

Perioperative glycaemic control in insulin-treated type 2 diabetes patients undergoing gastric bypass surgery

M. Cruijssen¹, P. Koehestani², S. Huttjes¹, K. Leenders², I. Janssen², H. de Boer^{1*}

Departments of ¹Internal Medicine and ²Surgery, Rijnstate Hospital, Arnhem, the Netherlands, *corresponding author: tel: +31 (0)6-3786735, fax: +31 (0)6-3786737, e-mail: hdeboer@rijnstate.nl

ABSTRACT

Background: Roux-and-Y gastric bypass (RYGB) rapidly reduces insulin requirements in patients with insulin-dependent type 2 diabetes mellitus (T2DMi). A too modest reduction in insulin dose may lead to hypoglycaemia in the early postoperative period.

Objective: To evaluate a regimen designed to maintain blood glucose levels between 5-15 mmol/l and to prevent hypoglycaemic events (blood glucose <3.5 mmol/l) after RYGB surgery.

Design: The effect of a 75% reduction in insulin dose was studied in 85 T2DMi patients during the first ten days after RYGB. Patients with severe β -cell failure (fasting C-peptide <0.3 nmol/l) were excluded. Primary outcome measures: percentage of patients exceeding the upper or lower blood glucose limits, and the number of hypoglycaemic events.

Results: The mean blood glucose level was 12.4 \pm 0.3 mmol/l (mean \pm SE) on the day of surgery (day 0), 10.7 \pm 0.3 mmol/l on day 1, 10.0 \pm 0.5 mmol/l on day 2, and 8.3 \pm 0.3 on day 10. Of all measurements performed during this ten-day period, 12.4% were above the target range, and 2.6% were <5 mmol/l. There were no hypoglycaemic events during the stay in hospital. During the first week at home 2% of the measurements were <3.5 mmol/l.

Conclusion: A 75% reduction in insulin dose is safe in T2DMi patients without severe β -cell failure, and prevents hypoglycaemia in the early postoperative period of RYGB in most cases.

KEYWORDS

Diabetes mellitus, insulin, gastric bypass, glucose control

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in patients with morbid obesity is about 20-30%.¹ Roux-and-Y gastric bypass (RYGB) is very effective in improving glucose control in these patients.^{2,3} Current guidelines state that T2DM patients with a BMI \geq 35.0 kg/m² should be offered the option of bariatric surgery, with RYGB as the method of choice.⁴ An improvement in glucose control can be observed within hours to a few days after surgery, before any significant weight loss has occurred.^{5,7} The underlying physiological changes leading to this rapid improvement have not been fully elucidated yet.⁸

About one-third of the T2DM patients presenting for bariatric surgery are treated with combinations of oral glucose-lowering drugs and subcutaneous insulin (T2DMi). It is not uncommon that massive doses of insulin are needed preoperatively to achieve at least some degree of glucose control. These patients on insulin are at risk to develop severe hypoglycaemia after RYGB if the insulin dose is not adjusted appropriately.

The main aim of perioperative glucose control is safety and stability of patient conditions. Hypoglycaemia is a powerful stimulus for catecholamine release, and may elicit strong haemodynamic responses such as tachycardia and hypertension. These alarming symptoms should be avoided during surgery. Postoperative hypoglycaemia should also be prevented because of patient discomfort, and the need for medical personnel emergency responses. On the other hand, marked hyperglycaemia is also undesirable because it is associated with delayed wound healing and increasing infection rates.⁹

To date, the actual incidence of post-RYGB hypoglycaemia has not been documented yet, and validated guidelines for

perioperative glucose control in T2DMi patients planned for RYGB are not available. We therefore decided to design a regimen for structured insulin dose reduction and to monitor its efficacy. The present study describes our experience in the first 85 patients.

MATERIAL AND METHODS

Patient selection

This is a single-centre observational study in T2DMi patients with a BMI ≥ 35.0 kg/m², scheduled for RYGB. Preoperatively, all patients were referred to the outpatient clinic of internal medicine to prepare for perioperative glucose control. Medical history and medication were recorded and a fasting blood sample was drawn between 08.00 and 10.00 hours to measure serum creatinine, glucose, and C-peptide levels. To minimise the risk of ketoacidosis in the perioperative period, only T2DMi patients with a fasting C-peptide level >0.3 nmol/l were included. Patients with a fasting C-peptide level <0.3 nmol/l were considered to have severe β -cell failure, and were not eligible for massive insulin dose reduction. Other exclusion criteria were not employed. The aim was to achieve blood glucose levels of 5-15 mmol/l in the early postoperative period, and to avoid hypoglycaemia (glucose <3.5 mmol/l). The upper limit of 15 mmol/l was chosen because rapidly progressive improvement in insulin action was anticipated in the days after surgery. Tuning of medication to induce tight glycaemic control during the brief in-hospital postoperative period would increase the risk of developing hypoglycaemia when returning home, in particular in patients resuming their normal daily physical activities.

