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Management of patients with type 2 diabetes before and after bariatric surgery: evolution and microvascular complications

L. L. Chuah and Carel W. le Roux

Imperial Weight Centre. Imperial College London. London. UK.

Abstract

Bariatric surgery is increasingly seen as a treatment option for patient with type 2 diabetes (T2DM) and severe complex obesity (SCO). There is however no consensus on how to manage this cohort preoperatively and postoperatively. Patients with T2DM having cardiac surgery benefit from glycaemic optimisation prior to surgery. National Health Service Diabetes in the United Kingdom recommends that glucose is optimised prior to all elective surgery. However, bariatric surgery such as gastric bypass (RYGB) is distinct from general surgery. Glycaemic control improves immediately after RYGB and thus all T2DM patients need a review of their glucose lowering medications postoperatively. Preoperatively most bariatric centres use a low calorie diet (LCD) which improved glycaemic control and may predisposed patients using insulin or sulphonylureas to risks of hypoglycaemia. There are no protocols and consensus among bariatric centres on how best to manage patients with T2DM preoperatively and postoperatively. Moreover patients with difficult to control T2DM are at risk of microvascular complications of diabetes. So far, there is little evidence on the impact of bariatric surgery on diabetes nephropathy, retinopathy and neuropathy.

In conclusion, bariatric surgery improves glycaemic control; however, there are limited studies, and no guidelines on how to manage patients with T2DM pre and postoperatively. Given the increasing proportion of T2DM patients referred for bariatric surgery, there is a need to review current practice on how to manage these patients in the short term and long term with a specific focus on improving end organ damage such as retinopathy, neuropathy and nephropathy.

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Key words: *Diabetes. Obesity. Bariatric surgery. Microvascular complications.*

Correspondence: Carel W. le Roux.
Imperial Weight Centre. Imperial College.
London W6 8RF.
E-mail: c.leroux@imperial.ac.uk

MANEJO DE PACIENTES CON DIABETES TIPO 2 ANTES Y DESPUÉS DE LA CIRUGÍA BARIÁTRICA: EVOLUCIÓN Y COMPLICACIONES MICROVASCULARES

Resumen

La cirugía bariátrica se considera cada vez más como una opción de tratamiento para los pacientes con diabetes tipo 2 (DM2) y obesidad severa compleja (SCO). Sin embargo, no hay consenso sobre cómo manejar este grupo de pacientes ni preoperatoria ni postoperatoriamente. Los pacientes con diabetes tipo 2 se benefician de los conocimientos procedentes de la cirugía cardiaca en la optimización de la glucemia antes de la cirugía. Por otra parte, el Servicio Nacional de Salud para la diabetes del Reino Unido recomienda que la glucosa haya sido optimizada antes de toda cirugía electiva. Sin embargo, la cirugía bariátrica como el bypass gástrico (BPG) es diferente de la cirugía general. El control glucémico del paciente intervenido mejora inmediatamente después de la cirugía (BGYR) y por lo tanto, todos los pacientes con DM2 necesita una revisión de sus medicamentos para el control de la glucosa durante el postoperatorio. Antes de la operación, la mayoría de los centros bariátricos utilizan una dieta baja en calorías (LCD) que mejora el control glucémico y si algunos de estos pacientes continúan usando sus fármacos antidiabéticos como insulina o sulfonilureas existe un alto riesgo de hipoglucemia. Hasta el momento no existen protocolos y no hay consenso entre los centros bariátricos sobre la mejor manera de tratar a los pacientes con diabetes tipo 2 antes de la cirugía y durante el postoperatorio. Además los pacientes con difícil control de la DMT2 se encuentran en riesgo de padecer complicaciones microvasculares debidas a la diabetes. Hasta el momento, hay pocas evidencias acerca del impacto de la cirugía bariátrica sobre la nefropatía diabética, retinopatía y neuropatía. En conclusión, la cirugía bariátrica mejora el control glucémico, sin embargo, hay pocos estudios, y no hay directrices sobre la manera de tratar a los pacientes con diabetes tipo 2 antes y después de la operación. Dado el creciente número de pacientes con DM2 que se someten a cirugía bariátrica, hay una necesidad de revisar las prácticas actuales sobre la forma de tratar a estos pacientes tanto a corto como a largo plazo con un enfoque específico en la mejora de daños tales como retinopatía, neuropatía y nefropatía.

