Diabetic retinopathy: an end of the century perspective

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In 1978 the late Kelly West wrote: 'The extent to which the level of hyperglycemia determines the risk of retinopathy is not all that clear.'[1] At that time, the 55% of persons with type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) took only one injection of long-acting insulin a day, essentially none did self blood glucose monitoring at least once per day, and the mean glycosylated haemoglobin A_{1c} level for this group was 10.1%.[2] The level of glycosylated haemoglobin in persons with type 2 disease, 9.0%, was also high. In addition, despite data from the Diabetic Retinopathy Study that showed panretinal photocoagulation resulted in a 50% reduction in severe visual loss (5/200 or worse) in eyes with severe proliferative retinopathy compared with eyes that were randomized to no treatment, only 54% of eyes with severe proliferative retinopathy in those with type 1 diabetes and 32% of those with type 2 diabetes had had such treatment.[3,4] Only 67% of those with type 1 diabetes and 50% of those with type 2 diabetes in the WESDR had been seen by an ophthalmologist within 2 years of the time they were studied in 1980–2.[5]

Twenty years later, the pathogenesis of diabetic retinopathy has become better understood, leading to new approaches to its treatment and prevention.[6,7] Epidemiological data from population-based studies[8] and clinical trials[9–11] have provided an answer to Kelly West's question. Data from the Diabetes Control and Complications Trial (DCCT) showed that in persons with type 1 diabetes, intensive treatment with insulin significantly reduced the risk of progression of retinopathy by 63%, of macular oedema by 26%, and the need for laser treatment by 51% compared with conventional treatment.[9] The WESDR showed that after adjusting for other risk factors in persons with type 2 diabetes a 1% decrease in glycosylated haemoglobin levels over the first 4 years of the study was associated with a 22% decrease in the odds of developing proliferative retinopathy and a 15% decrease in the odds of developing macular oedema at the 10-year follow-up.[8] In patients with type 2 diabetes, data from the United Kingdom Diabetes Prospective Study (UKPDS) showed that compared with the conventional group, the risk reduction for progression of diabetic retinopathy over a 12-year period in the intensive group was 21%.[12] In addition, there was a 29% reduction in the need for retinal photocoagulation in the intensive compared with the conventional group.

Understanding how hyperglycaemia mediates physiological and biochemical changes in the retina has resulted in the development of new strategies aimed at prevention and treatment of diabetic retinopathy. Hyperglycaemia has been hypothesised to: activate the diacylglycerol pathway with an increase in protein kinase C activity;[13] increase non-enzymatic glycosylation,[14] aldose reductase activity,[15] and secretion of vasoactive substances such as endothelin, prostanoids, histamine and nitrous oxide;[16] result in oxidant-induced free radical damage;[17] and release growth factors.[18] These biochemical changes have been postulated to lead to anatomical and functional changes in the retinal vasculature. The initiation and progression of retinopathy is probably due to a complex relationship among a number of these factors, that vary from person to person and at different stages of the retinopathy.

Data from the DCCT, UKPDS and epidemiological data from studies such as the WESDR resulted in the development by the American Diabetes Association of guidelines for glycaemic control in persons with type 1 and 2 diabetes.[19] In addition, data from the Early Treatment Diabetic Retinopathy Study suggested that severe visual loss of 5/200 could be prevented in 95% of patients with diabetes if there was early detection and timely photocoagulation treatment of clinically significant macular oedema and proliferative diabetic retinopathy.[20,21] This resulted in the development of guidelines by numerous groups, including the St Vincent Declaration,[22] which outlined approaches and set guidelines for early detection and timely treatment of vision-threatening diabetic retinopathy. A large body of literature has resulted describing the cost-effectiveness of such approaches, their implementation, and the success of such programmes.[23–25]

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The successful implementation of these guidelines for levels of glycaemic control has been difficult because achieving the levels of glycaemic control as recommended by the DCCT is associated with severe hypoglycaemia.[2,9] Other medical approaches to preventing or reducing the progression of retinopathy, such as control of hypertension, have recently been shown to reduce the progression of diabetic retinopathy in people with diabetes. A recently completed clinical trial suggested a benefit of the ACE inhibitor, lisinopril, in reducing the progression of diabetic retinopathy in persons with type 1 diabetes.[26] Tight blood pressure control resulted in a 34% reduction in the rate of progression of retinopathy, a 35% reduction in retinal photocoagulation, and a 47% reduction in the deterioration of visual acuity by three lines or more compared with conventional control in persons with type 2 diabetes participating in the UKPDS.[27] Other medical approaches to reducing the progression of retinopathy such as control of dyslipidaemia may be of benefit in reducing the incidence or microvascular and macrovascular complications. Clinical trials are under way to study the efficacy of control of dyslipidaemia and to further study the control of hypertension.[28] In addition, there are also randomised clinical trials under way to study the efficacy of new drugs such as protein kinase C inhibitors and anti-vascular endothelial growth factors, which may play a role in the pathogenesis of diabetic retinopathy, and clinical trials have been suggested to examine the benefits of vitamin E to prevent the incidence of retinopathy. If genetic susceptibility factors are found that explain variations in incidence and progression of retinopathy, then new treatments targeted to specific mechanisms administered at a specific stage in the natural history of the retinopathy might provide a complementary approach to glycaemic control in preventing the progression of retinopathy. Implementation of educational programmes, such as those developed by the National Eye Health and Education Program,[29] and developing cost-effective approaches, such as using newer computer-assisted approaches for detecting retinopathy in patients at risk for developing it, will probably result in a decline of diabetic retinopathy as an important cause of loss of visual acuity in the next century.

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