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Diabetic retinopathy: treatment and prevention

PAUL M DODSON

Abstract

Diabetic eye disease is the major cause of blindness and vision loss among working-age people in developed countries. Microangiopathy and capillary occlusion underlie the pathogenesis of disease. While laser treatment is regarded as the standard therapy, intensive medical management of glycaemia and hypertension is also a priority in order to reduce the risk of diabetic retinopathy. Recent data have prompted a re-evaluation of the role of lipid-modifying therapy in reducing diabetic retinopathy. The Fenofibrate Intervention for Event Lowering in Diabetes (FIELD) study demonstrated a significant 30% relative reduction in the need for first retinal laser therapy in patients with (predominantly early-stage) type 2 diabetes treated with fenofibrate 200 mg daily, from 5.2% with placebo to 3.6% with fenofibrate, $p=0.0003$. The benefit of fenofibrate was evident within the first year of treatment. These promising data justify further evaluation of the mechanism and role of fenofibrate, in addition to standard therapy, in the management of diabetic retinopathy.

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Key words: fenofibrate, FIELD study, management, retinopathy, type 2 diabetes.

Introduction

Diabetic eye disease is the leading cause of blindness among working-age adults in developed countries:¹ macular oedema and proliferative diabetic retinopathy are the main causes of vision loss.^{2,3} In the UK, retinopathy affects about 40% of the diabetes population, with about 10% having advanced, vision-threatening retinopathy.⁴ Of patients with type 2 diabetes, nearly 20% have a significant degree of retinopathy at the time of diabetes diagnosis.⁴ In the UK, people of AfroCaribbean and IndoAsian origin have a 2- to 5-fold higher prevalence of diabetes-related complications than those of European origin.⁵

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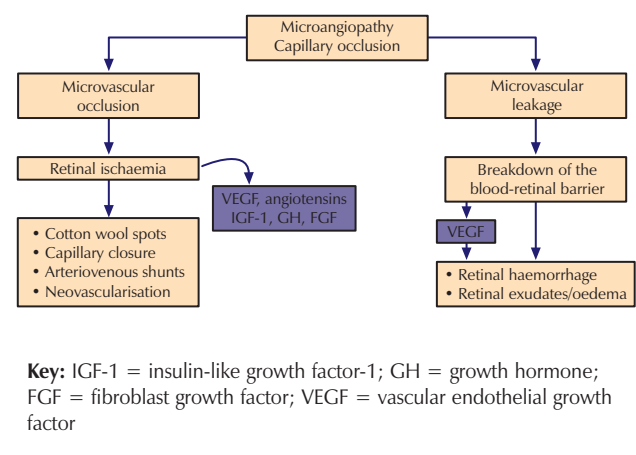
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Figure 1. Pathogenesis of diabetic retinopathy



Pathogenesis of diabetic eye disease

Microangiopathy and capillary occlusion underlie the pathogenesis of diabetic retinopathy (figure 1).^{1,6} Together, these lead to microvascular leakage and breakdown of the blood-retinal barrier, resulting in retinal haemorrhage, exudates and oedema, as well as the development of macular oedema. In addition, microvascular occlusion and ischaemia give rise to 'cotton wool' spots, capillary changes, arteriovenous shunts and neovascularisation. An increase in the level of vascular endothelial growth factor (VEGF) is probably one of the major angiogenic factors implicated in the pathogenesis of diabetic retinopathy.^{7,8}

Management priorities

Early identification and treatment are key priorities for reducing the morbidity of diabetic eye disease. However, while evidence supports the benefit of laser therapy, treatment is not completely effective. With respect to pan-retinal photocoagulation, event rates among laser-treated patients were substantially reduced (6% vs. 16% in untreated patients) according to the Early Treatment Diabetic Retinopathy Study Research Group 1991 report, and there was a 50% reduction in loss of visual acuity.⁹ More recent developments include the use of intra-vitreous injection of VEGF inhibitors (such as pegaptanib, currently licensed for age-related macular degeneration)¹⁰ and bevacizumab.¹¹ However, there are few data from randomised controlled trials for these newer treatments. Moreover, repeated injection increases the risk of endophthalmitis.

