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Review Article

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The Role of Hypertension and Dyslipidaemia in the Progression of Diabetic Retinopathy in Type 2 Diabetes

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Introduction

Despite the introduction of retinal laser photocoagulation and vitreoretinal surgery, diabetic retinopathy (DR) remains a significant source of sight disorders and blindness amongst individuals with Type 2 Diabetes Mellitus (T2DM) [1]. Visual impairment and blindness can add an additional burden to individuals with T2DM, thereby, affecting their quality of life and ability to self-manage their diabetes [2]. The number of people registered blind and those with moderate to severe sight complications due to DR rose from 0.2 million to 0.4 and 1.4 million to 2.6 million respectively between 1990 to 2015 [3].

Although the major risk factor of DR has been attributed to hyperglycaemia and diabetes duration, several other studies reported that DR can occur due to high blood pressure, abnormal serum lipids, smoking, abnormalities in glucose and lipids metabolism and atherosclerosis [3-5]. Other studies have considered high blood pressure and lipids disorders as independent risk factors to developing DR [6, 7].

In the light of the above, this report aims at examining the role of hypertension and dyslipidaemia in the progression of DR.

Classification and clinical presentation of DR

DR can be broadly classified into two categories. An earlier stage of non-proliferative DR (NPDR) and an advanced stage of proliferative DR (PDR). These two categories have been subdivided into mild NPDR, Moderate NPDR, proliferative DR and Severe PDR [8]. NPDR is characterized by micro aneurysms, dot haemorrhages, and hard exudates, vascular changes such as beading, looping and sausage like segmentation of the veins, cotton wool spots, intra-retinal micro vascular abnormalities (IRMA) and retinal oedema. Macular oedema can occur in patients with DR and is attributed to the major cause of visual loss in T2DM patients (Stitt et al., 2016). Besides the features seen in NPDR, PDR is characterized by the formation of new blood vessels and about 50% of patients with severe NPDR can progress to PDR within one year [8].

Screening and referral criteria for DR

DR is usually asymptomatic and early screening can help in early detection, assessment and treatment, thus helping in the prevention and reduction in DR related eye disorders and blindness [9-11]. Screening for DR can be done either by:
- A two field mydriatic digital photography which is used to examine the fundus of the retina to determine changes or disease progression, and - Optical coherence tomography used to examine the macular for changes such as oedema, retinal thickening, vitreoretinal traction or detachment [12, 13].

Screening for DR is recommended for T2DM patients at the time of diagnosis and the frequency of review would depend on the stage of retinopathy [13].

Referrals to ophthalmology

No DR- no finding	Review in 12 months
Mild NPDR	Review 6–12 months, depending on severity of signs, stability, systemic factors, and patient's personal circumstances
Moderate NPDR	Review in 6 months
Severe NPDR	Review in 4 months
Very severe NPDR	Review in 2–3 months High-risk PDR in up to 45% within a year
Mild–moderate PDR	Treatment considered according to severity of signs, stability, systemic factors, and patient's personal circumstances. If not treated, review in up to 2 months
High-risk PDR	Treatment should be performed immediately when possible, and certainly same day if symptomatic presentation with good retinal view

The pathogenesis and mechanism of progression of DR due to hypertension

Hypertension contributes significantly to the progression of DR. This process is multifactorial, and mainly involves the changes in

the retinal microvasculature and increased expression of Vascular Endothelial Growth Factor (VEGF) [14]. Blood flow distribution in the retina is controlled by autoregulation, which is the vessel's ability to keep blood flow constant with changing perfusion pressure. In diabetic patients, hyperglycaemia impairs this process, due to destruction of retinal pericytes [15]. Hypertension further disrupts autoregulation by causing basement membrane thickening and arteriolar hyalinosis [14]. Once this autoregulation has been disrupted, the retinal microvasculature become susceptible to changes in systemic blood pressure. Kohner et al. found that in the presence of hyperglycaemia, changes in mean arterial pressure by as little as 15% can cause more than 25% increase in retinal blood flow. Moreover, increased stretch of retinal microvasculature to accommodate changes in BP leads to up regulation of VEGF receptors [14]. VEGF receptors also increases by activation of the renin-angiotensin system, which augments angiotensin-II binding to AT-I receptor [16]. Increase in VEGF and its receptors leads to basement membrane thickening, increased vascular permeability and revascularization [14]. The IDF recommends target BP values <130/80 mmHg for patients with less than 70 years of age, <140/90 mmHg for patients of 70–80 years of age and <150/90 mmHg for patients over 80 years of age [17].

