Diabetic retinopathy: major unmet medical challenge

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Abstract

Since diabetes is now a global epidemic, the incidence of retinopathy, a leading cause of blindness in patients aged 20 to 74 years, is also expected to rise to alarming levels. The risk of development and progression of diabetic retinopathy is closely associated with the type and duration of diabetes, blood glucose, blood pressure and possibly lipids. It is an unmet medical need that can lead to severe and irreversible loss of vision in people of working age worldwide. The aim of this review is to give an overview of the clinical and anatomical changes during the progression of retinopathy, the underlying pathogenic mechanisms that link hyperglycaemia with retinal tissue damage, current treatments and the emerging pharmacological therapies for this sight-threatening complication of diabetes.

Introduction

Diabetes is now a global epidemic with recent surveys predicting that by 2025, the number of patients with diabetes will rise to staggering 380 million. This diabetes epidemic will lead to the increasing incidence of the two major types of long-term complications: macro vascular and micro vascular that contribute to morbidity and premature deaths. The macro vascular complications which affect the large vessels include cardiovascular, cerebrovascular and peripheral vascular disease. The micro vascular complications which affect the small vessels include neuropathy, nephropathy, and retinopathy. Diabetic retinopathy is one of the fastest growing causes of blindness and visual impairment in the working age population.

Sign and symptoms

Most diabetic patients may not experience any warning symptoms during the early stage of diabetic retinopathy. However, signs that may suggest the need for an urgent consulta-
tion with an eye care professional include blurred or sudden loss of vision and the presence of floaters and flashes.

Methods of examination

Early detection of diabetic retinopathy can prevent severe loss of vision and blindness. Diagnosis of diabetic retinopathy involves visual acuity tests, fundus examination (direct and indirect ophthalmoscopy) and retinal photography. Optical coherence tomography (OCT) examines the major layers of the retina with different reflectance of visible light. The technique is able to localise retinal lesions in relation to different retinal layers and quantify the retinal thickness. OCT can also be used to diagnose retinal oedema and measure retinal blood flow.

Classification, clinical features and anatomical changes

According to the International Clinical Diabetic Retinopathy Scale, retinopathy progresses from no retinopathy, nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Figure 1). This progression involves various clinical signs (Figure 2A) that include the formation of microaneurysms, dot and blot retinal haemorrhages, hard exudates, cotton wool spots, venous abnormalities, and the growth of new blood vessels.

NPDR is graded as mild, moderate, and severe (Figure 2B) according to the presence of these lesions. PDR (Figure 2C) involves the growth of new blood vessels in response to retinal ischaemia. These new vessels can develop from the disc (neovascularisation of the disc, NVD) or from elsewhere in the retina (neovascularisation elsewhere, NVE).

Along with PDR, diabetic macular oedema (MO) is a major cause of severe visual impairment in patients with diabetes. DMO (Figure 2D) can develop in NPDR and PDR and it is caused by leakage and build-up of fluid and proteins within 2 disc diameters of the macular region. The three types of diabetic maculopathy include exudative (focal), oedematous (diffuse or cystoid) and ischaemic. Focal exudative maculopathy is characterised by hard exudates present in a circinate pattern, with microvascular abnormalities (microaneurysms, haemorrhages) in the centre of the rings. Oedematous (diffuse, focal or cystoid) maculopathy is characterised by fluid accumulation in the perifoveal area and may result in cyst formation. Ischaemic maculopathy is characterised by enlargement of the perifoveal due to capillary closure and results in marked visual loss with microaneurysms, haemorrhages, mild or no intraretinal macular oedema and a few hard exudates.

If PDR is left untreated it eventually leads to advanced diabetic eye disease (Figure 2E). Advanced diabetic eye disease is characterised by vitreous haemorrhages, tractional retinal detachments, glaucoma and rubeosis iridis and eventually leads to complete blindness. The anatomical changes that occur during diabetic retinopathy have been well characterised and include the loss of pericytes and endothelial cells, formation of acellular capillaries, early thickening of the basement membrane, formation of microaneurysms and retinal neovascularisation.