Protocol

All patients were admitted to the hospital on the evening preceding surgery (day -1). In patients on bedtime long-acting (LA) insulin, the bedtime dose was reduced by 50% to minimise the risk of hypoglycaemia during the day of surgery. On the day of surgery (day 0), all oral antidiabetics were temporarily discontinued, and at 06.00 hours a saline-glucose infusion (NaCl 0.45% + glucose 2.5%) was started at a rate of 2 litres/24 hours, supplemented with potassium chloride 40 mmol/24 hours. Patients with a preoperative daily insulin dose <50 IU/day only received the saline-glucose infusion with potassium chloride during, whereas patients with a preoperative daily insulin dose >50 IU/day also started on continuous intravenous insulin by pump device at 06.00 hours. The insulin delivery rate was derived from the preoperative total daily insulin dose: Insulin delivery rate in IU/h = $(0.25 \times \text{preoperative total daily dose})/24$. During day 0 all patients remained in the fasting state, but from six hours

postoperatively they were allowed to drink water. During the next ten days food intake was limited to thickened fluids and minced foods with an approximate caloric intake of 800 kcal/day. Thereafter, a more regular diet was started, consisting of six small meals a day.

On the first day postoperatively (day 1), saline-glucose infusion and intravenous insulin were discontinued at 07.00 hours, and all patients previously on intravenous insulin now started a regimen of short-acting (SA) insulin three times a day (insulin aspart, TID), injected subcutaneously just before a meal. This was combined with metformin in the same dose as used preoperatively. SA insulin was given in a dose that was 75% lower than the preoperative mealtime doses. Bedtime LA insulin was discontinued permanently in all patients and replaced by glimepiride, taken at 20.00 hours, to achieve night-time glucose control. In patients with fasting C-peptide levels >0.3 nmol/l it has been shown that suppression of nocturnal hepatic glucose output can be achieved by raising portal insulin concentration with glimepiride administered at 20.00 hours.¹⁰ This approach was specifically chosen to avoid the effects of peripheral tissue overinsulinisation that is induced by LA insulin and is associated with inhibition of lipolysis and hindering of weight loss. In an uncontrolled study, the combination of SA insulin TID with glimepiride at 20.00 hours has been shown to provide long-term glycaemic control without weight gain, and we considered such a regimen preferable in the setting of morbid obesity.¹⁰ The glimepiride starting dose was 2 mg, and further adjustment was based on the mean of three consecutive fasting glucose levels. The maximum daily dose of glimepiride was set at 8 mg.

Three examples may serve to illustrate how the most common preoperative regimes were converted into an adjusted postoperative schedule on day 1. First, patients on a four times a day schedule resumed SA insulin in doses that were 75% lower than their preoperative mealtime doses. Their bedtime LA insulin was discontinued and replaced by glimepiride 2 mg at 20.00 hours, irrespective of the magnitude of the LA insulin dose. Second, patients on twice daily premixed insulin (30/70) also changed to a schedule of SA insulin TID, combined with glimepiride 2 mg at 20.00 hours. The amount of SA insulin prescribed for breakfast and lunch was 75% lower than their preoperative premixed morning dose. The dinner SA insulin dose was 75% lower than their formerly premixed evening dose. Third, patients using only LA insulin preoperatively were also put on a schedule of SA insulin TID with glimepiride 2 mg at 20.00 hours. The three mealtime SA doses were reduced to 1/12 of the preoperative total daily dose of LA insulin.

Capillary blood glucose levels were measured at 8.00, 12.00, 17.00 and 22.00 hours (Accu-Check®, Roche Diagnostics, Almere, the Netherlands). On the day of surgery, fasting glucose levels were measured at 06.00 hours instead of 08.00 hours, i.e. before the start of intravenous insulin infusion. Additional ad hoc measurements were performed if hypoglycaemia or severe hyperglycaemia was suspected. Medication was adjusted if glucose levels were <5 mmol/l or >15 mmol/l, for two consecutive measurements. Additional SA insulin was given if daytime glucose levels were >15 mmol/l. Discharge was considered safe if blood glucose levels had remained between 5-15 mmol/l. All patients had telephone contact with the diabetes nurse one week after discharge to discuss the management of their blood glucose levels. In case of markedly abnormal glucose levels they were free to advance this call. Ten days after surgery the medication was adjusted to obtain blood glucose levels in the order of 8-10 mmol/l for the next four weeks.