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Palabras clave: *Diabetes. Obesidad. Cirugía bariátrica. Complicaciones microvasculares.*

Introduction: the obesity epidemic

The exponential rise in obesity is predicted to increase the prevalence of Type 2 diabetes mellitus (T2DM) by 50%.[1] The total number of people with T2DM is projected to rise from 171 million in 2000 to 366 million in 2030.[2] Meantime, management of T2DM has also evolved, though at a much slower pace. Conventional medical treatment of T2DM such as use of sulphonylureas and insulin inevitably leads to weight gain which exacerbates insulin resistance, hence, the management of obese T2DM patients has been challenging. The newer drugs such as glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have a better weight profile. Increasingly, weight loss surgery has also been seen as a treatment for patients with T2DM and severe and complex obesity (SCO) defined as a body mass index above 35 kg/m² with life or limb threatening co-morbidities.[3] 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.[4]

Obesity surgery and diabetes

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.[5] 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). Gastric bypass involved division of the stomach into a small pouch which is drained by a proximal jejunum.[6] Food bypasses the gastric remnant and duodenum as a result. Gastric banding consists of the placement of a percutaneous adjustable band just distal to the gastro-oesophageal junction.[7] Sleeve gastrectomy involves stapling the stomach along its length to convert it into a tube, reducing its capacity down to 20% "sleeve" and removal of a large region of the stomach following the major curve.[8] All of these have also been termed as metabolic or diabetes surgery due to their effects in improving glycaemic control.[6,9,10] A randomised controlled trial of 60 patients with SCO and T2DM showed that bariatric surgery (gastric bypass or biliopancreatic diversion) achieved better diabetes remission (75% and 95% respectively) when compared to best medical therapy.[11] Despite its superior effect on diabetes remission, biliopancreatic diversion is not commonly performed[12] as in inexperienced hands it causes significant malabsorption and nutritional deficiencies. A meta-analysis by Buchwald (2009) showed that diabetes resolution was achieved in 80.3% of those undergoing RYGB.[6] It is important to note that the definitions used for remission of T2DM in all the above studies varied significantly. There was a lack of guidance on definition of remission of diabetes until the release of American Diabetes Association (ADA) guideline on "How do we define cure of diabetes" in November 2009. Since then, complete remission of diabetes has been defined as a return to normal glucose values (HbA1c < 6%, fasting glucose < 5.6 mmol/L) for at least one year after bariatric surgery without glucose lowering medication.[13] Pournaras et al. evaluated the proportion of patients achieving complete remission of T2DM using the stringent ADA guideline and found that of the 209 patients that had various types of bariatric surgery for their diabetes, only 34.4 % achieved complete remission of diabetes. The remission rate for gastric bypass was significantly lower with the new definition than with the previously used definition (40.6% *versus* 57.5 %; $P = 0.003$).[14] Schauer et al also found remission rate of 42%in their randomized controlled trial comparing gastric bypass and best medical treatment.[3] This new ADA definition therefore has therapeutic implication as more patients will have to remain on diabetes surveillance programs as well as on diabetes medication rather than the current practice of discontinuing treatment early.

The UK National Bariatric Surgery Registry showed that of 3,817 gastric bypasses performed in 2010, 27.5% of patients had T2DM.[15] This percentage is expected to rise, but there is no consensus in how to manage these patients preoperative, perioperative or postoperatively.

General surgery and diabetes outcome

Patients with T2DM are associated with a two to four fold increase in cardiovascular disease including hypertension, coronary artery disease and stroke.[1,16] The majority of people with T2DM planned for surgery are likely to have one or more cardiovascular risk factors and a significant number will have microvascular disease (retinopathy, nephropathy or neuropathy). These patients are at high risk of perioperative complications and even mortality.[1] The perioperative mortality rate is reported to be up to 50% higher than that of the non-diabetic population.[1,17] Diabetes patients are more at risk of poor wound healing, respiratory infection, myocardial infarction, admission to intensive care, and increased length of stay in hospital.[1,18,19] Perioperative poor glycaemic control has significant impact on postoperative infection.[17] The UK's National Health Service's department of Diabetes (NHS Diabetes) published: "Management of adults with diabetes undergoing surgery and elective procedures: improving standards" in April 2011. They recommended that all patients with diabetes undergoing elective surgery should have their glycaemic control optimised preoperatively.[1] However, 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.

