All 3 subjects who deteriorated had pre-existing retinopathy. There were no significant differences between the surgical and medical groups in the rates of patients who
deteriorated or improved after intervention [(p=0.70 and 0.67 respectively). See Figure 12]

Figure 12. Proportion of subjects who had at least two steps changes in retinal disease score from baseline to one year follow up.

8.3.3 Peripheral neuropathy

Nerve conduction study

Fifty-four subjects in the surgical group underwent nerve conduction studies. There was statistically significant changes in minimal latency tibial F-response which increased from 54.6 ± 0.9 ms to 56.3 ± 1.0 ms (p= 0.0028) at 1 year. This was not clinically significant. There were no statistically significant changes in other nerve conduction parameters (Table 20).

Qualitative analysis showed that 21 of the 54 surgical subjects had pre-existing neuropathy, of which 7 deteriorated over 1 year. No change was observed in the 14 subjects with pre-existing neuropathy, 33 subjects that had no neuropathy remained stable.
Thermal threshold testing

Forty-one subjects completed thermal threshold testing. Upper limb warm perception threshold improved from 36.0 (34.7-38.5) °C to 35.1 (33.7-36.7) °C (p=0.008), and lower limb cool perception threshold deteriorated from 29.5 (27.2-30.5) °C to 27.2 (23.7-30.2) °C, (p=0.0028). No other statistically significant changes were observed in other perception threshold parameters (Table 21).

Qualitative analysis showed that 18 (43.9%) subjects had normal thermal threshold perception, 23 (56.1%) had abnormal thermal threshold perception preoperatively. At 1 year after surgery, 17 subjects with known abnormal thermal threshold had worsened cool perception threshold in lower limb. Table 23 showed changes in thermal threshold perception in subjects with pre-existing abnormality.

There were no significant correlations between the changes in ACR and change in HbA1c (r=-0.046, p=0.75), BMI (r=-0.058, p=0.70), systolic (r=-0.079, p=0.61) and diastolic blood pressure (r=0.042, p=0.79) in either group.
Table 19. GLUCOSURG -Combine. Baseline characteristics and clinical parameters before and 1 year after RYGB surgery between surgical and medical groups.

<table>
<thead>
<tr>
<th></th>
<th>RYGB group (n=69)</th>
<th>Medical group (n=25)</th>
<th>P value (between groups at baseline)</th>
<th>P value (of change between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>69</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.7 ± 1.0</td>
<td>52.6 ± 1.9</td>
<td>-</td>
<td>0.26</td>
</tr>
<tr>
<td>Gender (% male, n)</td>
<td>51%, 35</td>
<td>44.0%, 11</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>Duration of T2DM (years)</td>
<td>10.0 (5.0 - 16.0)</td>
<td>13.0 ( 8.5 - 17.0)</td>
<td>-</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>43.6 (40.6 - 49.7)</td>
<td>42.0 (37.8 - 47.3)</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>32.9 (28.6 - 37.9)</td>
<td>41.9 (38.7 - 46.6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143 ± 2</td>
<td>139 ± 4</td>
<td>0.34</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>130 ± 3</td>
<td>134 ± 3.1</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 (79-90)</td>
<td>80 (76 - 88)</td>
<td>0.16</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>80 (75-88)</td>
<td>77 (71 - 86)</td>
<td>0.08</td>
<td>0.91</td>
</tr>
<tr>
<td>HbA1c (IFCC-mmol/mol)</td>
<td>81 (64 - 90)</td>
<td>62 (53 - 96)</td>
<td>0.22</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>9.6 (8.0 - 10.4)</td>
<td>7.8 (7.0 - 10.9)</td>
<td>0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol)</td>
<td>3.6 (1.7 - 9.3)</td>
<td>1.7 (1.0 - 4.9)</td>
<td>&lt;0.05</td>
<td>1.7 (1.1 – 4.9)</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>Retinal score</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>0.40</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Glucose lowering</td>
<td>2 (2-3)</td>
<td>1 (1-1)</td>
<td>P&lt;0.0001</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td>medications per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1 (1-2)</td>
<td>0 (0-1)</td>
<td>P&lt;0.0001</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>lowering</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI body mass index, HbA1c glycated haemoglobin, N/A not applicable, SBP systolic blood pressure, DBP diastolic blood pressure.
Table 20. Changes in medication classes before and 1 year after intervention in surgical and medical groups.

