Obesity Treatment/Obesity Comorbidity

Bariatric surgery and diabetic retinopathy: a systematic review and meta-analysis of controlled clinical studies

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Summary

Background: Uncontrolled studies have indicated appearance or progression of diabetic retinopathy in obese diabetic patients after bariatric surgery. The aim of this systematic review and meta-analysis was to compare the rate of appearance, as well as progression or regression of diabetic retinopathy in studies comparing medical and surgical treatment of obese type 2 diabetes.

Methods and findings: Intervention effect (new cases of retinopathy, and cases with any change of diabetic retinopathy score) was expressed as odds ratio (OR), with 95% confidence intervals (CIs); change of diabetic retinopathy score was expressed as standardized mean difference (SMD), with 95% CIs. Meta-analyses were performed by a random-effects model according to DerSimonian and Laird. Heterogeneity was assessed through Q and I2 statistics for each comparison, and potential sources of heterogeneity were discussed where appropriate. Appropriate methodology [preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement] was used. Seven studies were analyzed, and incident cases of retinopathy were fewer with bariatric surgery than with medical treatment; change of retinopathy score (three studies) was not different, while only two studies were available on numbers of patients showing progression or regression of retinopathy. Heterogeneity was not significant, and publication bias was not present.

Conclusions: Bariatric surgery seems to prevent new cases of diabetic retinopathy, but available studies are not sufficient to support progression or regression of retinopathy. Further studies are needed to draw firm conclusions on the effect of bariatric surgery on diabetic retinopathy.

Keywords: Diabetic retinopathy, bariatric surgery, meta-analysis, diabetes.

Introduction

Bariatric surgery has shown a great superiority to medical treatment in inducing remission of type 2 diabetes in morbidly obese patients (1,2), even though the basic abnormalities of beta cell function are not normalized (3–6). In addition, bariatric surgery has been shown to improve life expectancy (7), to reduce the development of cardiovascular disease (8) and to ameliorate kidney function in obese and in obese-diabetic patients (9,10).

Lesser attention has been paid to the development of diabetic retinopathy. A few uncontrolled studies, with conflicting results, have described retinopathy after bariatric surgery; some studies suggested that bariatric surgery can induce progression/deterioration of retinopathy, others suggested the opposite (11–20). A recent meta-analysis was based on consecutive obese diabetic patients undergoing bariatric surgery, in the absence of obese diabetic controls receiving medical treatment, concluding that progression of retinopathy was greater in patients with retinopathy at baseline than in patients without retinopathy at baseline (21). This meta-analysis was criticized by some of us because of its design and of its conclusions (22).

A few studies, appearing later on, included patients undergoing bariatric surgery and control patients receiving traditional medical treatment; these studies failed to show...
a significant risk of retinopathy in bariatric surgery patients versus controls (23–31).

The aim of this systematic review was to compare the impact of bariatric surgery on diabetic retinopathy, through evaluation of controlled studies including both bariatric surgery and standard medical treatment.

Materials and methods

Search strategy

Eligible studies were trials reporting appearance or deterioration/improvement of diabetic retinopathy in patients undergoing bariatric surgery in comparison with patients undergoing medical treatment. Only full reports, published in any language, were considered. Measures of effect of treatment were, in the whole sample and within each group of patients, the differences in appearance of diabetic retinopathy and in the change of score of diabetic retinopathy. Retrieval of studies was based on The Cochrane Library, MEDLINE and EMBASE (up to March 2016) using the terms diabetes mellitus, diabetic retinopathy, retina, retinopathy, surgery, bariatric surgery (laparoscopic adjustable gastric banding, gastric bypass, sleeve gastrectomy, biliopancreatic diversion, biliointestinal bypass) and obesity. A manual search was also performed on reference lists from articles, reviews, editorials and proceedings of international congresses. When results of one study were reported in more publications, only the most recent and complete data were considered. Additional contacts were attempted by mail to yield more details, and the authors of two publications (26,31) responded in a helpful manner, while other authors did not respond (23,25,29). Decisions on trials to include were taken unblindly by the authors (AEP, VC, CM and AM). Disagreements were resolved by discussion. Excluded trials were identified with the reason for exclusion (lack of controls). Seven studies fulfilled the inclusion criteria (23,24,26–28,30,31), all published as full reports (Table 1 shows details of the seven studies included in meta-analysis). The protocol of the meta-analysis has been registered (Prospero).

