

# BjO

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## Editorials

### Matrix metalloproteinases and their natural inhibitors

In this issue of the *BjO* an interesting study is presented by Salzmann *et al* (p 1092) in which they analyse, by immunohistochemistry, the epiretinal membranes in proliferative diabetic retinopathy (PDR) for the presence of certain matrix metalloproteinases (MMPs) and their inhibitors. MMPs are a group of zinc dependent proteolytic enzymes that play an important part in the degradation of extracellular matrix components during developmental, physiological, and pathological processes. These enzymes are naturally inhibited in the extracellular matrix by the tissue inhibitors of metalloproteinases (TIMPs), and expression of MMPs and TIMPs is regulated by a variety of growth factors, cytokines, oncogenes, and tumour promoters. Currently, at least 18 MMPs and four TIMPs have been identified, and their potential roles in vitreoretinal disorders have been discussed recently in a *BjO* perspective.<sup>1</sup>

MMPs are very likely to have an important role in the pathological processes underlying PDR. However, with such a complex system of enzymes and enzyme regulation, a tenet that is central to the work of Salzmann *et al* is that certain MMPs or TIMPs play a specific part in PDR; if these could be identified, then it may be possible to selectively modulate their actions in order to improve the treatment of this condition. Salzmann *et al* looked for the presence of MMP-1, MMP-2, MMP-3, MMP-9, TIMP-1, TIMP-2, and TIMP-3 in PDR membranes and essentially demonstrated the presence of all of them in a large proportion of membranes. In addition, they obtained similar data when proliferative vitreoretinopathy (PVR) membranes were analysed. These findings raise a number of issues that will now be discussed.

If the various MMPs and TIMPs found in the membranes are synthesised by cells contained within the pathological membranes this would tend to suggest that they have specific roles in the underlying pathological processes. It is quite possible that some or all of the MMPs and TIMPs are synthesised by the cells within the membranes, but other possibilities also exist. Some of the MMPs and TIMPs may be derived from the circulation as there is increased vascular permeability as a result of the neovascular process. It is also possible that they are derived from the vitreous as all of the MMPs and TIMPs identified in the PDR membranes by Salzmann *et al* have also been identified in the normal vitreous.<sup>2,3</sup> The vitreous MMPs were generally found to be in the inactive proform. However, it has been demonstrated that a single vitreous gel contained sufficient (latent) MMP2 to cause considerable structural damage when activated and introduced in

vitro into another vitreous gel.<sup>4</sup> Therefore, there is sufficient endogenous metalloproteinase in the normal vitreous to have a significant biological effect. The vitreous may therefore be acting as a source of MMPs and TIMPs that are used during PDR and PVR membrane formation. It is also possible that the MMPs and TIMPs that were identified as associated with PDR and PVR membranes were derived from the vitreous and may have been masking more specific and subtle expression patterns produced by cells within the membranes. These uncertainties can be addressed to some extent by looking at the proportion of active enzyme in the membrane and, indeed, a recent report showed that a significant proportion of the MMP-2 and MMP-9 in PDR membranes were in an active form.<sup>5</sup> An alternative approach would be to look at the expression of specific mRNAs for MMPs and TIMPs within the pathological membranes.

A difficulty with this study is that, inevitably, late stage membranes were analysed where much of the active growth and remodelling had already taken place. This is particularly a problem because the development of PDR membranes is a multistage process. Initially, there is an angiogenic process in which basement membrane degradation, endothelial cell migration, capillary tube formation, and endothelial cell proliferation occur. Then there is degradation of the internal limiting lamina (ILL) allowing the neovascular tissue to enter the vitreous cavity. Once in the vitreous cavity the neovascular tissue grows along and into the cortical vitreous gel and there is a second wave of cellular proliferation and extracellular matrix deposition which results in the formation of contractile fibrovascular tissue. Finally, the new blood vessels and associated fibrous tissue undergo remodelling. It is likely that by the time that PDR membranes are surgically removed these underlying pathological processes will be at a late stage in this sequence of events, while an understanding of the early events, such as initiation of angiogenesis and degradation of the ILL, is more likely to point the way towards new therapeutic strategies.

