Title: Short term impact of Roux-en-Y Gastric bypass surgery on Best Corrected Visual Acuity and Diabetic Retinopathy progression.

BRIEF Communication

Word count: 1109

References: 10

Figures: 3

BRIEF ABSTRACT

The immediate impact of rapid glucose lowering induced by bariatric surgery on diabetic retinopathy (DR) progression remains unclear. We present 3-year changes in the Best-Corrected Visual Acuity and DR grade in a retrospective observational study of 32 morbidly obese patients (64 eyes) who underwent Roux-en-Y-gastric bypass surgery. We found that despite overall benefits in vision, there was an initial progression from no retinopathy to background retinopathy in 18.9% and 21.7% at year 1 and 2 respectively. Patients with pre-proliferative DR at baseline were at increased risk of developing sight-threatening DR. We recommend that patients with diabetes undergoing bariatric surgery have a baseline visual acuity, macular Optical Coherent Tomography and diabetic retinopathy grading from wide-field digital imaging to identify those at risk of sight-threatening diabetic retinopathy.

Introduction

Bariatric surgery is recognised as an effective treatment for achieving significant weight loss and in inducing significant and rapid improvement in glycaemic control with, in some cases, remission of type 2 diabetes (T2D) [1]. The UK National Institute of Clinical Excellence (NICE) has recommended bariatric surgery as a treatment option for obese patients with T2D with a Body Mass Index of >35kg/m^2 and/or who are refractory to other weight-loss management options [2]. There are concerns regarding the acute impact of rapid glucose lowering induced by bariatric surgery on diabetic retinopathy (DR) progression, with some studies showing a paradoxical worsening of DR [3], no effect [4] or an improvement in DR [5]. Rapid and marked reductions in HbA1c, as a result of improved glycaemic control initiated during pregnancy or intensified insulin treatment, have previously been associated with a transitory worsening of DR [6].

To observe the impact of bariatric surgery on Best-Corrected Visual Acuity (BCVA) and DR grade, we present the results of a 3 year retrospective observational study of 32 morbidly obese patients (64 eyes) with T2D following Roux-en-Y-gastric bypass (RYGB) surgery at Derby Teaching Hospitals, a regional centre for bariatric surgery.

Methods All patients were registered with the Derbyshire Diabetic Retinopathy Screening programme and had given their informed consent for anonymised data to be used in audit and research. This consecutive series of 32 patients with T2D who underwent RYGB bariatric surgery in a single tertiary bariatric centre, had data collected retrospectively from the DRSS or diabetic retinopathy clinic notes at baseline, 12, 24 and 36 months post-surgery; specifically the LogMAR (logarithmic Minimum Angle of Resolution) BCVA and English Diabetic Eye Screening Programme grades of diabetic retinopathy based on 3, 50^o digital images. No diabetic retinopathy is termed R0, background diabetic retinopathy R1, pre-proliferative diabetic retinopathy R2, and stable or active proliferative diabetic retinopathy

termed R3s or R3a respectively. The presence or absence of diabetic maculopathy is termed M1 or M0 respectively. Descriptive analysis used the number of eyes and the un-paired 't'-test (Graphpad) was performed to compare means of BCVA, using patient numbers, not eyes.

Results

At baseline (Figure 1), R0 was present in 47 eyes (73.4%), 13 (20.2%) had R1, 3 (4.8%) had R2 and 1 (1.6%) had R3s. Of those with R0 at baseline, 9 (18.9%) had progressed to R1 at 12 months and 10 (21.7%) at both 24 and 36 months. Of those with R1 at baseline, 2 (15%) had regressed to R0 at 12 months, 11 (52%) at 36 months, with none developing R2 or worse. All eyes with R2 at baseline progressed to R3a within 2 years. At 36 months there was a net regression of diabetic retinopathy in most eyes with R0 present in 48 eyes (75%), R1 in 12 (18.6%), and 4 (6.4%) with active or stable R3.

