

The Effect of Bariatric Surgery on Diabetic Retinopathy: Good, Bad, or Both?

Dora M. Gorman¹, Carel W. le Roux^{1,2,3}, Neil G. Docherty^{1,2}

¹Diabetes Complications Research Centre, Conway Institute of Biomolecular and Biomedical Research, University College Dublin School of Medicine and Medical Sciences, Dublin, Ireland,

²Department of Gastrointestinal Research and Education, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden,

³Investigative Science, Imperial College London, London, UK

Bariatric surgery, initially intended as a weight-loss procedure, is superior to standard lifestyle intervention and pharmacological therapy for type 2 diabetes in obese individuals. Intensive medical management of hyperglycemia is associated with improved microvascular outcomes. Whether or not the reduction in hyperglycemia observed after bariatric surgery translates to improved microvascular outcomes is yet to be determined. There is substantial heterogeneity in the data relating to the impact of bariatric surgery on diabetic retinopathy (DR), the most common microvascular complication of diabetes. This review aims to collate the recent data on retinal outcomes after bariatric surgery. This comprehensive evaluation revealed that the majority of DR cases remain stable after surgery. However, risk of progression of pre-existing DR and the development of new DR is not eliminated by surgery. Instances of regression of DR are also noted. Potential risk factors for deterioration include severity of DR at the time of surgery and the magnitude of glycated hemoglobin reduction. Concerns also exist over the detrimental effects of postprandial hypoglycemia after surgery. *In vivo* studies evaluating the chronology of DR development and the impact of bariatric surgery could provide clarity on the situation. For now, however, the effect of bariatric surgery on DR remains inconclusive.

Keywords: Bariatric surgery; Diabetes mellitus; Diabetic retinopathy; Microvascular complications; Obesity

INTRODUCTION

This article aims to comprehensively review the impact of bariatric surgery on diabetic retinopathy (DR), a microvascular complication of type 2 diabetes mellitus (T2DM). Initially, an overview of epidemiology, classification, and pathogenesis of DR is presented. The relative benefits of medical and surgical treatment on glycemic control in T2DM are then briefly discussed. Following on from this the impact of medical management of hyperglycemia on DR is discussed, highlighting concerns about the effect of rapid reductions in blood glucose levels. Finally, the current evidence relating to the impact of bariatric surgery on DR in both the short- and long-term is discussed in detail.

DIABETIC RETINOPATHY-EPIDEMIOLOGY AND CLASSIFICATION

DR is the most common microvascular complication of T2DM worldwide and the leading cause of visual impairment among adults aged 20 to 74, with approximately 93 million people currently living with DR [1,2]. According to data from the United Kingdom Prospective Diabetes Study (UKPDS), 37% of patients with T2DM have evidence of retinopathy at the time of diagnosis [3]. After two decades of disease, >60% of patients with T2DM are expected to have some degree of retinopathy [4]. The principal risk factors for DR are degree and duration of hyperglycemia and the presence of comorbid hypertension with or without dyslipidemia [2]. DR is classified as

Corresponding author: Neil G. Docherty  <http://orcid.org/0000-0002-0961-2607>
Diabetes Complications Research Centre, Conway Institute of Biomolecular and Biomedical Research, University College Dublin School of Medicine and Medical Sciences, Belfield, Dublin 4, Ireland
E-mail: neil.docherty@ucd.ie

Received: Jun. 15, 2016; Accepted: Aug. 1, 2016

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) disease with reference to events occurring in the retinal capillary bed. DR is usually assessed using fundoscopic examination of a dilated pupil and retinal images can be recorded for future evaluation. Clinical evaluation in most centers is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) grading scheme [5].

A SUMMARY OF PATHOGENIC MECHANISMS

Early DR is usually asymptomatic but this belies structural and functional changes in the capillaries and supporting pericytes, which cause microvessel aneurysm, occlusion and leakiness and the onset of hypoxic injury. Pericytes are perivascular contractile cells that aid in the stabilization and maturation of endothelial cells. Pericyte loss is a hallmark of early DR and typically precedes endothelial cell loss [6]. Hypoxic stimuli trigger the formation of abnormally branched or dilated retinal vessels termed intraretinal microvascular abnormalities (IRMAs) in NPDR, and neovascularization in PDR [7]. Typically, neovascularization arises at the junction of nonperfused vessels and leaky vessels and at the optic disk, and can spread through the inner limiting membrane into the vitreous humor. These vessels exhibit increased permeability, raising the risk of vascular leakage and vitreous haemorrhage. Vessel permeability can result in diabetic macular edema (DME). DME, present in up to 25% of people with diabetes, presents with progressive impairment of visual acuity [8]. A fibrous component develops with neovascularization, increasing the risk of tractional retinal detachment [8]. Lipid deposition at the edges of small haemorrhages creates hard exudates, which contribute to microcystoid degeneration of the retina [9].

