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ORIGINAL CONTRIBUTIONS

Metabolic Changes and Diabetes Microvascular Complications 5 Years After Obesity Surgery

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Abstract

Background Obesity surgery has pronounced effects on metabolic profile of patients with type 2 diabetes mellitus (T2DM); however, reports on long-term remission rates based on the standardised and holistic criteria by the International Diabetes Federation (IDF) and effects on T2DM microvascular complications are scarce in the literature. In this retrospective clinical trial, our objectives were to assess these variables 5 years after surgery.

Methods Clinical data and direct measurements of renal and retinal damage were collected prospectively and analysed retrospectively for 82 patients with T2DM who underwent obesity surgery and were followed up for 5 years.

Results The cohort of 82 patients with T2DM that were followed up 5 years after obesity surgery was predominantly female (71%) with a median age of 51 years, weight of 133.5 kg, BMI of 46.8 kg/m^2 and pre-operative duration of T2DM of 8 years; 6% of patients had diet-controlled T2DM, 57% were on non-insulin treatment and 37% were on insulin treatment pre-operatively. Of the total 82 patients, 59 patients underwent Roux-en-Y gastric bypass, 15 sleeve gastrectomy and 8 patients underwent gastric band operations. At 5 years, 5% and 15% patients achieved optimisation and improvement of the metabolic state based on the IDF criteria respectively. Surgery was associated with almost halving of the albumin–creatinine ratio in 22 patients with pre-existing albuminuria (follow-up data available for 64 patients) and an overall stabilisation of retinopathy in 24 patients with retinal images available at 5 years.

Conclusion Whilst the findings on microvascular complications are encouraging, the rates of metabolic remission were lower than expected and raise the need for validated protocols to assist clinicians in managing these patients more aggressively post-operatively to achieve optimum cardio-metabolic risk factor control and hopefully further reduction in microvascular and macrovascular complications.

Keywords Obesity · Diabetes · Long-term · Remission

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Introduction

Obesity surgery has been shown to have impressive effects on the glycaemic control in obese patients with type 2 diabetes mellitus (T2DM) [1–3]; however, the definition of "diabetes remission" differs amongst the published RCTs. The American Diabetes Association (ADA) was the first to define "complete" and "partial" T2DM remission based on purely glycaemic markers [4]. The International Diabetes Federation (IDF) then introduced new more holistic criteria defining the "optimisation" and "substantial improvement" of the metabolic state using not only markers of glycaemia and medication usage but also weight loss, plasma lipids and blood pressure (BP) [5]. Evidence on 5-year T2DM "remission" rates using the IDF criteria and on the effects of the most common obesity surgery procedures on microvascular complications using *direct measurements* is relatively scarce in the literature (e.g. [6, 7]).

Our primary aim was to assess the rates of T2DM patients achieving the IDF criteria 5 years after obesity surgery in order to evaluate its long-term metabolic effects. Our secondary aim was to assess the long-term effect of obesity surgery on albuminuria and retinal appearances using *direct* measurements.

Methods

Data were collected prospectively and analysed retrospectively for 82 obese T2DM patients who underwent obesity surgery between 2006 and 2009 at the Imperial College Healthcare NHS Trust, UK, a centre of excellence for obesity surgery. Ethical permission was obtained from the Imperial College Healthcare NHS Trust Clinical Governance and Patient Safety Committee reference: 09/808. Data were collected pre-operatively and 5 years post-operatively for clinical parameters including body weight; HbA1c; fasting blood glucose and lipids; BP; rates of reported hypoglycaemia; and number of glucose, BP and lipid-lowering medications taken. Post-operatively, these patients are managed in the specialist obesity clinic for 2 years and then routinely discharged to primary care.

Partial or complete remission of T2DM and optimisation or improvement of the metabolic state at 5 years were defined based on the IDF and ADA criteria respectively (Supplemental Table 1).