The mean LogMAR BCVA at baseline was 0.18 in patients with R0. Those who did not develop any diabetic retinopathy had a significant improvement in mean BCVA when compared to baseline, being 0.13 at 12 months and 0.04 at both 24 and 36 months ($p>0.001$). Those with R0 at baseline who progressed to R1 at 12 months also had an initial improvement in the mean BCVA, being 0.08 at 12 months and 0.09 at 24 months but had deteriorated to 0.22 at 36 months which was significantly worse when compared to baseline ($p=0.001$, Figure 2). In patients with diabetic maculopathy at baseline the mean BCVA was 0.39 and 0.16 in those with no maculopathy but the mean BCVA in maculopathy patients improved so that there were no significant differences between groups at years 1,2 or 3 (figure 3).

Discussion

The beneficial effect of intensive glycaemic control on microvascular outcomes in the long term is well described. Optimization of glycaemic control remains the cornerstone of diabetes management and the prevention of microvascular complications such as DR. Our observation

is consistent with previous studies which have reported a greater risk of worsening of diabetic retinopathy as a result of rapid intensification of glucose control. Importantly, our present study employed a more sensitive assessment method of visual outcome by incorporating BCVA assessment with graded retinal imaging to chart the progression of DR.

While progression of DR observed in this study may be a manifestation of an "early worsening" phenomenon attributable to a large and rapid reduction in HbA1c, the long term benefits of improved glycaemic control may have overcome any short-term negative impact on DR outcomes as shown by a net regression to R0 and better mean BCVA at 3 years. However, the progression from R2 at baseline to R3a indicates that more severe levels of retinopathy at baseline may require closer observation and intervention. More recently, The SUSTAIN-6 clinical trial programme evaluated the efficacy and safety of semaglutide, a glucagon-like peptide-1 analogue, for the treatment of T2D. It reported that despite a significant reduction in HbA1c and weight loss, semaglutide was associated with a significant increase in the risk of DR complications vs placebo [7]. Post hoc analyses however revealed that the majority of the effect of DR progression with semaglutide vs placebo in this study may be attributed to the magnitude and rapidity of HbA1c reduction during the first 16 weeks of treatment in patients who had pre-existing DR and poor glycaemic control at baseline, and who were treated with insulin [8]. This concept is not dissimilar to other conventional agents which cause abrupt glycaemic improvement such as insulin which already have warnings in their prescribing information about the potential association with temporary worsening of DR. For example, in the insulin glargine clinical development programme, more frequent DR progression was reported with insulin glargine vs NPH insulin in patients with T2D [9]. However, a subsequent 5-year DR trial, employing a 7-field Early Treatment Diabetic

Retinopathy Study fundus photographic assessment, showed no detrimental effect with insulin glargine vs NPH on the long-term progression of DR [10].

In summary, although we found overall benefits in vision and retinopathy grade following bariatric surgery, our study showed that those who develop diabetic retinopathy or whose diabetic retinopathy progresses following bariatric surgery are at increased risk of developing sight-threatening diabetic retinopathy. Patients with R2 at baseline are specifically at risk of DR progression. We would recommend all patients with diabetes undergoing bariatric surgery have baseline visual acuity, macular Optical Coherent Tomography and grading of diabetic retinopathy from wide-field digital images to identify those at risk of progression to sight-threatening diabetic retinopathy. This group would require closer monitoring and intervention for up to 3 years. A prospective observational study would clarify the risk of development or progression of diabetic retinopathy following bariatric surgery in morbidly obese patients with type 2 diabetes.

STATEMENTS

a. A Conflict of Interest Statement:

Author 1 - "no conflict of interest."

Author 2- "no conflict of interest."

Author 3 - "no conflict of interest."

b. A Statement of Informed Consent (when reporting studies that involve human participants):

Not applicable. This was a retrospective evaluation of routine clinical practice. For this type of study formal consent is not required.

c. A Statement of Human and Animal Rights:

This was a retrospective evaluation of routine clinical practice. For this type of study formal consent is not required. Data collection was performed in accordance with the ethical standards of the Derby Teaching Hospital NHS trust

References.