Microvascular injury and neurodegenerative effects of hyperglycemia are considered to be central events in the development of DR in cases of chronically poor control of T2DM [10,11]. Hyperglycemia accelerates advanced glycation end products (AGE) formation. AGEs cross-link with proteins in the extracellular matrix, decreasing protein removal and enhancing deposition [12]. Activation of the AGE receptor results in the release of proinflammatory cytokines and growth factors, increased oxidative stress, procoagulant activity on endothelial cells and macrophages, proliferation of vascular smooth muscle cells and increased extracellular matrix synthesis [10]. Activation of the protein kinase C pathway leads to the

upregulation of vascular endothelial growth factor [13] and increased production of profibrogenic molecules involved in basement membrane synthesis. Cellular sorbitol accumulation increases osmotic stress, contributing to vascular damage [14]. Nicotinamide adenine dinucleotide phosphate consumption in the polyol pathway increases the susceptibility of cells to oxidative stress [1]. During hyperglycemia excess glycolytic fructose-6-phosphate is directed through the overflow hexosamine biosynthesis pathway, the end product of which causes aberrant posttranslational modification of cytosolic and nucleic proteins. This results in the increased expression of transforming growth factor β 1 and plasminogen activator inhibitor-1, adversely affecting endothelial cells [15]. Progressive microvascular injury promotes inflammation in the retina involving microglial activation and macrophage infiltration into the neural retina [8].

The constellation of pathogenic effects of hyperglycemia in the retina may be ameliorated by intensified therapies for T2DM. The relative impact of intensive medical and surgical interventions on control of diabetes and DR is described below.

CONTROL OF T2DM-RELATIVE EFFICACY OF MEDICAL AND SURGICAL APPROACHES

Medical management has traditionally been the mainstay of T2DM treatment. However bariatric surgery, originally intended as a weight-loss procedure for very severely obese individuals (body mass index [BMI] >40 kg/m²), has beneficial effects on glycemic control in obese patients with T2DM [16-18]. Typically, successful bariatric surgery results in a $>30\%$ reduction in total body weight within 1 year, making it the most effective treatment for weight loss [19].

Several randomized controlled trials (RCTs) and large case control, studies have additionally shown that bariatric procedures are superior to standard lifestyle intervention and pharmacological therapy for treatment of T2DM in obese patients [16-18,20-22]. Though these effects are not permanent, they are long lasting and when relapse occurs, good metabolic control can be achieved with relatively low intensity medical interventions.

MEDICAL MANAGEMENT: LONG-TERM EFFECTS ON DIABETIC RETINOPATHY

Several studies comparing the effect of intensified glycemic

Table 1. Major studies comparing intensive medical management to conventional medical management of type 2 diabetes mellitus and the associated DR outcomes

Study	No.	Follow-up, yr	New onset DR, %	Progression of DR, %
UKPDS [23]	718	12	-	Intensive: 38.6 Conventional: 48.7 (<i>P</i> =0.015)
Kumamoto study [24]	110	8	Intensive: 15.4 Conventional: 47.8 (<i>P</i> =0.022)	Intensive: 24 Conventional: 56 (<i>P</i> =0.023)
ADVANCE [25]	1,241	4	Absolute incidence and progression Intensive: 14 Conventional: 16.2 (<i>P</i> =0.27)	-
ACCORD [26]	2,856	4	-	Intensive: 7.3 Conventional: 10.4 (<i>P</i> =0.003)
VADT [37]	1,791	5.6	Intensive: 42.2 Conventional: 48.9 (<i>P</i> =0.27)	Intensive: 17 Conventional: 22.1 (<i>P</i> =0.07)

DR, diabetic retinopathy; UKPDS, United Kingdom Prospective Diabetes Study; ADVANCE, Action in Diabetes and Vascular Disease Preterax and Diamicon Modified Release Controlled Evaluation; ACCORD, Action to Control Cardiovascular Risk in Diabetes; VADT, Veteran's Administration Diabetes Trial.

control to standard treatment for T2DM have included secondary endpoints that focus on ophthalmic outcomes. These studies are summarized in Table 1. The UKPDS is a large RCT comparing intensive and conventional glycaemic control in patients with newly diagnosed T2DM. After 10 years, the intensive treatment cohort achieved a glycosylated hemoglobin (HbA1c) of 7.0% compared to 7.9% in the conventional treatment group. The risk of progression of retinopathy was reduced by 21% in the intensive treatment group after 12 years (*n*=718). The UKPDS group concluded that for every 1% decrease in HbA1c, the relative risk of developing microvascular complications decreased by 35% [23]. The Kumamoto study is a smaller study comprising of 110 Japanese patients with T2DM. Participants had no DR or mild NPDR at baseline and were randomized to intensive or conventional insulin therapy. After 8 years, this study found that the combined risk reduction for both the development and progression of DR with intensive treatment was 63% [24].

