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SHORT COMMENTARY

Retinal Ganglion Cell Loss in Diabetes Associated with Elevated Homocysteine

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Abstract: A number of studies have suggested that homocysteine may be a contributing factor to development of retinopathy in diabetic patients based on observed correlations between elevated homocysteine levels and the presence of retinopathy. The significance of such a correlation remains to be determined, and potential mechanisms by which homocysteine might induce retinopathy have not been well characterized. Ganapathy and colleagues[1] used mutant mice that have endogenously elevated homocysteine levels due to heterozygous deletion of the cystathionine-β-synthase gene to examine changes in retinal pathology following induction of diabetes. Their finding that elevated homocysteine levels hastens loss of cells in the retinal ganglion cell layer suggests that toxicity to ganglion cells may warrant further investigation as a potential mechanism of homocysteine enhanced susceptibility to diabetic retinopathy.

Keywords: homocysteine, diabetic retinopathy, retinal ganglion cells

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Background

A correlation between systemic and intraocular homocysteine levels and the presence of retinopathy in diabetic patients has been observed by a number of groups in the last two decades, although not in all studies. Indeed, in earlier studies such a correlation was only seen about half the time, leading to debate over whether a true correlation existed, but most studies in the last five years have found a significant correlation (Table 1).[2–12] Notable exceptions include de Luis and colleagues[5] who detected no difference in the prevalence of retinopathy between type 2 diabetics with or without hyperhomocysteinemia, and Nguyen et al[11] who did find a correlation between retinopathy and hyperhomocysteinemia, but this association was lost after controlling for other established risk factors for diabetic retinopathy.

While most studies suggest a correlation between homocysteine levels and diabetic retinopathy, few, if any, of these studies have examined whether elevated homocysteine may play a causative role, although this has been speculated based on the known potential of homocysteine to induce vascular endothelial cell damage and the recognized vasculopathy underlying retinopathy in many diabetics. In one study, a potential causative mechanism was examined by showing that elevated vitreal homocysteine levels in eyes with proliferative diabetic retinopathy were associated with decreased lysyl oxidase activity,[12] an oxidase important for extracellular matrix structural integrity and known to be inhibited by homocysteine. However, the demonstrated correlation between intravitreal homocysteine and lysyl oxidase did not examine a direct cause and effect relationship.

Commentary

Recent studies have provided evidence that homocysteine may indeed directly induce retinopathy, although predominantly through damage to retinal ganglion cells as opposed to other retinal neurons and photoreceptors. Homocysteine induces apoptosis of retinal ganglion cells in culture,[13,14] as well as following intravitreal injection.[15] Similar loss of retinal ganglion cells occurs in mice with endogenously elevated homocysteine levels due to deletion of cystathionine-β-synthase gene.[16] Currently, Ganapathy and colleagues have now extended their studies of this mouse model to examine the combined effects of elevated homocysteine and diabetes, induced by streptozotocin treatment of the mice, on the structure of various retinal layers and on the number of surviving cells in the ganglion cell layer.[1] Interestingly, they show that mice with moderately elevated homocysteine levels have significantly fewer cells in the ganglion cell layer 5 weeks after induction of diabetes, although by ten weeks after induction there is no difference in cell numbers between diabetic wild-type or cystathionine-β-synthase-deficient mice.

Ganapathy's results suggest that increased homocysteine levels may indeed be capable of causing, or at least

Table 1. Studies in the last five years examining correlation of homocysteine levels with diabetic retinopathy.

Authors	Year	Homocysteine association with diabetic retinopathy
Saeed et al[2]	2004	Positive association of homocysteinemia with retinopathy
Goldstein et al[3]	2004	Positive association of homocysteinemia with non-proliferative and proliferative diabetic retinopathy
Yucel et al[4]	2004	Positive association of homocysteinemia with preproliferative diabetic retinopathy and neovascular glaucoma
de Luis et al[5]	2005	No association of homocysteinemia with retinopathy
Soedamah-Muthu et al[6]	2005	Positive association of homocysteinemia with non-proliferative and proliferative diabetic retinopathy, dependent on albuminuria and glomerular filtration rate
Huang et al[7]	2006	Positive association of homocysteinemia with retinopathy
Brazionis et al[8]	2008	Positive association of homocysteinemia with retinopathy
Aydin et al[9]	2008	Positive association of homocysteinemia with macular edema
Aydemir et al[10]	2008	Positive association of homocysteinemia and high intravitreal homocysteine with proliferative retinopathy
Nguyen et al[11]	2009	Positive association of homocysteinemia with retinopathy, but association lost after controlling for established risk factors
Coral et al[12]	2009	Positive association of high intravitreal homocysteine with proliferative retinopathy

accelerating, retinopathy in some diabetic patients. It is important to note, however, that in their mouse studies there was significantly higher loss of retinal ganglion cells in all diabetic mice (with or without elevated homocysteine levels) as compared to non-diabetic mutant mice with moderately elevated homocysteine. This suggests that perhaps the observed ganglion cell loss is an unavoidable pathologic effect of the diabetes itself; while the elevated homocysteine may accelerate the damage, it does not appear to alter the longer-term outcome of the diabetic induced ganglion cell retinopathy. The authors also show that mice with even higher homocysteine levels, driven by their diet, also have significantly lower ganglion cell numbers 15 weeks following induction of diabetes as compared to non-diabetic mice with similar mutation and diet induced homocysteine levels. These findings are not compared to non-mutant diabetic mice fed the same diet, so it is unclear whether the full extent of ganglion cell loss can be explained by the diabetic retinopathy alone.

The fact that such significant levels of retinal ganglion cell loss are seen in the diabetic mice is worth noting. Most studies of diabetic retinopathy focus on vasculopathic damage from neovascularization or macular edema. However, increasing evidence has demonstrated that diabetes likely also induces direct neuronal damage, including to the retinal ganglion cells, amacrine cells, horizontal cells, and photoreceptors, and this neuronal damage can be associated with visual dysfunction.[17] Thus, the link between elevated homocysteine levels and accelerated retinal ganglion cell loss in diabetes suggests an interesting potential mechanism of ganglion cell loss that warrants further investigation.

Disclosure

The author reports no conflicts of interest.

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