Statistics

Results are shown as mean values ± standard error of the mean (SEM). Comparison of groups was done by unpaired t-test. A p-value <0.05 was considered to represent statistical significance.

RESULTS

Baseline characteristics

Eighty-five patients were included in the study. Baseline characteristics are summarised in *table 1*. Their mean age was 52.7±0.9 years, and they had a mean BMI of 42.8±0.6 kg/m². The interval between diagnosis of diabetes and the time of surgery was 11.3±0.7 years. Preoperative C-peptide levels ranged from 0.31-3.59 nmol/l. Seventy-two patients (85%) used metformin with a mean dose of 2024±79 mg/day. Seventy-one patients were on LA insulin (mean daily dose 75±5.4 IU/day) and in 59 patients this was combined with SA insulin (mean daily dose 89±5.5 IU). Eleven patients used premixed insulin preoperatively, with a mean daily dose of 81±9.8 IU/day. Three patients only used SA insulin T1D. The mean preoperative total daily insulin dose in all patients taken together was 133±8.4 IU. Ten patients used less than 50 IU/day, 21 patients used 50-100 IU/day, 22 patients used 100-150 IU/day and 32 patients used more than 150 IU/day.

Day of surgery (day 0)

Fasting glucose levels at day 0, the result of a 50% dose reduction of LA bedtime insulin on the night before, ranged from 3.9-16.1 mmol/l with a mean of 9.7±0.4 mmol/l (*figure 2*, day 0). At 06.00 hours the continuous

Table 1. Baseline characteristics of patients

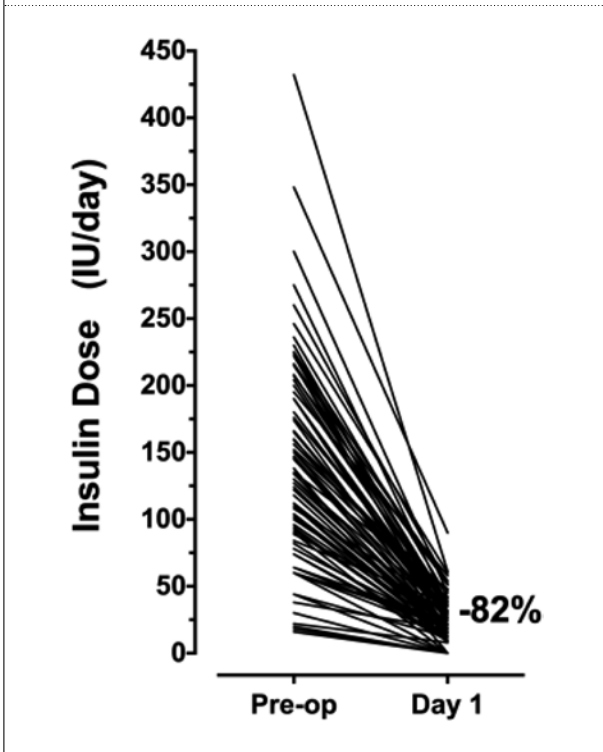
Characteristics	Patients (N=85)
Age (years)	52.7±0.9
Male / female ratio	1 / 1.7
BMI (kg/m ²)	42.8±0.6
Waist circumference (cm)	135.6±1.4
Oral glucose-lowering drugs	
Metformin	84.7%
Sulfonylureas	29.4%
Thiazolidinediones	2.4%
Insulin dose (IU/day)	136±8.5
Additional medication (%)	
Statins	70.6%
Diuretics	51.2%
ACE inhibitors	66.7%
β-blockers	30.6%
Calcium channel blockers	22.6%
Laboratory results	
Fasting glucose (mmol/l)	11.9±0.9
HbA _{1c} (mmol/mol)	67.4±1.7
Fasting C-peptide (nmol/l)	1.1±0.1
Creatinine (μmol/l)	74.3±4.6
Microalbuminuria (mg/l)	109.3±28.9
HDL (mmol/l)	1.2±0.1
LDL (mmol/l)	2.3±0.1
Triglycerides (mmol/l)	2.4±0.3

