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Morbidity and mortality of diabetes with surgery

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Abstract

The prevalence of Type 2 diabetes mellitus (T2DM) has increased; as a result the number of patients with T2DM undergoing surgical procedures has also increased. This population is at high risk of macrovascular (cardiovascular disease, peripheral vascular disease) or microvascular (retinopathy, nephropathy or neuropathy) complications, both increasing their perioperative morbidity and mortality. Diabetes patients are more at risk of poor wound healing, respiratory infection, myocardial infarction, admission to intensive care, and increased hospital length of stay. This leads to increased inpatient costs. The outcome of perioperative glycaemia management remains a significant clinical problem without a universally accepted solution.

The majority of evidence on morbidity and mortality of T2DM patients undergoing surgery comes from the setting of cardiac surgery; there was less evidence on non-cardiac surgery and bariatric surgery. Bariatric surgery is increasingly performed in patients with severe obesity complicated by T2DM, but is distinguished from general surgery as it immediately improves the glucose homeostasis postoperatively. The improvements in glycaemia are thought to be independent of weight loss and this requires different postoperative management. Patients usually have to follow specific preoperative diets which lead to improvement in glycaemia immediately before surgery.

Here we review the available data on the mortality and morbidity of patients with T2DM who underwent elective surgery (cardiac, non-cardiac and bariatric surgery) and the current knowledge of the impact that preoperative, intraoperative and postoperative glycaemic management has on operative outcomes.

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Key words: *Mortality. Morbidity. Perioperative management. Bariatric surgery.*

MORBI-MORTALIDAD EN PACIENTES DIABÉTICOS TIPO 2 TRAS CIRUGÍA ELECTIVA

Resumen

La prevalencia de la diabetes mellitus tipo 2 (DM2) ha incrementado en los últimos años, y como resultado, el número de pacientes con DM2 sometidos a procedimientos quirúrgicos también ha aumentado. Esta población posee un alto riesgo de complicaciones macrovasculares (enfermedad cardiovascular, enfermedad vascular periférica) o microvasculares (retinopatía, nefropatía o neuropatía), ambos incrementan tanto la mortalidad como la morbilidad perioperatoria de estos pacientes. Los pacientes con diabetes tienen un mayor riesgo de una mala cicatrización de las heridas, infección respiratoria, infarto de miocardio, ingreso en la UCI y mayor duración de la estancia hospitalaria. Todo esto incrementa los costes de tratamiento de este tipo de pacientes. El control de la glucemia perioperatoria sigue siendo un importante problema clínico sin una solución universalmente aceptada.

La mayoría de los conocimientos sobre la morbilidad y mortalidad de los pacientes con DM2 sometidos a cirugía proviene de la de la cirugía cardíaca, y algunos, aunque menos, de la cirugía no cardiaca y cirugía bariátrica. La cirugía bariátrica se realiza cada vez más en pacientes con obesidad mórbida complicado con diabetes tipo 2, y se diferencia de la cirugía general en que inmediatamente mejora la homeostasis de la glucosa tras la operación. Las mejoras en el control de la glucemia parecen ser independientes de la pérdida de peso y esto requiere un manejo postoperatorio diferente. Los pacientes por lo general tienen que seguir dietas específicas preoperatorias que conducen a la mejora de la glucemia inmediatamente antes de la cirugía.

En este artículos revisamos los datos disponibles sobre la mortalidad y la morbilidad de los pacientes con diabetes tipo 2 sometidos a cirugía (cirugía cardíaca, no cardíaco y bariátrica) y el conocimiento actual de los efectos preoperatorios, intraoperatorios y postoperatorios que el control de la glucemia tiene sobre los resultados operatorios.

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Palabras clave: *Mortalidad. Morbilidad. Control perioperatorio. Cirugía bariátrica.*

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Introduction

Type 2 diabetes mellitus (T2DM) is a very common metabolic disorder. More specifically, the prevalence of T2DM for all age-groups worldwide was estimated to be 2.8% in 2000 and to increase to 4.4% in 2030.[1] In developed countries, over the next decade, the exponential rise in obesity is predicted to increase the prevalence of T2DM.[2] This will have major implications for health services, with particular impact on inpatient care. A recent audit has shown that the prevalence of T2DM in the United Kingdom inpatient population now ranges from 10-28%, and this figure is certain to rise in the future.[3] T2DM related comorbidities increase the need for surgical and other operative procedures.[4-6]

T2DM is associated with a two to four fold increase in cardiovascular disease including hypertension, coronary artery disease and stroke.[7] 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). As a result, patients with T2DM are at high risk of perioperarative complications and even mortality.[8-10] The effect of preoperative, intraoperative and postoperative diabetes management and the effect of perioperative hyperglycaemia and hypoglycaemia in the short-term and long-term operative outcomes remains a significant clinical problem without a universally accepted solution.[2]