Despite these difficulties one very interesting observation made by Salzmann *et al* was that MMP9 expression was specifically seen within perivascular matrix in PDR membranes, perhaps suggesting a specific role for MMP9 in the neovascular process. These findings resonate with other work which has shown increased levels of MMP-9 (predominantly in the latent proform) in the vitreous of diabetic patients.<sup>6,7</sup> MMP-9 is one of the metalloproteinases that is capable of degrading type IV (basement membrane) collagen and as such may well be involved in the

basement membrane degradation that occurs during angiogenesis and breakdown of the ILL. In addition, a further, as yet unidentified 75 kDa metalloproteinase has been identified in PDR vitreous, whereas this enzyme was not commonly seen in controls.<sup>3</sup>

The work by Salzmann *et al* and others makes an important contribution to our understanding of the role of MMPs and TIMPs in PDR. How can we further enhance our understanding and what are the most direct paths to allow us to move from basic biomolecular research to improved clinical management? Much has still to be learnt about the functions of MMPs and TIMPs and the regulation of their expression. It is likely that genetic experiments will contribute greatly to this area; for example, generating and studying the phenotype of “knockout” mice where a specific MMP or TIMP gene has been removed will allow us to understand more about the individual functions of these proteins. Much of the current research on the role of MMPs and TIMPs in proliferative disorders is driven by the pharmaceutical industry in the hope that drugs that modulate their function could be used in the treatment of cancer. Already a number of synthetic MMP inhibitors are undergoing clinical trials and a pragmatic approach for

ophthalmic researchers may be to test these various pharmaceutical agents in experimental models of preretinal neovascularisation (and PVR) and to determine empirically whether these agents modify the disease process.

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## The conundrum of sweet hyperopia

The diabetic patient presenting with changing refractive error is not uncommon. We are taught to check for diabetes mellitus if a patient presents with rapidly changing refraction and advise them that spectacles should not be prescribed until the refractive state has stabilised.

A low degree of myopia (in the order of  $-2D$ ) is more common in metabolically stable adult diabetics<sup>1</sup> and is understood to be due to an increase in lens thickness<sup>2</sup> and surface curvature.<sup>3,4</sup> Although it is well recognised that transient refractive changes are common during periods of hyperglycaemia, or falling blood glucose during intensive glycaemic control, there has been some controversy about the nature of the changes and the underlying causes. It has been considered that myopia develops in hyperglycaemia,<sup>5,6</sup> and that following therapy there is an hyperopic shift.<sup>7–11</sup> Some investigators have suggested that acute changes may cause either myopia or hyperopia.<sup>12,13</sup> Most of these studies have been retrospective and the study by Okamoto *et al* in this issue of the *BJO* (p 1098) is helpful in clarifying some of these issues. In monitoring a group of poorly controlled diabetic patients during intensive glycaemic control there was an increase in hyperopia in all patients studied. The degree of hyperopia correlated with the level of hyperglycaemia and the rate of plasma glucose reduction.

The refractive power of the eye depends on the anterior and posterior corneal curvature, the corneal thickness, the anterior chamber depth, the lens thickness, the anterior and posterior curvature of the lens, the axial length of the eye, and the refractive index of the cornea, aqueous, lens, and vitreous. Okamoto *et al* report that there was no evidence of a change in lens or corneal curvature, lens thickness, or axial length of the eye, and conclude that a change in refractive index of the lens is responsible for the refractive changes. That the refractive changes are due to a change in the lens is supported by studies investigating refractive changes in both phakic and aphakic patients.<sup>14</sup>

The mechanism of the increased refractive index and why it takes so long to reverse (up to 20 weeks) remains

obscure. There is no knowledge of the biochemical changes occurring in the diabetic lens and any hypothesis is based on experimental studies. Current opinion favours the view that osmotic changes lead to changes in lens hydration.<sup>15</sup> Transient differences in osmotic pressure may occur across the blood-ocular barrier and the lens capsule. The lens membranes are permeable to glucose but much less so to sugar alcohols such as sorbitol. As hyperglycaemia stimulates sorbitol production in the lens it may be expected that a subacute rise in glucose levels in the aqueous would result in increased production of sorbitol in the lens and overhydration of the lens. On the other hand an acute rise in external glucose levels causes dehydration of the lens *in vitro*.<sup>16</sup> Depending on the changes in osmotic pressure across the lens membrane, owing to either differing glucose concentrations or sugar alcohol levels within the lens, arguments can be made for either swelling or dehydration of the lens. A change in refractive index must also be considered.