<table>
<thead>
<tr>
<th></th>
<th>RYGB group (n=69)</th>
<th>Medical group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operative</td>
<td>Post-operative</td>
</tr>
<tr>
<td>Patient use of glucose-lowering medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>58 (83%)</td>
<td>41 (59%)</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>15 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>4 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DPP4i/GLP-1</td>
<td>26 (37%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>46 (66%)</td>
<td>20 (29%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient use of BP-lowering medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/A2B</td>
<td>48 (69%)</td>
<td>26 (37%)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>18 (26%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Alpha blocker</td>
<td>7 (10%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>18 (26%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>6 (9%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

n refers to the number of patients in the cohort that were on the class of medications
A2B, angiotensin receptor 2 blocker; ACEi, ACE inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1
Table 21. Nerve conduction studies in the RYGB group: Baseline and one year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>RYGB group (n=54)</th>
<th>P value (change within group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operative</td>
<td>Post-operative</td>
</tr>
<tr>
<td>Sup radial SNAP (µV)</td>
<td>17.0 (11.0-23.3)</td>
<td>18.5 (12.2-25.6)</td>
</tr>
<tr>
<td>Sup radial CV (m/s)</td>
<td>62.0 (57.9-66.7)</td>
<td>61.3 (57.8-64.3)</td>
</tr>
<tr>
<td>Sural SNAP (µV)</td>
<td>9.0 (5.0-13.9)</td>
<td>9.9 (6.9-16.1)</td>
</tr>
<tr>
<td>Sural CV (m/s)</td>
<td>48.6 ± 0.8</td>
<td>48.6 ± 0.8</td>
</tr>
<tr>
<td>Common Peroneal CV (m/s)</td>
<td>44.6 ± 0.7</td>
<td>45.6 ± 0.7</td>
</tr>
<tr>
<td>Minimal latency tibial F-response (ms)</td>
<td>54.6 ± 0.9</td>
<td>56.3 ± 1.0</td>
</tr>
</tbody>
</table>

SNAP, sensory nerve action potential; CV, conduction velocity; CMAP, compound muscle action potential

Table 22. Result of thermal threshold testing in the RYGB group: Baseline and one year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>RYGB group (n=41)</th>
<th>P value (within group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operative</td>
<td>Post-operative</td>
</tr>
<tr>
<td>UL-WPT (°C)</td>
<td>36.0 (34.7-38.5)</td>
<td>35.1 (33.7-36.7)</td>
</tr>
<tr>
<td>UL-CPT (°C)</td>
<td>30.5 (29.5-31.0)</td>
<td>30.4 (30.0-31.0)</td>
</tr>
<tr>
<td>LL-WPT (°C)</td>
<td>40.1 (36.1-43.5)</td>
<td>39.8 (36.6-43.0)</td>
</tr>
<tr>
<td>LL-CPT (°C)</td>
<td>29.5 (27.2-30.5)</td>
<td>27.2 (23.7-30.2)</td>
</tr>
</tbody>
</table>

UL, upper limb; LL, lower limb; WPT, warm perception threshold; CPT, cool perception threshold
Table 23. Changes within each thermal threshold parameters in subjects with pre-existing abnormal thermal threshold result 1 year post surgery (n=23).

<table>
<thead>
<tr>
<th></th>
<th>Deterioration, n (%)</th>
<th>No deterioration, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limb WPT</td>
<td>4 (17.4%)</td>
<td>19 (82.6%)</td>
</tr>
<tr>
<td>Upper limb CPT</td>
<td>5 (27.8%)</td>
<td>18 (78.2%)</td>
</tr>
<tr>
<td>Lower limb WPT</td>
<td>6 (26.1%)</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>Lower limb CPT</td>
<td>17 (73.9%)</td>
<td>6 (26.1%)</td>
</tr>
</tbody>
</table>

*n refers to the number of patients within the each perception threshold parameter.
WPT, warm perception threshold; CPT, cool perception threshold
Chapter 9. Discussion

9.1 GLUCOSURG-pre

The intention to treat and as per protocol analysis shared similar results.

9.1.1 Summary of main findings

This study has shown that,

1. Intensive pre-operative glycaemic management of obese T2DM patients undergoing RYGB was not superior to conservative management in terms of glycaemic control at 1 year after surgery.