Data extraction

Data concerning trials, patient characteristics and treatment outcomes were abstracted by authors (AEP, VC, CM), and discrepancies were resolved by discussion. In two studies there were more than one arm, as more than one treatment was applied; in such cases, data were pooled (24,27). In some studies, not all items under evaluation were appropriately reported with measure of dispersion; therefore, meta-analysis was possible only for selected items. Retinopathy score was derived from published studies, and it was universally standardized as 0 = no retinopathy; 1 = background retinopathy; 2 = pre-proliferative retinopathy; 3 = proliferative retinopathy. The two methods used for assessment of diabetic retinopathy score were the International Clinical Diabetic Retinopathy Severity Scale (32), and the National Screening Committee Classification (33). The two methods are detailed in the Supplemental Appendix (Supplemental Table 1). Fundoscopy was employed in three studies, and retinal photography was used in three studies; the same technique was used at baseline and at follow-up. In one study (23), administrative data and vital records were used, and new diagnosis of blindness, laser eye or retinal surgery were considered as markers of incident cases of diabetic retinopathy. Quality of reports and risk-of-bias were assessed according to RoBANS (34), that is, risk of bias linked to selection of participants, confounding variables, performance, detection and measurement of exposure, attrition and reporting biases. A score was eventually built, indicating 0 = no risk, 1 = low risk, 2 = unclear risk and 3 = high risk, based on the number of the above criteria available for each paper. Appropriate methodology according to the preferred reporting items

<table>
<thead>
<tr>
<th>ref</th>
<th>Author (year)</th>
<th>study</th>
<th>f-u (years)</th>
<th>Intervention</th>
<th>BS (n)</th>
<th>C (n)</th>
<th>Age (y) BS</th>
<th>Age (y) C</th>
<th>BMI, body mass index (kg/m²); BPD, biliopancreatic diversion; BS, bariatric surgery; C, controls; CCS, case-control study; DM, diabetes mellitus; f-u, follow-up; GB, gastric banding; nd, not reported; RCS, retrospective cohort study; RCT, randomized controlled trial; RYGB, Roux en Y gastric bypass; SG, sleeve gastrectomy. Retinopathy Score: ICDRSS = International Clinical Diabetic Retinopathy Severity Scale (32); NSC = National Screening Committee Classification (33).</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Johnson (2013)</td>
<td>RCS</td>
<td>1.6 ± 0.5</td>
<td>GB/RYGB/SG/BPD</td>
<td>2,580</td>
<td>13,371</td>
<td>47.5 ± 10.6</td>
<td>52.1 ± 12.8</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Schauer (2014)</td>
<td>RCT</td>
<td>3.0 ± 0.0</td>
<td>RYGB + SG</td>
<td>97</td>
<td>40</td>
<td>47.9 ± 8.3</td>
<td>50.3 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Banks (2015)</td>
<td>CCS</td>
<td>2.0 ± 0.0</td>
<td>RYGB</td>
<td>21</td>
<td>24</td>
<td>54.4 ± 6.9</td>
<td>68.0 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Mingrone (2015)</td>
<td>RCT</td>
<td>5.0 ± 0.0</td>
<td>RYGB + BPD</td>
<td>40</td>
<td>20</td>
<td>43.0 ± 7.8</td>
<td>43.5 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Miras (2015)</td>
<td>CCS</td>
<td>1.0 ± 0.0</td>
<td>RYGB</td>
<td>56</td>
<td>21</td>
<td>50.7 ± 1.0</td>
<td>52.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Zakaria (2016)</td>
<td>RCS</td>
<td>13.8 ± 2.0</td>
<td>GB</td>
<td>20</td>
<td>36</td>
<td>44.7 ± 9.5</td>
<td>55.6 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Amin (2016)</td>
<td>RCS</td>
<td>3.0 ± 1.9</td>
<td>GB/RYGB/SG</td>
<td>152</td>
<td>155</td>
<td>50.7 ± 8.2</td>
<td>50.8 ± 8.8</td>
<td></td>
</tr>
</tbody>
</table>
for systematic reviews and meta-analyses (PRISMA) statement (35) was adhered to.