Albuminuria was assessed through the mean of two early morning spot urine albumin–creatinine ratio (ACR) values of 62 patients. This cohort was further divided into those with abnormal ACR values pre-operatively as defined by > 2.5 mg/mmol for men and > 3.5 mg/mmol for women. Retinal appearances were assessed in 24 patients with two-field digital retinal images obtained from the English National Screening Programme for Diabetic Retinopathy and graded by an independent ophthalmologist who was blinded to the patient clinical information, using a five-stage disease severity classification for diabetic retinopathy from the International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scales [8]. Improvement or worsening was defined as a decrease or increase of at least two steps in the same grading system, respectively.

Statistical Analysis

Descriptive statistics are presented as absolute values, percentages or median (25th–75th quartiles). As all datasets were not normally distributed, pre–post-surgery comparisons were made using the Wilcoxon-matched pairs test. Categorical data were analysed using chi-square testing. A p value < 0.05 was considered statistically significant. GraphPad Prism 6 and Sigmaplot version 12.0 statistical software packages were used.

Results

Our cohort of 82 patients with complete paired datasets at baseline and 5 years after obesity surgery was predominantly female (71%) with a median age of 51 years, median weight of 133.5 kg, median BMI of 46.8 kg/m^2 and pre-operative duration of diabetes of 8 years; 72% underwent Roux-en-Y gastric bypass (RYGB) (n = 59), 18% underwent vertical sleeve gastrectomy (VSG) (n = 15) and 10% underwent gastric band (BAND) (n = 8). Pre-operatively, 6% of patients had diet-controlled T2DM, 57% were on non-insulin treatment and 37% were on insulin treatment. No patients met the ADA or IDF criteria at baseline.

Pre-operative and 5-year post-operative data are shown in Table 1. BMI, HbA1c, fasting glucose, triglycerides, systolic and diastolic BP were all significantly decreased 5 years after surgery compared to baseline. There was a significant increase in HDL cholesterol. The decrease in total cholesterol and LDL cholesterol at 5 years did not achieve statistical significance. There was a significant decrease in the median number of glucose-lowering medications used at 5 years compared to baseline, but no significant change in BP and lipid-lowering medication usage. Forty-three percent of patients were on no T2DM medications, 43% on non-insulin treatment and 15% on insulin treatment 5-years post-operatively. During the 5-year post-operative period, 32% of patients experienced at least one episode of hypoglycaemia.

At 5 years post-operatively, 5% (n = 4) and 15% (n = 12) of patients met the IDF criteria for optimisation and improvement of the metabolic state respectively (Fig. 1). Twenty-three percent (n = 19) and 37% (n = 30) of patients met the ADA criteria for complete glycaemic remission of T2DM and partial remission respectively.

Table 1 Summary of the pre-operative and 5-year post-operative data from the cohort of patients studied ($n = 82$)

