Positive correlation between vitreous levels of advanced glycation end products and vascular endothelial growth factor in patients with diabetic retinopathy sufficiently treated with photocoagulation

Masahiko Yokoi, Sho-ichi Yamagishi, Masayoshi Takeuchi, Takanori Matsui, Yumiko Yoshida, Kazuhiro Ohgami, Tamami Amano-Okamoto and Shigeaki Ohno

doi:10.1136/bjo.2006.100198

Updated information and services can be found at:
http://bjo.bmj.com/cgi/content/full/91/3/397

These include:

References
This article cites 5 articles, 2 of which can be accessed free at:
http://bjo.bmj.com/cgi/content/full/91/3/397#BIBL

Rapid responses
You can respond to this article at:
http://bjo.bmj.com/cgi/eletter-submit/91/3/397

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to British Journal of Ophthalmology go to:
http://www.bmjjournals.com/subscriptions/
PostScript

Derek Stephens
Population Health Sciences, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Jane D Kivlin
Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Alex V Levin
Departments of Paediatrics and Ophthalmology and Vision Science, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Correspondence to: Dr A V Levin, Department of Ophthalmology and Vision Science, The Hospital for Sick Children, 555 University Avenue, M3B 3B7 Toronto, Ontario, Canada MSG 1X8; alex.levin@sickkids.ca
doi: 10.1136/bjo.2006.099481
Accepted 2 July 2006

Competing interests: None declared.

References


Positive correlation between vitreous levels of advanced glycation end products (AGEs) and vascular endothelial growth factor (VEGF) in patients with diabetic retinopathy sufficiently treated with photocoagulation

We investigated whether vitreous levels of advanced glycation end products (AGEs) were positively correlated with vascular endothelial growth factor (VEGF) in patients with diabetic retinopathy sufficiently treated with photocoagulation. Vitreous AGE and VEGF levels were significantly higher in patients with diabetes than in controls. Positive correlation between AGE and VEGF was found in patients with diabetic retinopathy sufficiently treated with retinal photocoagulation. Vitreous AGE and VEGF levels were significantly higher in patients with diabetes than in controls. Positive correlation between AGE and VEGF was found in patients with diabetic retinopathy sufficiently treated with retinal photocoagulation \((r = 0.26, p = 0.18)\). The present observations suggest that AGE may induce VEGF expression in an ischaemia-independent mechanism. AGE could be one of the important determinants of VEGF in diabetic retinopathy without obvious ischaemic regions.

Background

Vascular endothelial growth factor (VEGF) elicits retinal vascular hyperpermeability, thrombosis and angiogenesis, having a central role in the pathogenesis of diabetic retinopathy. Furthermore, vitreous VEGF levels are increased in proliferative diabetic retinopathy, whereas the levels are decreased after treatment with panretinal photocoagulation (PRP). These observations suggest that retinal ischaemia and resultant hypoxia could mainly contribute to VEGF induction in diabetic retinopathy.

Advanced glycation end products (AGEs), senescent macroprotein derivatives formed at an accelerated rate under diabetes, also stimulate VEGF expression in cell cultures and animal models. In addition, vitreous AGE levels are positively correlated with VEGF in patients with diabetic retinopathy, suggesting that AGEs may be a stimulant of VEGF in vivo. However, as AGEs predispose the retinal vessels to thrombogenesis, whether AGEs could induce VEGF expression in an ischaemia-independent manner remains unknown.

Therefore, in this study, we determined the relationship between vitreous levels of AGEs and VEGF in patients with diabetic retinopathy who were sufficiently treated with PRP for controlling retinal ischaemia.

Figure 1 Vitreous levels of advanced glycation end products (AGEs; A) and vascular endothelial growth factor (VEGF; B) in controls without diabetes and in patients with diabetes, including the sufficiently treated group with panretinal photocoagulation (S-PRP) and the insufficiently treated group with no or focal photocoagulation (IS-PRP). Data analysed by Mann–Whitney U test. All samples were analysed by the Mann–Whitney U test. All samples were analysed by the Mann–Whitney U test.

Figure 2 Correlation between the vitreous levels of advanced glycation end products (AGEs) and vascular endothelial growth factor (VEGF) in the sufficiently treated group with panretinal photocoagulation (S-PRP: A) and in the insufficiently treated group with no or focal photocoagulation (IS-PRP: B). Spearman’s correlation coefficient calculated by rank test.