In this review, we summarize the knowledge regarding the mortality and morbidity in patients with T2DM who underwent elective surgery in three major surgical categories: cardiac surgery, non-cardiac surgery and bariatric surgery. The stronger body of evidence regarding T2DM and perioperative glucose management comes from the setting of cardiac surgery.[11-15] We have less evidence for the non- cardiac surgeries or specifically bariatric surgeries which are a separate category as they immediately improve glucose homeostasis postoperatively. The improvements in glycaemia after bariatric surgeries are often thought to be independent of weight loss and this should require different postoperative management regimens. Moreover, patients who come for bariatric procedures have often followed low calories diets preoperatively,[16,17] this can lead to improvement in glycaemic control.

Mortality and morbidity after cardiac surgery in patients with T2DM

Long term mortality

A prospective study of 9,125 survivors of isolated coronary artery bypass graft (CABG) surgery found that cardiac-specific survival at 5 and 10 years was lower in patients who required insulin compared to patients who only needed oral medications for T2DM and patients without diabetes.[18] The need for insulin, chronic kidney disease, peripheral vascular disease, and a low ejection fraction were all independent risk factors for late cardiac death.[18] Another study, of 1025 patients (45 with diabetes) who underwent CABG and were followed up for a mean of 7.4 years, showed that long-term mortality was increased in patients with T2DM despite similar early mortality.[9] Furthermore, 3,707 patients who were investigated over a 12 year period after isolated CABG included 250 patients on diet or oral therapies for T2DM and 162 T2DM patients on insulin. The survival and the cardiac event-free curves revealed no difference between the groups with T2DM. However, there was a significant difference between both groups with T2DM and patients without diabetes.[8] Finally, Marcheix et al in a retrospective study with 1,000 patients (722 without and 278 with T2DM) reports that after off-pump coronary artery bypass graft (OPCABG) the ten-year survival and the free survival of major adverse cardiac events was decreased significantly in the group with T2DM.[10]

Early mortality (30-days mortality)

The data regarding the early mortality after CABG show conflicting results.[8-10] Risum et al and Marcheix et al have reported that the early mortality was not significantly higher when comparing patients with and without T2DM.[9,10] On the other hand, Salomon et al found that the perioperative mortality after CABG was greater in patients with T2DM compared to patients without diabetes.[8]

Morbidity

Cardiac surgery in patients with T2DM is associated with longer hospital stay, higher health care resource utilization, and greater perioperative morbidity than in subjects without T2DM.[4-6,11] The higher morbidity in patients with T2DM is related in part to the heightened incidence of comorbid conditions including coronary heart disease, hypertension, and renal insufficiency, as well as the adverse effects of hyper- and hypoglycaemia in clinical outcome.[4,8,19,20] More specifically, patients with T2DM have worse outcomes after percutaneous coronary intervention than patients without T2DM.[20] A recent study which compared patients with T2DM to patients without T2DM, after implantation of drug-eluting stents or bare metal stents, found that the 2-year risk of myocardial infarction was 6.9% greater in the T2DM patients.[20] Moreover, the 2-year risk of target lesion revascularization was significantly higher for patients with T2DM. Thus 2 years after drug-eluting stent or bare metal stent implantation, patients with T2DM had a greater risk of myocardial infarction and death.[20]

As regards to coronary artery bypass graft (CABG), patients with T2DM had a higher incidence of postoperative death (3.9% *versus* 1.6%) and stroke (2.9%

versus 1.4%), but not Q wave myocardial infarction (1.8% *versus* 2.9%) compared to patients without T2DM (19). They also had lower survival (5 years, 78% *versus* 88%; 10 years, 50% *versus* 71%) and lower freedom from percutaneous transluminal coronary angioplasty (5 years, 95% *versus* 96%; 10 years, 83% *versus* 86%). In the same study, the authors reported that patients with T2DM and patients without T2DM had similar freedom from myocardial infarction events (5-years, 92% versus 92%; 10-years, 80% *versus* 84%) and similar freedom from additional coronary artery bypass grafting (5-years, 98% *versus* 99%; 10-years, 90% *versus* 91%) (19).

