Is diabetic retinopathy an inflammatory disease?

A P Adamis

More work remains to prove this hypothesis

Inflammation may represent the inciting and final common pathway leading to the complex pathology that is diabetic retinopathy

If diabetic retinopathy is an inflammatory disease, then one would expect that anti-inflammatory drugs would have a beneficial effect. This seems to be the case. In 1964, it was observed that patients with rheumatoid arthritis receiving high doses of aspirin tended to have less severe diabetic retinopathy. Recently, Kern and Engerman directly tested the effect of aspirin in the relevant dog model of diabetic retinopathy. When started shortly after the onset of diabetes and given for 5 years, aspirin prevented certain classic histopathological features of diabetic retinopathy. Acellular capillary formation, retinal haemorrhage development, and capillary sudanophilia (a non-specific indicator of cellular degeneration) were all inhibited. A trend towards microaneurysm and pericyte ghost suppression was also observed, although statistical significance was not achieved. The moderately high doses utilised (20–25 mg/kg) were anti-inflammatory in nature and more than twice the antiplatelet dose utilised in the negative Early Treatment Diabetic Retinopathy Study aspirin trial (650 mg/day). Recent data in a rodent model complement and extend these findings by showing that a variety of anti-inflammatory drugs can be effective. High dose aspirin (50 mg/kg), meloxicam (cyclo-oxygenase-2 inhibitor), and etanercept (soluble tumour necrosis factor α receptor) each potently suppressed diabetic retinal ICAM-1 expression, leucocyte adhesion, and blood-retinal barrier breakdown. An inflammatory drug testing in human diabetic retinopathy has begun. Envision, a sustained release formulation of fluocinolone implanted into the vitreous, appears to resolve refractory diabetic macular oedema in early clinical testing (Andrew Pearson, MD, Foundation Fighting Blindness Drug Delivery Meeting, San Francisco, 2001).

How is the slowly evolving nature of diabetic retinopathy reconciled with the finding of early onset inflammation? As noted above, the inflammation is, at first, mild and subclinical in nature. It does not result in an overt vasculitis. However, because the inflammation is chronic in nature, the damage to the vascular endothelium is cumulative. The endothelial cells of the diabetic retinal vasculature proliferate and die at rates much higher than normal. The vascular injury, in large part, is leucocyte induced. As first proposed by Mizutani and coworkers, we hypothesise that the chronic low grade endothelial injury of early diabetes is reparable, but as diabetes progresses, the vascular endothelium reaches its Hayflick number and can no longer proliferate and repair the damaged endothelial lining. Acellular capillary formation ensues at this point. We speculate that with the formation of acellular capillaries, irreversible ischaemia develops, leading to marked retinal VEGF upregulation and transition to the proliferative stage of retinopathy.

How is VEGF, a molecule causally linked to the pathogenesis of diabetic retinopathy, connected to the inflammation? It is known that retinal VEGF expression is correlated with diabetic blood-retinal barrier breakdown and ischaemia related neovascularisation in animals and humans. Moreover, the inhibition of VEGF prevents these processes in relevant experimental models. New data now indicate that VEGF can also trigger inflammation.
In the retina and elsewhere, VEGF can induce ICAM-1 expression and leucocyte adhesion. Further, monocytes, via VEGF receptors on their surfaces, migrate in response to VEGF. When retinal ICAM-1 bioactivity is blocked, VEGF induced blood-retinal barrier breakdown is almost completely prevented, demonstrating the mechanistic link between the permeability and inflammation enhancing effects of VEGF.

In experimental diabetes, retinal VEGF levels increase within one week. When the human retinal VEGF bioactivity is blocked with a soluble receptor, the ICAM-1 upregulation, leucocyte adhesion, and blood-retinal barrier breakdown are all prevented. Taken together, these data strongly suggest that retinal VEGF upregulation occurs early in diabetes and serves as an important upstream inducer of early retinal inflammation. What triggers VEGF expression in the first place? There are no definitive answers as yet. However, changes in glucose concentration per se can alter VEGF expression and may represent a direct proximal upstream stimulus. As diabetes progresses, other stimuli, including advanced glycation end products and reactive oxygen intermediates, probably serve to further increase VEGF expression.