2. Intensive pre-operative glycaemic management of obese T2DM patients undergoing RYGB was not superior to conservative management in terms of 30-day peri-operative surgical complication and LOS.

Other findings

Both conservative and intensive groups showed significant reduction in BMI and HbA1c. SBP was significantly reduced in the conservative group only. The use of glucose–lowering medications and BP lowering medications were reduced in both groups of patients. There was no difference in hypoglycaemic event between both groups.

ACR was significantly reduced in the conservative group only. There were no significant changes in retinal score and NCS parameters in both groups. TTT showed worsening of lower limb cool perception threshold in the conservative group. The change is statistically significant but not clinically significant, as it is still within normal limits.

Overall, there were no statistically differences when compared the changes between the conservative and intensive groups. The postoperative glucose trend in both groups were not significantly different. The reduction in BMI, HbA1c, SBP, use of glucose and BP lowering medications, and urine ACR were the result of the RYGB, as evidenced
by other studies (Schauer et al., 2012b, Heneghan et al., 2013, Miras et al., 2012, Ribaric et al., 2014). Further intensive optimisation had not yielded added benefit.

9.1.2 Factors influencing the result

This study suggested that the reduction of “glycaemic burden” in the months preceding bariatric surgery did not translate to better clinical outcomes either in the short or the medium term. This might be influenced by the following factors:

Pre-op low calorie diet

Despite glucose optimisation in the intensive cohort 3 months before surgery, both conservative and intensive groups underwent a low-calorie diet for 2 weeks pre-operatively. Although the two groups were exposed to different glucose levels for the 3 months pre-surgery, it is likely that glucose readings were similar on the day of surgery. This may explain the lack of difference in the rates of peri-operative complications.

At 1 year, there was a non-significant trend for the conservatively treated group to have a greater reduction in glycaemia; this may be due to the non-significantly higher baseline HbA1c. Nonetheless, glycaemic optimisation remains crucial in T2DM.

Challenge in optimising glucose control

Even though in our study the intensively treated group managed to improve glycaemic control, on the day of surgery their HbA1c was still elevated at 8.4% (68mmol/mol). This reflects real life practice in that the vast majority of diabetes patients referred for bariatric surgery have exhausted non-surgical glucose-lowering treatments and there is less room for additional optimisation. Instead, any pre-operative interventions could be focused on improving other obesity-associated comorbidities.

Lack of difference in microvascular complications

Albuminuria improved in the conservative group but no significant change in intensive group at 1 year. This could be explained by the smaller sample size in intensive group. We did not observe improvement in retinopathy or NCS parameters at 1 year follow up. This might be limited by the small sample size, and short duration of follow up.
9.1.3 Comparison with similar work

The finding of this study is in contrast to the study by Perna et al. who retrospectively categorised 468 patients by their pre-operative HbA1c, and compared it to the outcomes. The study reported that the cohort with poor glycaemic control (HbA1c>8%) before bariatric surgery was associated with worse glucose control postoperatively, with fewer diabetes remission and less weight loss by 18 months (Perna et al., 2012).

In another of our retrospective cohort study we found no difference in post-operative complications between patients with or without diabetes (Neff K, 2013). The discrepancies may be due to differences in study design (i.e. retrospective vs. prospective randomised trials).

There were many studies assessing effect of perioperative glucose control on surgical outcomes but these were limited to non-bariatric surgery cohorts. No study has compared effect of intensive and conservative glucose management before bariatric surgery on diabetic nephropathy, retinopathy and neuropathy.

9.1.4 Originality

This is the first prospective RCT comparing the effect of intensive glucose control 3 months before RYGB on glycaemic outcome and microvascular complications of T2DM.

9.1.5 Translation to clinical practice

I expected to find that intensification of glucose-lowering regimes pre-operatively would be beneficial for longer term glycaemic control, but my pilot study did not support this. However, my study data do not support withholding or delaying surgery from patients with poorly controlled glycaemia when all medical and lifestyle interventions have already been optimised. Physicians and anaesthetists who are not familiar with the impact of bariatric surgery may be turned down patients with poorly controlled diabetes for bariatric surgery. Although their approach is understandable, given the wealth of data on poor outcomes in patients with poorly controlled T2DM undergoing non-bariatric surgery, our data questions whether this is the case for bariatric surgery. The only option available currently for this group of patients may be bariatric surgery when all other interventions failed.
9.1.6 Future directions

1. This study could be used to pilot a larger sample size RCT with at least 6 months of intensive therapy compared against best medical therapy before RYGB. Both conservative and intensive groups should avoid pre-operative LCD, to maintain the difference in blood glucose control at time of surgery. However, taking into account the effect size was small, a larger trial focussing on glycaemic outcome may thus be challenging. In order to assess if better perioperative glycaemic control improves post-operative complications, a very large RCT will be required, because even if the effect size of the intervention is large, the number of post-operative complications is low. The lack of any statistical trends suggests that a larger number of subjects may not have altered the final result.