In the Action in Diabetes and Vascular Disease Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) RCT, participants were randomised to an intensive glycaemic control target HbA1c of 47.5 mmol/mol (6.5%) or a standard care target of 53 mmol/mol (7%). At the start of the study the participants had a mean duration of T2DM of 6 years. After 4 years, no significant difference in incidence and

progression of DR was observed between groups (*n*=1,241) [25]. Progression of DR was evaluated in the glycaemic control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (*n*=2,856). Participants had a mean duration of T2DM of 10 years at study entry. Intensive glycaemic control targeted an HbA1c of 42 mmol/mol (6%), lower than other studies. After 4 years, retinopathy progression occurred in 7.3% of the intensive treatment group compared to 10.4% of the standard therapy group [26]. The Veteran's Administration Diabetes Trial (VADT) studied 1,792 patients who had a mean duration of T2DM of 11.5 years. After a mean follow-up of 5.6 years, HbA1c was 8.4% in the standard therapy cohort compared to 6.9% in the intensive therapy cohort. There was a nonsignificant trend suggesting beneficial effect with intensive-therapy as the increase in DR severity was greater in the standard-therapy group (*P*=0.07). However, there were no differences between groups in the incidence of new onset DR or in progression to PDR or clinically relevant DME [27].

MEDICAL MANAGEMENT: CONCERNS OVER RAPID IMPROVEMENT IN HYPERGLYCEMIA

Although overall improvements in glycaemic control are associated with reduced development and progression of DR in the

long-term, initial worsening of DR has been reported as a consequence of rapid improvement of hyperglycemia. Without any change in blood glucose levels, the risk of progression from severe NPDR or early PDR to high-risk severe PDR is approximately 25% over 4 to 6 months. This risk may increase to 50% with intensive glucose-lowering treatment [28].

Initiation of treatment in patients with type 1 diabetes mellitus resulting in a substantial decrease in HbA1c has been associated with the development of severe retinopathy, vitreous haemorrhage or macular edema within 1 year in patients who had little or no retinopathy at baseline [29]. The Diabetes Control and Complications Trial (DCCT) documented the phenomenon of transient, early worsening of DR with intensive glycemic control ($n=1,439$). At 6, 12, and 18 months progression by three steps or more on the ETDRS retinopathy scale was more common with intensive treatment. The 13.1% of the intensive group and 7.6% of the conventional group experienced 'early worsening,' defined as the development of soft exudates, IRMAs, or clinically important retinopathy within the first 12 months. Approximately half of these patients had recovered at the 18-month follow-up. The magnitude of the decrease in HbA1c in the first 6 months of treatment was the most important risk factor for early worsening. Each percentage point drop in HbA1c is associated with a 1.6 times increase risk of early worsening. Severity of retinopathy at baseline is also associated with the risk of worsening [30]. Proposed mechanisms for this phenomenon include a decrease in the availability of nutrient substrate, a reduction in the ability of retinal circulation to autoregulate and also in increase in growth factors [30-34]. Unfortunately, a similar trial has not been conducted in T2DM. However, Henricsson et al. [35] did find a relationship between the degree of HbA1c improvement and deterioration of DR in insulin-treated patients with T2DM ($n=45$) over a 2-year period. This paradoxical deterioration of retinal function with improved glycemic control has also been observed with intensified insulin treatment in pregnancy. The deterioration of background retinopathy correlated with the magnitude of glycemic control [36]. In a retrospective 1 year study of 165 patients treated with glucagon-like peptide-1 (GLP-1) receptor agonist (exenatide), overall 29.7% of patients treated had new or worsening DR while 19.4% of the cohort showed an improvement in pre-existing DR. Interestingly there was a significant difference in DR progression rates between those patients with an improved HbA1c profile (35.3% progression rate) versus those in whom HbA1c profile deteriorated

(6.2% progression rate) [37]. The recently published Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) RCT examined prospectively, with a mean follow-up of 3.8 years, the longer-term effects of treatment with a GLP-1 analogue on DR. This showed no significant impact the incidence of DR (hazard ratio, 1.15; 95% confidence interval, 0.87 to 1.52), despite evidence of a significant reduction in nephropathy [38].

Despite reports of early worsening, the beneficial effects of intensive glycemic control are substantial in the long term. By inference, this apparently contradictory data is suggestive of longer-term adaptation of the retina to lower glycemic levels. In the brain, adaptation to hypoglycemia occurs via up-regulation of glucose transporter 1 (GLUT1), a glucose transporter protein, and it may be speculated that an analogous phenomenon may be implicated in long-term adaptation in the retina [39].

SURGICAL MANAGEMENT OF T2DM AND DR OUTCOMES

Since 2012, data has been emerging on the effect of bariatric surgery on DR. Data was collected following systematic interrogation of PubMed using the following terms: "bariatric surgery," "Roux-en-Y gastric bypass," "gastric bypass," "bilio-pancreatic diversion," "gastric band," "vertical sleeve gastrectomy," and "diabetic retinopathy." This strategy generated 36 results and after removal of duplicates, review articles, anecdotal case reports, and letters, 13 relevant studies remained. These studies are included in the following section and are summarised in Table 2.