How relevant are the experimental data to human diabetic retinopathy? Rodent retinas, although lacking the ability to develop bone fide proliferative diabetic retinopathy, exhibit almost all the biochemical, pathophysiological, and histopathological features of background retinopathy. These include blood-retinal barrier breakdown, altered blood flow, vessel dilatation, microaneurym formation, basement membrane thickening, intraretinal microvascular abnormalities (IRMA), accelerated endothelial cell proliferation and death, pericyte loss, neural cell death, acellular capillary formation, haemorrhage formation, platelet microthrombi, and VEGF upregulation. However, care must be taken when extrapolating data generated in rodents to humans. An ongoing anti-ICAM-1 trial in Crohn's disease is showing some promise in humans. However, anti-CD18 trials for stroke and myocardial infarction, although supported by rodent data, failed quite spectacularly in humans. Yet the body of correlative evidence in the case of human diabetic retinopathy is greater than that for stroke and myocardial infarction.

McLeod and coworkers, in a landmark early study, found a marked increase in leucocyte density and retinal vascular ICAM-1 immunoreactivity in human eyes with diabetic retinopathy. Others have shown that human diabetic leucocytes are more activated and less deformable, and that patients with diabetic retinopathy have a more pronounced stimulus induced expression of leucocyte adhesion molecules. In addition, circulating adhesion molecule levels, shed from activated leucocytes and endothelium, are elevated in patients with progressively worsening retinopathy. Nevertheless, more evidence is needed.

Taken together, a body of data has been generated indicating that diabetic retinopathy is a low grade inflammatory disease. Inflammation, specifically leucocyte adhesion to the retinal vasculature, may represent the inciting and final common pathway leading to the complications that is diabetic retinopathy. However, more work remains to directly prove this hypothesis, especially in human diabetic retinopathy. The latter, after all, is the only model that really counts.

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Diabetic retinopathy

Blood pressure control and diabetic retinopathy

R Klein, B E K Klein

New insights

It is nearly 25 years since the Diabetic Retinopathy Study, a multicentred controlled clinical trial, first reported the efficacy of treatment by photocoagulation of proliferative diabetic retinopathy with high risk characteristics for visual loss.1 In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated the beneficial effects of focal laser treatment for clinically significant macular oedema in patients with diabetes.2 Based on data from these studies, it was estimated that timely detection and photocoagulation treatment of vision threatening retinopathy could prevent nearly 95% of severe visual loss in patients with diabetes.3 Despite the resulting development of guidelines and education and screening programmes for early detection and treatment of these problems, diabetic retinopathy still remains an important cause of visual loss.4 More recently, the Diabetic Control and Complications Trial (DCCT)5-7 and the United Kingdom Prospective Diabetes Study (UKPDS)8-11 have demonstrated the efficacy and cost effectiveness of glycaemic control in reducing the incidence and progression of retinopathy. However, data from these and other studies4-17 have confirmed how difficult it is to achieve and maintain good glycaemic control over a long period. For this reason, intervention on other risk factors such as hypertension have been studied in an effort to decrease the risk of visual loss due to diabetic retinopathy. The purpose of this commentary is to briefly describe new findings regarding the role of blood pressure control in the prevention of visual loss in people with diabetes and to review whether specific classes of antihypertensive medications are associated with reduced incidence and progression of retinopathy even in normotensive people with diabetes.

IS BLOOD PRESSURE ASSOCIATED WITH DIABETIC RETINOPATHY AND MACULAR OEDEMA?

Increased blood pressure has been hypothesised, through the effects of increased blood flow, to damage the retinal capillary endothelial cells in eyes of people with diabetes.18 This hypothesis has been supported by observations from clinical studies which showed an association between hypertension and the presence and severity of retinopathy in people with diabetes.19-22 While cross sectional data suggest that hypertension is associated with diabetic retinopathy, longitudinal data have been inconsistent.23-24 The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure.25 Of the 1919 patients with older onset (type 2) diabetes from that study with retinal photographs taken at diagnosis and 6 years later, systolic blood pressure was significantly associated with retinopathy incidence (type 2). Those in the top tertile range was found to be associated with a 330% increased 4 year risk of developing macular oedema compared to the first tertile range. The difference between treatment groups was no longer statistically significant (p=0.06). There was no significant interaction with blood glucose control. It has been postulated that ACE inhibitors, such as lisinopril, might have an effect independent of blood pressure lowering through a number of possible mechanisms which included a beneficial haemodynamic effect, enhancement of nitric
oxide resulting in a reduction of endothelial dysfunction, blockage of vascular endothelial growth factor receptors, and reduction in metalloproteinase activity improving the blood-retinal barrier. It may also be true that higher blood pressure, even in the “normal range,” is still associated with risk, and thus lowering blood pressure at all levels might be beneficial to the retina. This is consistent with observations from the UKPDS which reported that there was no evidence of a threshold effect of systolic blood pressure on the incidence of microvascular complications in people with type 2 diabetes mellitus.

