Epidemiology of diabetic retinopathy

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Diabetic retinopathy is associated with a number of systemic risk factors, namely hyperglycaemia, elevated blood pressure and dyslipidaemia. Patients with diabetes should be vigorously treated for these modifiable risk factors to prevent the development and progression of diabetic retinopathy.

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Diabetic retinopathy is one of the leading causes of vision loss in adults aged 20 years and older in a number of western countries. Patients with type 1 diabetes are at a higher risk of developing more severe retinal complications and visual loss. Patients with type 2 diabetes have a lower prevalence of retinopathy and tend to have less severe retinopathy. However, type 2 diabetic patients account for approximately 90% of the population with diabetes, and they comprise a larger proportion of those affected with diabetic retinopathy.

Data from population-based studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) provide valuable information on the prevalence of diabetic retinopathy and the risk factors associated with its development. In the younger-onset patients, whose age at diagnosis of diabetes was under 30 years and who were taking insulin at the time of examination (presumably type 1 diabetes), some degree of retinopathy was seen in 13% of patients with diabetes of less than 5 years' duration and in 90% of patients with diabetes of 10–15 years' duration (Klein et al, 1984a) (*Table 1*). Proliferative diabetic retinopathy, the most vision-threatening form of the disease, is present in approximately 25% of patients with type 1 diabetes of 15 years' duration.

For patients with onset of diabetes at 30 years of age or older (type 2 diabetes) and less than 5 years of known duration of diabetes, 40% of the insulin-taking and 24% of the non–insulin-taking patients have retinopathy (Klein et al, 1984b). These rates increase to 84% and 53% respectively by 15–19 years of diabetes. Proliferative retinopathy develops in 2% of patients with less than 5 years of diabetes and 25% of patients with 25 or more years of diabetes.

The 4-year incidence of diabetic macular oedema did not vary as much by diabetes type, approximately 8% in patients with either type 1 or type 2 diabetes and taking insulin. The incidence was 3% in those patients with type 2 diabetes not taking insulin (Klein et al, 1989).

TABLE 1.
Prevalence of diabetic retinopathy by onset and duration of diabetes

	Type 1 diabetes Onset <30 years of age		Type 2 diabetes Onset 30 years or older	
	Duration of diabetes		Duration of diabetes	
	<5 years	10–15 years	<5 years	>15 years
Any retinopathy	13%	90%	40%*	84%*
			24%†	53%†
Proliferative retinopathy		25%	2%	25%

* Insulin taking; † Non-insulin taking. From Klein et al (1984a,b)

RISK FACTORS FOR PROGRESSION OF DIABETIC RETINOPATHY

Modifiable medical risk factors

Glycaemic control: The relationship of glucose control to the chronic complications of diabetes has been extensively investigated in observational studies (Krolewski et al, 1986, 1992; Teuscher et al, 1988; Janka et al, 1989; Marshall et al, 1993; Arfken et al, 1994; Klein et al, 1988, 1994, 1996; Lloyd et al, 1995). These studies demonstrated that increased severity of diabetic retinopathy is associated with poorer glucose control. Randomized controlled clinical trials of glycaemic control were designed to address the causal role of glucose control in diabetic complications. In the Diabetes Control and Complications Trial (DCCT), 1441 patients with type 1 diabetes were randomly assigned to either conventional or intensive insulin treatment and followed for 4–9 years (mean of 6.5 years) (DCCT Research Group, 1993, 1995a,b, 1996; Reichard et al, 1993). This resulted in a median haemoglobin A_{1c} (HbA_{1c}) of 9.1% for the conventional treated group and 7.2% for the intensively treatment group. The DCCT demonstrated that intensive insulin treatment is associated with a decreased risk of either the development or progression of diabetic retinopathy in patients with type 1 diabetes.

In patients without any visible retinopathy when enrolled in the DCCT, the 3-year risk for development of retinopathy was reduced by 75% in the intensive insulin treatment group compared with the standard treatment group. However, even in the intensively treated group, retinopathy could not be completely prevented over the 9-year course of the study.

The benefit of strict control was also evident in patients with existing retinopathy (50% reduction in the rate of progression of retinopathy compared with controls). At 6- and 12-month visits, a small adverse effect of intensive treatment on retinopathy progression was seen, similar to that described in other trials of glucose control. However, in eyes with little or no retinopathy at the time of initiating intensive glucose control, this is unlikely to threaten vision. When the DCCT results were stratified by HbA_{1c} levels, there was a 35–40% reduction in the risk of retinopathy progression for every 10% decrease in HbA_{1c} (e.g. from 8% to 7.2%). This represented a fivefold increase in the risk for patients with an HbA_{1c} of approximately 10% *vs* those with 7%. Furthermore, there was a statistically significant reduction in both diabetic neuropathy and nephropathy with intensive blood glucose control in the DCCT.

