Is diabetic retinopathy an inflammatory disease?

A P Adamis

More work remains to prove this hypothesis

Last year an ARVO symposium organised by Tim Kern was titled “Is diabetic retinopathy an inflammatory disease?” It is a timely question. Chronic subclinical inflammation may underlie much of the vascular pathology of diabetic retinopathy. Nomenclature is critical to this discussion, so the definition of inflammation bears repeating here. Macroscopic inflammation comprises the classic signs of pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (funcio laesa). None of these signs, except for swelling and loss of function, clearly applies to diabetic retina. However, at a microscopic level, inflammation consists of vessel dilatation, altered flow, exudation of fluids, including plasma proteins, and leucocyte accumulation and migration. Given the recent data that have been generated in relevant models of diabetic retinopathy, the latter definition appears to fit. A brief overview of the evidence illustrates this point.

Within one week of experimental diabetes, leucocytes adhere to and accumulate within the vasculature of the retina. A subpopulation of these leucocytes exits the vasculature and transmigrates into the neural retina. The leucocyte increases are moderate in nature and precede any overt clinical evidence of retinopathy. However, they progress with time. Monocytes and neutrophils predominate, although preliminary data suggest that lymphocytes may be involved as well (Ahmed, Ishida, Adamis, et al, unpublished observation). The leucocytes actively tether themselves to the endothelial cell lining via classic adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) on the vasculature and β2 integrins on the leucocytes. The expression levels for these adhesion molecules increase in early diabetes and correlate with the leucocyte increases. Additional adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and VLA-4 may also be involved, but here the data are more preliminary.

The leucocyte increases coincide with the onset of diabetic vascular dysfunction. At first, the dysfunction is subclinical in nature, probably because of the lack of sensitivity of our current clinical detection methods. However, when more powerful experimental techniques are applied, the early alterations uncovered include a subtle breakdown of the blood-retinal barrier, premature endothelial cell injury and death, and capillary ischaemia/reperfusion.

The leucocytes appear to be causal for these pathologies. When diabetic rats are treated with ICAM-1 or β2 integrin neutralising antibodies, leucocyte adhesion is suppressed, blood-retinal barrier breakdown is normalised, and endothelial cell injury and death are prevented. When mice deficient in the ICAM-1 or β2 integrin gene CD18 are made diabetic and followed for 11 months, the retinal vasculature is indistinguishable from age matched normal control mice (Joussen, Poulik, Adamis, et al, unpublished data). In contrast, the retinas from diabetic ICAM-1 and CD18 competent mice exhibit marked increases in leucocyte density, blood-retinal barrier breakdown, and endothelial cell injury and death. Since 11 months represents almost half of the normal mouse life span, these data suggest that the inhibition of leucocyte adhesion provides effective long-term suppression of certain diabetes related pathologies.

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. Anti-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 Hayfllick 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 leukocyte 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, leukocyte 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, microaneurysm 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 leukocyte density and retinal vascular ICAM-1 immunoreactivity in human eyes with diabetic retinopathy. Others have shown that human diabetic leukocytes are more activated and less deformable, and that patients with diabetic retinopathy have a more pronounced stimulus induced expression of leukocyte adhesion molecules. In addition, circulating adhesion molecule levels, shed from activated leukocytes 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, especially leukocyte adhesion to the retinal vasculature, may represent the initiating and final common pathway leading to the complex pathology 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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Blood pressure control and diabetic retinopathy

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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 and is nearly 25 years since the Diabetic Retinopathy Study.4,5

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.6,7 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.8–11 While cross-sectional data suggest that hypertension is associated with diabetic retinopathy, longitudinal data have been inconsistent.12–18 The UKPADS showed that the incidence of retinopathy was associated with systolic blood pressure.19 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 of blood pressure were 2.8 times (95% confidence interval) as likely to develop retinopathy as people in the lowest tertile range (systolic blood pressure >140 mm Hg). There was no significant difference in the progression of retinopathy.19

Does control of blood pressure reduce the risk of incidence and progression of retinopathy? If so, is the type of medication used to control blood pressure important?