2. It would be interesting to follow up the group of patients with abnormal NCS to assess if peripheral neuropathy become symptomatic, and whether NCS helped to identify those at high risk of developing neuropathy. Effect of RYGB on reversibility of neuropathy would warrant longer term follow up given UKPDS only showed beneficial effect of intensive glycaemic control on neuropathy at 15 years follow up.
9.2 GLUCOSURG-post

The similarities and differences between intention to treat and as per protocol analysis were discussed below.

9.2.1 Summary of main findings

In this study I have shown that:

1. Intensive post-operative glycaemic management of obese T2DM patients undergoing RYGB was not superior to conservative management in terms of glycaemic control at 1 year after surgery.

2. Intensive post-operative glycaemic management of obese T2DM patients undergoing RYGB was not superior to conservative management in terms of 30-day peri-operative surgical complication and LOS.

Other findings

Intention to treat analysis

Intensive group had T2DM for 5 year longer than the conservative group following randomisation. Both conservative and intensive groups showed significant reduction in BMI and HbA1c. The use of glucose−lowering medications and BP lowering medications were reduced in both groups of patients.

There were no significant reduction in urine ACR, retinal score and TTT at 1 year. Within NCS, superficial radial conduction velocity reduced. This was not clinically significant as it was still within the normal range.

The postoperative glucose trend in both groups were not significantly different, despite best effort to control glucose within conservative group post-surgery. 10 subjects in conservative group achieved intensive glucose target post-surgery, which is the result of RYGB.
As per protocol analysis

There was no difference in duration of diabetes when the group was analysed using as per protocol analysis. SBP showed significant reduction at 1 year. This was explained by the significantly higher SBP at baseline. There was no significant reduction in use of BP lowering medications in conservative group, likely due to the small sample size of 10 subjects. Except this, all groups showed reduction in glucose and BP lowering medications.

There were no significant reduction in urine ACR, retinal score, NCS and TTT at 1 year. Overall, there were no significant differences when compared the changes between the conservative and intensive groups. The postoperative glucose trend in both groups were only different in as per protocol analysis.

9.2.2 Factors influencing the result

Effect of RYGB on postoperative glucose control

Unlike other elective surgical procedures following which hyperglycaemia is common and predominantly due to surgical stress, RYGB is different in that it has a substantial effect in improving glucose levels within days after surgery. Consequently, the glucose levels of our conservatively treated group were still in the intensive glucose range. This may explain the lack of significant difference in the short and medium term clinical outcomes between the groups.

The hypoglycaemic rate was low, a post-operative glucose management algorithm that maintain fasting glucose <7.5mmol/L therefore appears to be safe. Further intensification may not therefore confer clinical benefits nor does it decrease complications. An overzealous glucose management approach may increase hypoglycaemic risk.

The reduction in BMI, HbA1c, use of glucose and BP lowering medications were the result of RYGB, as evidenced by other studies (Schauer et al., 2012b, Heneghan et al., 2013, Miras et al., 2012, Ribaric et al., 2014). Significant reduction in SBP was only observed in the group with higher baseline SBP.
Lack of difference in microvascular complications

Urine ACR had not shown improvement as they were within normal range at baseline. Retinal and neuropathy changes as discussed in 9.1.2

9.2.3 Comparison with similar work

A retrospective study by Perna et al. reported that the cohort with poor glycaemic control (HbA1c>8%) before bariatric surgery was associated with worse glucose control postoperatively, fewer diabetic remission and less weight loss by 18 months (Perna et al., 2012). In my study, I had not observed any worsening in HbA1c, remission of diabetes or BMI differences between both groups. The discrepancies may be due to differences in study design (i.e. retrospective vs. prospective RCT), the different target glucose range for intensive and conservative groups postoperatively.