Bariatric surgery and diabetes outcome

There is no data on whether preoperative glycaemic control could influence the outcome of bariatric surgery and remission of diabetes. In non-bariatric surgery (orthopaedics, spinal, vascular, colorectal), elevated HbA1c preoperative has been associated with increased hospital length of stay (LOS) and worsen postoperative outcome.[20-24] There is also a belief amongst clinicians that optimised glycaemic control before surgery would aid wound healing and reduce immediate postoperative complications.

However, 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.[25] Moreover, these patients often followed low calorie diets preoperatively[26,27] 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 should we manage their diabetes differently? Would the preoperative, perioperative and postoperative glucose management impact on improvement and remission of diabetes?

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 ($p = 0.04$).[28]

Remission of diabetes

Although remission of diabetes after gastric bypass surgery is well recognised, there is a paucity of data on when remission occurs, how to manage diabetes in patients that are not in immediate postoperative remission, and how to optimise patients going into remission of diabetes. Scopinaro et al showed that giving a low dose of long acting insulin analogue therapy for the first few weeks after biliopancreatic diversion improves the number of patients achieving remission.[29] Another 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 one year.[30] It is possible that the pancreas undergoes a period of regeneration within the early postoperative period, and a healthy glucose environment is beneficial for 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.[31,32]

Complications of diabetes

Management of diabetes is not confined to glycaemic control only. Diabetes is characterised by micro- and macrovascular complications which could lead to significant morbidity and mortality.[33-35] United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that early intensive glycaemic control reduced the risk of developing microvascular complications in patients with T2DM.[36] The UKPDS follow up study further demonstrated that early intensive glycaemic control has long term beneficial effects on both micro and macrovascular complications.[37] However, there are some uncertainties around rapid intensive glycaemic management as the Diabetes Control and Complications Trial (DCCT) reported a paradoxical deterioration in microvascular complications such as retinopathy and neuropathy after rapid glucose lowering in Type 1 diabetes.[38,39] The safety and effectiveness of intensive glycaemia were also questioned by recent trials.[40-42] Hence, the question remains whether diabetes surgery alter the course of diabetes complications? Would the rapid improvement in glycaemic control cause more harm to retinopathy, as seen in pregnancy?[43] It is therefore important to assess the influence of bariatric surgery on the progression of diabetes complications.

Macrovascular complications such as cardiovascular disease were reduced following bariatric surgery[44] with improvements in coronary heart disease (CHD).[45] Similar results were also reported in the Swedish Obesity Subject (SOS) study and by Adam et al.[46,47] The SOS study is a prospective controlled cohort study comparing bariatric surgery to medical treatment for long-term mortality. The study compared 2,010 subjects who underwent bariatric surgery with 2,037 subjects receiving conventional treatment for their weight. Both groups were matched to 18 variables including gender, age, weight, height, waist circumference and blood pressure. The study found that the adjusted hazard ratio was 0.71 in the surgery group ($p = 0.01$) as compared with the control group.[48] Surgery was associated with a reduced number of cardiovascular death compared to the control group (28 *vs* 49 events, adjusted HR 0.47, $p = 0.02$).[46] The only group that had a cardiovascular benefit from surgery was those with baseline plasma insulin above the median of 17 IU/L. The microvascular complications in another case-controlled study with 10-years' follow-up comparing bil-

iopancreatic diversion versus those associated with conventional therapy on microalbuminuria, and glomerular filtration rate (GFR) in 50 newly diagnosed T2DM showed all surgical treated subjects recovered from microalbuminuria; whereas there was progression of microalbuminuria in non-operated subjects.[45] Metabolic complications such as hypertension, hyperlipidaemia, and obstructive sleep apnoea were all improved following bariatric surgery.[49] However, there had been case report of worsened diabetes neuropathy after RYGB;[38,50] and retinopathy[51] had been noted to deteriorate after very rapid improvement of glycaemic control. One year data after RYGB does however suggest that neither retinopathy nor microalbuminuria deteriorates, with the latter possibly showing some improvement.[52]