The UKPDS also sought to determine whether lower blood pressure achieved with either a β blocker or an ACE inhibitor was beneficial in reducing macrovascular and microvascular complications associated with type 2 diabetes mellitus. A total of 1048 patients with hypertension (mean blood pressure 160/94 mm Hg) were randomised to a regimen of tight control of blood pressure with either captopril or atenolol and another 390 patients to less tight control. The aim in the group randomised to tight control was to achieve blood pressure values <150/<85 mm Hg. If these goals were not met with maximal doses of a β blocker or ACE inhibitor, additional medications were prescribed, including a loop diuretic, a calcium channel blocker, and a vasodilator. The aim in the “control” or conventionally treated group was to achieve blood pressure values <180/<105 mm Hg. Tight blood pressure control resulted in a 35% reduction in retinal photocoagulation compared to conventional control. After 7.5 years of follow up, there was a 34% reduction in the rate of progression of retinopathy by two or more steps using the modified ETDRS severity scale and a 47% reduction in the incidence of deterioration of visual acuity by three lines or more using the ETDRS charts (for example, a reduction in vision from 20/30 to 20/60 or worse on a Snellen chart). It is assumed that the effect was largely due to a reduction in the incidence of diabetic macular oedema. Atenolol and captopril were equally effective in reducing the risk of developing these retinal microvascular complications. The effects of blood pressure control were independent of those of glycaemic control. These findings support the recommendations for tight blood pressure control in patients with type 2 diabetes mellitus as a means of preventing visual loss from diabetic retinopathy.

The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial was a prospective randomised masked clinical trial comparing the effects of intensive (diastolic blood pressure goal of 75 mm Hg) and moderate (diastolic blood pressure of 80-89 mm Hg) blood pressure control in 470 hypertensive subjects (baseline diastolic blood pressure of ≥90 mm Hg) with type 2 diabetes mellitus. People were randomised to nisoldipine 10 mg/day (titrated up to 60 mg/day as needed), enalapril 5 mg/day (titrated up to 40 mg/day as needed), or placebo as the initial hypertensive medication. If single study medication alone did not achieve the target blood pressure, then metoprolol followed by hydrochlorothiazide was added until the target blood pressure was achieved. The mean blood pressure achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate control group. Over a 5 year follow-up period, there was no difference between the intensive and moderate groups with regard to progression of diabetic retinopathy. There was no difference in nisoldipine versus enalapril in progression of retinopathy. The authors concluded that lack of efficacy in their study compared to the UKPDS might have resulted from the shorter time period of the ABCD trial (5 years versus 9 years on average for the UKPDS), lower average blood pressure control in the ABCD trial (144/82 mm Hg versus 154/87 mm Hg in the UKPDS), and poorer glycaemic control in the ABCD trial than the UKPDS. It is possible that there is a threshold effect below which there is no or minimal effect of reducing the risk of progression of retinopathy by further reduction of blood pressure. Results from other clinical trials that are currently underway should provide more information regarding the relative efficacy of blood pressure control and specific antihypertensive medications in reducing the progression of retinopathy in people with diabetes.

CONCLUSIONS

Hypertension in people with diabetes is common, affecting 30% of people with younger onset diabetes mellitus and 75% with older onset diabetes mellitus (Klein R, unpublished data). It is often poorly controlled with only about 60% of those with younger onset diabetes mellitus and 42% of those with older onset diabetes mellitus achieving normal blood pressure (Klein R, unpublished data). While observational longitudinal data show an association of blood pressure with long term incidence and progression of retinopathy, there is no clinical trial evidence that blood pressure control prevents the incidence and progression of retinopathy in those with type 1 diabetes mellitus. The data for people with type 2 diabetes mellitus are not consistent. The efficacy of blood pressure control for retinopathy in people with hypertension and diabetes may be a moot point because of the known serious systemic sequelae (for example, higher risk of cardiovascular disease, nephropathy, and amputation) of uncontrolled hypertension. For these reasons the American Diabetes Association has issued guidelines for targeted systolic blood pressure levels of <130 mm Hg and diastolic blood pressure levels of <85 mm Hg. Whether lowering of blood pressures already in the normal range is beneficial, is still unknown.

