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Early worsening of diabetic retinopathy due to intensive glycaemic control

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ABSTRACT

The prevalence of diabetes and diabetic retinopathy is increasing around the world. Glycaemic control is important in reducing the long-term risk of complications of diabetes, however intensive glycaemic control, particularly in patients with longstanding and poorly controlled diabetes, is associated with the risk of early worsening of diabetic retinopathy and vision loss. We present two clinical cases to illustrate the presentation of early worsening and to highlight a role for intravitreal anti-vascular endothelial growth factor therapies in ameliorating this phenomenon, as well as a review of the current understanding of this phenomenon. We emphasise the importance of identifying individuals at risk of early worsening of diabetic retinopathy and recommend regular ophthalmological review during the period of intensive glycaemic control to ensure optimal visual outcomes.

Key words: diabetic retinopathy, early worsening phenomenon, glycaemic control, anti-vascular endothelial growth factor

INTRODUCTION

Diabetes and diabetic retinopathy continue to rise in prevalence in Australia and around the world.[1] In 1993, the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glycaemic control reduced the risk of microvascular complications in patients with type 1 diabetes mellitus (T1DM).[2] The authors showed that intensive control of blood glucose levels delayed the onset of diabetic retinopathy (DR) with a 76% risk reduction compared to conventional therapy. In those with mild non-proliferative diabetic retinopathy (NPDR), intensive glycaemic control reduced the risk of DR progression by 54%. This was supported by data from the United Kingdom Prospective Diabetes Study (UKPDS) which demonstrated that every percentage point reduction in haemoglobin A1c (HbA1c) in individuals with type 2 diabetes (T2DM) was associated with a 35% reduction in the relative risk of developing microvascular complications.[3]

However, despite the association between overall improvements in glycaemic control and reduced risk of development and progression of DR in the long term, the DCCT revealed a side effect in a small subset of patients. Consistent with results from previous trials,[4-6] initial worsening of diabetic retinopathy occurred with intensive therapy. This 'early worsening' (EW) phenomenon has been reported in both T1DM[4,7,8] and T2DM[9-11], and consisted mainly of increases in cotton wool spots and intraretinal microvascular abnormalities and/or diabetic macular oedema (DMO), indicating retinal ischaemia. In the DCCT, EW mainly affected the secondary-intervention cohort (ie those with T1DM for 1 to 15 years, very mild to moderate NPDR at baseline and urinary albumin excretion of <200mg/24hr) during the first year of therapy, of which 22 percent in intensive therapy group experienced EW versus 13 percent in the conventional therapy group. The characteristic fundus abnormalities often disappeared by 18 months.[2]

Herein we report the clinical course of two patients, in whom rapid lowering of HbA1c resulted in deterioration of their diabetic retinopathy, and in whom use of anti-vascular endothelial growth factor (anti-VEGF) was associated with regression of this EW. We provide a review of the current understanding of this phenomenon.

CASE 1:

A 52-year-old male truck driver was referred by his general practitioner (GP) to the ophthalmology clinic for diabetic retinopathy screening. He was newly diagnosed with T2DM two months prior, with a HbA1c of 16.0%. He was also found to have stage three diabetic nephropathy and peripheral neuropathy, and was commenced on oral hypoglycaemic agents and insulin. Fundus examination revealed severe NPDR without associated DMO. His best corrected visual acuity at the time was 6/9 in both eyes. His other vascular risk factors included hypertension and hypercholesterolemia. He was advised to improve his glycaemic and blood pressure control and a review was scheduled in three months' time.

Five months later, he presented with a three-week history of deteriorating vision in both eyes. His best corrected visual acuity was reduced to 6/60 in his right eye and 6/120 in his left eye. He reported rapid tightening of his glycaemic control, with a reduction of his HbA1c from 16.0% to 6.9% in the preceding five months. Fundus examination revealed multiple cotton wool spots bilaterally, gross DMO and featureless peripheral fundi, without evidence of proliferative disease. Hypertension was excluded as a cause of retinopathy.

Optical coherence tomography (OCT) confirmed bilateral centre-involving DMO with subretinal fluid but without disorganisation of the inner retinal layers (Figure 1). The

right and left thicknesses (CMT) were measured as 1155μm and 915μm respectively. Fluorescein angiography revealed bilateral macular ischaemia, with more extensive perifoveal capillary closure in the left eye than in the right eye (Figure 2). In view of the likely better prognosis of the right eye, the patient promptly received an intravitreal injection of bevacizumab (1.25mg/0.05ml) in his right eye (on-label anti-VEGF agents were not available at that time).

The patient demonstrated a marked response to the initial dose of bevacizumab – his visual acuity improved from 6/60 to 6/24 and his CMT decreased from 1155μm to 321μm (Figure 1). The visual acuity in his untreated left eye remained at 6/120. He received a second intravitreal injection of bevacizumab in his right eye.