SURGICAL MANAGEMENT: SHORT TERM OUTCOMES

Changes in DR are unpredictable following bariatric surgery. Given the reported impact on DR of rapid correction of glycemic control using pharmacological approaches, concerns have been raised about the rapid and substantial decreases in blood glucose levels that occur after bariatric procedures. Concerns also exist about the detrimental effects of episodes of postoperative reactive hypoglycemia [40]. A number of studies investigating the effect of bariatric surgery on retinal outcomes in patients with T2DM and obesity have been carried out. In the Mannheim obesity study ($n=30$) in 2012, the arteriole-to-venule ratio, a marker of retinal inflammation/endothelial dys-

Table 2. Summary of studies reporting on the surgical management of type 2 diabetes mellitus and the associated DR outcomes

Study	No.	Follow-up	New onset DR	Progression of pre-existing DR	Regression of pre-existing DR	No change in DR status
Varadhan et al. (2012) [42]	22	6–12 mo	2/15 (13%)	2/7 (29%)	2/7 (29%)	16/22 (73%)
Miras et al. (2012) [43]	67	12–18 mo	0/39 (0%)	1/28 (3.6%)	5/28 (17.8%)	61/67 (91%)
Thomas et al. (2014) [45]	38	12 mo	4/26 (15%)	3/12 (25%)	5/12 (42%)	26/38 (68%)
Amin et al. (2016) [46]	S: 152 M: 155	3 yr	29/106 (27%)	5/41 (12%)	5/41 (12%)	113/152 (74%)
Miras et al. (2015) [47]	S: 56 M: 21	1 yr	S and M: 0/77 (0%)	S: 6/56 (11%) M: 3/21 (14%)	S: 6/56 (11%) M: 1/21 (5%)	S: 44/56 (78%) M: 17/21 (81%)
Murphy et al. (2015) [48]	318	334 day	38/218 (17%)	12/100 (12%)	35/100 (35%)	232/318 (73%)
Kim et al. (2015) [49]	20	12 mo	2/12 (16.6%)	7/8 (87.5%)	1/8 (12.5%)	10/12 (83.3%)
Banks et al. (2015) [50]	S: 21 M: 24	2 yr	Surgery: mean deterioration of 0.24 grades ($P=0.135$) Controls: mean deterioration of 0.38 grades ($P=0.026$)			
Zakaria et al. (2016) [53]	S: 21 M: 24	13 yr	Surgery: 0/20 (0%) Controls: 1/20 (5%)	-	-	Surgery: 1/1 (100%) Controls: 4/4 (100%)
Abbatini et al. (2013) [54]	33	3 or 5 yr	No new incidences of DR (32/32)	-	-	NPDR: 1/1 (100%)
Brynskov et al. (2016) [51]	56	1, 3, 6, and 12 mo	12 mo: 0/32 (0%) At 6 mo: 1/32 (3%)	12 mo: 3/24 (13%) 5/24 (21%) at any follow-up visit	12 mo: 4/24 (17%) 6/24 (25%) at any visit	12 mo: 49/56 (87.5%)
Singh et al. (2015) [52]	150	2 yr	No difference between bariatric surgery and intensive medical management			86.5% of all participants ($n=150$)
Johnson et al. (2013) [44]	15,951	20 mo	Surgery vs. Controls Diagnosis of blindness: <0.1% vs. 0.3% Laser eye/retinal surgery required: 0.2% vs. 0.6%			

DR, diabetic retinopathy; S, surgical; M, medical; NPDR, non-proliferative diabetic retinopathy.

function, improved significantly in obese patients with cardiovascular risk factors at 9 months postbariatric surgery [41].

Varadhan et al. [42] conducted a small, retrospective, pilot study in 2012 to investigate to effect of vertical sleeve gastrectomy (VSG) or Roux-en-Y gastric bypass (RYGB). Retinal images were taken presurgery and from 6 to 12 months after surgery. Of those without preoperative DR ($n=15$), two developed new DR. Of those with preoperative DR ($n=7$), two progressed, two regressed and three remained stable. Despite the small numbers included ($n=22$), considering 18% of patients developed new DR or experienced deterioration of their existing DR, this pilot study identified the need for further investigation into the implication of bariatric surgery on ophthalmic outcomes [42].

A retrospective study with a mean follow up of 1 year was conducted by Miras et al. [43] in 2012 ($n=67$). The main effect observed overall was stabilization (91%). A significant improvement was observed in a subgroup that had established

preoperative DR, with 17.8% improving and 3.6% deteriorating [43].