intravenous insulin pump was started in 75 patients, according to protocol, with a mean infusion rate of 1.2±0.1 IU/h, or 29 IU/day. This resulted in a mean 24-hour blood glucose level of 12.4±0.3 mmol/l. Twenty-six percent of all glucose measurements were >15 mmol/l, the highest level being 23.1 mmol/l (*figure 2*). Only two measurements (1%) were <5 mmol/l. No hypoglycaemic events were observed. As shown in *figure 3*, variability in glucose levels during insulin infusion was acceptable. There was a trend of progressively declining glucose levels, in particular during the night, but hypoglycaemia did not occur. The fasting glucose levels on day 1 varied from 6.1-23.1 mmol/l. Three of the four patients with a day-1 fasting glucose level >15.0 mmol/l were found to have a postoperative surgical complication.

Ten patients were not treated with insulin on the day of surgery because their preoperative insulin dose had been <50 IU/day. Their preoperative fasting glucose levels were comparable with those on high-dose insulin (9.7±1.2 mmol/l versus 12.2±1.0 mmol/l, p=0.13), but their preoperative C-peptide levels had been significantly higher (1.6±0.3 nmol/l versus 1.0±0.1 nmol/l, p<0.05). In this

subgroup not receiving insulin infusion during surgery, mean glucose levels varied from 8.8-15.5 mmol/l. Twenty percent of these measurements were >15 mmol/l and none were <5 mmol/l.

Figure 1. Insulin dose reductions in individual patients with type 2 diabetes mellitus: preoperative daily dose versus daily dose on day 1



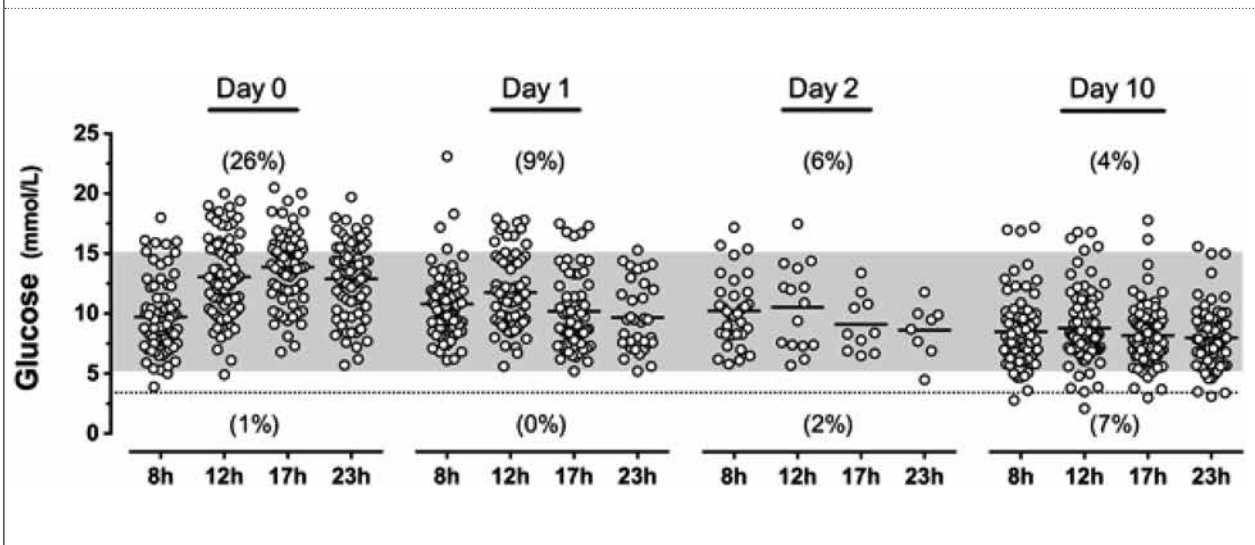
Day 1

The first day after surgery, all 75 patients using a preoperative insulin dose >50 IU/day started subcutaneous SA insulin TID, combined with glimepiride if indicated by protocol, and metformin in the same dose as used preoperatively. The mean total insulin dose was 24.4±1.9 IU/day, i.e. 82% lower than preoperatively (figure 1). Glimepiride was resumed in all 25 patients who had been using it preoperatively in a dose >2 mg/day. In 45 patients who had been on evening or bedtime LA insulin preoperatively, LA insulin was replaced by glimepiride 2 mg at 20.00 hours. This 2 mg dose replaced a mean dose of LA insulin of 75±5.4 IU. The regimen produced a mean glucose level of 10.7±0.3 mmol/l. Nine percent of measurements were >15 mmol/l, none were <5 mmol/l. Six patients had one glucose measurement >15 mmol/l, six patients had two measurements >15 mmol/l, and one patient had three glucose measurements >15 mmol/l. Seven percent of patients received an extra dose of subcutaneous insulin.