Epidemiology and risk factors

According to the World Health Organization (WHO) diabetic retinopathy is responsible for 4.8% of the 37 million cases of blindness worldwide. The results from various epidemiological clinical studies including the Wisconsin Epidemiological Study on Diabetic Retinopathy...
(WESDR), Diabetic Retinopathy Study (DRS), Early Treatment of Diabetic Retinopathy Study (ETDRS), Diabetes Control and Complications Trial (DCCT), Diabetic Retinopathy Vitrectomy Study (DRVS), UK Prospective Diabetes Study (UKPDS) have identified various risk factors for understanding the development and progression of diabetic retinopathy.8-13

The major risk factors for diabetic retinopathy are hyperglycaemia, high blood pressure, and duration of diabetes. A number of studies have confirmed the pathogenic link between hyperglycaemia and the onset and progression of diabetic retinopathy. The DCCT and UKPDS provided conclusive evidence that tight control of blood glucose can delay the onset and progression of diabetic retinopathy in patients with type 1 and type 2 diabetes, respectively.11,14 However, if blood glucose is rapidly controlled in patients with previous poor control, it can worsen diabetic retinopathy.15

The duration of diabetes is an important risk factor for diabetic retinopathy. In patients with type 1 diabetes, the incidence of retinopathy in the first 3-5 years is very rare, but thereafter there is a rapid rise, so that by 20 years over 90-95% of patients have some degree of retinopathy.16,17 PDR in this group of patients is almost always absent for the first 10 years, again with a rapid rise to 60% by 20 years of duration. In comparison, 60-70% of the

Figure 1. Natural progression of diabetic retinopathy according to the International Clinical Diabetic Retinopathy (DR) Disease Severity Scale.

Figure 2. Diabetic retinopathy. (A) Schematic diagram defining the retinal lesions in diabetic retinopathy. (B) Fundus photograph showing severe non-proliferative (NPDR) diabetic retinopathy: microaneurysms, venous abnormalities, intraretinal microvascular abnormalities, cotton wool spots and hemorrhages. (C) Proliferative diabetic retinopathy: New vessels are present at the optic with blot haemorrhages in the macular area. (D) Diabetic retinopathy with exudative maculopathy showing hard exudates. (E) Advanced eye disease. New vessel on the optic disk, blot haemorrhages, and preretinal haemorrhage (arrow). Hard exudates are present near the fovea indicate the presence of clinically significant macular oedema (DMO).
Pathogenesis

Surgical management with laser surgery and vitrectomy is effective in reducing vision loss and useful for late stage of retinopathy, but it is devastating. The continual growing understanding of the pathogenesis of diabetic retinopathy is helping to facilitate new and early treatments and preventive strategies.

The DCCT and UKPDS clinical trials confirmed the role of chronic hyperglycaemia in diabetic retinopathy, but the underlying mechanism of how glucose causes microvascular damage remains unknown. Research worldwide has established various biochemical mechanisms that potentially link hyperglycaemia and diabetic retinopathy. These proposed and tested mechanisms include polyol pathway flux, activation of diacylglycerol (DAG)-PKC pathway, increased expression of growth factors (vascular endothelial growth factor, VEGF; insulin-like growth factor-1, IGF-1), accelerated formation of advanced glycation end products (AGEs), oxidative stress, haemodynamic or retinal blood flow changes, activation of the RAS pathway and sub-clinical inflammation.1,1

Polyol pathway

In cellular glucose metabolism a small percentage of glucose is metabolised through the polyol pathway. In diabetes, the flux of glucose through this pathway increases. The polyol pathway is controlled by two enzymes. The first enzyme, aldose reductase (AR) using nicotinamide adenine dinucleotide phosphate (NADPH) reduces glucose to sorbitol, which is then converted to fructose by the second enzyme, sorbitol dehydrogenase (SDH). The excessive build-up of sorbitol in cells is thought to cause osmotic damage to the retinal vascular cells leading to diabetic retinopathy. Genetic polymorphism studies suggest a link between AR and diabetic retinopathy. However, the role of AR in diabetic retinopathy remains controversial.

Non-enzymatic glycation

Glycation is a chemical reaction in which glucose binds to proteins and lipids leading first to the formation of the Schiff’s bases, then Amadori products and finally, after slow and complex rearrangements, to irreversible AGEs. The accelerated accumulation of AGEs in diabetes can cause cross-linking of long-lived proteins leading to stiffness and vascular dysfunction. In addition, the binding of AGEs with specific cell surface AGE receptors including the receptor for advanced glycation end product (RAGE), can induce intracellular signaling, oxidative stress and the production of key pro-inflammatory and pro-sclerotic cytokines. Several studies indicate that serum AGE levels are associated with incidence of diabetic retinopathy amongst other vasculopathies.