1 Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 2009; 122(3): 248–256. e5

2 National Institute For Health and Clinical Excellence (NICE). Obesity: identification, assessment and management (CG189). 2014. Available from https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925. accessed 10 June 2018.

3 Murphy R, Jiang Y, Booth M, Babor R, MacCormick A, Hammodat H et al. Progression of diabetic retinopathy after bariatric surgery. Diabet Med 2015; 32(9): 1212–1220

4 Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Bariatric surgery and diabetic retinopathy: a systematic review and meta-analysis of controlled clinical studies. *Obes Rev* 2017; **18**: 309–316.

5 Coleman KJ, Haneuse S, Johnson E, Bogart A, Fisher D, O'Connor PJ *et al*. Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: evidence for the legacy effect of surgery. *Diabetes Care* 2016; **39**: 1400–1407

6 Feldman-Billard S, Larger É, Massin P; Standards for screening and surveillance of ocular complications in people with diabetes SFD study group. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab. 2018; 44:4-14.

7 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844

8 Vilsboll T, Bain SC, Leiter LA et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab. 2018; 20:889-897.

9 Davis MD, Beck RW, Home PD, Sandow J, Ferris FL. Early retinopathy progression in four randomized trials comparing insulin glargine and NPH [corrected] insulin. Exp Clin Endocrinol Diabetes. 2007;115(4):240-243. [PubMed]

10. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Diabetologia. 2009;52(9):1778-1788

Figure legends

Figure 1

The percentage of eyes with retinopathy grades following bariatric surgery showing a net progression from R0 to R1 in years 1 and 2, with regression back to R0 by year 3. All R2 patients progressed to R3 by year 2. Abbreviations: PRE-OP, pre-operative; YR1, 1year post-surgery; YR2, 2 years post-surgery; YR3, 3 years post-surgery; R0, no diabetic retinopathy; R1, background diabetic retinopathy; R2, pre-proliferative diabetic retinopathy; R3, active or stable proliferative diabetic retinopathy

Figure 2

The mean BCVA in those remaining at R0 was significantly improved compared to baseline at 12*, 24# and 36# months. In those who progressed to R1, the mean BCVA was improved at 12# and 24# months from baseline but was significantly worse at 36# months (unpaired 't'-test with 32 patients, not 64 eyes, * p= 0.007, # p= 0.0001). Abbreviations: LogMAR BCVA, logarithmic minimum angle of resolution best-corrected visual acuity; R0, no diabetic retinopathy; R1, background diabetic retinopathy.

Figure 3

At baseline the mean BCVA in patients with maculopathy was reduced compared to those without maculopathy, but at all post-operative visits there was no significant difference between those with or without maculopathy. Abbreviations: LogMAR BCVA, logarithmic minimum angle of resolution best-corrected visual acuity; M0, no diabetic maculopathy; M1, diabetic maculopathy**.**

Figure 1

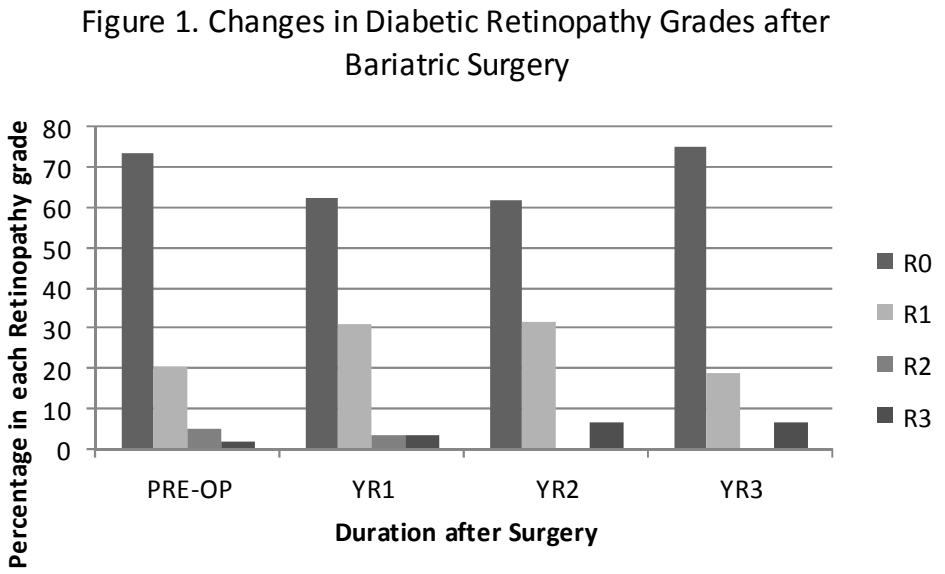
Figure 1. Changes in Diabetic Retinopathy Grades after Bariatric Surgery
Percentage in each Retinopathy grade
80
70
60
50
40
30
20
10
0
PRE-OP
YR1
YR2
YR3
Duration after Surgery
R0
R1
R2
R3