Johnson et al. [44] conducted a large retrospective study in 2013 ($n=15,951$). Less ophthalmic manifestations, defined as new diagnosis of blindness in ≥ 1 eye/laser eye or retinal surgery, were reported in the bariatric surgery group (<0.1%/0.2%) than in the non-surgical group (0.3%/0.6%) after a follow-up of less than 2 years. However caution should be taken when interpreting these results as the endpoints examined are rare and very severe [44].

Thomas et al. [45] conducted a 12-month retrospective pilot analysis in 2014 ($n=40$). Of those without preoperative DR ($n=26$), 22 still had no evidence of DR postsurgery. The remaining four developed minimum background diabetic retinopathy (BDR). Five out of nine participants with minimum BDR before surgery deteriorated, while the other four did not change. The only participant with moderately severe BDR ($n=1$) progressed to preproliferative diabetic retinopathy

(PPDR). Two of those with PPDR ($n=4$) before surgery deteriorated, with the other two lost to follow-up [45].

In 2015, Amin et al. [46] conducted a retrospective cohort study ($n=152$) with a mean follow-up duration of 3 years. Results revealed that the risk of developing sight-threatening DR was lower after bariatric surgery (5.7%) compared to non-surgical management (12.1%). However, the absence of evidence of DR prior to surgery did not eliminate the risk of developing sight-threatening diabetic retinopathy postoperatively [46].

A retrospective case-control study carried out by Miras et al. [47] in 2015 revealed that after 1 year there were no significant differences in retinal outcomes in participants who underwent RYGB compared to medical treatment. In the surgical cohort ($n=56$), 44 participants experienced no change, six improved, and six deteriorated. In the medical group ($n=21$), 17 patients experienced no change, one improved, and three deteriorated [47].

In 2015, a retrospective observational study conducted by Murphy et al. [48] ($n=318$) revealed that 73% of patients undergoing bariatric surgery had no change in their retinopathy grade after a mean of 334 days, a moderate or higher-grade retinopathy postoperatively was associated with the magnitude of HbA1c reduction, a higher preoperative retinopathy grade and male gender.

A small pilot study carried out by Kim et al. [49] in 2015 ($n=20$) identified that two out of 12 participants without preoperative DR and two out of three participants with mild NPDR developed moderate NPDR after surgery. All five participants who had moderate NPDR preoperatively experienced progression that required further intervention. Although 30% of participants who underwent surgery entered remission of T2DM, the risk of progression of DR was not eliminated in this cohort [49].

Banks et al. [50] conducted a retrospective case-control pilot study investigating the progression of DR after RYGB ($n=21$) compared to medical therapy ($n=24$). DR progressed significantly in the medical therapy group, but not in the RYGB group. However, there was no significant difference when the change in DR scores was compared between groups. Results from this study were inconclusive due to heterogeneity of group characteristics [50].

Brynskov et al. [51] conducted a prospective observational study of patients undergoing RYGB or VSG ($n=56$). Overall, six patients experienced worsening of DR at any time within 1 year, but this only persisted in three patients at 12 months. In

patients with preoperative DR ($n=24$), 17 participants experienced no change, three deteriorated, and four improved. For those without preoperative DR, one out of 30 participants experienced a transient worsening at 6 months, but at 12 months all 30 were unchanged from baseline. This study concluded that retinopathy was clinically stable in the first year after bariatric surgery [51].

The Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) RCT was the first study that compared the effects of intensive medical management to bariatric surgery on DR in a large population of patients with T2DM ($n=150$). After 2 years, this study found that RYGB/VSG did not significantly impact DR. Of all participants, surgical and medical, 86.5% experienced no change in their retinopathy scoring postoperatively [52].

There is significant heterogeneity in the data relating to the shorter term impact of bariatric surgery on DR. Some of the variability in the data may be explained by differences in the incidence of hypoglycaemia, a phenomenon not systematically tracked after surgery, or by the type of bariatric procedure performed.

SURGICAL MANAGEMENT: LONG-TERM OUTCOMES

There is a paucity of data on the long-term effects of bariatric surgery on DR. A retrospective analysis with a 13-year follow-up, focusing on the effects of laparoscopic adjustable gastric band (LAGB) in morbidly obese patients ($BMI \geq 35 \text{ kg/m}^2$), with or without diabetes, was carried out by Zakaria et al. [53]. Despite the long follow-up, no new cases of DR were recorded in the LAGB group ($n=87$) compared with a single case in the control group ($n=87$). These results indicate that LAGB is not associated with an increased risk of DR and that outcomes are similar to medical treatment in the long term [53].

Abbatini et al. [54], evaluated the long-term effects of VSG on T2DM severely obese patients retrospectively. Thirty-three patients had a 3-year follow-up and 13 of these were also followed up at 5 years. No new incidences of DR were reported, supporting the concept of bariatric surgery having a preventative effect on DR development. The single case of preoperative DR had not progressed when assessed at the 3-year follow-up point [54].