The pathogenesis and mechanism of progression of DR due to dyslipidaemia

There has long been evidence on the correlation between hard exudates formation and lipids levels (Keinding et al., 1950). Although dyslipidaemia has been linked with diabetic DR, the exact pathogenesis remains unknown and lipids are not known to affect the proliferative phase of DR. It is postulated that permeability differences in retinal blood vessels result in extra vascular deposits of lipoproteins in the retina [18]. While, in DR the atherosclerotic changes induced by lipids are thought to play a role, in DME, the pathology is thought to result from leakage of lipids through broken blood-retinal barrier [6]. The human retina has very high expression of fatty acids (FA) elongates that help in retinal FA metabolism through de novo lipogenesis and polyunsaturated (PUFA) remodeling pathways [19]. In patients with diabetes, elongase activation is reduced due to disturbed insulin levels. This result in reduced remodeling of FA particularly n-3 PUFA [20]. The activation of sphingolipids and ceramides in the retina result in pro-apoptotic and pro-inflammatory effects which cause endothelia cells damage in the retina [21]. Oxidized & glycated LDL in the retina are shown to induce retinal pericyte apoptosis thereby causing DR [22, 23].

Hard exudates which are characteristic of development and progression of DR are thought to develop from the interaction between raised lipids and BP in addition to suboptimal glycaemic control [18]. Studies that investigated the association of lipids and DR progression revealed mixed findings. While some studies demonstrated that elevated lipids levels increase the risk of retinal exudates, others found no significant association between lipids and DR [6]. A meta-analysis by Zhou et al. (2018) showed no significant differences in lipid levels in patients with and without DR, although in DR patients, LDL levels were slightly higher. One meta-analysis showed that total cholesterol, triglycerides, and LDL were higher in patients with diabetic maculopathy [18].

The effect of dyslipidaemia and BP control in the progression of DR Lipid-lowering drugs have shown to retard the progression of DR, predominantly DME and exudation. Fenofibrate is indicated to treat elevated triglycerides and dyslipidaemia in T2DM patients with DR. Fenofibrate reduces total and LDL cholesterol, increase HDL cholesterol and lower triglyceride levels. There is wealth of evidence that fenofibrate can slow the progression of DR and reduces the requirement for laser treatment in T2DM patients [24]. Nonetheless, The FIELD and ACCORD study found that fenofibrate cannot preserve vision or prevent the development of DR [18]. Fenofibrate was found to reduce hard exudates and is highly recommended in T2DM patients with DR [6, 25]. Common side effects of fenofibrate include diarrhoea, nausea, vomiting and abdominal pain [26]. Statins treatment for hypercholesterolemia had no significant impact on DR progression [18]

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BP reduction exhibits a fundamental role in the prevention and management of DR. The UKPDS reported that a reduction of micro aneurysm, hard exudates and cotton-wool spots at 4.4 years and 7.5 years follow-up respectively were recorded when BP was reduced from 154 to 144 mmHg. A reduction in BP was also linked with decrease in DR deterioration and reduced requirement for photocoagulation treatment [27].

The EUCLID study examining the efficacy of ACE inhibitors in decreasing the progression of DR revealed that, over two years, patients taking Lisinopril had a 50% reduction in progressing to DR compared to patients on no medication for hypertension. An 82% reduction in the progression to PDR was seen in patients taking Lisinopril compared to the placebo group [28]. ACE inhibitors are associated with adverse effects such as hair loss, angina pectoris, cough, hyperkalaemia and dizziness [29].

Laser treatment and intravitreal surgery can be used in patients who progresses to PDR and DME despite hypertension and dyslipidaemia treatment. The aim of laser treatment is to halt the growth of abnormal new blood vessels in the retina. The risk of sight loss and progression of PDR was reduced by 50% with the use of laser treatment [30]. Laser treatment is associated with defects to the peripheral visual-field [6].

Anti VEGF injections can also be used to treat PDR and DME. Studies using this treatment have shown improvements in visual acuity and reduction in the need for laser treatment [31]. A temporary rise in intraocular pressure and floaters are common side effects of Anti VEGF injections treatment [6, 32-35].

Conclusion

In conclusion, DR remains a significant burden to both the individual and healthcare system. Beside hyperglycaemia, hypertension and abnormal serum lipids have shown to be independent predisposing factors in the development of DR in patients with T2DM. Hypertension and dyslipidaemia are associated with an additional risk of NPDR and DME. The optimal preventative approach for DR in patients with T2DM is therefore the prevention of diabetes through the support of social and healthcare systems. Beside optimal glycaemic control, tight BP control, frequent eye examination and timely laser therapy for PDR and DME can significantly minimize the risk of eye sight disorders and blindness among patients with T2DM. Appropriate structured education in retinal screening can enhance patient compliance with retinal examination and facilitate subsequent eye reviews.

Timely intervention and treatment of dyslipidaemia and hypertension with medications such asfenofibrate, statins and ACE inhibitors can retard the progression of DR in patients with T2DM. These available therapies can enable the patient to attain a normal or near normal BP target and serum lipids status. The control of the risk factors that can result in the progression of DR in patients with T2DM can indisputably minimize diabetes complications.

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