Role of pre-operative low calorie diet

Low calorie diet (800-1,200 kcal/day) and very low calorie diet (≤ 800 kcal/day) lead to rapid weight loss and improvement in T2DM.[53] It has also been shown to place type 2 diabetes in remission.[54] The diet has been used preoperatively in many bariatric centres to induce acute weight loss before surgery. The duration of preoperative diet varied between 2 to 6 weeks depending on practices. Low calorie diet(LCD) has shown to reduce visceral fat, liver volume and intrahepatic fat.[55] Reduction in liver size may have safety implication, as it facilitates the use of laparoscopic approach in obesity surgery.[55]

Despite the wide use of preoperative diet, Vargas et al. (2011) found a lack of evidence to supports its benefits as most of these studies were retrospective and could be underpowered.[26] Van Nieuwenhove et al. carried out a prospective, randomised multicentre study which randomised 273 patients to preoperative LCD or control before laparoscopic RYGB. The study reported no differences in mean operating time, estimated blood loss and intraoperative complications. However, the 30 days postop complications were lower in the LCD group.[27]

The use of LCD in patients with T2DM improves glycaemic control, and in some patients, may predispose them to the risk of hypoglycaemia especially if insulin doses were not reduced. Thus far, there is no published data on management of glucose during the perioperative period whilst on LCD or immediately after surgery. Some bariatric units may discontinue insulin treatment while others reduce the dose; some units may even discontinue all glucose lowering agents.

Management of hypertension post-surgery

The Copenhagen study showed that for each 10% increase in BMI, there was a 2-6 mm Hg raise in systolic pressure, and a 1-3 mmHg raise in diastolic blood pressure.[56] There was a significant correlation between mass of visceral adiposity and the level of blood pressure.[56] Consequently, patients with hypertension and diabetes are more at risk of developing end stage renal failure. A study looking at Austrian dialysis transplant registry showed that of the 50,000 patients, cardiovascular mortality was significantly higher for BMI 30-35 kg/m^2, compared to less than 30 kg/m^2.[56]

Aetiology of obesity related hypertensions are multifactorial. Hyperlipidaemia, activation of sympathetic nervous centre and renin-angiotensin activities have all been suggested as possible causes. Studies had shown that weight loss could improve hypertension.[57] A meta-analysis by Buchwald (2004) showed that hypertension resolved in 61.7% of total populations with hypertension following bariatric surgery; and it improved or resolved in 78.5% of the population.[49] Sarkhosh et al. reviewed 32 studies of laparoscopic sleeve gastrectomy and concluded that hypertension resolved in 58% of patients, and improved or resolved in 75% of patients at one year follow up. Each one percent reduction in body weight decreased systolic blood pressure by 1 mmHg, and diastolic blood pressure by 2 mmHg.[57] The SOS study showed that at 2 years, 34% of the surgical group recovered from hypertension, as compared to 21% of control group, but at 10 years only 19% of surgical group recovered from hypertension, as compared to 11 % of the control.[58]

Bariatric surgery has a positive effect on hypertension; however, its effect in the long term is less clear. Blood pressures therefore need to be monitored and antihypertensives titrated accordingly. Thus far, there is no study looking at management of changes in blood pressure after weight loss surgery. In diabetes patients, medications such as angiotensin converting enzyme inhibitor (ACE inhibitor) maybe initiated for renal protective effect rather than blood pressure lowering effect. Therefore physicians and surgeons need to be mindful when titrating blood pressure medication. As the SOS study illustrated, blood pressure might progress with time, and therefore one has to be vigilant in monitoring of these patients.

Management of hyperlipidaemia post surgery

Obesity and hyperlipidaemia are associated with higher cardiovascular risk as the Framingham Heart Study showed there was an increase in cardiovascular disease in overweight men and women.[59] Angina and myocardial infarctions are more common in overweight individuals. There are correlations between lipids concentration and development of coronary heart disease.[59] The most commonly encountered dyslipidaemia in obese individuals are a cluster of interrelated plasma lipid and lipoprotein abnormality including hypertriglyceridemia, low high-density lipoprotein cholesterol(HDL-C), raised small-density lipoprotein cholesterol (LDL-C).[60]