Prevention of AGE formation using aminoguanidine (pimecolimide) has been shown to prevent retinopathy-like changes (pericyte loss and acellular capillaries) in diabetic rats. Although the significance of AGEs and their inhibition can be appreciated based on experimental diabetes, there is limited information available supporting the clinical application of these agents in the development and progression of diabetic retinopathy. Furthermore, the use of aminoguanidine is associated with adverse effects that arise from an imbalance of the vitamin B6 metabolism and side effects related to the kidneys, the gastrointestinal tract and the liver.

Protein kinase Cβ1/2

In diabetes, glucose-induced activation of protein kinase C beta 1/2 (PKCβ1/2) via DAG leads to changes in endothelial permeability, contractility, extracellular matrix protein synthesis, haemodynamics (retinal blood flow) changes, production and intracellular signalling of VEGF. Glucose induced PKCβ1/2 activation is also thought to contribute to the loss of capillary pericytes.

Inflammation

Recent clinical research indicates the impact of sub-clinical inflammation in the development and progression of diabetic complications. Increase in serum concentrations of pro-inflammatory cytokines, adhesion molecules and activation of immune cells together contribute to an enhanced inflammatory response. In the retinal vasculature this leads in leukostasis and increased vascular permeability via VEGF, important early features of diabetic retinopathy. The extent of leukostasis, which in turn leads to capillary occlusion and non-perfusion, greatly influences the prognosis in diabetic retinopathy.

Haemodynamics changes

Loss of autoregulation and increased retinal blood flow has been suggested as a potential mechanism in the onset and progression of diabetic retinopathy. In contrast, other groups have reported reduced retinal blood flow or no significant change in diabetes.

Current management and treatment

Tight control of blood glucose, blood pressure and possibly lipids are important management strategies to reduce the onset and progression of diabetic retinopathy. The uses of anti-hypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors were investigated by several groups. The EURODIAB Controlled Trial of Lisonpril in Insulin-Dependent Diabetes Mellitus (EUCLID) study group found the ACE inhibitor, lisonpril, reduced the progression of diabetic retinopathy by 50% and the progression of PDR by 82% in normotensive type 1 diabetes patients. This can be interpreted as the involvement of a cellular role of the renin-angiotensin system (RAS) pathway that contributes to pathogenesis in the retinal tissue independent of blood pressure.

The Action in Diabetes and Vascular Disease Controlled Evaluation Retinal Measurement (ADVANCE-ADREM) study also investigated the effect of the ACE inhibitor perindopril and indapamide in type 2 diabetes patients. While the ACE inhibitors had some effect in reducing the progression of retinopathy, this number was considerably different from the EUCLID study. This disparity maybe a result of the difference in the patient cohort of the two studies, since all patients in EUCLID were normotensive.

Clinically it is difficult to achieve and maintain near normal levels of glucose and blood pressure, and laser photocoagulation and possibly vitrectomy may be needed to reduce the risk of severe visual loss from sight threatening diabetic retinopathy. Laser photocoagulation with argon green laser is effective for PDR and diabetic maculopathy. Vitrectomy may be indicated for PDR and advanced diabetic eye disease with severe visual loss.
Emerging treatments

Inhibition of some of the biochemical mechanisms linking hyperglycaemia and diabetic retinopathy has produced encouraging results in animal and/or clinical patients. The drugs tested include inhibitors of aldose reductase, oral protein kinase Cβ2/1 inhibitor, somato-statin analogs, anti-VEGF agents, angiotension receptor blocker (ARB), anti-inflammatory drugs and hyaluronidase.

Aldose reductase inhibitors

Although clinical trials have failed to confirm therapeutic potential of AR inhibitors (ARIs) in diabetic retinopathy, new and more effective ARIs are being developed.75-77

Protein kinase Cβ2/1 inhibitor

Ruboxistaurin mesylate (Arxxant, Eli Lilly, Indianapolis, USA), a specific inhibitor of PKCβ2/1, was developed and tested for the treatment of diabetic retinopathy in animal studies, ruboxistaurin delayed the progression of diabetic retinopathy.80-82 Encouraging animal data led to two multi-centre, placebo-controlled, phase 3 clinical trials of ruboxistaurin: the PKC DR study (PKC-DRS) and the diabetic Macular Edema Study (PKC-DMES).83,84 The PKC-DRS trial reported that ruboxistaurin did not prevent the progression of diabetic retinopathy or the need for laser photocoagulation, but significantly reduced the occurrence of sustained moderate visual loss. This effect was greatly influenced by the extent of glycaemic control, such that in patients with HbA1c≤10, the effect of ruboxistaurin was more pronounced and clinically significant.85 In the PKC-DMES trial, ruboxistaurin was found to significantly reduce the progression to DMO.86