Salomon et al. reports that the extent of diffuse coronary disease as judged angiographically and at CABG was significantly greater in patients with T2DM as compared to those without.[8] No difference was noted in the incidence of localized coronary disease between the groups and the average number of grafts was greater in patients with T2DM. The incidences of sternotomy complications, renal insufficiency and total hospital length of stay were significantly greater in the group with T2DM when compared to those without.[8] Moreover, this study indicates that patients with T2DM have quantitatively and qualitatively more coronary artery disease than non- diabetes patients and therefore higher perioperative morbidity and mortality, and a lower long-term survival rate when compared to patients without T2DM.[8] In contrast, a recent study reports that T2DM patients had no increased risk of perioperative myocardial infarction, or of low-output syndrome necessitating intraortic balloon pumping, and no excess incidence of late non-fatal myocardial infarction or late chronic heart failure after CABG compared to patients without diabetes.[9]

Finally, a comparison between patients with T2DM on oral medications or diet and those requiring insulin showed that the mean number of complications per patient was higher in patients who needed insulin.[21] The major differences in perioperative complication rates were found in the need for prolonged (> 24 hours) ventilation, occurrence of respiratory or renal insufficiency, and mediastinitis. The mean length of stay in the intensive care unit and for total hospitalization were longer in patients with T2DM treated with insulin compared to diet/oral medications (4.3 ± 2.8 days *versus* 2.8 ± 2.7 days and 11.1 ± 2.2 days *versus* 7.2 ± 2.4 group, respectively).[21] Moreover, overall late cardiac and non-cardiac complication rates were significantly higher in patients with T2DM needing insulin compared to those on oral medications and diet.

Impact of perioperative glycaemic control on mortality and morbidity after cardiac operations

Evidence from observational studies suggests that in surgical patients, with and without T2DM, improvement in glycemic control positively affects morbidity and mortality postoperatively.[22,23] After cardiac surgery, a retrospective study which analysed 8,727 adults found that inadequate postoperative blood glucose control was a predictor of in-hospital mortality and morbidity.[24] Randomised controlled trials for patients with T2DM undergoing CABG have investigated the effect of tight glycemic control compared to conservative glucose management on perioperative outcomes. Patients were prospectively randomised to tight glycemic control (serum glucose 125 to 200 mg/dL) with a modified glucose-insulin- potassium (GIK) solution or standard therapy (serum glucose < 250 mg/dl). Patients with tight control had a significant lower incidence of atrial fibrillation (16.6% *versus* 42%), a shorter postoperative length of stay, a significant survival advantage over the initial 2 years after surgery, significant decreased episodes of recurrent ischemia (5% *versus* 19%) and they developed fewer recurrent wound infections (1% *versus* 10%).[14] Another randomised controlled trial evaluated if aggressive glycaemic control (90-120 mg/dL) would result in more optimal clinical outcomes and less morbidity than moderate glycemic control (120-180 mg/dL) using continuous intravenous insulin solutions in patients with T2DM undergoing CABG surgery. The results showed that patients with aggressive control had a lower mean glucose at the end of 18 hours of insulin infusion, higher incidence of hypoglycemic events, but there were no differences in the incidence of major adverse events between the groups.[15]

Impact of preoperative glucose control on mortality and morbidity after cardiac surgery

Increased haemoglobin A1c (HbA1c) and inadequate preoperative glycaemic control could be a predictor of adverse outcomes after CABG.[25,26] A study on 3,555 consecutive patients who underwent CABG reported that an elevated HbA1c level predicted the in-hospital mortality after CABG.[25] More specifically, an HbA1c greater than 8.6% was associated with a 4-fold increase in mortality and for each unit increase in HbA1c, there was a significantly increased risk of myocardial infarction and deep sternal wound infection.[25] Moreover, renal failure, cerebrovascular accident, and deep sternal wound infection occurred more commonly in patients with elevated HbA1c. Preoperative HbA1c levels in patients with T2DM were not predictive of long-term outcomes after OPCABG as shown in 306 patients that had undergone OPCABG and were divided in 3 groups according to their preoperative HbA1c.[27]

Mortality and morbidity after non-cardiac surgery in patients with T2DM

Long term mortality

A retrospective study of 179 patients with T2DM undergoing non cardiac surgery (plastic, abdominal,

orthopaedic, ophthalmic, gynaecology, urological), reported a postoperative mortality of 24% at 10 months after surgery, with one third of the fatalities occurring during the first 30 days. Established ischaemic heart disease before the operation was associated with a postoperative mortality of 44%, which was significantly higher compared to patients with T2DM, but without pre-existing cardiovascular disease.[28] Another study of patients undergoing non-cardiac surgery with 7-year follow–up showed mortality was higher in patients with T2DM as compared to those without, 37.2% *vs* 15% ($p < 0.00001$). Cardiovascular disease was the main causes of death in the T2DM population, 56.8% *vs* 18.6% ($p < 0.0001$). Therefore in non-cardiac surgery, patients with T2DM also appear to have a higher mortality rate as compared to the non-diabetes group.[29]

Short term mortality

A study that compared 274 patients with T2DM and 282 non diabetes patients having non-cardiac surgery (abdominal, gynaecological, orthopaedic, otolaryngological, thoracic, vascular, urology) showed significantly higher short term mortality (≤ 21 days) in the diabetes group, 3.5% *vs* 0% ($p < 0.05$).[29] A study in non-cardiac surgery (general surgery, neurosurgery, surgical oncology, orthopaedic, vascular, thoracic, urology, otolaryngology except tonsillectomy, gynaecology) comparing 2,469 non-diabetes and 643 patients with T2DM, showed a 30-day mortality of 2.3% (72 of 3,112 patients). The diabetes group showed a trend towards higher mortality as compared to non-diabetes patients, 3.1% *vs* 2.1% ($p = 0.11$).[4] The multivariate analysis, suggested that the risk of death increased in proportion to perioperative glucose level, but this was only significant in those not known to have T2DM.

