RESEARCH ARTICLE

SERUM HOMOCYSTEINE AS A RISK FACTOR IN DIABETICS WITH COLOUR VISION DEFICIENCY AND FOR DEVELOPING RETINOPATHY

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ABSTRACT

Background: Diabetic retinopathy causes vascular complications of retina causing blindness. Macular edema is the crucial cause of visual impairment and may occur at any stage of diabetic retinopathy. Patients suffering from diabetes mellitus can show alterations in their colour perception. Colour vision testing provides a sensitive method to assess macular damage. Deterioration in colour vision often precedes changes in other clinical measures such as visual acuity and morphological changes. Elevated homocysteine levels play a causative role in inducing vascular endothelial cell damage and causing retinopathy in diabetics.

Aims & Objective: This observational study was intended to examine if serum homocysteine is a risk factor for developing colour vision defects in diabetes and worsening of retinopathy.

Material and Methods: A total of 92 patients with established diabetic retinopathy and having colour vision defects visiting hospital were examined and a detailed history of duration of diabetes was taken. Retinal examination for evidence of diabetic retinopathy and colour vision patterns on Ishihara colour vision chart were noted. OCT was performed on these patients.

Results: 92 of patients with diabetic retinopathy under study had a gross colour vision deficiency. The average macular thickness on OCT of patients with total colour vision deficiency was 279 microns. Prevalence of colour vision deficiency increased with duration of diabetes and severity of retinopathy. The average serum homocysteine level in these patients was 21.98 µM/L which was above the normal range. Serum homocysteine levels ranged from 11.0 µM/L to 30.2 among males and 11.1to 41.0 in females.

Conclusion: Higher prevalence of colour blindness was observed in patients of diabetes with macular oedema and high circulating serum homocysteine levels. Impaired colour vision was more in patients with average macular thickness of 228 micron and raised homocysteine levels thus suggesting it could be a possible risk factor.

Key-Words: Colour Vision; Diabetic Retinopathy; Serum Homocysteine

Introduction

Diabetic retinopathy (DR) is a major vascular complication of diabetes mellitus often leading to blindness. Poor glycemic control, vascular endothelial cell injury, hypercoagulability, ischemia and anoxia of retina, and genetic factors may contribute to formation of diabetic retinopathy.[1] Macular edema (ME) is the crucial cause of visual impairment and may occur at any stage of DR.[2-4] Colour vision testing provides a sensitive, non-invasive method to assess macula damage. Deterioration in colour vision often precedes changes in other clinical measures such as visual acuity and morphological changes.[5] Several studies have shown a correlation between tritan colour vision deficiency and stage of diabetic retinopathy.[6]

Patients suffering from diabetes mellitus can show alterations in their colour perception. Metabolic alterations caused by chronically raised blood glucose levels cause capillary degeneration, hypoxia, and cell death in the retina of diabetics. The role of hypoxia in the colour vision changes has recently been stressed by the findings of Dean et al.[7] Several studies have shown that fasting plasma total homocysteine concentrations are increased in the presence of micro and macrovascular complications in patients with Type 1 or Type 2 diabetes mellitus (DM).[8,9]

An analysis of colour vision defects done by Kinnear et al who found colour discrimination among diabetics was poorer than non-diabetic population.[10] A correlation between systemic and intraocular homocysteine levels and the presence of retinopathy in diabetic patients has been observed by a number of studies.[11-15] While most studies suggest a correlation between homocysteine levels and diabetic retinopathy, few, of these studies have examined whether elevated homocysteine may play a causative role, to induce vascular endothelial cell damage and the recognized vasculopathy causing retinopathy in many diabetics. But a few studies by De Luis et al.[14] and Nguyen et al.[16] have shown no significant correlation between hyperhomocystinemia and diabetic retinopathy.

Hence we intend to study the impact of serum homocysteine in diabetics with colour vision deficiency. The aim of this study was to, (i) ascertain correlation between duration of diabetes, macular thickness on OCT and serum homocysteine levels in diabetes; and (ii) know if serum homocysteine is a possible risk factor for colour

vision deficits in diabetics.