Medical management of risk factors, specifically inten-

Table 1. Priorities for medical management to reduce the risk of diabetic retinopathy

- Tight control of glycaemia ($\text{HbA}_{1\text{C}} < 7\%$)
- Tight blood pressure control ($< 130/80$ mmHg)
- Control of lipids (total cholesterol < 4.0 mmol/L, LDL cholesterol < 2.0 mmol/L, triglycerides < 1.7 mmol/L and HDL cholesterol > 1.0 mmol/L)

Key: $\text{HbA}_{1\text{C}}$ = haemoglobin $\text{A}_{1\text{C}}$; HDL = high-density lipoprotein; LDL = low-density lipoprotein

sive control of glycaemia and blood pressure, is important in the prevention of diabetic retinopathy. There is evidence to support this intensive control from major prospective studies such as the UK Prospective Diabetes Study (UKPDS) (table 1).^{12,13} In the UKPDS, the risk of microvascular complications in type 2 diabetes was shown to be associated independently and additively with hyperglycaemia and hypertension, with risk reductions of 21% per 1% decrement in glycosylated haemoglobin ($\text{HbA}_{1\text{C}}$) and 11% per 10 mmHg decrease in systolic blood pressure. Intensive treatment of both risk factors was associated with a significant trend for reduction in microvascular events, thereby reinforcing the importance of achieving current targets for glycaemic control and blood pressure to minimise the risk of complications.¹⁴

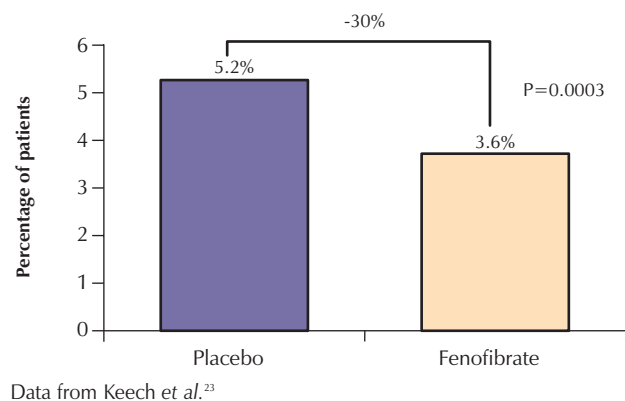
Role of lipids

Dyslipidaemia management may also have a role in reducing the risk of microvascular complications associated with type 2 diabetes. Early evidence that patients with combined dyslipidaemia (but not familial hypercholesterolaemia) had an increased incidence of retinal abnormalities led to the hypothesis that abnormal levels of triglycerides and cholesterol might be implicated in the pathogenesis of diabetic retinopathy.¹⁵ In addition, epidemiological studies showed that elevated serum lipids, notably elevated triglycerides, were related to the development of macular hard exudates.¹⁶⁻¹⁹

Together, these data prompted investigation of the potential of lipid-modifying therapy, specifically fibrates, in the management of diabetic retinopathy. Early preliminary studies demonstrated reduction in macular exudates with fibrate treatment; there were no changes in visual acuity, which was not surprising given that the patients recruited to these studies had advanced retinopathy at baseline.²⁰⁻²²

FIELD: reduction in retinal laser therapy

More recently, prospective data from studies investigating the role of lipid-modifying therapy in diabetes patients have been more promising. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a total of 9,795 patients with type 2 diabetes and adequate glucose and blood pressure control were randomised to treatment with fenofibrate 200 mg daily or placebo for a median of five years. Notably, these patients were predominantly in early-

Figure 2. Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that fenofibrate for five years significantly reduced the rate of first retinal therapy

stage diabetes, with a low prevalence of retinopathy (8%) and cardiovascular disease (22%) at baseline.²³

After five years, treatment with fenofibrate produced a significant 30% relative reduction in the rate of first laser therapy for retinopathy (from 5.2% with placebo to 3.6% with fenofibrate, $p=0.0003$) (figure 2). The benefit of fenofibrate was evident within the first year of treatment and continued thereafter. The effect of fenofibrate was similar in subjects without previous history of diabetic retinopathy at baseline.²³ This treatment effect could not be explained by changes in $\text{HbA}_{1\text{C}}$ or concomitant medication, or by the minor reduction in blood pressure observed in the fenofibrate treatment group. The FIELD study provides the first evidence that a lipid-modifying therapy, fenofibrate, impacts significantly on the progression of microvascular complications associated with type 2 diabetes. These findings justify further evaluation of the mechanism and role of fenofibrate, in addition to standard therapy, in the management of diabetic retinopathy. Recent experimental data indicate that fenofibrate regulates retinal endothelial cell survival via the signal transduction pathway, suggesting an effect of fenofibrate on retinal leakage, independent of lipid effects.²⁴

Conclusion

Diabetic retinopathy is a major cause of blindness and vision loss among adults of working age in developed countries. While laser therapy is of proven benefit in treating diabetic eye disease, this treatment is not completely effective. Management should therefore be aimed at reducing the risk of diabetes-related microvascular disease, via intensive control of glycaemia, blood pressure and lipids. Recent data from the FIELD study, which demonstrated a significant reduction in the rate of retinal laser therapy in type 2 diabetes patients treated with fenofibrate (from 5.2% with placebo to 3.6% with fenofibrate, $p=0.0003$), are promising and warrant further evaluation.

Conflicts of interest statement

None declared.

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