	Pre-operatively	5 year post-operatively	*P* value
Age (years)	51.1 ± 10.0 (28.0–70.0)	n/a	n/a
Gender F/M (*n*)	58/24	n/a	n/a
Weight (kg)	133.5 [113.7–150.0] (84.0–235.0)	100.4 [82.2–115.0] (62.0–165.0)	< 0.0001
% total weight loss	n/a	24.0 ± 11.8 (−3.0–50.7)	n/a
BMI (kg/m^2)	46.8 [41.9–52.7] (32.1–76.7)	35.3 [30.0–40.6] (24.9–60.2)	< 0.0001
HbA1c (%)	7.7 [6.7–9.3) (5.2–12.6)	6.3 [5.6–7.2] (5.0–9.6)	< 0.0001
HbA1c (mmol/mol)	61.0 [50.0–78.0) (33.0–114.0)	45.0 [38.0–55.0] (31.0–81.0)	< 0.0001
Glucose (mmol/l)	7.1 [5.3–9.4] (3.0–19.4)	6.0 [5.0–8.0] (3.1–16.0)	0.0014
Total cholesterol (mmol/l)	4.7 [4.0–5.4] (2.1–8.8)	4.4 [3.8–5.1] (2.0–9.1)	0.21
HDL cholesterol (mmol/l)	1.1 [0.9–1.3] (0.5–2.1)	1.4 [1.2–1.6] (0.7–2.5)	< 0.0001
LDL cholesterol (mmol/l)	2.6 [1.9–3.6] (0.4–5.2)	2.3 [1.8–3.0] (1.0–6.2)	0.16
Triglycerides (mmol/l)	1.8 [1.3–2.4] (0.6–7.4)	1.3 [0.9–1.8] (0.4–4.4)	< 0.0001
Systolic BP (mmHg)	142 [130–150] (103–195)	128 [120–139] (104–196)	< 0.0001
Diastolic BP (mmHg)	84 [80–90] (63–114)	76 [70–80] (57–110)	< 0.0001
Number of glucose lowering medication	2 [1–2] (0–4)	1 [0–1] (0–3)	< 0.0001
Number of BP lowering medication	1 [0–2] (0–5)	1 [0–2] (0–5)	0.48
Number of lipid lowering medications	1 [0–1] (0–3)	1 [0–1] (0–1)	0.86
Hypoglycaemia (%)	n/a	32%	n/a
ACR (mg/mmol)	1.8 [0.8–4.9] (0.2–312.4)	1.2 [0.7–4.3] (0.1–413.4)	0.48
ACR in cohort with albuminuria at baseline, $n = 62$, (mg/mmol)	7.1 [4.6–29.5] (2.9–312.4)	3.6 [0.6–18.1] (0.3–413.4)	0.020

Descriptive statistics are presented as absolute values, percentages, or median [interquartile range] and (range). Pre–post-comparisons were performed using Wilcoxon-matched paired tests. Glucose and lipids were assessed in the fasting state. Medication usage refers to the number of glucose, BP and lipid-lowering drugs used per day and hypoglycaemia to the percentage of patients with episodes in which capillary glucose readings of < 4.0 mmol/l at any stage during the 5-year post-operative period. The cohort has been divided into those with abnormal ACR values pre-operatively as defined by > 2.5 mg/mmol for men and > 3.5 mg/mmol for women

BMI body mass index, *HbA1c* glycated haemoglobin, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *BP* blood pressure, *ACR* albumin/creatinine ratio, *n/a* not applicable

A pre-operative duration of T2DM of less than 5 years was associated with an increased likelihood of complete remission based on the ADA criteria 5 years post-operatively. Patients treated with insulin pre-operatively were less likely to achieve ADA complete remission compared to non-insulin treated patients. Age, gender, pre-operative BMI, HbA1c, duration of T2DM and insulin use did not significantly predict the achievement of optimisation of the metabolic state based on the IDF criteria (Supplemental Table 2). Weight loss did not predict the achievement of any of the criteria.

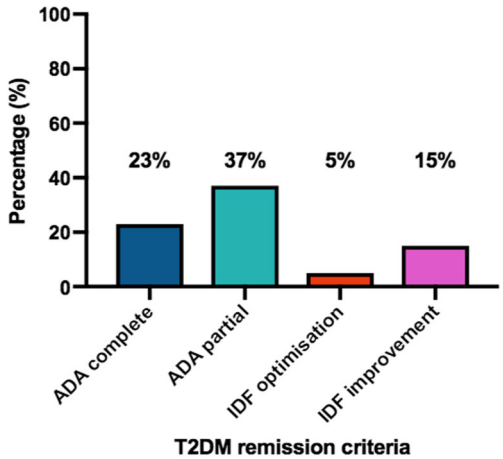

Fig. 1 Percentage of patients meeting the American Diabetes Association (ADA) criteria for complete or partial remission of type 2 diabetes mellitus (T2DM) and the International Diabetes Federation (IDF) criteria for optimisation or improvement of the metabolic state at 5 years after obesity surgery ($n = 82$)

Amongst the surgical procedures, 5% of RYGB patients, 0% of BAND patients and 7% of VSG patients met the IDF criteria for optimisation of the metabolic state. Twenty-five percent of RYGB patients, 25% of BAND patients and 13% of VSG patients met the ADA criteria for complete remission of T2DM. The sample size did not allow for statistical comparisons between the three groups.