Figure 2

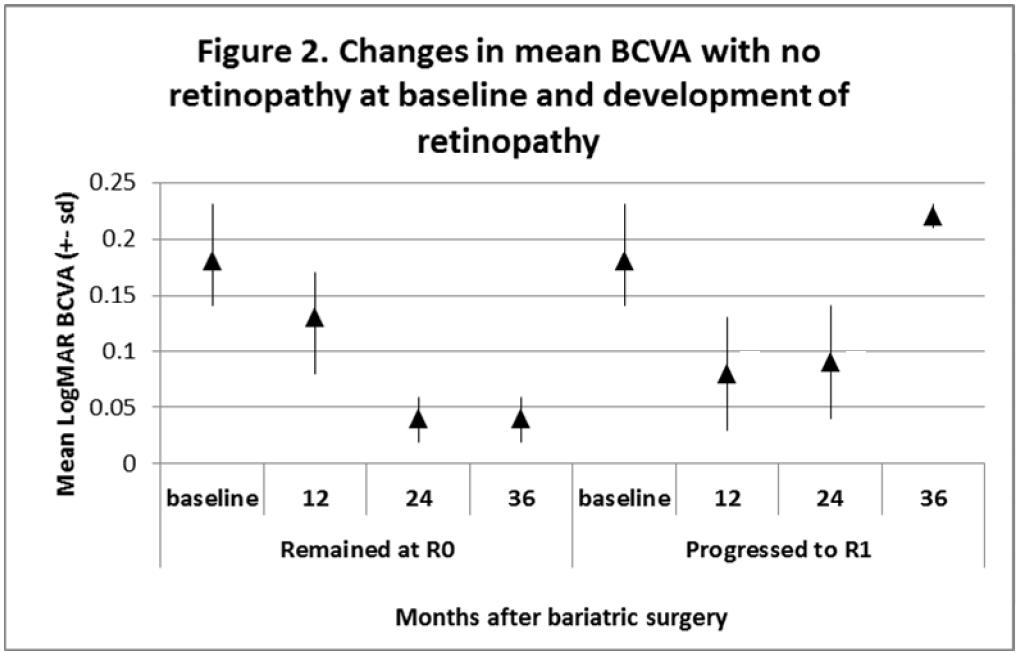
Figure 2. Changes in mean BCVA with no retinopathy at baseline and development of retinopathy
Mean LogMAR BCVA (+- sd)
0.25
0.2
0.15
0.1
0.05
0
baseline
12
24
36
baseline
12
24
36
Remained at R0
Progressed to R1
Months after bariatric surgery

Figure 3

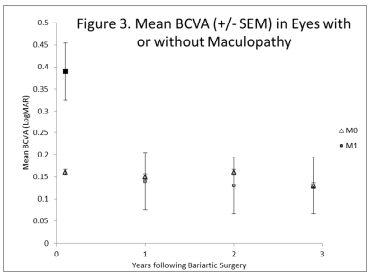
Figure 3. Mean BCVA (+/- SEM) in Eyes with or without Maculopathy
Mean 3CVA (LogMAR)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
1
2
3
Years following Dariartic Surgery
△ M0
▪ M1