The production of sorbitol via the polyol pathway in the human lens has been questioned in relation to the refractive changes seen in diabetics.<sup>15</sup> Reduction of sugar to sugar alcohol requires the presence of the enzyme aldose reductase, the levels of which are very low in the human lens. The enzyme is located in the lens epithelium and to a lesser extent in the superficial fibres.<sup>17</sup> Aldose reductase activity to glucose is poor and it has been suggested that sorbitol may be produced in the human lens from fructose.<sup>15</sup>

Hyperglycaemia may also affect the permeability of the lens membrane<sup>18</sup> and may influence lens metabolism through yet unknown mechanisms.

The refractive power of the lens is affected by the refractive gradients across the cortex and nucleus and is dependent on the protein (crystallin) gradients across serial layers of lens fibres. The refractive index and protein concentration is lower in the cortex than the nucleus.<sup>19,20</sup> Changes in refractive index therefore may partly depend on how excess water is distributed in the lens.

Although the basic pathophysiology remains puzzling the paper by Okamoto *et al* is helpful in establishing the natural history of the refractive changes and is welcome.

Does this influence what advice we give our patients? Patients may have significant problems with everyday tasks including driving. They may require frequent changes of spectacle prescription to function normally till stabilisation. With regard to patients considering refractive surgery, diabetes mellitus remains a relative contraindication to excimer laser photoablative surgery.<sup>21</sup>

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### Cover illustration: You have an eagle eye

Eagles are majestic birds, and their feeding methods often betoken their majesty. The African fish eagle (*Haliaeetus vocifer*) is an aerial killer and a robust fisher, although it certainly can be a scavenger or even a pirate of other bird's prey. Few species of birds fish on the wing, but *H vocifer*, and its North American counterpart, the bald eagle (*H leucocephalus*), are thoroughly equipped to do so. These bifovate birds rely upon their visual abilities to facilitate their spectacular foraging methods. As can be seen in the photographs, *H vocifer* will follow its prey throughout the approach and, at the instant of strike, the bird will redirect its gaze to keep the fish in stereoscopic visualisation. The head down position, seen in the photographs on the cover, allows the eagle to use both temporal foveae for binocular stereopsis. The second, or more nasal, fovea in each eye is probably used to spot the prospective prey and perhaps keep the prey in alignment during the initial flight approach. The connecting infula (linear strip fovea connecting the nasal and temporal fovea of each eye), allows the eagle to begin stereoscopic tracking at some point during the approach to help assure that the fish will not be lost in the three dimensional peregrinations within its watery home. The infular strip allows for foveal quality vision as the image swings from the nasal fovea to the temporal fovea in each eye. Although it is not clear when the image becomes stereoscopic, ray tracing would suggest that the infula would allow this stereopsis especially in the later stages of approach.

The eyes are large, both absolutely and relatively, with a globular shape approaching our own. Many eagles have a photoreceptor concentration of over one million/mm<sup>2</sup> photoreceptors in the fovea, compared with our own 200 000/mm<sup>2</sup>. The steep walled temporal foveae may even afford additional linear magnification increasing visual acuity further.

Combine this with a clearer visual axis, increased amacrine cell concentration in the retina, and absent vascular system in front of their retinas, and one has a formidable ocular system with an “eye mindedness” quality.

Usually male and female fish eagles will fish and share their catch with each other in and out of breeding season as they live in lifelong pairs. They have rarely been seen drinking despite their close association with water.

An endearing quality of these birds is their spectacular nuptial display. A mated pair will soar over their territory, calling to each other. The male will dive towards the female, and she will turn over in flight and grasp his talons with hers. Once united with wings outstretched and legs straight, they will spin in graceful cartwheels towards earth breaking contact as they approach ground, only to begin a climb to a suitable height to repeat the performance. This display is often done outside the breeding season and perhaps is a method of re-establishing their mutual bond.

As with the bald eagle in North America, the African fish eagle will utilise piracy (especially from the osprey) and scavenging (carrion) for food. *H vocifer* has been known to prey upon weaker birds, such as flamingoes and young water birds, especially if these prey species are injured or separated from their flocks. None the less, fish make up 90% of its diet. This eagle has been known to take fish weighing up to 2 kg, a tremendous burden to lift out of the water since even the larger female has a maximum weight of approximately 3½ kg.

Although found in large flocks when food is plentiful, fish eagles are frequently seen as a single pair or an individual bird and are concentrated along rivers, lakes, and wooded sea coasts of sub-Saharan Africa. Their regal appearance and dramatic feeding habits make this species an unforgettable emblem of Africa.—IVAN R SCHWAB, *University of California, Davis, Medical School, Department of Ophthalmology*



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