In the subgroup of 62 patients (76% of total patient cohort) with urinary ACR, measurements were available for follow up; there was no significant change at 5 years after surgery compared to baseline (Table 1). However, there was a significant reduction in ACR in the 22 patients with albuminuria at baseline.

In the subgroup of 24 patients (29% of total patient cohort) with available retinal images, retinal appearances remained

stable in 13, worsened in 6 and improved in 5 patients 5 years after obesity surgery (Supplemental Figure 1). We did not identify any factors that predicted the worsening of retinopathy.

Discussion

In this study, we have demonstrated that obesity surgery is associated with statistically significant improvements in BMI, HbA1c, fasting glucose, HDL cholesterol, triglycerides and BP even at 5 years post-operatively. However, the percentage of patients achieving the holistic IDF criteria at 5 years was lower than expected. The vast majority of available studies and RCTs report remission based on the glucocentric ADA criteria (e.g. [7]). To our knowledge, this is the first time the IDF criteria have been applied to this population. Surgery was associated with almost halving of ACR in patients with pre-existing albuminuria and an overall stabilisation of retinopathy.

Although surgery is still effective at 5 years and there is a significant improvement in many cardio-metabolic factors, 15% of patients achieved the more holistic IDF criteria for optimisation of not only glycaemia but also other cardio-metabolic risk factors. The ADA criteria for complete remission were met by 23% of patients in our cohort at 5 years. This is consistent with the findings of the only other RCT that used similar criteria in which 22% of patients treated in a USA centre of excellence in bariatric surgery achieved this long-term complete remission of T2DM [7].

The relatively low remission rates reported in our study may be due to the stringency of the IDF criteria themselves or due to suboptimal long-term management of T2DM patients due to the absence of validated treatment algorithms to guide clinicians and patients. It is not uncommon practice to withdraw all or most glucose, BP and lipid-lowering medication soon after obesity surgery in anticipation of a "cure" of these comorbidities. In the UK, these patients are cared for in secondary care for 2 years before discharge to primary care. Failure to reintroduce these medications after the first 2 years, i.e. when this is usually required, may have resulted in the under-treatment of cardio-metabolic risk factors. This reluctance may be driven at least in part by medication usage as a criterion for "metabolic success" as defined both by the IDF and ADA and fear that restarting medications would suggest treatment failure. On the contrary, our findings raise the hypothesis that a synergistic approach between surgery and medical therapy may be more effective in achieving optimal control of these risk factors and may translate in better micro and macrovascular outcomes. Ultimately, meeting these targets is far more important than the number of medications used to achieve this.

Our novel and encouraging 5-year data on microvascular complication using *direct* measurements are in line with those published from the SOS study using *indirect* measurements [9] and suggest that albuminuria is more sensitive than retinopathy to the numerous physiological effects of surgery. Particular attention should be paid to those patients whose retinal appearances deteriorate and identify predictive factors.

Limitations of our study include the bias introduced by its retrospective analysis, lack of a control group and missing data on microvascular complications, which reduced our sample size. The main reason for missing data on albuminuria and retinal images was that unfortunately patients often do not attend these appointments on a regular yearly basis. Additional reasons for the rather low optimisation/remission rates were that the long average duration of T2DM before surgery and that patients were not offered procedures like the single anastomosis duodeno–ileal bypass with sleeve gastrectomy and duodenal switch.

In conclusion, although there were sustained improvements in cardio-metabolic risk factors, the proportion of patients achieving IDF criteria for optimisation of the metabolic state at 5 years following obesity surgery was lower than expected. These findings may indicate the need for validated protocols to assist clinicians in managing these patients more aggressively post-operatively to achieve optimum cardio-metabolic risk factor control and reduction in microvascular and macrovascular complications.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval Ethical permission was obtained from the Imperial College Healthcare NHS Trust Clinical Governance and Patient Safety Committee reference: 09/808.

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