He continued to respond well to bevacizumab in his right eye, achieving a best corrected visual acuity of 6/12 after 5 injections. Buoyed by this favourable outcome, a trial of monthly left intravitreal bevacizumab injections was commenced at this point. Significant improvement in his DMO, as indicated by a reduction in the CMT on OCT from 915μm to 486μm, was not accompanied by an improvement in vision. He underwent panretinal photocoagulation to both eyes over three sessions, in addition to focal laser to microaneurysms in his right eye in an attempt to reduce the need for intravitreal anti-VEGF treatment. At the final review, following 6 bevacizumab injections in his right eye, his visual acuity was 6/18 and 3/60 in his right and left eyes, respectively. Unfortunately he did not attend further appointments and subsequently passed away from diabetic complications, hence his final visual outcome was unable to be determined.

CASE 2:

A 54 year old man was referred by his optometrist in February 2013 for a recent decrease in his visual acuity in the context of poorly controlled type 2 diabetes mellitus, hypertension and dyslipidaemia. At presentation, his HbA1c was 9.1%. His blood pressure was within normal limits. His best corrected visual acuity was 6/9.5 in the right eye and 6/15 in the left eye. Clinical examination revealed bilateral severe non-proliferative diabetic retinopathy and DMO (Figure 3). OCT confirmed centre-involving macular oedema, more marked in the right eye than in the left (CMT of 793μm and 785μm respectively) (Figure 4). Fluorescein angiography of the right eye showed moderate peripheral retinal capillary closure without significant macular capillary occlusion. There was confluent capillary closure in all four retinal quadrants in the left eye and significant perifoveal capillary closure indicative of macular ischaemia (Figure 5).

The patient was commenced on monthly intravitreal bevacizumab (1.25mg/ 0.05ml) injections in both eyes to treat sight-threatening macular oedema (on-label anti-VEGF agents were not available at that time). In addition, he underwent panretinal photocoagulation to his left eye over four sessions given the extent of the capillary closure. He opted for a low glycaemic index, high protein diet to control his blood sugar. Remarkably, his HbA1c reduced from 9.1% to 5.3% within three months, during which time he was receiving monthly bevacizumab injections to both eyes.

Three months after commencing monthly intravitreal bevacizumab therapy, his best corrected visual acuity was 6/6 in his right eye, and 6/7.5 in his left eye. There was complete resolution of the DMO in both eyes (Figure 4). Apart from a minor increase in cotton wool spots (Figure 3), there was overall stabilisation of his diabetic retinopathy and his visual acuity was maintained at baseline levels.

After three sessions of monthly bevacizumab, the frequency of injections was reduced to two-monthly. However, this resulted in worsening of his DMO (CMT increased from 277μm to 523μm in his right eye, and from 255μm to 369μm in his left eye) with an associated reduction in visual acuity to 6/12 in both eyes. He was advised to return to a monthly regimen of bevacizumab injections and panretinal photocoagulation to right eye. However, he was lost to follow-up and his long term visual outcome is unknown.

DISCUSSION

Case 1 serves to demonstrate the potential adverse impact of EW on vision, and emphasises that people with longstanding, poorly controlled T2DM and established retinopathy, may be at increased risk. A dramatic reduction in HbA1c occurred in both cases, with 1.8% per month in case 1 and 1.3% per month in case 2 and both benefited from intravitreal anti-VEGF therapy. Case 2 highlights a potential role for anti-VEGF therapy in ameliorating or preventing EW. Even though the fundus images of these two cases do not offer direct before and after image comparisons following tightening of blood sugar control, these images support the effect of anti-VEGF therapy in situations of intensive glycaemic control.

The risk of progression from severe NPDR or early proliferative DR (PDR) to high-risk severe PDR is approximately 25% over 4 to 6 months, and this risk may increase to 50% with intensive glycaemic control.[12] Initial worsening in the DCCT occurred within 12 months,[7] consistent with other studies showing worsening within 3 to 12 months of the commencement of intensive insulin treatment.[5,6,8,10,13-20]

Despite having been described in the literature, the pathogenesis of EW is not well understood. It has been shown that frequency and severity of EW was associated

with more advanced DR at baseline, higher HbA1c levels, and longer duration of diabetes.[7,9,20] In addition, whilst the rapidity of blood glucose control and accompanying reduction in retinal blood flow have been implicated as important risk factors for EW,[5,6,21] others have proposed that the magnitude, but not the rapidity, of reduction of HbA1c during the first 6 months of intensive blood glucose control plays a more important role.[7,9] The DCCT showed that every percentage point drop in HbA1c was associated with 1.6-fold increase in the risk of EW. This was also supported by studies showing that poor initial control paired with a dramatic reduction in HbA1c increases the risk of retinopathy progression significantly,[15,22] with this having an even greater effect than prior duration of diabetes.[22] The magnitude of HbA1c reduction is however closely related to the baseline HbA1c, hence cannot be regarded as an independent factor.