The DCCT study was extended as a follow-up study, Epidemiologic Study of Diabetes Intervention and Complications (EDIC) (DCCT/EDIC Research Group, 2000). All patients were informed of the beneficial results of tight glycaemic control and those in the conventional treatment group were offered intensive therapy. The care of all patients was then transferred to their own physicians. At 4 years follow up, the difference in HbA_{1c} narrowed (8.2% for the conventional group and 7.9% for the intensive group) but the beneficial effects of tight glycaemic control persisted despite the increased hyperglycaemia. The proportion of patients who had worsening retinopathy, including proliferative diabetic retinopathy, macular oedema and the need for laser therapy, was reduced in the intensive treatment group compared with the conventional treatment group (odds reduction 72% to 87%, $P<0.001$). During the fourth and sixth subsequent years of follow up, the beneficial effects of glycaemic control persisted despite the decrease in the difference in HbA_{1c} among the treatment groups (8.1% *vs* 8.2%, $P=0.09$) (DCCT/EDIC Research Group, 2000, 2002). It appears that a period of good glycaemic control results in a decrease in the progression of both diabetic retinopathy and nephropathy, despite increasing hyperglycaemia.

The effect of glycaemic control on the incidence and progression of diabetic retinopathy is similar in patients with type 2 diabetes, as assessed in observational studies and randomized studies conducted in Japan and the UK (Ohkubo et al, 1995; Klein et al, 1996; UK Prospective Diabetes Study, 1998a,b). A study of Japanese patients with type 2 diabetes showed that multiple insulin injection treatment reduced the onset of retinopathy from 32% to 8% and reduced a two-step progression in retinopathy from 44% to 19% compared with people receiving conventional insulin treatments over 6 years (Ohkubo et al, 1995).

In the UK Prospective Diabetes Study (UKPDS), the largest and longest study of patients with type 2 diabetes, there was a 25% reduction in the risk of the 'any diabetes-related microvascular endpoint', including the need for retinal photocoagulation, in the intensive treatment group compared with the conventional treatment group. After 6 years follow up, a smaller proportion of patients in the intensive treatment group than in the conventional group had a two-step progression (worsening) in diabetic retinopathy ($P<0.01$). Epidemiological analysis of the UKPDS data showed a continuous relationship between the risk of microvascular complications and glycaemia, such that for every percentage point decrease in HbA_{1c} (e.g. 9% to 8%), there was a 35% reduction in the risk of microvascular complications.

The results of both the DCCT/EDIC and UKPDS show that although intensive therapy of blood glucose control does not prevent retinopathy completely, it does reduce the risk of the development and progression of diabetic retinopathy (*Table 2*). This may be translated clinically to both preservation of vision and reduction in therapies such as laser photocoagulation.

Hypertension: The findings of observational studies assessing the importance of blood pressure in the progression of non-proliferative diabetic retinopathy are inconsistent. However, in the UKPDS, a randomized comparison of more intensive *vs* less intensive blood pressure control in people with type 2 diabetes showed that intensive blood pressure control was associated with a decreased risk of retinopathy progression. Of the 1148 hypertensive patients in the UKPDS, 758

TABLE 2.
Reduction in retinopathy progression with intensive glycaemic control

	Decrease in haemoglobin A_{1c}	Reduction in progression of diabetic retinopathy
Diabetes Control and Complications Trial (DCCT)	10% decrease (i.e. 8% to 7.2%)	35–40%
UK Prospective Diabetes Study (UKPDS)	Every point decrease (i.e. 9% to 8%)	35%

From DCCT Research Group (1996); UKPDS Group (1998a)

were allocated to tight control of blood pressure and 390 to less tight control with a median follow up of 8.4 years (UKPDS Group, 1998c). Tight blood pressure control resulted in a 37% reduction in microvascular diseases, predominantly reduced risk of retinal photocoagulation, compared with less tight control. An earlier study of blood pressure medication in diabetic retinopathy suggested a specific benefit of angiotensin-converting enzyme (ACE) inhibition and blood pressure reduction, even in 'normotensive' people, on the progression of diabetic retinopathy (Chaturvedi et al, 1998). UKPDS included a randomized comparison of β-blockers and ACE inhibitors in the tight blood pressure control arm. Benefits from tight blood pressure control were seen in both treatment groups, with no statistically significant difference between them. This suggests that the effect is more likely to be secondary to blood pressure reduction than to a specific effect of ACE inhibitors.