PKC-DRS2 a multi-centre, 36-month, placebo-controlled, phase III clinical trial reported the potential of ruboxistaurin to reduce sustained moderate visual loss by 40% after 3 years.87 Although ruboxistaurin is a well tolerated drug with few significant adverse effects which has shown some clinical effectiveness, it is not available as a therapy for diabetic retinopathy.

Renin angiotensin system

The renin-angiotensin system (RAS) is the hormone system which regulates blood pressure and fluid balance. The RAS system has been shown to be disturbed in patients with diabetes.70 It has been demonstrated that in angiotensin type 1 and 2 receptors.71,72 VEGF is a heparin-affin growth factor which exists in four homodimeric molecular species, each monomer having respectively 121, 165, 189 or 206 amino acids. VEGF via its interaction with flt-1 and KDR receptors plays a key role in angiogenesis and vascular permeability. Studies over many years have implicated VEGF, particularly the 165 isoform, in the development of both PDR and DMO.82-84 VEGF levels are higher in patients with diabetic retinopathy and the levels have been shown to decrease after laser therapy.85-86

Blocking VEGF prevents development of proliferative disease in an oxygen-induced retinopathy (OIR) mouse model.86 Injection of VEGF165 into the vitreous of healthy primates leads to the formation of microaneurysms, hemorrhage, capillary closure, vascular leakage, and retinal angiogenesis.

Oxidative stress

Oxidative stress is the imbalance between the production of reactive oxygen species (ROS) and the cells ability to remove or neutralise the ROS using anti-oxidants. Oxidative stress results in damage to cellular components and contributes to the pathogenesis of certain diseases. It is now established that diabetes is associated with increased production of ROS such as the superoxide anion and a decrease in the level of antioxidant enzymes.66-67 The production of ROS is thought to lead to the activation of several other detrimental pathways such as the PKCβ2/1, and hexosamine pathways and the formation of AGEs.68-69

Fenofibrate

Fenofibrate is a lipid-regulating drug commonly used for the treatment of hyperlipidaemia. Beyond its lipid lowering effects, the recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial found that patients with type 2 diabetes receiving fenofibrate required less photoacoagulation for PDR and DMO.88 The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study showed that treatment of type 2 diabetic patients with fenofibrate in combination with simvasatin was able to reduce the odds of having progression of retinopathy by 40% over 4 years compared to treatment with simvasatin alone.89 Further work is still needed to under-
stand the underlying mechanism by which fenofibrate has a positive effect in DR and DMO. A number of potential mechanisms have been proposed which include: inhibition of the VEGF pathway, reduction in the levels of proinflammatory cytokines and adhesion molecules and sustained activation of the AMP-activated protein kinase pathway.68

Somatostatin analogues

Somatostatin is an endogenous polypeptide hormone of 14 or 28 aminoacids with potent anti-angiogenic properties. The somatostatin analogue octreotide has proved beneficial in preventing the progression to high-risk PDR, haemorrhage and the requirement for photoocoagulation and vitrectomy.93-102 No adverse side effects have been found with octreotide treatment in these studies. It has been hypothesised that the effects of octreotide are due to the direct neuroprotective and anti-angiogenic effects rather than its ability to indirectly lower IGF-1.103 From the current studies it appears that treatment with octreotide is beneficial in severe NPDR and PDR, although further greater powered studies are required to confirm this. Current efforts are focusing on the development of improved somatostatin analogues with increased selectivity.104

Anti-VEGF agents

Currently, pegaptanib, bevacizumab, ranibizumab and VEGF trap are being tested for the potential treatment of diabetic retinopathy. Recent evidence from clinical trials suggests beneficial effect of anti-VEGF agents in DMO and PDR.105-110 In DMO VEGF-trap was shown to have clinically significant improvement on the visual acuity of patients compared to photoocoagulation,111,112 Recently the use of intravitreal bevacizumab as a pre-operative adjunctive therapy for vitrectomy patients has been investigated. Promising results have demonstrated pre-treatment with bevacizumab accelerates vitreous clear up, reduces intraoperative bleeding, post operative hemorrhages and active neovascularisation.113,114 Despite promising results with anti-VEGF therapy, there are questions regarding its long-term safety in patients and repeated intravitreal injections may be associated with side-effects such as uveitis, cataract, retinal detachment, and endophthalmitis.62,112 Reducing VEGF levels in mice was found to cause death of photoreceptors and Muller glia involved required for normal visual function.115