Proposed mechanisms for this phenomenon include a decrease in availability of cellular energy substrates, a reduction in the ability of retinal circulation to autoregulate, and increase in growth factors.[6,7,21,23] One prominent hypothesis is the upregulation of insulin-like growth factor 1 (IGF-1), a potent angiogenic and mitogenic hormone.[24,25] Several studies showed that circulating IGF-1 levels are low in most people with type 1 diabetes.[26,27] This is partly due to the lack of portal venous insulin in these people, as the secretion of IGF-1 by the liver varies according to insulin levels. Intensive glycaemic control results in upregulation of circulating IGF-1 with a brief overshoot, which may be due to insulin effects on IGF-binding proteins and IGF-1 bioavailability.[28,29]An increase in IGF-1 contributes to an increase in microvascular permeability and augmentation of the effects of angiogenic factors.[25,30,31] IGF-1 has been demonstrated to induce the expression of vascular endothelial growth factor (VEGF), an angiogenic factor central to the pathogenesis of DR, and to enhance the downstream effects of VEGF.[32,33] In experimental models, the intravitreal injection of IGF-1 results in microvascular abnormalities resembling

those of DR, including increased basement membrane thickening, vasodilatation, vascular tortuosity, microaneurysms, intraretinal haemorrhage and neovascularisation.[41,42]

Increased serum IGF-1 levels have been correlated with rapidly accelerating DR and increased frequency of PDR,[9,23,30,34] and 3-fold higher vitreous levels of IGF-1 have been found in people with PDR than in those without diabetes.[35,36] A clinical trial of systemic IGF-1 administration to improve metabolic control in diabetes demonstrated progression of retinopathy and optic nerve neovascularisation.[43,44]Chantelau *et al*. demonstrated that the cessation of insulin and intensive glycaemic control led to the stabilisation of retinopathy in individuals with T2DM and EW, and this was associated with reductions in serum IGF-1.[24,37] Use of octreotide, a growth hormone and IGF-1 antagonist, has also been shown to delay or prevent disease progression in severe NPDR and early PDR.[36,38-40] However, growth hormone and IGF-1 antagonists nor somatostatin analogues have not been studied specifically in the context of the EW phenomenon.

Recent work suggests that acute reductions in retinal glucose levels that accompany intensive glycaemic control may compound the effects of the hypoxia that is associated with capillary closure in DR. Hypoxic retinal injury may be reduced by hyperglycaemia as glucose is the major cellular energy source. Casson *et al*. demonstrated the glucose confers a neuroprotective effect in the setting of retinal hypoxia, through the glycolytic synthesis of adenosine triphosphate (ATP) and a reduction in the production of reactive oxygen species via glucose entry into the pentose phosphate pathway.[50-52] A sudden dramatic tightening of glycaemic control may compromise this 'protective' effect, rendering retinal neurons vulnerable to injury. Nevertheless, while glucose may be protective to neurons in the context of

retinal hypoxia, long-term hyperglycaemia is deleterious to both to retinal neurons and the microvasculature.[53]

Clinical reports of severe visual impairment associated with EW[14,16-19,54] are balanced by those that describe transient and apparently reversible effects on vision.[4-6,8,55] Moskalets *et al*. reported 6 of 122 patients with T1DM who had little or no retinopathy at baseline developed severe retinopathy, neovascularisation despite laser photocoagulation and vitreous haemorrhage within 1 year intensive glycaemic control.[17] Mean HbA1c in these 6 patients reduced from 14.9% to 10.0% at 12 months, with initial rate of decline of HbA1c level at approximately 1% per 47days.[17] In the DCCT, EW was associated with the development of high-risk PDR in 2 patients and clinically significant macular oedema in 3, all of which responded well to treatment.[7] Approximately 50% of people with EW at 3 months had recovered by 6 months, and more than 60% of those with any EW at 3 or 6 months had recovered by 12 months. EW occurred earlier and recovery was more frequent in those who received intensive therapy than in those who underwent to conventional therapy.