Results from three clinical trials have recently been published regarding the association of blood pressure control and type of antihypertensive medication used with the incidence and progression of retinopathy.20–23 The EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus (EUCLID) Study sought to examine the role of an angiotensin converting enzyme (ACE) inhibitor in reducing the incidence and progression of retinopathy.24 The subjects included a group of largely normotensive younger onset diabetic patients of whom 85% did not have microalbuminuria at baseline. The study showed a statistically significant 50% reduction in the progression of retinopathy in those taking lisinopril over a 2 year period compared to those not on blood pressure medication, after adjustment for glycaemic control. Progression to proliferative retinopathy was also reduced by 82% in the group taking lisinopril compared to the group treated with the placebo. After controlling for study site, 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
oxida resulting in a reduction of endothelial dysfunction, blockade of induction of vascular endothelial growth factor receptors, and reduction in monocyte adhesion activity improving the blood-retinal barrier.\(^{10}\) 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.\(^{55}\)

The UKPDS also sought to determine whether lower blood pressure achieved with either \(\beta\) blocker or an ACE inhibitor was beneficial in reducing macrovascular and microvascular complications associated with type 2 diabetes mellitus.\(^{57}\) A total of 1048 patients with hypertension (systolic 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 \(\beta\) 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 photoocoagulation 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.\(^{36}\) 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.\(^{37}\) 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 under way 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.\(^{58}\) 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.\(^{59}\) The UKPDS data show no difference in the efficacy of ACE inhibitors and \(\beta\) 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.\(^{60}\) 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 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.\(^{46-48}\) 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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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.

Angiogenesis is... thought to be a central event in growth of ocular neoplasms... where a high tumour vascularity index carries increased risk of metastasis and poor prognostic outcome.

In this issue of the BJO, Boyd et al (pp 440 and 448) present data that confirm an important role for vascular endothelial growth factor-A (VEGF-A) and, to a lesser extent, basic fibroblast growth factor (bFGF) in angiogenic growth in and around uveal melanomas. Using a range of approaches, they assayed these factors in ocular fluids and postmortem specimens from patients, grew co-cultures of tumour cells and endothelium in vitro, and concluded that anti-angiogenic therapy may be a worthwhile approach for treatment of eyes harbouring uveal melanomas. In many of these tumours VEGF-A was expressed at high levels, and this was especially true in patients who developed secondary retinal and iris neovascularisation following ionising radiation treatment of their tumours. VEGF-A expression was shown to be particularly high in the ocular fluids of this subset of patients and Boyd et al conclude that this phenomenon makes the case for anti-VEGF-A treatment as an adjunctive therapy in the treatment of uveal melanoma and secondary neovascularisation. While this may be so, the authors acknowledge that the situation is still extremely complex and interpatient variability remains surprisingly high. Furthermore, it should be considered that increased levels of VEGF following irradiation of the tumour could represent a classic response to tissue hypoxia following enhanced destruction of vascular endothelial cells that, in the case of melanoma, may be more radiosensitive than the tumour they serve.

While anti-angiogenic therapies continue to be developed at an ever increasing pace, 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. Agents such as anti-VEGF antibodies, VEGF receptor or integrin antagonists, VEGF antagonists, matrix metalloproteinase (MMP) inhibitors, antisense oligonucleotides to growth factor mRNAs, and established drugs such as thalidomide are already in various stages of clinical trial and may offer therapeutic benefits. Given the proliferation of these anti-angiogenics and the prolonged nature of many trials we will soon discover the validity of such an approach. However, it should be considered that growth factors such as VEGF-A represent single members of highly complex and interrelated families, many of which can also contribute to ocular angiogenesis. Even more importantly, many of these peptides are proved survival factors, especially in the retinal microvasculature. And their effective depletion in a delicately balanced system could have serious long term and unwanted vasodegenerative effects in non-target tissue.

Another potentially negative consequence of an anti-angiogenic strategy for uveal melanomas and/or secondary neovascularisation, especially as an adjunct to radiation therapy, may be the inadvertent promotion of a more aggressive tumour phenotype. It has been demonstrated in various malignant tumours that induction of hypoxia, by restricting vascular supply, may actually promote selection of hypoxia resistant tumour cells with decreased apoptotic potential. An initial reduction in tumour size may be followed by a more malignant counterpart (for a review of this concept see Hockel and Vaupel). It is clear, therefore, that during treatment of the neovascular consequences of uveal melanomas with anti-angiogenics, their effects on tumour growth and stability will need to be carefully monitored. In addition, recent evidence also points towards anti-angiogenic therapy (in particular through blocking VEGF-A bioactivity) that serves to "normalise" tumour vasculature, which in turn promotes effective delivery of oxygen that is essential for efficacious radiotherapy. In short, it may be important to make use of anti-angiogenic approaches in a carefully planned and titrated manner that can enhance therapy of solid tumours.

Uveal melanomas represent a serious ocular problem and much research is needed in order to advance the established ophthalmic approaches to these
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 the presence of 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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New BJO online submission and review system

I am pleased to inform authors and reviewers that as of 17 April 2002, BJO will be using a new online submission and review system. Developed by Highwire Press (CA, USA), Bench>Press is a fully integrated electronic system which utilises the web to allow rapid and efficient submission of manuscripts. It also allows the peer review process to be conducted entirely online. The aim, apart from saving trees, is to speed up the frequently frustrating progress from submission to publication.

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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.