Day 2

On the morning of the second day after surgery (day 2), 70 of all 85 patients were discharged. Patients who remained in hospital either had a surgical complication or blood glucose levels outside the target range. Discharge reduced the total number of in-hospital glucose measurements on day 2 to 66. A complete 24-hour glucose profile was available in ten patients. The mean fasting glucose level was 10.3±0.5 mmol/l. The mean glucose level of all measurements performed at day 2 was 10.0±0.5 mmol/l.

Figure 2. Glucose levels on the day of surgery (day 0) and 1, 2 and 10 days later. Grey area: target range, glucose levels of 5-15 mmol/l. Numbers in parentheses: percentage of glucose measurements >15 mmol/l or <5.0 mmol/l. Black interrupted line refers to a glucose level of 3.5 mmol/l



Eight percent of all measured glucose levels were outside the target range, 6% because of a glucose level above 15 mmol/l. Hypoglycaemic events were not observed.

Surgical complications and blood glucose levels

Seven patients (8.2%) had surgery-related complications requiring re-laparoscopy: four patients had a leaking anastomosis, and three patients had postoperative bleeding. Blood glucose levels in these patients were markedly higher than in the group without surgical complications. Forty-six percent of their glucose levels were >15 mmol/l on day 0, 35% on day 1 and 13% on day 2. Hypoglycaemic events were not observed. Preoperative glycaemic control was comparable in patients with and without surgical complications: HbA1c 64.3±3.4 versus 67.7±1.8 mmol/mol (p=0.70).

