Systemic Approaches and Considerations in the Management of Diabetic Retinopathy

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INTRODUCTION

Diabetes mellitus is a growing global epidemic. It is a disease of absolute insulin deficiency, type 1, or insulin resistance, type 2 [1]. In the UK more than 3.2 million people have been diagnosed with diabetes mellitus; this number is expected to rise as long as poor diet, obesity and sedentary lifestyles continue [2].

All health professionals but especially General Practitioners (GPs), diabetic nurses, optometrists and obstetricians are most involved in the care of diabetic patients. Thus, they all have the responsibility to recognise, educate and advise patients about factors that can accelerate their disease progression. This review will focus on these factors and their relationship to diabetic retinopathy (DR).

BLOOD GLUCOSE

Two landmark clinical trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have conclusively demonstrated the beneficial effects of tight glycaemic control in patients with type 1 and type 2 diabetes respectively [3,4].

DCCT randomly allocated 1441 type 1 diabetics to an ‘intensive’ and ‘conventional’ treatment group and followed them up for 6.5 years [3]. Their most important finding demonstrated that in the ‘intensive’ group, which had a mean glycated haemoglobin (HbA1c) of 7.2%, had a 54% reduction in incidence and a 76% reduction in progression of DR when compared to the ‘conventional’ group, which had a mean HbA1c of 7.8%.
of 9.2% [3]. The investigators also noted that the effect of HbA1c changes with the duration of disease (with earlier tighter control clearly being more beneficial). In their follow up study, Epidemiology of Diabetes Interventions and Complications (EDIC), they reported that patients from the ‘intensive’ group maintained the reduction in risk for 4 years, even though HbA1c levels in the two groups gradually converged [5]. This coined the term “metabolic memory” which describes a long lasting benefit of previously intense glucose control.

The UKPDS conducted a similar trial in type 2 diabetics (4). They randomly allocated 3867 patients to an ‘intensive’ therapy and ‘conventional’ therapy group for 6 years. Results of the study showed that intensive glycaemic control (with a mean HbA1c of 7.0%) had a 21% reduction in the progression of DR when compared to conventional glycaemic control (with HbA1c of 7.9%) [4].

One disadvantage of intensive glycaemic control reported in both trials was the increased incidence of hypoglycaemic attacks, with a threefold increase of severe hypoglycaemia in the ‘intensive’ group [3,4]. Another drawback recognised in the DCCT was an early initial worsening in retinopathy status. However after 18 months this reversed, with patients in the intensive group faring better in the longer term [4].

As a result of the above studies the overall recommendations are early intensive treatment of systemic disease, as safely as possible, for as long as possible with a goal of maintaining levels of glycaemia close to normal [3,4]. Although good glycaemic control is paramount to the management of diabetic patients to limit complications, the overall contribution of glycaemia on retinopathy amounts to 11% when evaluating total risk [6]. This means that other factors exist that contribute to the pathogenesis of diabetic retinopathy.

**BLOOD PRESSURE**

Retinal vasculature has two distinguishing features, both affected by diabetes and hypertension. The first one is the blood-retina barrier created by the tight junctions of the endothelium and the surrounding pericytes. The second is the lack of autonomic innervation and thus modulation of blood flow is dependent on local signalling mechanisms. Increased blood pressure (BP) is known to accelerate the progression of DR by disrupting endothelial function, impairing vascular auto-regulation and, ultimately, increasing the expression of vascular endothelial growth factor (VEGF) [7]. Hypertension is a common concomitant finding in diabetics and is an independent predictor of DR [4]. Over two-thirds of DR clinical trials related to hypertension have shown an association with diastolic pressure, systolic pressure, or both [7].

The UKPDS trial reported on the effect of tight BP control by studying 1148 hypertensive type 2 diabetics for 8.4 years [4]. They found the patients who had tight BP control (with a mean of 144/82 mmHg) had a 34% reduction in progression of DR and 47% reduced risk of deterioration of visual acuity, compared to the less controlled group (with a mean BP of 154/87 mmHg). The Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and the Action to Control Cardiovascular Risk in Diabetes mellitus (ACCORD Eye study group) both showed that control of BP in type 1 and type 2 diabetics, respectively, was less effective when retinopathy advanced beyond a “point of no return” [8,9]. Therefore, it is clear that the favorable effects of reduced BP are more significant in the early stages of diabetic retinopathy. Finally, there is a continuous debate whether angiotensin converting enzyme inhibitors offer a greater risk reduction of DR in comparison to other BP lowering medications, independent of their pressure lowering effect.

Hypertension appears to be a significant risk factor in the development and progression of DR and should be rigorously controlled on an ongoing basis by the patient and medical teams.

**RENNIN–ANGIOTENSIN SYSTEM**

The Renin-Angiotensin System (RAS) is a growing therapeutic target in patients with diabetes. Along with its BP lowering effects, blocking the RAS has BP independent mechanisms that delay the progression of retinopathy [10]. This observation has been attributed to RAS being unregulated in diabetic retinopathy, which directly increases the expression of VEGF and other growth factors [10].