The Swedish Obese Subjects study did reveal that bariatric surgery was associated with a decrease in the incidence of mi-

crovascular complications compared to medical treatment. After a mean follow-up of 17.6 years, the incidence in the non-surgical cohort ($n=55$) was 41.8 per 1,000 person-years compared to 20.6 per 1,000 person-years in the surgery cohort ($n=288$). Unfortunately the composite end-point incorporated renal, retinal and neural endpoints, including whichever complication occurred first. Therefore, it was not possible to specify the effect of surgical intervention on retinal outcomes in this long-term study [17].

CONCLUSIONS

The current evidence suggests that the risk of progression of pre-existing DR or the development of new DR are not elimi-

nated by bariatric surgery or by the remission of T2DM and that surgical intervention may be more beneficial at an earlier stage of disease development. In the literature, the majority of patients with established DR at the time of surgery had no change in their DR grade after surgery. However, instances of regression and progression have also been recorded [42-46,48-55]. This trend was also observed in a systematic review and meta-analysis by Cheung et al. [56] that comprised of four primary studies ($n=148$). Raw data was sought from all relevant studies. In Table 3, data that was successfully obtained was collapsed to determine the number of cases that deteriorated, improved or remained stable depending on DR status at baseline. Possible risk factors for progression of DR include severity of DR at time of surgery and the magnitude of the reduction of

Table 3. Summary of DR status at baseline and the associated retinal outcomes after bariatric surgery

Preoperative DR status	Deteriorated	Stable	Improved
No retinopathy ($n=443$)			
Thomas et al. (2014) [45]	4/26	22/26	
Amin et al. (2016) [46]	29/106	77/106	
Murphy et al. (2015) [48]	38/218	180/218	
Kim et al. (2015) [49]	2/12	10/12	
Zakaria et al. (2016) [53]	0/20	20/20	
Abbatini et al. (2013) [54]	0/32	32/32	
Brynskov et al. (2016) [51]	0/29	29/29	
Total no. (%)	73/443 (16.5)	370/443 (83.5)	
Non-proliferative retinopathy ($n=179$)			
Thomas et al. (2014) [45]	1/10	4/10	5/10
Amin et al. (2016) [46]	5/42	32/42	5/42
Murphy et al. (2015) [48]	12/99	52/99	35/99
Kim et al. (2015) [49]	5/6	1/6	0/6
Zakaria et al. (2016) [53]	0/1	1/1	0/1
Abbatini et al. (2013) [54]	0/1	1/1	0/1
Brynskov et al. (2016) [51]	2/20	15/20	3/20
Total no. (%)	25/179 (14.0)	106/179 (59.2)	48/179 (26.8)
Proliferative ($n=12$)			
Thomas et al. (2014) [45]	2/2	0/2	0/2
Amin et al. (2016) [46]	0/4	4/4	0/4
Murphy et al. (2015) [48]	0/1	1/1	0/1
Kim et al. (2015) [49]	2/2	0/2	0/2
Zakaria et al. (2016) [53]	0/0	0/0	0/0
Abbatini et al. (2013) [54]	0/0	0/0	0/0
Brynskov et al. (2016) [51]	1/3	1/3	1/3
Total no. (%)	5/12 (41.6)	6/12 (50)	1/12 (8.3)

DR, diabetic retinopathy.

HbA1c.

The retina is one of the most metabolically active tissues in the body. Neural tissue is solely dependent on glucose for energy rendering the retina more vulnerable than the kidney to periods of hypoglycemia. Concerns remain over the effect of the rapid decrease of HbA1c after surgery on retinal outcomes. This rapid correction of blood glucose, along with postsurgical reactive hypoglycemia potentially contributes to worsening of DR.

Avoiding postprandial hypoglycemia may prevent hypoglycemia detracting from the beneficial effect of removal of hyperglycemia. Deepening our understanding of the complex pathophysiology of postprandial hypoglycemia after bariatric surgery and optimizing appropriate therapy may prove crucial in improving retinal outcomes.

The data on DR are thus much less coherent than the picture developing with regard to diabetic kidney disease (DKD). Bariatric surgery is uniformly associated with a reduction in urinary albumin excretion, leading indicating improvement in DKD [57]. Parity of the measurements available for DKD is not achievable clinically for DR. Therefore, in-depth animal studies comparing chronology of DR progression and the impact of surgery could provide clarity on the situation. However, for now, whether the effect of bariatric surgery on DR is good, bad or both remains inconclusive.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

D.M. Gorman is an intercalated M.Sc student from the University College Dublin medical degree programme (MB BCh BAO). Work in the group on microvascular complications of diabetes is supported by a Science Foundation Ireland President of Ireland Young Researcher Award to C.W. le Roux (12/YI/B2480). C.W. le Roux (PI) and N.G. Docherty are co-investigators on a grant from the Swedish Research Council (Medicine and Health) (2015-02733).