Serum lipid levels: The WESDR, a population-based study, and the Early Treatment Diabetic Retinopathy Study (ETDRS) found that elevated serum cholesterol levels were associated with increased severity of retinal hard exudates (Klein et al, 1991; Chew et al, 1996). Independent of accompanying macular oedema, the severity of retinal hard exudate at baseline was associated with decreased visual acuity in ETDRS. The severity of retinal hard exudate was also a significant risk factor for moderate visual loss (loss of 15 or more letters on the visual acuity chart) during the course of the study. The most severe retinal hard exudates had double the risk of moderate vision loss in 5 years (*Figure 1*). Having severe hard exudates was the strongest risk factor for development of subretinal fibrosis in ETDRS patients with diabetic macular oedema (Fong et al, 1997).

Elevated serum triglyceride levels were also associated with a greater risk of developing high-risk proliferative diabetic retinopathy in the ETDRS patients (Davis et al, 1998). In a study in Pittsburgh, elevated triglycerides and elevated low-density lipoprotein cholesterol levels were found to be associated with proliferative diabetic retinopathy (Kostraba et al, 1991). Although these are all observational findings, the data strongly support lowering elevated serum lipids in patients with diabetic retinopathy to reduce the risk of vision loss. In addition to reducing cardiovascular risk, reducing the risk of vision loss should be a further motivating factor for patients to decrease elevated serum lipid levels.

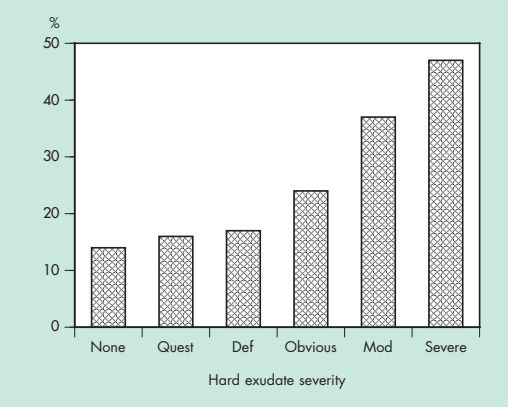

Figure 1. Per cent of patients with doubling of baseline visual angle at 5 years. Quest = questionable (not certain that there are hard exudates in the retina); Def =definite evidence of retinal hard exudate; Mod = moderate severity of retinal hard exudate.

Other risk factors

In addition to the modifiable risk factors presented previously, there are other risk factors that may be associated with the progression of diabetic retinopathy and some of these may also be modifiable.

Diabetic neuropathy: The risk of proliferative diabetic retinopathy was five times more common in patients with diabetic neuropathy compared with those without neuropathy in a cross-sectional analysis of approximately 2500 European patients (Tesfaye et al, 1995). In a case-control study of patients with or without proliferative diabetic retinopathy after 15–21 years of insulin-dependent diabetes at the Joslin Clinic, the odds of having cardiovascular autonomic neuropathy were 30–40-fold greater for those with proliferative diabetic retinopathy than those without (Krolewski et al, 1986). In ETDRS, the presence of neuropathy increased the risk of developing proliferative diabetic retinopathy by 26% to 32% ($P<0.0009$) (Davis et al, 1998).

Anaemia: In the ETDRS, a progressive increase in the risk of developing high-risk proliferative diabetic retinopathy was associated with decreasing haematocrit (Davis et al, 1998). In the lowest category of haematocrit for both men and women, there was a 52% increased risk ($P<0.0038$). Similar findings were seen in a cross-sectional study of patients in a diabetes clinic in Finland (Qiao et al, 1997).

Fibrinogen and albumin: In the DCCT, elevated fibrinogen and decreased albumin were associated with increased risk of diabetic retinopathy progression (McMillan et al, 1986, 1995). In the ETDRS, elevated fibrinogen increased the risk of proliferative diabetic retinopathy and this was of borderline statistical significance (Davis et al, 1998).

CONCLUSIONS

Diabetic retinopathy is a microvascular complication that is associated with a number of systemic risk factors, namely hyperglycaemia, elevated blood pressure, dyslipidaemia and others such as anaemia and elevated serum fibrinogen. Increased

fibrinogen suggests a possible inflammatory pathogenesis of diabetic retinopathy. Treatment of systemic factors, e.g. hyperglycaemia and blood pressure, has been proven in controlled clinical trials to prevent or reduce the rate of progression of diabetic retinopathy. Treatment of anaemia and dyslipidaemia may also be important in preventing or retarding the progression of diabetic retinopathy. Further clinical trials in these areas will increase our understanding of the aetiology of diabetic retinopathy. **HM**

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KEY POINTS

- Diabetic retinopathy is a leading cause of blindness in adults in many countries.
- Diabetic retinopathy increases with increasing duration of diabetes.
- The most important risk factor that is associated with both the development and progression of diabetic retinopathy is poor glycaemic control.
- Hypertension also increases the risk of progression of diabetic retinopathy.
- Other risk factors that may impact on unfavorably on the progression of diabetic retinopathy include dyslipidaemia, anaemia and elevated serum fibrinogen.