Materials and Methods

This observational study was done on 92 patients with diabetes mellitus having colour vision deficiency attending outpatient department of ESIC Medical College and PGIMSR Bangalore over one year and five months between April 2012 and September 2013. Ethical committee of our institution had cleared our study. Diabetic retinopathy was classified based on the international clinical diabetic retinopathy disease severity scale as in the American academy of ophthalmology October 2002 guidelines.

- *Inclusion Criteria:* (i) All patients with diabetes mellitus with visual acuity of 6/24 or better; (ii) Presence of at least mild diabetic retinopathy; (iii) Presence of tritan, deuteran, or total colour vision deficiency.
- *Exclusion Criteria:* (i) Diabetic patients with visual acuity 6/36 or lesser as the Ishihara interpretation may not be accurate; (ii) Known cases of colour vision deficiency, Central serous retinopathy, optic neuritis; (iii) Patients on Anti Tubercular therapy; (iv) Chronic uveitis, glaucoma; (v) Family history of colour vision disorders; (vi) History of any vitreoretinal surgeries in the past; (vii) Presence of cataract

After obtaining informed consent, a detailed history on demographic data, ocular, and medical history was taken. All the participants underwent a complete ophthalmic examination, including visual acuity (VA) measurement, refraction, and slit lamp examination, dilated fundus examination by indirect ophthalmoscopy, +90D and direct ophthalmoscopy .IOP measurement by Goldmann applanation, gonioscopy using three mirror lens and macular thickness on 3D OCT. blood investigations including fasting and post prandial blood glucose levels were tested. Colour vision testing was done using standard Ishihara's colour vision plates. All findings were tabulated. Optical coherence tomography was performed using commercially available equipment through a dilated pupil by an experienced examiner who was aware of the clinical findings.

The OCT examination comprised six radial 6-mm-long scans of each eye, cantered on the patient's fixation point, at intervals of 30 degrees. Retinal thickness was computed automatically, using OCT retinal mapping software (A5). This mapping averaged the six scans to give the central macular thickness in an area 500 micron in diameter. The average macular thickness was noted for the study. Complete blood count, fasting serum homocysteine levels was done.

Results

A total of 92 patients with diabetes mellitus having colour vision deficiency were included in the study. The age group varied from 42 years to 69 years among males and 44 yrs to 62 among females. The average age duration of diabetes among males was 7.45 years and 7.8 years among females. Diabetic retinopathy causing colour vision deficiency had a higher prevalence among men was about 67.4% and 32.6 % in females in the study group .The prevalence of colour vision defects was found to be more in men 62 of the 92 patients than women 30 of 92 as shown in Table 1. Colour vision deficiency observed was maximum for red green patterns. About 42 of subjects had deficient red green pattern, 26 had protanopia, 8 had deuteran defect and 16 had total colour blindness. The macular thickness determined on OCT of patients varied from 198 micron to 388 micron among males with an average of 276 micron and ranged from 188 to 488 in females with an average of 281 micron. Colour vision defects increased with duration of diabetes and had significant association with severity of diabetic retinopathy too. Increasing macular thickness on OCT was associated with higher prevalence of colour vision defects. Patients with an average macular thickness of 270 (males) and 274 (females) showed protan and deuteran colour defect. The average central macular thickness in males with red green defect was 274 micron in males and 260 in females but above 290 micron showed total colour vision defects. Patients with proliferative diabetic retinopathy showed a higher incidence of colour vision defects 34 out of 92 (37%) showing colour defect followed by 26 of 92 i.e. 28 % in severe NPDR, mild NPDR was seen in 14 cases (13.0%) and moderate NPDR was in 18 patients (19.6%). Serum homocysteine levels ranged from 11.0 to 30.2 µM/L among males with an average of 21.71 µM/L and 11.1to 41.0 in females and average of 22.54 µM/L. The normal range of serum homocysteine levels range between 5.46 to 16.2 in males and 4.44 to 13.56 in females.

