Diabetic retinopathy: pathogenesis, prevention, and treatment

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Introduction
It is estimated that diabetes mellitus affects about 4% of the global population, almost all of whom may have some degree of diabetic retinopathy at any given time. Retinopathy is the most severe ocular complication of diabetes. Despite advances in treatment it remains an important problem with about 700,000 persons having proliferative diabetic retinopathy, and overall 63,000 new cases each year. The risk is directly related to the degree and duration of hyperglycaemia. Almost all persons who have had diabetes for 20 years or more, and in whom the onset occurred before the age of 30 years, have some evidence of retinopathy. Those who are 30 years of age or older when diabetes develops are at a lower risk. In these older patients, those who require insulin are at a higher risk for retinopathy than those who do not require insulin. This review article provides a current and concise review of retinopathy, its pathogenesis, prevention, and treatment.

Pathogenesis
Attention has been focused on pathogenic mechanisms in the development and progression of retinopathy, including non-enzymatic protein glycation, the sorbitol pathways, and growth factors. Recently, some researchers reported that benfotiamine, a thiamine derivative, blocked three major pathways of hyperglycaemic damage and prevented experimental retinopathy. These pathways are: the hexosamine pathway, the diacylglycerol-protein kinase, and the up-regulation of the transcription factor NF-κB.

Vascular endothelial growth factors (VEGFs) have been implicated in pathogenesis. Several features of VEGFs make them a possible mediator of retinal neovascularisation and vascular permeability in ischaemic ocular conditions. They are thought to enhance vasculogenesis and increase vascular permeability. The expression of VEGF is enhanced by hypoxia which is a major stimulus for retinal neovascularisation. The demonstration of elevated levels of VEGF in the vitreous humour of patients undergoing vitrectomy in the presence of active retinal neovascularisation, has provided some degree of evidence that VEGF has a role in proliferative retinopathy (PDR). In addition, exogenous VEGF injected into the vitreous of the eyes of monkeys caused neovascularisation of the iris and retina.

Pigment epithelium-derived factor (PEDF) inhibits neovascularisation. Animal studies showed that systemic administration of PEDF protein inhibits retinal neovascularisation in hyperoxygenated neonatal mice. There is evidence that PEDF levels decrease in PDR.

Inhibitors of growth hormone
Much interest has been generated on the beneficial effect of cessation of growth hormone secretion or inhibition of growth hormone action on the treatment of PDR. A small-scale trial showed that high doses of octreotide, a somatostatin analogue, prevented progression to the proliferative stage of retinopathy; while a larger trial is in progress.

Genetic predisposition
Some observations have been made on a possible genetic role in the risk of development of retinopathy. The Diabetes Control and Complications Trial (DCCT) revealed familiar clustering of certain severe forms of retinopathy. Also of importance is its continued progression after the institution of normoglycaemia in many human subjects and in laboratory animals.

Clinicopathologic features
Retinopathy results from five fundamental processes. These are: formation of retinal capillary microaneurysms, development of excessive vascular permeability, vascular occlusion and ischaemia, neovascularisation with accompanying fibrous tissues, and contraction of fibrovascular structures and the vitreous.

Retinal capillary microaneurysms
These are saccular outpouchings from the retinal capillary walls. Although retinal capillary microaneurysms are the first clinical manifestation, the earliest histological...
lesion is the loss of intramural capillary pericytes and development of acellular capillaries. The presence of microaneurysms alone has no apparent clinical importance except as a marker of retinopathy development. However, there is a correlation between the number of microaneurysms in the retina and the risk of further progression.\textsuperscript{26,27}

**Excessive vascular permeability**
Excessive vascular permeability results in the formation of hard exudates. These are well-defined, yellow-white lipid deposits often found within the outer retina.\textsuperscript{28} The extent of hard exudates correlates with serum lipid concentrations. Fluorescein angiography can be used to identify patients with excessive vascular permeability.

**Vascular occlusion**
Vascular occlusion occurs as small areas of confluent acellular capillaries and/or occluded terminal arterioles. Capillary occlusion leads to retinal microinfaracts which appear as off-white to grey patches with poorly defined margins.\textsuperscript{29} This description represents cotton-wool spots. Progressive vascular occlusion is associated with increased intraretinal haemorrhages and retinal venous dilatation.\textsuperscript{30}

**Neovascularisation**
Proliferative retinopathy is characterised by the formation of new blood vessels that develop from the retinal circulation. These new vessels are accompanied by fibrous tissues. When new vessels are on or within one disc diameter of the optic disc, it is described as neovascularisation near the disc and is associated with worse prognosis. Traction on the new vessels from the fibrous tissues causes haemorrhage into the vitreous and/or retinal detachments.\textsuperscript{31,32} Vitreous haemorrhages may range from unnoticeable bleeding to complete filling of the eye with blood, causing loss of vision except for light perception. Haemorrhage often occurs during sleep, but can occur at any time. Late in the course of the disease, neovascularisation and fibrosis may occur within the stroma of the iris and the structures that drain the anterior chamber angle of the eye causing neovascular glaucoma. The prevalence of retinopathy is directly associated with duration of diabetes and degree of blood glucose control.\textsuperscript{33}

**Macular oedema**
Another important change that can occur as retinopathy progresses is diabetic macular oedema, which involves the breakdown of the blood–retinal barrier, with leakage of plasma from small blood vessels in the macula.\textsuperscript{34,35} Macular oedema is defined as retinal thickening resulting from the accumulation of fluid and can best be seen with the use of a binocular slit lamp or stereoscopic fundus photography. Resorption of the fluid elements from plasma leads to the deposition of its lipid and lipoprotein components and the formation of hard exudates. Although diabetic macular oedema does not cause total blindness, it frequently leads to severe loss of central vision.