Blockade of the RAS with the angiotensin converting enzyme inhibitor Lisinopril in the EUCLID Controlled trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EURODIAB) showed promising results [11]. They demonstrated a significant reduction in the progression of retinopathy in type 1 diabetes (although not of incidence of retinopathy) and the effect remained irrespective of BP reduction. This was further supported by a larger trial, the Diabetic Retinopathy Candesartan Trial (DIRECT) involving type 1 diabetics focusing both on prevention and progression [12]. They reported 18% reduction in the incidence of early stage retinopathy but failed to show a significant effect on progression.

From these studies there is evidence that RAS blockade may offer beneficial effects beyond the lowering of BP and even in normotensive patients.

**SERUM LIPIDS**

Dyslipidaemia is a recognised risk factor for cardiovascular morbidity and diabetic renal disease but its association with DR is not so conclusive. In addition, current studies fail to agree as to whether it is cholesterol, triglycerides or LDL levels that is mainly linked to diabetic eye disease.

The Hoorn Study and EURODIAB found raised cholesterol and triglycerides to be significantly associated with severity of DR when corrected for blood glucose levels [11,13]. In contrast, the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) and Early Treatment Diabetic Retinopathy Study (ETDRS) both argued that the link between dyslipidaemia and DR severity is not so evident [14,15], Although they did describe a relationship between increased levels of cholesterol and the presence of retinal hard exudates, in WESDR this failed to translate to a significant effect on retinopathy progression.

There have been several studies investigating specifically the effects of fenofibrate on DR. Fenofibrate mainly increases HDL and reduces triglycerides with a much less significant effect on LDL lowering in comparison to statins. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and ACCORD studies...
showed that fenofibrate slowed down the progression of retinopathy and reduced the need for laser photocoagulation [9,16]. In both studies fenofibrate achieved a modest lipid reduction and this alone was unlikely to explain the exceptional effects on DR [17]. This implies that an alternative mechanism exists outside of serum lipid control. Multiple pathways have been suggested to explain fenofibrate’s favourable outcomes such as protecting against the detrimental effect of oxidative stress and inflammation, inhibitory effects on the VEGF pathway and a role in regulating endothelial cell survival [10,17].

Despite the controversial results on dyslipidaemia and DR, it still remains an important risk factor for cardiovascular morbidity; therefore control of serum lipid levels is recommended.

**NEPHROPATHY**

The term Renal-Retinal Syndrome was used in 1980 to describe the group of diabetic patients that suffered from both kidney and eye damage as a result of glomerular and retinal microvasculopathy [18]. This prompted many to question whether the presence of one had an effect on the pathogenesis of the other. Epidemiological studies since have shown DR to take a more aggressive course in the presence of diabetic kidney disease [19,20]. Yet, it was unclear whether this was a direct effect of diabetic nephropathy or due to concomitant factors such as the duration of diabetes and hypertension [1].

A Scandinavian study explored the relationship between nephropathy and retinopathy in 110 type 1 diabetics [21]. Results showed that patients with proteinuria were 5 times more likely to have proliferative retinopathy. The authors of this study were aware of the confounding factors associated with both conditions and had matched patients accordingly. Further, a study which followed up subjects who had taken part in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) found that patients with gross proteinuria had a 95% increased risk of developing maculopathy [22]. The exact pathogenesis that links these two microvascular complications is not fully understood. There is evidence that alteration in prorenin, renin, angiotensin, aldosterone, aldosterone synthase, aldosterone receptor, and a role in regulating endothelial cell survival [10].

Although we now have a better understanding of the Retinal-Renal Syndrome, researchers are still exploring the possibility of separating and even reversing their effects. For now though, patients diagnosed with DR should have their kidney function assessed, as early diagnosis and management may well benefit their underlying nephropathy as well as the progression of their retinopathy.

**SMOKING**

Diabetes and smoking, independently, are definitive risk factors for cardiovascular disease, nephropathy and hypertension. However, the effect of smoking on the development and progression of DR is inconclusive [1].

Mühlhauser reviewed scientific papers published between 1989 and 1993 exploring the risk factors of DR [23]. Following critical analysis of the publications, the author concluded that the association between smoking and retinopathy was weak and inconsistent [23]. The relationship was further diminished when a 14-year follow-up study found smoking status to be irrelevant in the progression and incidence of DR [22].

Although no direct associations have been made, the studies mentioned did not assess the indirect effects of smoking such as carotid artery occlusion leading to secondary ocular under perfusion, aggravating retinal ischaemia and proliferative disease. Furthermore, life-threatening effects of smoking on other organs cannot be ignored, especially in diabetics, considering their concurrent vascular risks. Therefore, smoking should always be discouraged.

**CONCLUSION**

The aim of this review was to discuss specific factors that may influence diabetic retinopathy. The findings discussed above need to be known by the patient and critical members involved in the patient’s care; this is to ensure that when these challenges arise the correct advice, care and follow-up is provided.

**REFERENCES**