REFERENCES

- Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013;93:137-88.
- Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556-64.
- Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44:156-63.
- Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R; American Diabetes Association. Retinopathy in diabetes. *Diabetes Care* 2004;27 Suppl 1:S84-7.
- Heng LZ, Comyn O, Peto T, Tadros C, Ng E, Sivaprasad S, Hykin PG. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments. *Diabet Med* 2013;30:640-50.
- Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003;26:2653-64.
- Moreno A, Lozano M, Salinas P. Diabetic retinopathy. *Nutr Hosp* 2013;28 Suppl 2:53-6.
- Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med* 2012;366:1227-39.
- Gandorfer A, Rohleder M, Grosselfinger S, Haritoglou C, Ulbig M, Kampik A. Epiretinal pathology of diffuse diabetic macular edema associated with vitreomacular traction. *Am J Ophthalmol* 2005;139:638-52.
- Sena CM, Pereira AM, Seica R. Endothelial dysfunction: a major mediator of diabetic vascular disease. *Biochim Biophys Acta* 2013;1832:2216-31.
- Villarreal M, Ciudin A, Hernandez C, Simo R. Neurodegeneration: an early event of diabetic retinopathy. *World J Diabetes* 2010;1:57-64.
- Sharma Y, Saxena S, Mishra A, Saxena A, Natu SM. Advanced glycation end products and diabetic retinopathy. *J Ocul Biol Dis Infor* 2013;5:63-9.
- Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005;54:1615-25.
- Fowler MJ. Microvascular and macrovascular complications of

- diabetes. *Clin Diabetes* 2008;26:77-82.
15. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci U S A* 2000;97:12222-6.
 16. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Nanni G, Castagneto M, Bornstein S, Rubino F. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015;386:964-73.
 17. Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, Bouchard C, Carlsson B, Karason K, Lonroth H, Naslund I, Sjostrom E, Taube M, Wedel H, Svensson PA, Sjöholm K, Carlsson LM. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014;311:2297-304.
 18. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE, Kashyap SR; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes: 3-year outcomes. *N Engl J Med* 2014;370:2002-13.
 19. Docherty NG, Canney AL, le Roux CW. Weight loss interventions and progression of diabetic kidney disease. *Curr Diab Rep* 2015;15:55.
 20. Courcoulas AP, Goodpaster BH, Eagleton JK, Belle SH, Kalarchian MA, Lang W, Toledo FG, Jakicic JM. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg* 2014;149:707-15.
 21. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, Vella A, Chuang LM, Bessler M, Sarr MG, Swain JM, Laqua P, Jensen MD, Bantle JP. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013;309:2240-9.
 22. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. *Diabetes Res Clin Pract* 2013;101:50-6.
 23. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
 24. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;23 Suppl 2:B21-9.
 25. Beulens JW, Patel A, Vingerling JR, Cruickshank JK, Hughes AD, Stanton A, Lu J, McG Thom SA, Grobbee DE, Stolk RP; AdRem project team; ADVANCE management committee. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. *Diabetologia* 2009;52:2027-36.
 26. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233-44.
 27. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129-39.
 28. Davis MD. Diabetic retinopathy. A clinical overview. *Diabetes Care* 1992;15:1844-74.
 29. Moskalets E, Galstyan G, Starostina E, Antsiferov M, Chantelau E. Association of blindness to intensification of glycemic control in insulin-dependent diabetes mellitus. *J Diabetes Complications* 1994;8:45-50.
 30. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol* 1998;116:874-86.
 31. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagaenae O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br Med J (Clin Res Ed)* 1985;290:811-5.
 32. Grunwald JE, Brucker AJ, Schwartz SS, Braunstein SN, Baker L, Petrig BL, Riva CE. Diabetic glycemic control and retinal blood flow. *Diabetes* 1990;39:602-7.
 33. Ernest JT, Goldstick TK, Engerman RL. Hyperglycemia im-