Meta-analysis of weight loss through diet showed a significant reduced total cholesterol(TC), LDL-C, very

low-density lipoprotein cholesterol (VLDL-C), and triglyceridaemia.[61] A retrospective observational study of 114 patients undertaking RYGB shared similar results. TC improved from 211.2 ± 3.8 mg/dL to 172.3 ± 5.5 mg/dL, $p < 0.001$ at 18 months; LDL-C reduced from 131.7 ± 3.3 mg/dL to 96.6 ± 4.0 mg/dL, $p < 0.001$; triglycerides reduced from 132.3 ± 5.3 mg/dL to 69.7 ± 3.7 mg/dL, $p < 0.001$; HDL-C increased from 52.9 ± 1.2 mg/dL to 63.1 ± 2.7 mg/dL, $p < 0.001$. There was significant association between changes in lipid profile and weight loss.[60] In another non randomised prospective cohort study assessing lipid profile of 102 patients undertaking VSG and RYGB, weight loss and reduction of triglycerides were similar between both procedures at one year. RYGB group has significant reduction in LDL-C (125.9 ± 29.3 to 100.3 ± 26.4 mg/dl, $p < 0.001$), as compared to VSG group (118.6 ± 30.7 to 114.6 ± 33.5 mg/dl, $p = 0.220$). However, VSG group showed significant increase in HDL-C of 15.4 ± 13.1 mg/dl compared to RYGB group (9.4 ± 14.0 mg/dl, $p = 0.032$).[62]

The concern is always that while patients are in a negative energy balance dyslipidaemia will improve, but may return to previous set points when patients become weight stable and there are limited studies with long term follow up. Gleysteen reported changes in lipid profiles for 2 cohorts of patients after RYGB and were followed up for different length of time.[59] The 1980-1981 cohort (N = 33) were followed up for up to 5-7 years; while 1985-1986 cohort (N = 23) were followed up for 1 year. Both cohorts showed significant increase in mean HDL-C at 1 year and 5-7 years. Both cohorts also showed significant reduction in the TC: HDL-C ratio at follow up. In the 1980-1981 cohort, significant weight reduction was noted at 1 year, but there was a mean weight regain of 11% at 5-7 year. Despite these, the changes in lipid profiles were maintained. The magnitude in weight loss does not correspond to changes in lipid profiles.[59] SOS study which compared 2,010 bariatric surgery patients with controls showed that the rate of recovery from hypercholesterolaemia did not differ significantly between surgical and control groups at 2 years and 10 years follow up. Rate of recovery from hypertriglyceridaemia and HDL-C were more frequent in the surgical group. In the surgical group, triglycerides improved by 27.2% at 2 years, the effect reduced to 16.3% at 10 years follow up; whereas HDL-C increased by 22 % at 2 years and 24% at 10 years.[58] Data on the long term follow up of lipids post bariatric surgery are limited. There is thus no logical reason why patients should stop treatment for dyslipidaemia or those who had discontinued lipid lowering treatment not to be monitored yearly and lipid lowering medication restarted as per usual protocol.

Conclusion

Diabetes is a disease which involves multiple systems. Management of T2DM has long term implications on macrovascular complications such as coronary heart disease and microvascular complications (retinopathy, nephropathy, neuropathy) and should not be limited to glucose management alone. A holistic approach to patients care is needed. Blood pressure and lipid control, as well as management of diabetes eye, kidney and nerve disease should not be overlooked. Glucose control improved following bariatric procedures such as gastric bypass surgery, but very little effort has focused on the long term cardiovascular risk and progression of microvascular complications.

Currently, there are no recognised guidelines in managing glycaemic control before and after bariatric surgery. More specifically, the effect of tight or more relaxed glucose control and the adjustment of insulin in the perioperative and early postoperative period could impact on long term outcomes in diabetes remission, mortality and diabetic microvascular and macrovascular complications. Whether patients would benefit from glycaemic optimisation before bariatric operations in order to decrease mortality and perioperative morbidity has not yet been determined. Each bariatric procedure has different effect on insulin secretion and insulin resistance and may also have differential effects on macrovascular and microvascular complications. The lessons learned from diabetes management in cardiac surgery necessitates us to evaluate management strategies in patients with T2DM scheduled for bariatric surgery especially as more patients are encouraged to consider surgery as a treatment for T2DM.

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