Bariatric surgical procedures can cause prompt and sustained normoglycaemia in up to 80% patients with T2DM[57,58] and episodes of post-operative reactive hypoglycaemia are not uncommon, making EW of DR a potential concern in this group.[59] Retrospective studies have demonstrated variable effects of bariatric surgery on DR with worsening reported in between 1% and 45% of subjects 1 year after surgery.[11,60-63] In a prospective observational study, 13% of patients exhibited progression of DR in the first 12 months post-operatively, but only 5% of those persisted at 12 months.[64] The Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study compared the effects of intensive medical management with bariatric surgery on DR in T2DM. It was found that bariatric surgery did not significantly impact DR, and 86.5% of all patients had no change in

their retinopathy 2 years post-operatively.[65] There is considerable variability in the literature reporting on the short-term impact of bariatric surgery on DR, likely due to differences in incidence of hypoglycaemia, which is not systematically tracked after surgery, or due to variations in the type of bariatric surgery performed.[66] Whilst DR appears to remain relatively stable in most people after bariatric surgery, a pre-operative retinal examination and careful monitoring of retinopathy post-operatively may be advisable, particularly in people with established retinopathy who undergo pronounced reductions in blood glucose levels. Similarly, studies have shown that pancreas or islet transplantation does not induce EW, but reduces the risk of DR progression instead.[67-71]

Despite the EW phenomenon, the long-term benefits of intensive glycaemic control are compelling and the occurrence of EW does not appear to compromise these. The DCCT showed that 'intensive' glycaemic control (mean HbA1c of 8.6% versus 12.8% in the conventional treatment group) was associated with a 2-fold increase in risk of EW, and the risk of sustained DR progression was 2-4 times higher in those that had EW than in those that did not develop EW.[7] Importantly, people who received intensive therapy and developed EW still had a lower long-term risk of DR progression than did those who received conventional therapy and did not develop EW.[7]

In addition, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a follow-up to DCCT study, demonstrated the phenomenon of "metabolic memory"[72] -- a phenomenon related to the sustained effects of prior glycaemic control on risk of vascular complications, irrespective of the level of glycaemic control later in the disease. People from both DCCT groups (intensive control group and conventional control group) went on to receive intensive therapy in the EDIC study, and mean HbA1c levels of 8.0% were achieved for both groups. The group

with initial intensive therapy continued to have substantial reductions in the risks of DR progression (70% reduction), PDR, macular oedema and requirement for laser treatment, compared with those who started with conventional therapy.[2,72] This protective effect of early intensive control persisted even 10 years later, emphasising the long-term benefit of early intensive therapy despite the risk of EW. Altered expression of retinal glucose transporter 1 (GLUT1), as has been observed in the brain, may contribute to this effect.[73]

RECOMMENDATIONS

- The risk of EW has been demonstrated in those with dramatic reduction in HbA1c levels, hence identification of patients at high risk of EW, such as those with long history of poorly-controlled diabetes or previous advanced DR, is important.
- We recommend closer retinal follow-up before intensive therapy is initiated, as well as over the following 12 months.
- Retinal examinations at least every 3 months should be performed in those at high risk of EW.
- Particular attention should be paid to young patients with longstanding poorly controlled T1DM even in the absence of DR due to their high risk of rapidly progressive DR.
- There is no consistent evidence that controlling the speed of HbA1c reduction will decrease the risk of EW, moreover, controlling the speed of decrease is difficult and unpredictable in clinical practice. This highlights the importance of close ophthalmological monitoring during this period of blood glucose control.

CONCLUSIONS

While the early worsening of DR may accompany rapid and marked blood glucose lowering, the existing evidence suggests that the long-term benefits of the early initiation of intensive glycaemic control outweigh this risk in most circumstances. As has been illustrated in the two cases described in this paper, the use of intravitreal anti-VEGF therapies may offer a useful approach to minimise or perhaps even prevent the morbidity associated with EW of DR. The influence of EW on inner retinal neuronal injury is not well understood at present and warrants further study. Forewarning of the potential for worsening of retinopathy should be given to people in whom the intensification of glycaemic control is considered, and regular ophthalmological review is advised in high risk individuals. A collaborative relationship between endocrinologists, general practitioners, bariatric surgeons and eye health professionals will ensure optimal outcomes for people at risk of EW.

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Figure 1. OCT macula demonstrating dramatic response to intravitreal bevacizumab in the right eye