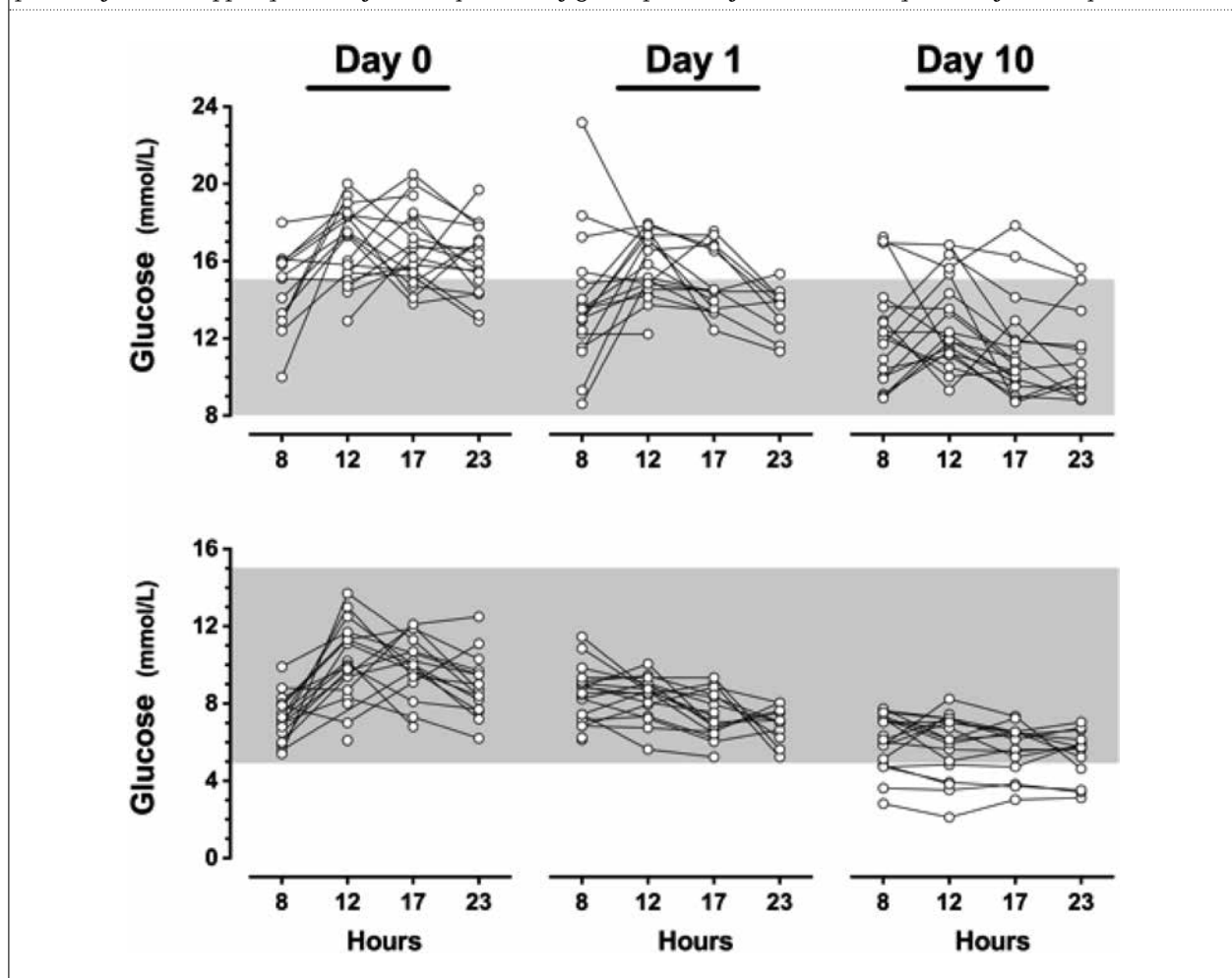
One week after discharge

Seven patients (8.2%) were lost to follow-up. In the remaining 78 patients, the fasting glucose level ranged

from 2.8-17.5 mmol/l, and the mean daily glucose level was 8.3±0.3 mmol/l. Four percent of all measurements were >15 mmol/l, and 7% were <5 mmol/l. Blood glucose levels of patients with values in the lowest quartile were fairly stable throughout that day (figure 3). Glucose levels <3.5 mmol/l were observed on five occasions, and occurred in two patients (figure 3). Severe hypoglycaemia requiring the help of a third party was not reported. Seventy-six percent of patients were advised to continue glibenclamide as before. The glibenclamide dose was raised in ten patients (13%) because of a fasting blood glucose level >8 mmol/l. In four patients (5%) the dose of glibenclamide was reduced because of a fasting glucose <4 mmol/l, and in three patients (4%) glibenclamide was discontinued.

Forty patients (51%) were advised to continue the dose of insulin as prescribed at discharge, 23 patients (30%) were advised to lower their insulin dose by a mean of 6.0±1.1 IU/day, and 14 patients (18%) were advised to stop insulin treatment. In one patient, the insulin dose was raised by 6 IU/day.

Figure 3. Variability in glucose levels in individual patients on the day of surgery (day 0), day 1, and day 10. Top figures: patients from the upper quartile of that day. Bottom figures: patients from the lowest quartile of that day



Prediction of glucose levels at day 10

Ninety-one percent of patients demonstrated a decline in mean blood glucose levels between day 1 and day 10. The mean decrease was 3.0 ± 0.3 mmol/l. Interindividual variability was large, with individual changes ranging from +7.4 to -13.5 mmol/l (figure 4). Mean 24-hour glucose levels at day 1 were weakly correlated with levels at day 10 ($R^2=0.15$, $p<0.001$). At day 10, five patients (6%) had developed a mean glucose level ≤ 5 mmol/l, this had occurred after declines in mean glucose levels between day 1 and 10 of 1.0-11.6 mmol/l (figure 4). The mean glucose levels at day 10 were not correlated with preoperative or postoperative insulin doses.