In another of our prospective cohort study comparing postoperative protocol driven glucose management to a standard glycaemic regime; the protocol driven group which aimed for fasting capillary glucose of 5.5-6.9mmol/L achieved better glycaemic control and remission of diabetes at 1 year (Fenske et al., 2012). The lack of significant difference in my study could be due to the narrow range of target fasting capillary glucose, and the substantial effect of RYGB on glycaemic control.

9.2.4 Originality

Management of T2DM post RYGB varied extensively across different centres. There are limited prospective studies that assess if perioperative glucose optimisation would have favourable glycaemic outcomes in the future. This study is the first study that assess if postoperative glucose optimisation would have an impact on diabetic nephropathy, retinopathy and neuropathy.

9.2.5 Translation to clinical practice

I expected to find that intensification of glucose-lowering regimes post-operatively would be beneficial for longer term glycaemic control, but my study did not support this. The effect of RYGB is substantial and therefore further intensification of glucose management will not confer further benefits. It shows that the use of a post-operative glucose management algorithm that maintain fasting glucose <7.5mmol/L appears to
be safe. This study, in conjunction with GLUCOSURG-pre support that RYGB as a metabolic surgery, should be distinguished from other gastrointestinal surgery. RYGB should therefore warrant its own preoperative glucose management recommendation rather than a generalised guideline based on prior studies on non-bariatric surgeries. This would have implication on patients’ access for surgeries as some patients might have been denied surgery due to their poor control.

9.2.6 Future directions

1. This study could be used as a pilot to compare different glucose management protocols between centres to assess its effect on diabetes outcomes.
9.3 GLUCOSURG-combine
9.3.1 Summary of main findings

In this study I have shown that:

1. RYGB had beneficial effect on progression of diabetic nephropathy at 1 year when compared to medical group that received best medical care.
2. RYGB had not shown significant beneficial effect on progression of retinopathy at 1 year when compared to medical group that received best medical care.
3. RYGB had not shown significant beneficial effect on progression of neuropathy at 1 year.
4. RYGB had not shown significant deterioration in retinopathy and neuropathy 1 year after surgery.

Other findings

RYGB group showed significant reduction in BMI, HbA1c, and SBP when compared to the medical group at 1 year following intervention. There was also a large proportion of RYGB subjects that achieved remission of diabetes. Significant reduction in glucose lowering and blood pressure lower medications were also observed in the surgical group. These results are consistent with other studies (Mingrone et al., 2012a, Ribaric et al., 2014, Schauer et al., 2012b)

Urine ACR improved significantly in the surgical group, whereas medical group showed significant deterioration at 1 year. Eighty-one percent of those with pre-existing albuminuria in the surgical group showed improvement, of which 73% normalised their ACR at 1 year. This was not observed in the medical group. The deterioration of albuminuria and the new incidence of albuminuria were not significantly different between surgical and medical groups.

There was no significant difference in the changes of retinal score between surgical and medical groups. Most subjects in both groups had no change in retinal score. Four of the 6 subjects in surgical group and all 3 subjects in medical group who deteriorated, had pre-existing retinopathy. There were no differences between the groups in the rates of deterioration and improvement.
NCS showed statistically significant change in minimal latency tibial F response, which was not clinically significant. There was no change in other nerve parameters. On qualitative analysis, 2 of the 11 subjects with pre-existing peripheral neuropathy showed deterioration; no change was observed in those without neuropathy.

TTT showed improvement in upper limb warm perception threshold; but deterioration in lower limb cool perception threshold. The change in upper limb was within normal range. Qualitative analysis showed 13 subjects who had pre-existing abnormal thermal threshold perception had deterioration in lower limb cool perception threshold.

There were no significant correlations between the changes in ACR and change in HbA1c, BMI, SBP, and DBP in surgical group.

9.3.2 Factors influencing the result

Effect of RYGB on BMI, HbA1c and SBP are well known. Numerous studies have looked into metabolic effect of RYGB on weight loss and remission of diabetes. The proposed mechanisms include weight dependent and weight independent factors. These have been discussed in Chapter 1.3.4. These mechanisms, working in concerted manner reduce weight, improves hepatic insulin sensitivity and reverse islet cell dysfunction. Immediately post-surgery, hepatic sensitivity improved secondary to energy restriction (Dirksen et al., 2012, Lim et al., 2011); exaggerated postprandial insulin response which restored the impaired acute phase insulin response in T2DM is also observed. This is in conjunction with altered gut hormone response including exaggerated release of postprandial GLP-1. Peripheral insulin sensitivity improves later after established weight loss. Other mechanisms such as altered bile acid passage, altered gut microflora, altered food preferences to less energy dense diet had been observed (Dirksen et al., 2012, Behary and Miras, 2015). Many studies continue to explore the mechanisms of RYGB on remission of diabetes.