Angiotensin receptor blocker

In light of the success of ACE inhibitors in the treatment of DR, other approaches to target the RAS pathway such as angiotensin receptor blockers (ARBs) have also been considered.116 The Diabetic Retinopathy Candesartan Trials (DIRECT), a large multicentre trial, consisted of three arms; the DIRECT- Prevent 1, DIRECT-Protect 1 and DIRECT-Protect 2.117,118 The first two groups determined whether ARB blocker candesartan prevented the incidence and progression of retinopathy in type 1 patients, while the third group investigated the effect of the drug on the progression of retinopathy in type 2 patients. Findings demonstrated significant reduction in the incidence of retinopathy in patients with type 1 diabetes, and the progression of retinopathy in patients with type 1 and type 2 diabetes. However, it is unclear if the beneficial effect was via RAS blockade, or lowering of blood pressure.

More recently, the RAS Study trial (RASS) has investigated the effect of ACE inhibitor enalapril against ARB losartan in normo tensionive patients to elucidate the mechanism of protection/prevention against retinopathy, and whether it is indeed independent of hypertension.119 Although, the ACE inhibitor was effective in reducing the progression of retinopathy, losartan was more potent in exerting this effect. This study highlighted the significance of RAS blockade in patients with NPDR or early stages of retinopathy, and can offer a novel approach to diabetes management and prevention of retinopathy in the future.

Antioxidants

A small number of studies on the effects of antioxidants on diabetic retinopathy have been performed; however whether the treatment is beneficial remains contentious. A small study demonstrated that diabetic patients with little or no diabetic retinopathy had a reversal in blood flow abnormalities after treatment with a high-dose of vitamin-E.120 Recently a 5 year follow up study indicated that antioxidant supplementation was able to cause retardation in the progression of retinopathy compared to a control group.121 However, two other clinical trials have shown that vitamin C and E treatment had no benefit on diabetic retinopathy.122 Further work needs to be performed to ascertain whether antioxidant treatment is a viable therapy for diabetic retinopathy.

Inhibitor of carbonic anhydrase

A recent study has introduced carbonic anhydrases, an enzyme that converts carbon dioxide to bicarbonate and protons, in the pathogenesis of diabetic retinopathy.123 The finding that inhibition of carbonic anhydrase prevents retinal vascular permeability in an animal model of diabetes suggests this enzyme as a potential therapeutic target in diabetic retinopathy.

Enzymatic vitreolysis

A recent addition to vitrectomy has been enzymatic vitreolysis to clear vitreous haemorrhage.124 Intravitreous ovine hyaluronidase (Vitrase; ISTA Pharmaceuticals, Inc., CA, USA) has been tested and shown to be effective in the management of persistent vitreous haemorrhage from PDR.125,126 Other potential vitreolysis enzymes include plasmin, and microplasmin.127

Combination therapy

Based on the comprehensive information and investigations over the years that target pathways in the prevention and protection against diabetic retinopathy, it has become evident that there is no one magic bullet and combination therapies may pave the way for a novel and more effective approach to the management and treatment of diabetic retinopathy. The combination of triamcinolone and the anti-VEGF agent, bevacizumab, has shown promise in patients with DMO who fail to respond to laser treatment.128 Several clinical trials have already demonstrated greater benefit of combined anti-VEGF and laser on visual acuity than just laser treatment.111,129,130

Conclusions

Diabetic retinopathy, a leading cause of blindness and visual impairment in the working age population, remains a major unmet medical challenge. However, research efforts worldwide have led to the introduction of various novel therapeutic targets in diabetic retinopathy. These include specific inhibitors of aldose reductase, PKCζ, anti-VEGF drugs (e.g., pegaptanib, bevacizumab, ranibizumab and VEGF trap), fenofibrate, renin-angiotensin system blockers, anti-inflammatory drugs, car bonic anhydrase inhibitors, and hyaluronidase. These emerging drug therapies individually or most likely in combination with standard treatments (laser photoocoagulation) may offer hope to diabetic patients by preventing and treating diabetic retinopathy.

References


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