Results

Vitreous levels of AGEs and VEGF were significantly higher in patients with diabetes than in controls (mean (SD) 0.13 (0.07) v 0.04 (0.03) U and 2.15 (2) v 1.21 (0.23) ng/ml, respectively; \(p < 0.01\)). As fig 1A and B shows, vitreous VEGF levels were higher in IS-PRP than those in S-PRP (2.75 (2.3) v 1.4 (1.3) ng/ml, respectively; \(p < 0.05\)), whereas there was no significant difference of vitreous levels of AGEs between IS-PRP and S-PRP (0.13 (0.07) v 0.13 (0.06) U, respectively). A positive correlation was found between AGEs and VEGF in S-PRP \((r = 0.44, p < 0.05)\), but not in IS-PRP \((r = 0.26, p = 0.18)\).

Comment

Our observations suggest that AGEs may induce VEGF expression in an ischaemia-independent mechanism. In this study, the
positive correlation between vitreous AGEs and VEGF levels disappeared when retinal ischaemia was not sufficiently controlled. Therefore, it may become a major determinant of VEGF.

**References**

1. Telenino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and subsequent hypoxia was not sufficiently controlled. Therefore, VEGF levels disappeared when retinal ischaemia was not sufficiently controlled. Therefore, it may become a major determinant of VEGF.

**Postoperative subconjunctival 5-fluorouracil in the management of recurring pterygium**

The treatment of choice for pterygium is surgical excision. Recurrence is the most common undesirable treatment outcome. Surgery and other modalities of treatment including β-irradiation, topical thiotepa, intraoperative and postoperative use of mitomycin C, 5-fluorouracil (5-FU) and daunorubicin, have been described to reduce recurrence. Multiple surgery is itself a risk factor for recurrence. We present a case in which the fourth surgery for recurrent pterygium resulted in further recurrence, which was thwarted by multiple intralesional injections of 5-FU.

**Case report**

A 34-year-old Afro-Caribbean woman was referred to us in October 2004 for the management of recurrent pterygium in the right eye. She had two previous surgeries, the first in 2002 with conjunctival autograft and the second in 2003 leaving behind bare sclera. A third attempt at removal in 2004 was aborted owing to excessive intraoperative bleeding. Her unaired visual acuity was 6/9 right eye and 6/6 left eye. The right eye showed a highly vascularised, fleshy nasal pterygium measuring 11×8 mm. It had encroached 2.5 mm into the cornea (fig 1A). The recurrent pterygium in the right eye was excised for the third time in March 2005. On this occasion, mitomycin C (0.04%) was applied intraoperatively to the scleral bed for 5 min and a double-layered amniotic membrane was grafted to cover the conjunctival defect. A recurrence at the original site was noted 2 months later (fig 1B), and in an attempt to arrest progression, topical 0.02% mitomycin C was given four times daily for 7 days (three cycles with an interval of 10 days between cycles). The recurrent pterygium, however, progressed to encroach on to the cornea (fig 1C). At this point, subconjunctival injections of 5-FU into the advancing lesion, under topical anaesthesia, was started. A 26-gauge needle was used to deposit the injection in the core of the fibrovascular tissue away from the cornea. Over 5 months, she received 10 injections of 5-FU (5 mg in 0.2 ml/injection) given 1–2 weeks apart until the recurrent pterygium became less vascular and atrophic. No complications were noted. Now, 8 months after the last injection, there is no progression (fig 1D).

**Comment**

Pterygium recurrence is thought to be due to fibroblast proliferation and migration and hence use of 5FU, which inhibits fibroblastic activity, is believed to reduce recurrence rates. 5-FU is toxic only to proliferating cells and is considered to be safer than other agents. Postoperative use of 5-FU to halt the progression of recurrence has been described before, but involved a maximum of four injections with a maximum dose of 3 mg. Our patient received 10 injections totalling 50 mg of 5-FU with no complications.

In cases with a high risk of recurrence, such as the one described, intralesional subconjunctival injection of 5-FU even at large doses seems to be safe, effective and well tolerated by the eye. Such an intervention should be considered as an option in the management of difficult cases of recurrent pterygium.