**Statistical methods**

Intervention effect (new cases of retinopathy) was expressed as odds ratio (OR), with 95% confidence intervals (CIs); change of score of diabetic retinopathy was analysed in patients with retinopathy at baseline, and expressed as standardized mean difference (SMD), with 95% CIs: next, patients with deterioration and improvement of retinopathy score (any deterioration or any improvement) was expressed as OR, with 95% CIs; all meta-analyses were performed by a random-effects model according to DerSimonian and Laird (36). Heterogeneity was assessed through Q and I2 statistics for each comparison, and potential sources of heterogeneity were discussed where appropriate (37). A p value <0.05 was considered indicative of statistically significant heterogeneity. We also explored, through a meta-regression analysis, the potential effect of several patients or study characteristics on incidence of new cases of retinopathy, on change of score and on numbers of patients with any deterioration or improvement of retinopathy score. This was performed independently of statistically significant heterogeneity. The dependent variable was either incidence of new cases of retinopathy or change of score for any deterioration or improvement of retinopathy score. This was performed independently of statistically significant heterogeneity. The dependent variable was either incidence of new cases of retinopathy, or change of score for any deterioration or improvement of retinopathy score from each study. The role of each covariate in heterogeneity was expressed by Wald test estimated by the meta-regression. The following covariates were included in the meta-regression analysis: number of patients enrolled, age, kind of study (prospective or retrospective), RoBANS score, duration of diabetes, duration of follow-up, body mass index (BMI) of each study (weighted means of intervention and control patients), amount of weight lost and efficacy of treatment (vs. controls) in each study. Meta-regression was performed considering all studies together. In a secondary analysis, we also evaluated the existence of a potential publication bias, defined as the tendency of authors and editors to handle studies in which the experimental results achieved statistical significance more favourably than in studies in which the results failed to reach significance, which would ultimately introduce bias into the overall published literature (38). Funnel-plot asymmetry was evaluated by using the Egger’s test for small study effects through the metabias routine (38). All statistical analyses were performed by Stata 12 (Stata Corporation, College Station, TX, USA) for MacIntosh (Fig. 1).

**Results**

Table 2 shows that both bariatric surgery and medical treatment were able to improve HbA1c and systolic and diastolic blood pressure; BMI decreased significantly with bariatric surgery, not with medical treatment. Drop-out of patients was reported in the studies (23,24,27,28,31), not in other studies (26,30); the drop-out rate varied between 2.38% (23) and 11.7% (27), with an average rate around 5%.

Figure 2A shows that incident new cases of retinopathy were fewer with bariatric surgery than with medical treatment; the study by Johnson et al. (23) was responsible for this difference, although a similar trend was observed for all other studies, except for the study by Schauer et al. (24). In contrast, Fig. 2B shows that change of retinopathy score could be analyzed in only four studies (one of which excluded), and was not different with bariatric surgery and with medical treatment. Other meta-analyses (number of patients with any deterioration or of patients with any improvement of retinopathy score) could not be performed because made of two studies each (details in Supplemental Appendix). Presence of maculopathy and evaluation of sight-threatening-diabetic-retinopathy (STDR) appeared in only one study (31). Heterogeneity was not statistically significant. At meta-regression analysis, none of the independent variables explored was associated with any of the outcomes. Details of risk-of-bias are shown in the Supplemental Appendix.

No publication bias was present for the number of patients with incident cases of retinopathy, nor for the change of retinopathy score (details in Supplemental Appendix).
No significant correlation was found between change of BMI, HbA1c, systolic and diastolic blood pressure (on one side) and new cases of retinopathy, and change of retinopathy score (not shown). No difference whatsoever was observed when considering different surgical approaches (not shown).

**Table 2** Details of the patients in studies considered in this meta-analysis. Means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Bariatric surgery at baseline</th>
<th>Bariatric surgery at follow-up</th>
<th>Control treatment at baseline</th>
<th>Control treatment at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>2,966</td>
<td></td>
<td>13,685</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.4 ± 3.88 *</td>
<td></td>
<td>53.2 ± 7.41</td>
<td></td>
</tr>
<tr>
<td>Duration of DM (y)</td>
<td>6.7 ± 3.02</td>
<td></td>
<td>9.3 ± 5.43</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.8 ± 4.81</td>
<td>34.4 ± 5.08 *</td>
<td>37.6 ± 5.23</td>
<td>39.1 ± 3.53</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 ± 3.2</td>
<td>7.0 ± 3.1 *</td>
<td>8.4 ± 2.5</td>
<td>7.9 ± 2.9 *</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>68.0 ± 11.69</td>
<td>52.7 ± 10.69 *</td>
<td>68.3 ± 4.18</td>
<td>62.6 ± 7.98 *</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140.2 ± 7.91</td>
<td>131.6 ± 1.39 *</td>
<td>143.2 ± 9.87</td>
<td>136.1 ± 4.28 *</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85.7 ± 5.57</td>
<td>79.3 ± 1.83 *</td>
<td>85.3 ± 8.04</td>
<td>79.1 ± 3.69 *</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin.