Table-1: Sex wise distribution of colour defects

Total Under Study (92)	Males	Females
Colour defects	62	30
%	67.4	32.6

Table-2: Colour defects with severity of retinopathy and homocysteine levels

	Mild NPDR	Moderate NPDR	Sever NPDR	PDR
Total	14	18	26	34
% of Colour Blind	15	19.6	28.3	37
Average Homocysteine (µM/L)	19.27	20.3	24.33	22.18

Discussion

Homocysteine is a by-product formed in the biologic transmethylation reactions and detoxified with the methionine synthetase, which is the enzyme depending on vitamin B12, B6, and folate as coenzymes for proper functioning S-adenosylmethionine and methylation.[17,18] High plasma homocysteine level has been also reported as an independent risk factor for atherosclerosis, cardiovascular disease, and venous thrombosis.[19-21] Homocysteine- stimulated vascular problems may be multifactorial, including direct toxic damage to the endothelium, stimulation of smooth muscle cells proliferation, enhanced low density lipoprotein peroxidation, increased platelet aggregation, and activation of coagulation system.[22]

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, as well as following intravitreal injection.[23-25] Macular Oedema occurs because of the breakdown of the tight blood–retinal barrier in the retinal capillaries and increased fluid accumulation in the outer layers of the retina. An increase in homocysteine plasma level is considered an independent risk factor for the development of vascular damage.[26] Studies suggest homocysteine which mediates oxidative stress in endothelial cells, as inducing intimal damage and activating a serine elastase in arterial smooth muscle cells. Then activation of matrix metalloproteinase 2 causes elastolysis of elastin and fibrillar collagen in arterial media.[27,28] Endothelial-cell–derived nitric oxide relaxes vascular smooth muscle cells, causes vasodilatation, and inhibits platelet aggregation .[29] Homocysteine demonstrates an indirect inhibitory effect on receptor-mediated, non-receptor-mediated, and L-arginine stimulated nitric oxide (NO) release by endothelial cells.[30]

Plasma homocysteine levels are elevated in patients with diabetes, particularly in patients with type 2 diabetes as well as in individuals in prediabetic states. In present study we found hyperhomocystinemia in patients of diabetes mellitus with the male predominance and it is consistent with the study of Schalinske.[31] Elevated levels of plasma homocysteine have been found in patients suffering from peripheral vascular occlusions, such as coronary artery disease, cerebral vascular accidents and deep-vein thrombosis as well as from ocular vascular occlusions such as retinal vein and retinal artery and anterior ischaemic optic neuropathy .Recent studies have shown higher concentrations of homocysteine in patients with diabetes.[32]

To our knowledge, this is the first report that explores the relationship of plasma homocysteine and the severity of DR and ME in patients with Type 2 diabetes having colour vision deficiency. Even though Albdella et al.[33] determined that there was no association between plasma homocysteine levels and diabetic retinopathy severity in patients with Type 2 diabetes, which was similar to the study of Agardh et al.[34] in our study, we detected significantly increased homocysteine levels in severe NPDR groups rather than Proliferative Diabetic Retinopathy groups, and least among patients with mild retinopathy as in Table 2. Huang et al. found no significant difference between plasma homocysteine levels of PDR and NPDR groups since both of these groups had patients with similar mean duration of diabetes.[35] This finding was contrary to our study; we found significant difference between severe NPDR than PDR.

It is well established that colour vision is affected by diabetic retinopathy. Colour vision is a function of the cones, and patients with exudative maculopathy would be expected to demonstrate the most marked defects of colour vision when central macular on OCT was above 260 micron. Our results confirm this; 92 patients with maculopathy and macular thickness more than 260 microns had an abnormal colour vision. In some cases of proliferative retinopathy areas of capillary closure may be situated peripherally in the retina where they might be expected not to influence colour vision, while in other patients intraretinal microvascular abnormalities or capillary closure may affect the macular circulation and lead to a deterioration of colour vision.[36]

Conclusion

In the present study, we investigated an association between hyper homocysteinemia in patients with diabetics having acquired colour vision deficiency and macular thickness. It is well known that many factors contribute to the development and severity of diabetic retinopathy and some of them are unknown. It seems as if high homocysteine levels are among the contributing factors in formation of ME. Therefore, homocysteine levels should be evaluated in all patients with diabetes.

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