Diabetic nephropathy

Effects of RYGB on microvascular complications are less known. Among the microvascular complications, diabetic nephropathy is the best studied. Mechanisms of
obesity and kidney disease are less well known. Renal lipotoxicity, inflammatory cytokines, altered renal hemodynamics had been proposed (Wahba and Mak, 2007, Currie et al., 2011).

UKPDS study reported that intensive blood glucose control resulted in 33 % reduction in relative risk of developing microalbuminuria or proteinuria at 12 years (Bilous, 2008). Kumamoto study also reported a lower incidence of nephropathy in intensive glycaemic group after 6 years (Ohkubo et al., 1995). This was also supported by ADVANCE trial where intensive glycaemic group had less incidence of microalbuminuria (Patel et al., 2008).

Obesity is associated with renal hyperfiltration and hyperperfusion, independent of hypertension (Currie et al., 2011). Animal studies suggested that obesity is associated with increase intra-abdominal pressure leading to increase renal venous pressure, systemic blood pressure and vascular resistance. This activated the juxtaglomerular apparatus and the renin-aldosterone system, leading to hypertension, hyperfiltration, and proteinuria (Currie et al., 2011, Heneghan et al., 2013). Chagnac et al reported that study on non-diabetic subjects with obesity-related glomerular hyperfiltration ameliorated after weight loss further supported the critical role that obesity played in nephropathy (Chagnac et al., 2003). Amor et al. also reported that a stepwise logistic regression analysis on 255 subjects who had bariatric surgery, of which 96 had T2DM, weight loss was the only independent predictor of ACR normalisation at 12 months post-surgery (Amor et al., 2013).

Fenske et al showed reduction in CRP, urinary ACR and cytokines at 12 months after RYGB, AGB or SG. The study proposed that the reduction in inflammatory marker is due to weight loss rather than type of procedures (Fenske et al., 2013). Reduction in total body fat and visceral fat post RYGB may also have impact on renal function and inflammatory state. The presence of GLP-1 receptors on kidney and animal study suggested that GLP-1 might have renoprotective effect independent of glucose homeostasis (Kodera et al., 2011).

My study reported an improvement in albuminuria after RYGB. Of this, 73% of the subjects in fact normalised their ACR at 1 year. This showed the combination effects
of weight loss, improved glucose control, as well as weight independent factors achieved by RYGB.

_Diabetic retinopathy_

There were no significant changes in retinal score between the surgery and medical groups. This was surprising considering UKPDS (1998b), Kumamoto study (Ohkubo et al., 1995) and ACCORD Eye study (2010) had all shown that intensive glucose management reduce the risk of diabetic retinopathy. VADT trial had not observed similar effect and this might be due to limited numbers of subjects and follow up time as compared to UKPDS (Duckworth et al., 2009). Other factors such as hypertension are also critical in influencing progression of retinopathy.

My study showed that those with pre-existing retinopathy were more at risk of deterioration and would therefore warrant more intensive retinal surveillance. It was reassuring that none of the subjects reported worsening vision or retinopathy post-surgery. The lack of changes in my study is limited by the number of subjects and the short follow up period.

_Diabetic neuropathy_

There were no clinically significant changes in NCS parameters in the surgical groups. The change in lower limb cool perception threshold, however, was unexpected. In diabetic neuropathy, lower limb small nerve fibres are affected before upper limb. However, the first thermal modality usually affected is lower limb warm perception threshold which is innervated by unmyelinated small fibres, and followed by lower limb cool perception threshold, which is innervated by thinly myelinated small fibres. This would then followed by warm perception threshold changes in hand (Personal communication, Dr Alessia Nicotra). The change in thermal threshold perception was out of what is expected in clinical practice. An abstract reporting quantitative sensory testing on 10 subjects who had bariatric surgery had not reported any changes in their parameters although the type of quantitative sensory testing was not known. There was no other publication on assessment of small nerve fibres post bariatric surgery so far.
Thermal threshold testing, however, is a psychophysical test which could be influenced by patient’s perception of the change in temperature, patient’s response to the changes, and interoperator variability (Heldestad et al., 2010, Devigili et al., 2008). We have attempted to limit the variability by having a single operator, using the same machine and conduct the test in a temperature controlled room.