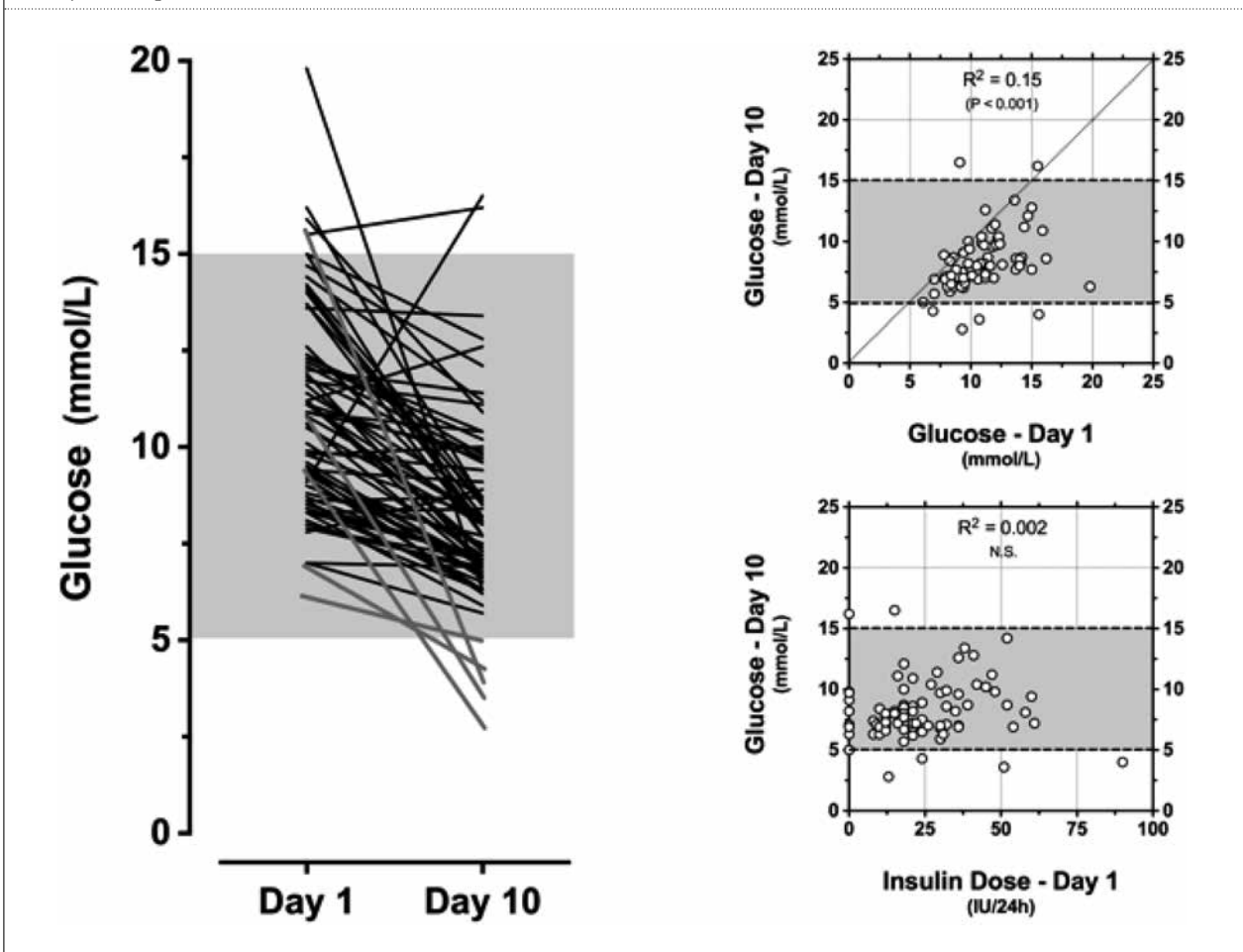
DISCUSSION

The results of this study indicate that a 75% lowering of the daily insulin dose is safe after RYGB in patients with T2DMi and proven residual β -cell function. This regimen

was very effective in avoiding hypoglycaemia during the first ten days after surgery in the majority of patients. The study also illustrates that there is room for improvement. Extension of the in-hospital period to allow a full 48-hour monitoring on subcutaneous insulin may help to achieve a more stable blood glucose level at discharge and might improve the prediction of changes in blood glucose levels in the days after discharge. Secondly, patients with in-hospital postoperative blood glucose levels of 5-10 mmol/l are at increased risk to develop hypoglycaemia at home (figure 3), and their insulin doses should be reduced at discharge to avoid that. Finally, advancing the first telephone contact from the 7th to the 3rd day after discharge may help to detect patients with rapidly declining glucose levels at an earlier stage and further reduce the risk of hypoglycaemia.

The present study has investigated five aspects of perioperative glucose control in morbidly obese patients with T2DMi: 1) The effect of a 50% reduction of bedtime LA insulin on the evening before surgery, 2) The efficacy

Figure 4. Changes in mean 24-hour glucose levels between day 1 and day 10 after surgery, and the correlation between mean glucose levels measured on day 10 and those on day 1. Grey lines: patients developing mean glucose levels <5 mmol/l on day 10



of low-dose intravenous insulin pump delivery during the day of surgery in patients using a preoperative insulin dose >50 IU/day, 3) The glucose response to withholding perioperative intravenous insulin in patients using a preoperative insulin dose <50 IU/day, 4) The safety of a major reduction in postoperative subcutaneous insulin treatment, and 5) The efficacy of replacing LA insulin by glimepiride at 20.00 hours to obtain nocturnal glucose control.