- pairs retinal oxygen autoregulation in normal and diabetic dogs. *Invest Ophthalmol Vis Sci* 1983;24:985-9.
34. Merimee TJ, Zapf J, Froesch ER. Insulin-like growth factors. Studies in diabetics with and without retinopathy. *N Engl J Med* 1983;309:527-30.
 35. Henricsson M, Berntorp K, Berntorp E, Fernlund P, Sundkvist G. Progression of retinopathy after improved metabolic control in type 2 diabetic patients. Relation to IGF-1 and hemostatic variables. *Diabetes Care* 1999;22:1944-9.
 36. Phelps RL, Sakol P, Metzger BE, Jampol LM, Freinkel N. Changes in diabetic retinopathy during pregnancy. Correlations with regulation of hyperglycemia. *Arch Ophthalmol* 1986;104:1806-10.
 37. Varadhan L, Humphreys T, Hariman C, Walker AB, Varughese GI. GLP-1 agonist treatment: implications for diabetic retinopathy screening. *Diabetes Res Clin Pract* 2011;94:e68-71.
 38. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-22.
 39. Kumagai AK, Kang YS, Boado RJ, Pardridge WM. Upregulation of blood-brain barrier GLUT1 glucose transporter protein and mRNA in experimental chronic hypoglycemia. *Diabetes* 1995;44:1399-404.
 40. Cohen R, Pechy F, Petry T, Correa JL, Caravatto PP, Tzanno-Martins C. Bariatric and metabolic surgery and microvascular complications of type 2 diabetes mellitus. *J Bras Nefrol* 2015; 37:399-409.
 41. Lammert A, Hasenberg T, Kraupner C, Schnulle P, Hammes HP. Improved arteriole-to-venule ratio of retinal vessels resulting from bariatric surgery. *Obesity (Silver Spring)* 2012;20: 2262-7.
 42. Varadhan L, Humphreys T, Walker AB, Cheruvu CV, Varughese GI. Bariatric surgery and diabetic retinopathy: a pilot analysis. *Obes Surg* 2012;22:515-6.
 43. Miras AD, Chuah LL, Lascaratos G, Faruq S, Mohite AA, Shah PR, Gill M, Jackson SN, Johnston DG, Olbers T, le Roux CW. Bariatric surgery does not exacerbate and may be beneficial for the microvascular complications of type 2 diabetes. *Diabetes Care* 2012;35:e81.
 44. Johnson BL, Blackhurst DW, Latham BB, Cull DL, Bour ES, Oliver TL, Williams B, Taylor SM, Scott JD. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. *J Am Coll Surg* 2013;216: 545-56.
 45. Thomas RL, Prior SL, Barry JD, Luzio SD, Eyre N, Caplin S, Stephens JW, Owens DR. Does bariatric surgery adversely impact on diabetic retinopathy in persons with morbid obesity and type 2 diabetes? A pilot study. *J Diabetes Complications* 2014;28:191-5.
 46. Amin AM, Wharton H, Clarke M, Syed A, Dodson P, Tahrani AA. The impact of bariatric surgery on retinopathy in patients with type 2 diabetes: a retrospective cohort study. *Surg Obes Relat Dis* 2016;12:606-12.
 47. Miras AD, Chuah LL, Khalil N, Nicotra A, Vusirikala A, Baqai N, Graham C, Ravindra S, Lascaratos G, Oliver N, le Roux CW. Type 2 diabetes mellitus and microvascular complications 1 year after Roux-en-Y gastric bypass: a case-control study. *Diabetologia* 2015;58:1443-7.
 48. Murphy R, Jiang Y, Booth M, Babor R, MacCormick A, Hammodat H, Beban G, Barnes RM, Vincent AL. Progression of diabetic retinopathy after bariatric surgery. *Diabet Med* 2015; 32:1212-20.
 49. Kim YJ, Seo du R, Kim MJ, Lee SJ, Hur KY, Choi KS. Clinical course of diabetic retinopathy in Korean type 2 diabetes after bariatric surgery: a pilot study. *Retina* 2015;35:935-43.
 50. Banks J, Adams ST, Laughlan K, Allgar V, Miller GV, Jayagopal V, Gale R, Sedman P, Leveson SH. Roux-en-Y gastric bypass could slow progression of retinopathy in type 2 diabetes: a pilot study. *Obes Surg* 2015;25:777-81.
 51. Brynskov T, Laugesen CS, Svenningsen AL, Floyd AK, Sorensen TL. Monitoring of diabetic retinopathy in relation to bariatric surgery: a prospective observational study. *Obes Surg* 2016;26:1279-86.
 52. Singh RP, Gans R, Kashyap SR, Bedi R, Wolski K, Brethauer SA, Nissen SE, Bhatt DL, Schauer P. Effect of bariatric surgery versus intensive medical management on diabetic ophthalmic outcomes. *Diabetes Care* 2015;38:e32-3.
 53. Zakaria AS, Rossetti L, Cristina M, Veronelli A, Lombardi F, Saibene A, Micheletto G, Pontiroli AE; LAGB10 working group. Effects of gastric banding on glucose tolerance, cardiovascular and renal function, and diabetic complications: a 13-year study of the morbidly obese. *Surg Obes Relat Dis* 2016;12: 587-95.
 54. Abbatini F, Capoccia D, Casella G, Soricelli E, Leonetti F, Basso N. Long-term remission of type 2 diabetes in morbidly obese patients after sleeve gastrectomy. *Surg Obes Relat Dis* 2013;9:

- 498-502.
55. Miras AD, le Roux CW. Metabolic surgery: shifting the focus from glycaemia and weight to end-organ health. *Lancet Diabetes Endocrinol* 2014;2:141-51.
56. Cheung D, Switzer NJ, Ehmann D, Rudnisky C, Shi X, Karmali S. The impact of bariatric surgery on diabetic retinopathy: a systematic review and meta-analysis. *Obes Surg* 2015; 25:1604-9.
57. Jackson S, le Roux CW, Docherty NG. Bariatric surgery and microvascular complications of type 2 diabetes mellitus. *Curr Atheroscler Rep* 2014;16:453.