An important unanswered question is: do specific types of antihypertensive agents, such as ACE inhibitors, have a beneficial effect in preventing the incidence and progression of retinopathy in diabetic people who are normotensive? The EUCLID data are suggestive for people with type 1 diabetes mellitus, but the findings are not conclusive owing to the small sample size in that study. The UKPDS data show no difference in the efficacy of ACE inhibitors and β blockers with regard to retinopathy progression in people with type 2 diabetes mellitus, suggesting that blood pressure lowering and not the type of medication was more important in people with moderately severe hypertension. Thus, ophthalmologists at this point should not be recommending a specific type of antihypertensive medication, such as ACE inhibitors, be used for reducing the risk of progression of diabetic retinopathy in normotensive or normotensive individuals. The medications may be costly and are not without risk. However, for diabetic people with cardiovascular disease, microalbuminuria, or nephropathy, this too may be a moot point. Data from the Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril, an ACE inhibitor, substantially lowered the risk of death from cardiovascular disease by 37%, stroke by 33%, myocardial infarction by 22%, need for revascularisation procedure by 17%, and overt nephropathy by 24% in a group of diabetic patients (n=3577, of whom 56% had known hypertension) participating in that study.

These findings resulted despite a very small reduction in blood pressure. A large randomised controlled clinical trial, the DIRECT study, has just begun with its major objective to examine the efficacy of use of ACE inhibitors to prevent incidence and progression of retinopathy in people with type 1 and type 2 diabetes mellitus.

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REFERENCES
Anti-angiogenic therapy for uveal melanoma—more haste, less speed

A W Stitt, T A Gardiner

Tumour angiogenesis is a key concept that supports investigations in a range of clinically relevant research areas

Uveal melanoma represents a serious ophthalmic problem and much research is under way to optimise the range of available treatment options. Recent reviews have highlighted the key role of angiogenesis to tumour growth and metastasis. 

Angiogenesis continues to be developed as an ever increasing range of anti-angiogenic therapeutic approaches. As a result, it is perhaps worth considering the pros and cons of such approaches. As a case in point, uveal melanomas carry a serious risk of metastasis and enucleation remains a necessary, if last resort, option. Therefore, there are real pressures to take radical steps that may reduce growth and metastatic potential of these aggressive tumours and prevent secondary neovascularisation.

Anti-angiogenic agents play a key role in the treatment of uveal melanomas. However, their effectiveness has been limited.

Angiogenesis is...
tumours. Using fundamental laboratory and clinic based research, the angiogenic characteristics of the vasculature in uveal melanomas should be carefully determined. This is important, since residence in a highly oxygenated microenvironment such as the choroid may make uveal melanomas distinct from cutaneous counterparts. Also, recent research, indicates that the vasculature of many tumours exists in a dynamic equilibrium of mature and immature vessels and that highly malignant varieties (such as glioblastomas) have a very high ratio of immature vessels. This subpopulation of vessels is often the specific target of anti-angiogenic agents. This being the case, new tumour specific and tumour vasculature specific targets should be identified that can ultimately allow precisely targeted treatments, that will not significantly upset the delicate angiogenic balance that exists in many ocular tissues. Following on from this, novel delivery systems should be developed, which will allow tumours lodged in the posterior uvea to have efficacious agents delivered at appropriate concentrations while minimising risk to the non-involved retina or choroid. Efficient transcleral delivery is being researched and, if possible, may provide a approach that is particularly relevant to uveal melanomas.

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We are very excited with this new development and I would encourage authors and reviewers to use the online system where possible. It really is simple to use and should be a big improvement on the current peer review process. Full instructions can be found on Bench>Press http://submit-bjo.bmjjournals.com/ and BJO online at http://www.bjophthalmol.com/. Please contact Natalie Davies, Project Manager, ndavies@bmjgroup.com for further information.