The observation that fasting and daytime glucose levels on the day of surgery were never <3.5 mmol/l indicates that the preoperative 50% lowering of bedtime LA insulin was effective in avoiding hypoglycaemia. This dose adjustment also did not result in clinically significant hyperglycaemia, the highest fasting glucose level being 16.1 mmol/l (figure 2). It is therefore concluded that a 50% reduction on the night before surgery is appropriate in these patients.

Ten patients used insulin in a dose <50 IU/day. It was, prospectively but arbitrarily, decided that insulin treatment on the day of surgery was not likely to be necessary. The present data suggest that this appraisal was correct. The highest glucose level was 16.9 mmol/l, and glucose levels <5 mmol/l did not occur. Preoperative fasting C-peptide levels indicated that β -cell function was better in this subgroup. Apparently, their β -cell function was sufficient to maintain blood glucose levels with an acceptable range while fasting. However, the first day after surgery three of these patients required a restart of insulin at a dose of 8-18 IU/day.

Seventy-five patients were given intravenous insulin by pump device on the day of surgery. The dose was 78% lower than the subcutaneous dose used preoperatively. This major reduction in insulin prevented hypoglycaemia in all patients. However, 26% of the measurements were >15 mmol/l. The surgical complication rate was markedly higher in patients with glucose levels >15 mmol/l than in patients with glucose levels <15 mmol/l: 18.2% versus 6.4%. As preoperative glycaemic control was similar in patients with and without surgical complications, the high glucose levels are considered a consequence and not a cause of these complications.

The first day after surgery all patients on intravenous insulin were put on a regimen of insulin aspart TID, combined with glimepiride 2 mg at 20.00 hours, and metformin was resumed in the same dose as before surgery. Discontinuation of LA insulin is attractive in T2DM patients because it reduces the risk of hypoglycaemia and may be associated with better RYGB-induced weight loss because overinsulinisation with inhibition of lipolysis is avoided. As described previously, glimepiride was used for night-time glucose control with its dose titrated based on fasting glucose levels.¹⁰ In view of glimepiride's plasma half-life of 5-8 hours, several days of use are required to reach a steady state. The fasting

glucose levels at ten days after surgery are therefore a good indication of its efficacy. The results are promising: 89% of patients had fasting glucose levels within the desired range.

The present study has some limitations. First, it is a single-centre study and it lacks comparator arms. Future studies might consider inclusion of a treatment arm with continued use of bedtime LA insulin at an adjusted dose to examine the hypothesis that glimepiride at 20.00 hours is preferred over LA insulin because of its presumed lower risk of hypoglycaemia and less hindering of RYGB-induced weight loss. In addition, inclusion of a study arm with gliclazide instead of glimepiride might be useful to examine whether gliclazide is associated with a lower risk of hypoglycaemia than glimepiride in this particular setting.^{11,12} Another limitation is the low number of in-hospital observations on day 2. A 48-hour postoperative in-hospital observation period on subcutaneous insulin may be required to ensure a higher degree of stability in glycaemic control and a better predictability of glucose levels during the first week at home. Future studies focusing on the results of treatment on day 1 and 2 and studying their correlation with glucose control during the first week out-of-hospital may reveal subcategories of patients who can be safely discharged on the morning of day 2, based on the glucose measurements of day 1. However, as long as this information is lacking, we advocate a postoperative in-hospital two-day observation period on subcutaneous insulin, for reasons of safety, particularly in those on high-dose insulin. Finally, the perioperative glucose upper target limit of 15 mmol/l used in this study is higher than the generally recommended upper limit of 11 mmol/l.¹³ Although postoperative wound infections did not occur, the current number of patients is too small to exclude a negative impact on infection rates.¹⁴ The issue of preoperative glycaemic control and its consequences for postoperative infection rates after gastric bypass is still under debate. Studies evaluating this aspect have produced conflicting results.^{15,16}

In conclusion, a perioperative 75% reduction in daily insulin dose in T2DMi patients with residual β -cell function appears to be appropriate to avoid hypoglycaemia and marked hyperglycaemia after bariatric surgery. Confirmation of this observation in a controlled, multicentre study is recommended to increase the evidence of safety and efficacy and to allow comparison with other regimens.

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