*Significantly different from baseline ($p < 0.05$ or less).
*Significantly different from controls ($p < 0.05$).
Discussion

With bariatric surgery, a new concept arose, that is remission/resolution of type 2 diabetes; several studies have indicated that resolution of diabetes is frequent with bariatric surgery, in a manner proportional to the decrease of body weight (39,40), more than with traditional or intensified medical treatment (1,2), even though the basic abnormalities of beta cell function are not normalized (3–6). In addition, bariatric surgery reduces the development of cardiovascular disease (8) and improves life expectancy, with similar efficacy between different surgical approaches (7), and with similar efficacy in diabetic and non-diabetic patients (41).

Less studied is the possible role in the prevention of retinopathy; uncontrolled studies on consecutive patients undergoing bariatric surgery yielded conflicting results, suggesting that retinopathy could improve, deteriorate or be stable after bariatric surgery (11–20). Recent controlled studies, coming from retrospective or prospective studies, were the basis for this meta-analysis (23,24,26–28,30,31). We see that new cases of retinopathy are fewer after bariatric surgery than after medical treatment; however, no effect was seen on progression–regression of retinopathy, considered as change of retinopathy score. This agrees with what was suggested by Varadhan et al. (11), that, if any, bariatric surgery prevents new cases of retinopathy.
Bariatric surgery is the most effective preventive measure for development of type 2 diabetes (42); when diabetes and retinopathy are present, acute improvement of metabolic control can be dangerous for retinopathy, at least in the short run, as indicated by intervention trials aimed at normalization of metabolic control (43), or by the use of GLP-1 agonists (44), at least temporarily. These adverse events might somehow counteract the benefits induced by weight loss, masking the effects on retinopathy. With bariatric surgery, improvement of metabolic control can be acute with some surgical procedures (biliopancreatic diversion and gastric bypass), slower with gastric banding; in addition, low-calorie diet usually precedes surgery, and this can acutely improve metabolic control per se. However, a recent retrospective study in a large cohort of obese diabetic patients undergoing bariatric surgery has shown that the incidence of new cases of retinopathy is lower in patients experiencing remission of diabetes than in patients with persisting diabetes; in addition, the different incidence is proportional to the duration of remission (45), suggesting the existence of a beneficial legacy effect of bariatric surgery on retinopathy.

This study has limitations. The first limitation is that studies were few, some of retrospective nature and the main study showing prevention of new cases was of retrospective nature. Even though kind of study (retrospective vs. prospective), quality of studies at RoBANS score and duration of follow-up were not associated with any of the outcomes at meta-regression, caution is needed in interpretation of data. Given the low incidence of new cases of retinopathy (0.7% with bariatric surgery vs. 1.01% with medical treatment during the entire follow-up period), a large single study of long duration would be necessary to detect a significant difference in the appearance of new cases of retinopathy between bariatric surgery and medical treatment. This view is supported by data recently presented in poster format (46). An additional limitation is that there were too few cases to show meaningful differences between different surgical approaches, and the follow-up period was in general short, 1 to 5 years, with the exception of the study by Zakaria et al. (30). Drop-outs were not frequent, but drop-outs, together with short duration of studies, might have hidden other cases of retinopathy, and we cannot exclude that additional cases of retinopathy might become evident with longer follow-ups. Age of bariatric surgery patients was younger than in controls, while duration of diabetes was not different; even though these co-variates were not statistically significant at meta-regression, caution is required before excluding these potential confounding factors. Also, data on retinopathy score and on patients with any change of retinopathy score were limited, so that no conclusion is possible. Even though this meta-analysis was based on the incidence of new cases of retinopathy and on changes of diabetic retinopathy score, one should remember that what really affects patients is the development of STDR; a move from no retinopathy to background disease is far less important than moving to a proliferative disease. Also, most of STDR comes from maculopathy rather than retinopathy. Unfortunately, only one study described these two aspects of retinopathy [31]. Finally, management of diabetes after surgery was looked at in only a few studies (24,27,28,30,31).

In conclusion, available data coming from controlled studies indicate that bariatric surgery prevents new incident cases of retinopathy, but available studies are not sufficient to support progression or regression of retinopathy. Because of the multiple limitations of the studies included in this meta-analysis, we need further studies to draw firm conclusions on the effect of bariatric surgery on diabetic retinopathy. In addition, strict ophthalmological follow-up of diabetic patients undergoing bariatric surgery seems to be mandatory, even because it can help in screening hazards linked to bariatric surgery (47).

Conflict of interest statement

The authors have no conflict of interest with the contents of this manuscript. CM, VC and AEP researched data and wrote manuscript; AM performed statistical analysis and contributed to discussion; AEP, CM, VC and AM reviewed/edited manuscript.

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Transparency declaration

Antonio E. Pontiroli (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12490

References