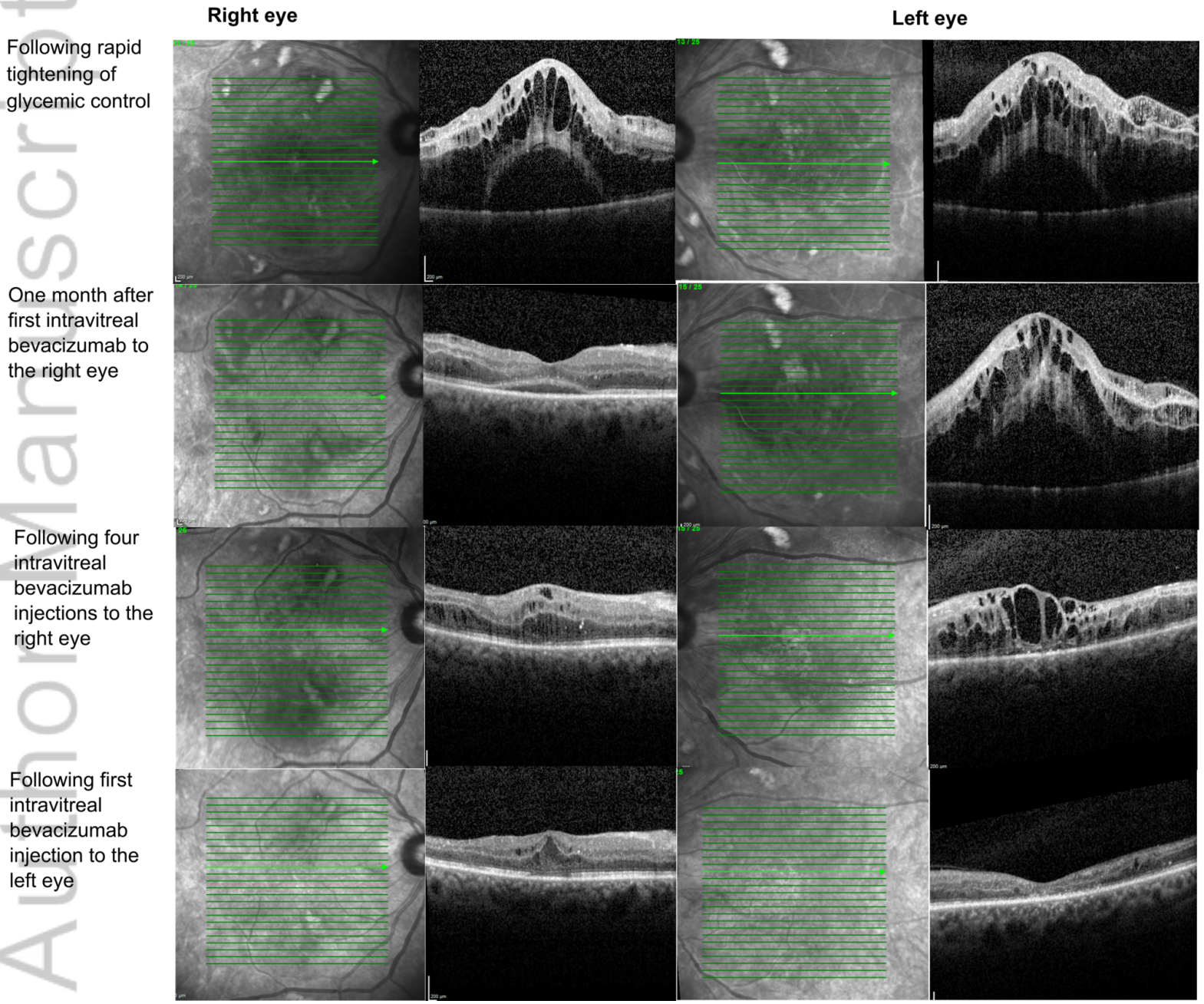

Figure1.png

Figure 2. Fundus fluorescein angiogram demonstrating significant retinal ischemia

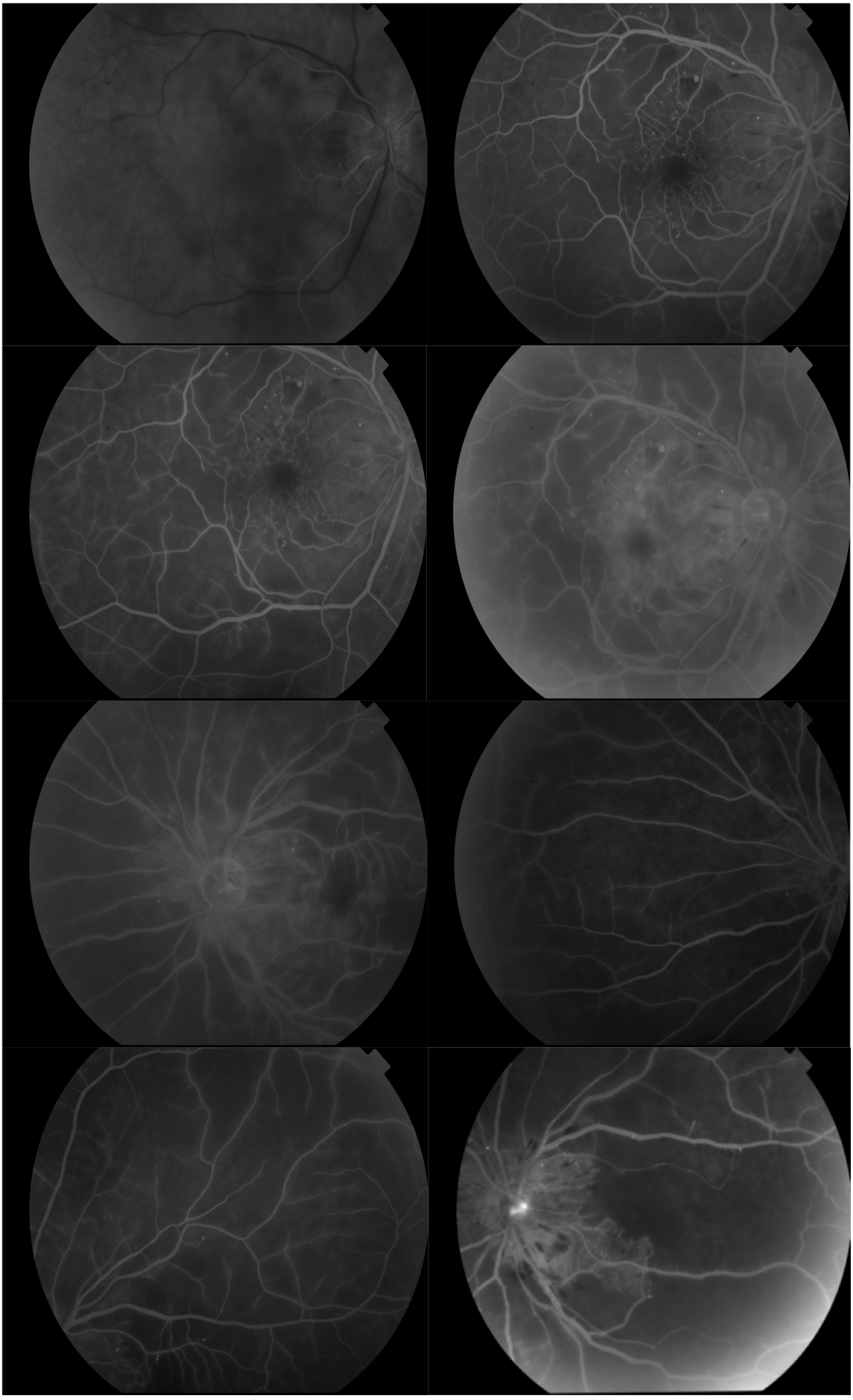

Figure2.png

Figure 3. Initial fundus photographs and at three months

Initial presentation

Three months after monthly bevacizumab injections along with a dramatic reduction in HbA1c

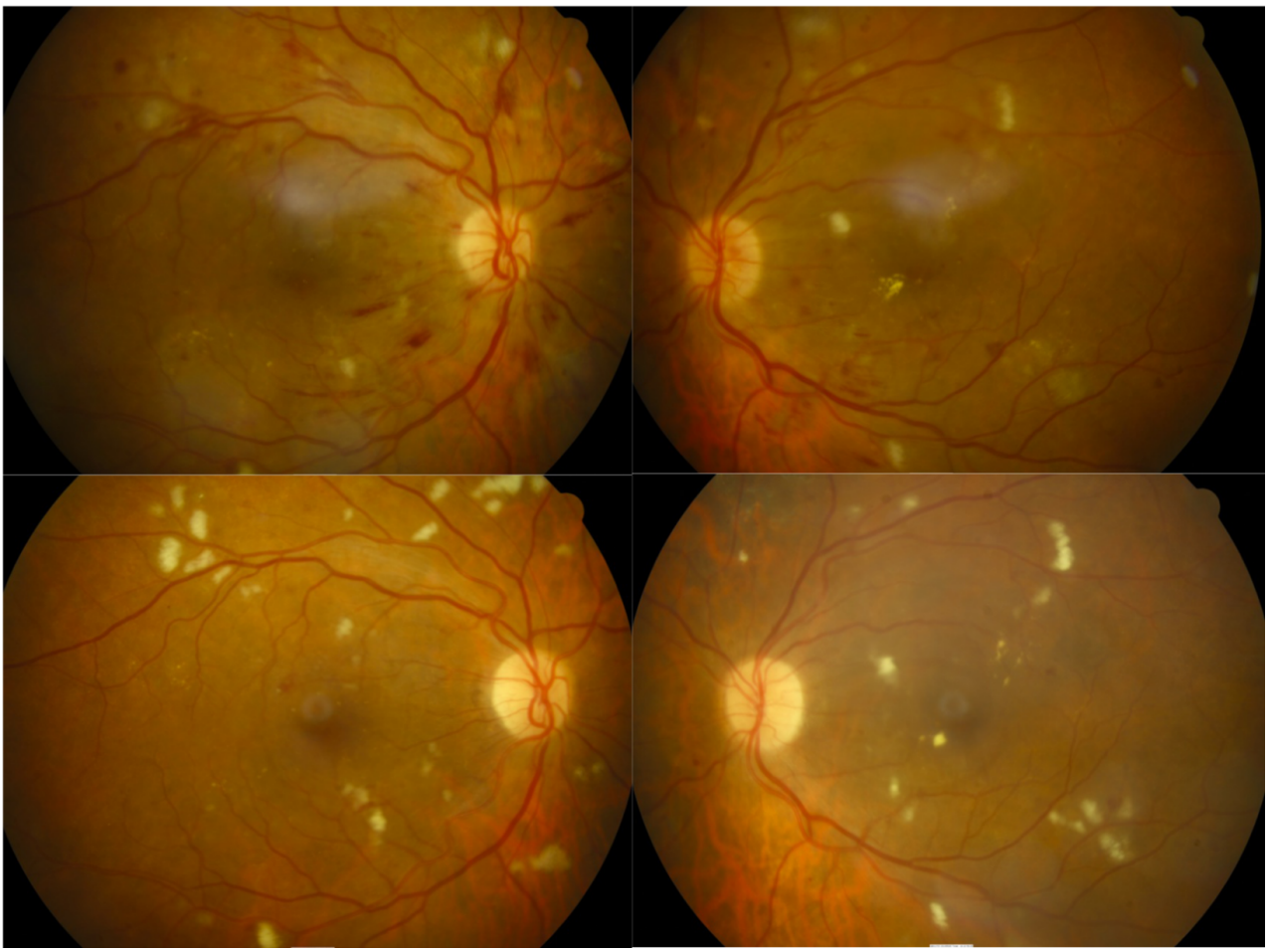

Figure3.png

Figure 4. OCT macula demonstrating good response to intravitreal bevacizumab injections

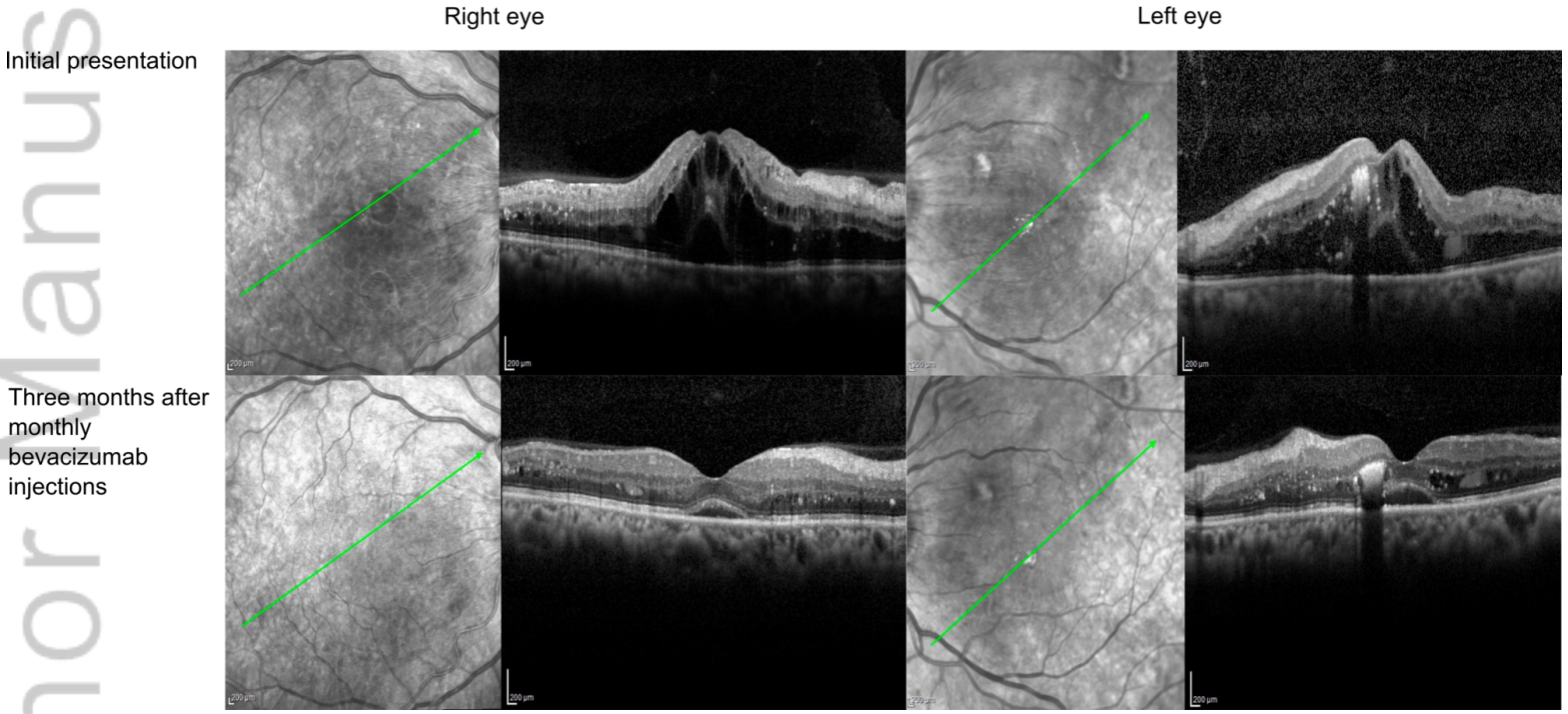

Figure4.png

Figure 5. Fundus fluorescein angiogram on initial presentation demonstrating severe degree of retinal ischemia

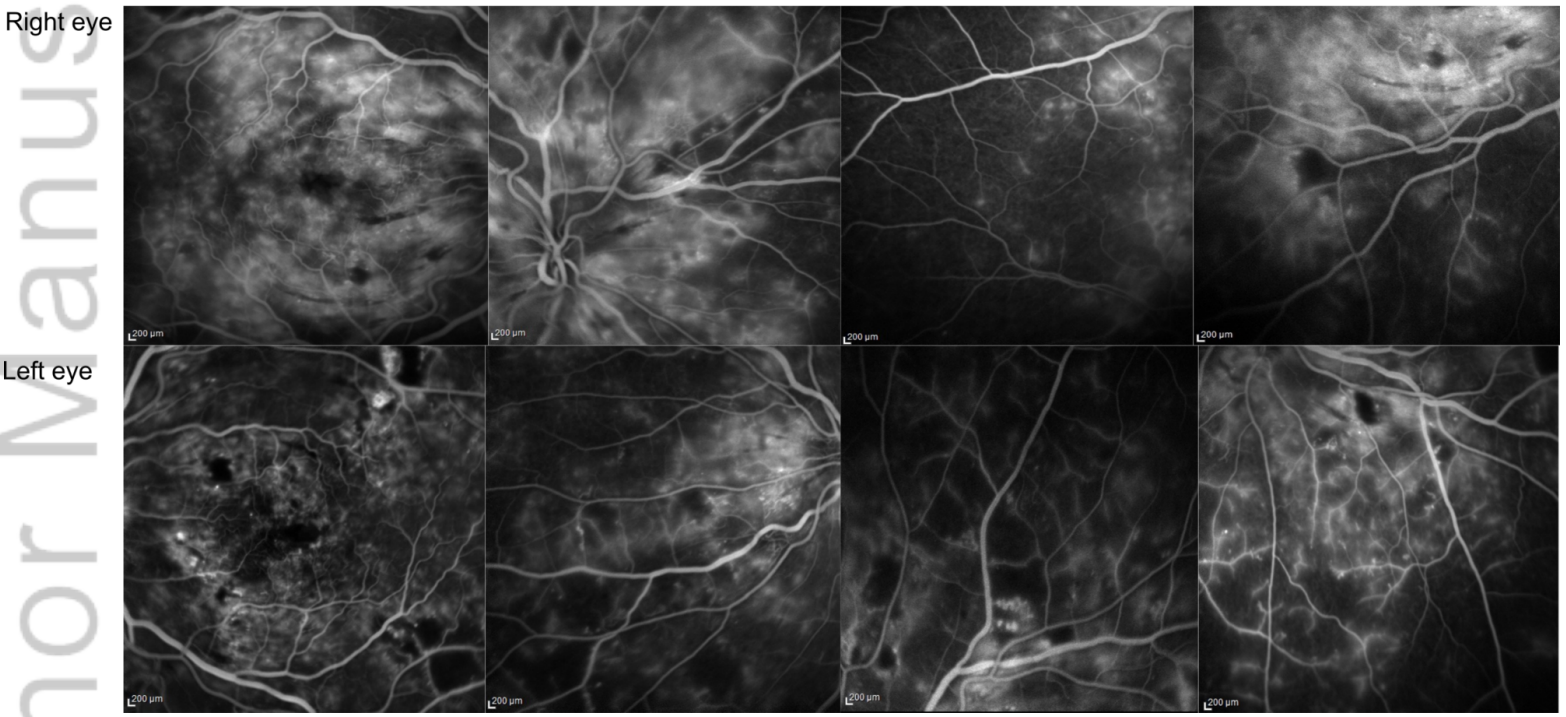

Figure5.png