It appeared that deterioration in NCS were more likely in the group that had pre-existing neuropathy. There was no worsen of symptoms in those with normal NCS at baseline. The changes in TTT and NCS were subclinical. Although we had not undertaken a formal clinical neurological evaluation assessment, all patients were asked if they have neuropathy symptom before surgery and at one year follow up. There were 3 subjects that had symptom consistent with carpal tunnel syndrome, but none have reported neuropathy previously or during follow up. The changes we detected on NCS and TTT might precede the development of symptoms, therefore future longer term follow up of this group of patients to assess progression of symptom would be warranted. The tests might be a useful tool to predict the proportion of subject that would develop neuropathic symptoms in the future.

NCS is an objective test, and we have attempted to limit the interoperator variability by having only single neurophysiologist to carry out the testing. Although some nerve conduction parameters showed statistically significant changes, the changes were within normal limit, and hence of no clinical significance.

As compared to T1DM where EDIC study showed intensive glycaemic control reduced the risk of neuropathy by 64%, its effect on T2DM is not as robust (Martin et al., 2006). Of the T2DM studies, UKPDS is the only study that showed intensive glycaemic control was associated with reduction in neuropathy, albeit only at 15 years follow up(1998c). It is therefore likely that factors other than glycaemic control is more critical in influencing progress of neuropathy. Other factors such as obesity, lipids, and
inflammation had been implicated previously. Given the duration of time it takes to show beneficial effect in UKPDS study, it might be that the nerve fibres take longer time to recover.

Although the 3 microvascular complications shared similar pathogenesis, their rate of progression and reversibility appeared to differ, and factors influencing their recovery may not be similar either. Nutritional deficiency has been implicated in a few trials post bariatric surgery (Thaisetthawatkul et al., 2004). We haven’t observed this in our cohort. The group of patients that showed worsening in neuropathy all had pre-existing neuropathy on electrophysiology testing even before the surgery. All our patients were prescribed multivitamins and minerals supplement after RYGB.
9.3.3 Comparison with similar work

Diabetic nephropathy

Several retrospective and prospective studies including our own, had reported improvement in albuminuria following RYGB (Miras et al., 2012, Heneghan et al., 2013, Navaneethan et al., 2010). Iaconelli et al followed up newly diagnosed T2DM for 10 years following BPD reported that all 7 patients with microalbuminuria had normalised ACR, whereas microalbuminuria progressed to macroalbuminuria in control group (Iaconelli et al., 2011).

Navaneethan et al compared effect of different bariatric surgery on 15 subjects and reported RYGB improved albuminuria and insulin sensitivity as compared to other procedures (Navaneethan et al., 2010). Heneghen et al retrospectively reviewed changes in urine ACR in T2DM subjects completed 5 years follow up, and reported diabetic nephropathy resolved in 58.3% at 5 year follow up (Heneghan et al., 2013). The study also reported a significant correlation between postoperative urine ACR and systolic blood pressure.

My study confirmed similar finding that RYGB improves diabetic nephropathy at 1 year follow up. However, I did not find correlation between changes in ACR and SBP. The discrepancy might be associated with different design in study (retrospective vs prospective).

Diabetic retinopathy

STAMPEDE trial which randomised 150 T2DM subjects to either RYGB, VSG and medical therapy reported no change in retinopathy score at 2 years. Longer term follow up data is awaited (Singh et al., 2015).

Murphy et al retrospectively reviewed 318 T2DM subjects who had bariatric surgery and reported that 73% of subjects had no change in retinopathy 11% regressed, and 16% progressed. The probability of progression of retinopathy was associated with the magnitude of change in HbA1c, more severe pre-existing eye disease (Murphy et al., 2015). Similar finding was also reported by Thomas et al (Thomas et al., 2014).
This is consistent with my finding that majority of subjects had no change in retinopathy at 1 year follow up.

_Diabetic neuropathy_

Muller-Stich et al reported a study of 20 non-severely obese subjects who had RYGB which showed significant improvement in neuropathy symptom score and neuropathy deficit score post-surgery. All patients had shown improvement (Muller-Stich et al., 2013).