Morbidity after non-cardiac surgery

Perioperative hyperglycaemia is associated with increased length of stay (LOS) and postoperative pneumonia.[4] Patients with T2DM compared to non diabetes had a significantly higher rate of complications including pneumonia (12.1 *vs.* 5.4%), wound and skin infections (5 *vs.* 2.3%), systemic blood infection (3.6 *vs.* 1.1%), urinary tract infections (4.5 *vs.* 1.4%), acute myocardial infarction (2.6 *vs.* 1.2%), and acute renal failure (9.6 *vs.* 4.8%). In addition, patients with T2DM had significantly higher LOS in the hospital and significantly higher ICU LOS compared to non-diabetes subjects (8.8-10.6 days *vs.* 7-10.8 days and 2.3-6.2 days *vs.* 1.8-6.5 days respectively).[4] A retrospective study of 183 patients with T2DM who underwent colorectal resection showed that 28 (15%) patients developed surgical site infections postop. Hyperglycaemia, use of drains, and the use of prophylactic antibiotics for more than 24 hours were associated with surgical site infections.[30]

Mortality and morbidity in patients with T2DM after bariatric surgery

Mortality

Bariatric surgery is effective in improving weight loss and glycaemic control in patients with T2DM and severe & complex obesity. 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.[31] 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.[32] The most common cause of death was myocardial infarction. The recently published SOS data on bariatric surgery and long term cardiovascular events showed that surgery was associated with a reduced number of cardiovascular death compared to control group (28 *vs* 49 events, adjusted HR 0.47, $p = 0.02$).[33] 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.[34] 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.

Morbidity

Perioperative complications

A prospective study aimed to assess outcome of laporoscopic Roux-en Y gastric bypass on T2DM reported that of the 191 subjects, there were 8.4% early major complications, most commonly due to pneumonia and gastrojejunal leaks. There were also 29 early minor complications including gastrojejunal leaks without peritonitis, and wound infections. Approximately 5.2% of patients presented with late major complications due to small bowel obstruction and deep vein thrombosis, and 9.9% of patients reported late minor complications most commonly prolonged emesis and marginal ulcers. The overall major complication rate was 13.6%, and minor compli-

cations rate was 24.9%.[35] These had not been compared to the non-diabetes cohort. However, an earlier study by Schauer that looked at outcomes after LRYGB in 275 patients, of which 22% had T2DM, showed early major complications of 3.3%, which is lower than the diabetes cohort. However, the study showed 27% of the cohort had early minor complications, and 47% of the cohort had late complications and side effects. These raised complication rate coincided with the introduction of laparoscopic approach to RYGB, and may be explained by the relative inexperience of surgeons at that time. The LABS study reported that of the 2,975 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%.

Complications of diabetes

Macrovascular complications such as cardiovascular disease were reduced following bariatric surgery[32] with improvements in coronary heart disease (CHD).[36] Similar results were reported in the SOS study and by Adam et al.[33,34] The microvascular complications in a case-controlled study with 10-years' follow-up comparing biliopancreatic diversion versus those associated with conventional therapy on renal microvascular outcome (macro- and microalbuminuria, and glomerular filtration rate/GFR) on 50 newly diagnosed T2DM showed all surgical treated subjects recovered from microalbuminuria, whereas there was progression of renal microalbuminuria in non-operated subjects.[36] Metabolic complications such as hypertension, hyperlipidaemia, and obstructive sleep apnoea were all improved following bariatric surgery.[37] However, there had been case report of worsen diabetes neuropathy;[38,39] and retinopathy[40] following LRYGB and improved glycaemic control. The safety and effectiveness of intensive glycaemia were also questioned by recent surgical trials.[41-43]

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

Elevated HbA1c has been associated with increased hospital LOS and worsen postoperative outcome in non-bariatric surgery patients.[44] 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 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 failure (p = 0.04)[44]. 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.[45]

Conclusion

Diabetes management preoperatively, and in the early postoperative period after non- cardiac surgery, and bariatric surgery are not protocol driven. More specifically, the effect of tight or more relaxed glucose control and the adjustment of insulin in the perioperative and early postoperative period could have a result on the long term outcomes in diabetes remission, mortality and diabetic microvascular and macrovascular complications. Whether patients would benefit from glycaemic optimisation before non-cardiac 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 therefore 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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