**Clinical features**
Often there are no symptoms in the early stages of retinopathy, but it is very important to have a comprehensive ophthalmologic examination at least once a year. In proliferative retinopathy, there may be bleeding into the eye which may appear at first as few specks of blood, or spots. Sometimes, the spots may clear spontaneously. However, bleeding can reoccur and cause severely blurred vision.\textsuperscript{36} Untreated proliferative retinopathy can cause severe vision loss and even blindness.

**Non-invasive diagnostic techniques**
There are several new, non-invasive techniques with potentials for improved diagnostic sensitivity and enhanced investigations of retinopathy.

**Optical coherence tomography**
Optical coherence tomography can be used for the evaluation and follow-up of patients with diabetic macular oedema.\textsuperscript{37} An advanced version of this device, which uses a different optical system and a titanium–aluminum oxide laser, provides enhanced image resolutions of the retinal layers which resemble the detail of a histologic section.\textsuperscript{38}

**Retinal blood flow measurements**
Several newer techniques are in the pipeline to measure retinal blood flow in humans. The laser Doppler flowmeter uses Doppler methods to measure blood flow in the retinal vessel. Another device, the scanning laser ophthalmoscope, produces a video fluorescein angiogram, from which the rate of flow of the plasma column in the retinal blood vessel can be calculated. Retinal oxygenation has until recently been measurable only with intraretinal oxygen electrodes, an invasive technique that cannot be used in humans.\textsuperscript{39,40} A new, non-invasive method, functional magnetic resonance imaging (fMRI), provides an indirect measurement of the retinal partial pressure and can detect changes in retinal oxygenation even in very small regions of the retina.\textsuperscript{41}

**Prevention and treatment**
**Tight blood glucose control**
Prevention of retinopathy or stopping its progression is one of the major overall goals of effective and proactive diabetes treatment. The DCCT showed unequivocally that tight blood glucose control remarkably reduced the rate of the development or progression of retinopathy. A smaller randomised clinical study of 102 patients with type 1 diabetes who were followed for more than 7 years also found that intensive treatment reduced the prevalence of retinopathy.\textsuperscript{42} The conclusion is that effective glycaemic control has a beneficial effect on the incidence and progression of retinopathy in both type 1
and type 2 diabetes, but may take years to become clinically significant.43-46 Therefore, the goal of treatment is to lower blood glucose levels if possible to the near-normal range (HbA1c levels of <7.0%) and to maintain them in this range. However, tight blood glucose control is not advisable in some categories of patients. These include: elderly patients with a life expectancy of <5 years, patients with a terminal disease, and patients with hypoglycaemia unawareness.

Treatment of co-morbidities
Treatment of coexisting high blood pressure has also been shown to slow down the progression of retinopathy.46 Patients with hyperlipidaemia have an increased risk of retinopathy and correcting it may lower this risk.

Aldose-reductase inhibitor
Cellular accumulation of sorbitol, a glucose by-product, is one of the pathogenetic pathways implicated in the development of long-term complications of diabetes.47 Animal studies have shown that aldose-reductase inhibitors may slow the development of retinopathy.48 However, this finding has not been replicated in human studies.

Photocoagulations
Although photocoagulation was introduced in the 1950s, it was not until the early 1970s when a few trial studies showed that it might be an effective treatment approach for neovascularisation and macular oedema.49 Scatter photocoagulation consisted of photocoagulation throughout the middle and peripheral portions of the retina, with each burn separated from its neighbours by one burn width. Panretinal laser coagulation, which destroys areas of peripheral retina but preserves central vision, is the current treatment for proliferation. It is, however, associated with unavoidable side-effects, such as diminished peripheral and night vision, and misdirected or excessive burns.50 In general, the argon-laser burns were smaller and less intense than the xenon-arc burns. Photocoagulation with the argon laser rather than the xenon is recommended, because the former has fewer side-effects.50

Vitrectomy
This is a surgical technique whereby access is made into the eye and the vitreous gel is removed and replaced with an aqueous solution. Fibrous bands can be removed and areas of retinal detachment flattened. Patients with severe and non-clearing vitreous hemorrhages or tractional retinal detachments may benefit.31-33 Over the years, the techniques of vitrectomy and the instruments used have been refined considerably, the side-effects have been reduced, and photocoagulation can now be carried out concomitantly.35

Experimental therapeutic options
The development of strategies to block the formation of VEGF or its specific receptors has become a subject of intense research and a potentially useful therapeutic option. However, systemic anti-VEGF therapy would have potential clinical disadvantages, and direct intraocular administration of agents that block neovascularisation may be preferable.54 Other experimental antiangiogenic approaches to counter ocular neovascularisation are antitrigens, antimetalloproteinases, inhibitors of insulin-like growth factor I, and inhibitors of protein kinase C.55

Conclusion
Diabetic retinopathy has been a focus of extensive basic and clinical research since the 1960s. There is no doubt that retinal laser photocoagulation and vitrectomy are effective for the treatment of this disease. The value of effective control of blood glucose, blood pressure and blood lipid abnormalities in the prevention and/or delay of retinopathy cannot be overemphasised. Continuous health education of diabetic patients on all management issues, including eye care, forms the bedrock of overall effective care. There is hope that new therapeutic approaches that are being developed may ultimately improve the outcome for patients with diabetic retinopathy.

References


31. Caird FI, Burditt AF, Draper GJ. Diabetic retinopathy: a further