My study had not shown similar result. This is interesting as the subjects in my study were not symptomatic, hence the abnormal findings on NCS were subclinical, yet the results had not improved after intensive glycaemic control following RYGB. Muller-Stich et al, however studied a group of subjects who were symptomatic, by definition would be more severe in degree of neuropathy. The major discrepancy in the study would be the investigations used. Electrophysiological study is an objective measurement of large nerve fibres, whereas neuropathy score is a subjective test. Secondly, both studies were limited by the small sample size. Thirdly, the other study had a cohort with lower BMI of 25-35kg/m².

9.3.4 Originality

This study is the first study that prospectively assessed the effect of RYGB on all 3 components of microvascular complications (diabetic nephropathy, retinopathy and neuropathy) using objective measurements.

9.3.5 Translation to clinical practice

Results of this study showed that despite improved glycaemic control following RYGB, only diabetic nephropathy improved at 1 year follow up. Diabetic retinopathy and subclinical changes in diabetic neuropathy had not altered. The study has clinical implications on follow up of this group of patients. Patients as well as physician need to be aware of the importance of continuing with annual retinal and foot surveillance despite improvement or remission of diabetes.
9.3.6 Future directions:

1. A longer term follow up to assess changes in retinopathy and neuropathy would allow assessment on reversibility of the complications.

2. Future study should include NCS and TTT assessment in the obese T2DM medical treated group as control.
9.4 Limitations

GLUCOSURG -pre and GLUCOSURG -post

Due to the design of both studies, limitations on both studies are similar. These include the number of patients in each group being relatively small, but even so, the effect size was small, which suggests that there was only a small chance of the data representing a type II statistical error. A larger trial focussing on glycaemic outcome may thus be challenging. Whether better perioperative glycaemic control improves post-operative complications requires a very large RCT, because even if the effect size of the intervention is large, the number of post-operative complications are low. The lack of any statistical trends suggests that a larger number of subjects may not have altered the final result. In both trials the follow-up was limited to 1 year, and therefore differences in clinical outcomes between the groups in the longer term cannot be excluded. My study based the post-operative management of patients on fasting CG readings only and continuous glucose monitoring may have been superior for assessing glycaemic excursions and enabled detection of hypoglycaemia more effectively. Despite randomisation in the GLUCOSURG-post trial, the intensively treated group had a longer duration of T2DM. This may have limited the impact of the intervention on the 1 year glycaemic outcome endpoint, although my study did not detect any trends that would have suggested this even in the smaller number of patients that had similar duration of diabetes.

GLUCOSURG -combine

This study is limited by the small sample size, the non-randomised design and lack of information on peripheral neuropathy for the medically treated patients. I cannot exclude that some patients may have had an acute deterioration in retinopathy which occurred before 12 months and then partially recovered. I am however, reassured that the surgical patients who were all followed at 3, 6 and 9 months after surgery did not complain of deteriorating vision. Moreover the retinopathy findings at one year were also reassuring. The study is also limited by its short follow up of 1 year, which is not adequate to assess changes in microvascular complications. However, my findings could be used to power larger randomised controlled trials with longer term follow up that are necessary in this field.
Chapter 10 Conclusion

In summary, I have shown that RYGB had an early and substantial effect on glucose control, and additional intensive glucose-lowering interventions before and after RYGB did not appear to confer any clinical benefits. My pilot randomised controlled trials did not confirm the two previous cohort studies that intensive management of glycaemia for the first two weeks after RYGB resulted in better glycaemic control one year after surgery. I also did not find evidence that intensive management of glycaemia in the 3 months before surgery made a difference. There was no difference in LOS or incidence of surgical complications between the conservative and intensive groups. My study did show improving peri-operative glycaemia was feasible, but a much larger randomized controlled trial would be required to address whether such an approach reduces the already low post-operative complications of RYGB.

The combine study has shown that, as compared to a group of patients receiving best medical care, patients treated with bariatric surgery experience substantial reductions in albuminuria. The rates of retinopathy progression were similar to those observed in a medically treated group whilst there were no significant changes in peripheral nerve function 1 year after RYGB surgery. A longer term follow up on retinopathy and neuropathy changes would provide insightful information on the disease progression. The result of my studies reaffirm the importance of retinal and neuropathy surveillance in the face of improving glycaemic control following RYGB.
Chapter 11 References


Appendix 1. Publication arising from the thesis:
