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Worsening of Diabetic Retinopathy and Maculopathy with Rapid Tightening of Glycaemic Control

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Abstract

Early worsening of diabetic retinopathy following rapid tightening of glycaemic control is well described. However, no consensus guidelines available to date regarding management of this condition. We report two patients with diabetes whose diabetic retinopathy worsened soon after intensification of their glycaemic control. A 33-year-old lady with type 2 diabetes started insulin resulting in a drop of the HbA1c by 5.7% over 7 months. Her retinopathy deteriorated rapidly and progressively from background retinopathy and maculopathy to active proliferative retinopathy and maculopathy within 6 months of intensive treatment. In a second case, a 31-year-old male with type 1 diabetes had more intensive insulin intensification and his HbA1c dropped by 2.9% over 12 months. His retinopathy deteriorated rapidly and progressively from background retinopathy without maculopathy to bilateral active proliferative retinopathy and maculopathy within 12 months of starting more intensive treatment. Worsening of retinopathy after tightening of glycaemic control is not uncommon and the progression was very rapid and significant requiring repeated ophthalmologic interventions. Agreements on the evaluation and management of diabetic retinopathy and maculopathy during rapid tightening of glycaemic control is a timely need in the current era of new and effective glucose lowering medications and technologies.

Keywords: Early worsening of diabetic retinopathy; Rapid glycaemic control; Diabetic retinopathy

Abbreviations: EWDR: Early Worsening of Diabetic Retinopathy; IDDM: Insulin Dependent Diabetes Mellitus; CSII: Continuous Subcutaneous Insulin Infusion; DR: Diabetic Retinopathy; DCCT: Diabetes Control and Complications Trial; GLP 1RA: Glucagon like Peptide-1 Receptor Agonist

Introduction

Diabetic retinopathy is a leading cause of blindness globally. A recent meta-analysis reported worldwide prevalence of diabetic retinopathy being as high as 22.3% (95% confidence interval: 19.7-25.0%) among individuals with diabetes [1]. Several factors are associated with an increased risk of worsening of diabetic retinopathy, including sub-optimal glycaemic control, hypertension, and dyslipidaemia [2]. Despite the evidence of tighter glycaemic control leading to favourable retinopathy outcomes [3], paradoxical worsening of diabetic retinopathy with rapid improvement of glycaemic control was first described in 1980s. In patients with type 1 diabetes, several studies show early worsening of diabetic retinopathy (EWDR). Lauritzen *et al* described progression of background retinopathy to proliferative retinopathy in patients with insulin dependent diabetes who had improvement of HbA1c within 2 years of initiation of continuous subcutaneous insulin infusion compared to conventional insulin treatment [4]. In the landmark DCCT study, 13.1% of 711 patients who received intensive treatment had EWDR, compared to 7.6% of 728 patients who received conventional treatment during the initial 6 and/or 12 months follow up visits (odds ratio, 2.06; $P<0.001$) [5].

In patients with type 2 diabetes, evidence for early worsening of diabetic retinopathy is limited to non-randomized trials, as

most of the landmark randomized controlled trials only measured the retinopathy outcome at the end of the trial. In a retrospective case control study by Shurter *et al*, 34 patients who had an HbA1c drop of 1.5% over 1-2 years had worsening retinopathy (P=0.0025) and loss of vision (P=0.003) compared to 35 patients whose HbA1c was stable [6]. In a systematic review by Feldman-Billard *et al,* 10-20% of patients with uncontrolled type 1 or type 2 diabetes undergoing intensive treatment developed EWDR within 3 months of the start of intensive treatment. The risk of EWDR was twice as high in patients who already had diabetic retinopathy at baseline [7]. Here, we present two patients who had early deterioration of their diabetic retinopathy following rapid glycaemic control.

Case 1

A 33-year-old woman with type 2 diabetes for 14 years had persistently above target HbA1c 110–134mmol/mol (12.2–14.3%)] for more than 11 years before presentation to a specialist diabetes centre. Her glycaemic control was intensified by starting insulin which resulted in drop of HbA1c of 34mmol/mol from 134mmol/mol (13.4%) to 100mmol/mol (11.3%) by 3 months and further fall to 61mmol/mol (7.7%) by 7 months. Her diabetic retinopathy deteriorated progressively and rapidly, from bilateral background retinopathy and maculopathy at presentation, to active proliferative retinopathy and maculopathy (right eye) and pre proliferative retinopathy and maculopathy (left eye) after 4 months of insulin treatment. The retinopathy further deteriorated and within next 6 months to bilateral active proliferative retinopathy and maculopathy requiring bilateral pan retinal photocoagulation and vitrectomy in her right eye.

Case 2

A 31-year-old male with type 1 diabetes since the age of 8 had persistently elevated HbA1c over at least 8 years prior to presentation [HbA1c range:74mmol/mol – 88mmol/mol (8.9%-10.1%)]. His glycaemic control was intensified (lifestyle modifications and flash glucose monitoring) resulting in drop of his HbA1c from 85mmol/mol (9.9%) to 66mmol/mol (8.2%) over 4 months with a further drop to 53mmol/mol (7%) over 12 months. His retinopathy was stable with only background retinopathy and no maculopathy for at least 8 years prior to presentation. Within 4 months of glycaemic intensification, his retinopathy rapidly deteriorated to pre-proliferative retinopathy and maculopathy in his right eye and background retinopathy and maculopathy in his left eye. Within the next 8 months, his retinopathy further worsened to bilateral active proliferative retinopathy and maculopathy requiring pan retinal photocoagulation. During the period of progression of retinopathy, his blood pressure was tightly controlled on lisinopril and amlodipine (130/80mmHg or lower), and his LDL cholesterol remained below 1.7mmol/L on atorvastatin. He was a non-smoker.

Discussion

In both cases presented, diabetic retinopathy and maculopathy progressed rapidly and significantly following intensification of glycaemic control. There are several risk factors known to associate with EWDR. Increased risk of worsening of retinopathy is linked with the magnitude of the drop in HbA1c or blood sugar levels, with a larger drop being associated with a higher risk. Funatsu *et al* in a case control study revealed the relative risk of progression of DR increased by 1.7, 2.8 and 4.7 when HbA1c dropped within 6 months by 1%, 2% and 3% respectively [8]. Longer duration of diabetes is also associated with EWDR, and the risk was higher if blood glucose remains elevated for a longer period before intensification [5,9]. The progression of retinopathy is more likely in patients who already have diabetic retinopathy, compared to patients who had no retinopathy at baseline [5,9,10]. Both of our patients had retinopathy at baseline, a longer period of poor glycaemic control before intensification and demonstrated a significant drop of their HbA1c very rapidly (5.7% over 7 months and 2.9% over 12 months).

Apart from insulin, which is the commonest reason for tighter glycaemic control in studies demonstrating EWDR, other treatment modalities such as glucagon like peptide-1 receptor agonists (GLP1 RA) are thought to associate with EWDR phenomenon [11]. However, *post hoc* analysis suggests that this effect is more likely related to rapid improvement of glycaemic control rather than a direct drug effect of GLP1 RA [12]. There is heterogenous evidence for EWDR in bariatric surgery [13]. Pregnancy is also associated with rapidly worsening retinopathy [14]. Improvement of diabetic retinopathy has been reported after pancreatic and islet cell transplant, however, most studies have reported retinopathy status only 2 years after the transplant and so no comment can be made about early worsening of the retinopathy [7]. Mechanisms of early worsening of retinopathy are yet to be elucidated and there are several hypotheses described in the literature. One theory is the *"osmotic force theory"*: glucose is an osmotically active substrate and rapid changes in blood glucose may alter the osmotic pressures resulting in water retention within the retina [15]. The *"synergistic hypothesis"* proposes that insulin and VEGF act synergistically on the retinal blood vessels and trigger proliferation of arterioles resulting in worsening of the diabetic retinopathy [16]. In the *"VEGF hypothesis"*, retinal ischemia during poor glycaemic control results in reduced VEGF production. Subsequent reperfusion (due to improved glycaemic control) leads to a surge of VEGF resulting in increased vascular permeability and retinopathy progression [15].

There are several controversies and uncertainties in the management of EWDR with rapid tightening of glycaemic control. Firstly, there is no consensus definition of "rapid tightening". Thresholds for rapid tightening of glycaemic control used in the studies vary from a 1.5% drop over 1 year to >2% over 6 months

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[7]. Defining the rapidity and the degree of HbA1c drop would enable the prioritization of patients who need closer surveillance of their retinopathy. Despite a reasonable amount of evidence being available on EWDR, there are no consensus guidelines available for evaluation and management. By slowing down the rapidity of glycaemic control, can the deterioration of retinopathy be halted or reversed? This remains unanswered. However, it would also be difficult to conduct such studies to evaluate the benefit because of ethical concerns.

In the long term, tighter glycaemic control has undoubted benefits in improving overall macrovascular and microvascular complications and DM. With regards to the long-term outcome following EWDR, regression of the diabetic retinopathy was observed at 18 months in both intensive and conventional groups by 51% and 55% respectively in the DCCT trial. Despite the initial worsening of retinopathy, risk of diabetic retinopathy worsening was significantly lower in the intensive group at 10 years which persisted even at 18 years of follow up [5]. This highlights the importance of cautious management during rapid tightening of glycaemic control targeting to minimize the acute complications while trying to maximize the overall long-term benefits. Further large-scale studies on both type 1 and type 2 patients are warranted to evaluate this further. Over the past 4 decades, more than 40 new antidiabetic drugs alongside technological advances in insulin delivery and monitoring have revolutionized current diabetes treatment for people with both type 1 and type 2 diabetes [17]. These new therapeutic modalities can be associated with a rapid and significant tightening of glycaemic control. As such, the phenomenon of EWDR is likely to be a growing concern when treating patients with diabetes in current era. We highlight the timely need for consensus guidelines on evaluation and management.

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Declaration of Interest

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