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Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Role of hyperhomocysteinemia in the progression of diabetic retinopathy

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ARTICLE INFO

Article history:
Received 27-09-2021
Accepted 17-08-2023
Available online 30-03-2024

Keywords:
Diabetes mellitus
Hyperhomocysteinemia
Proliferative diabetic retinopathy
Homocysteine
Endothelium

ABSTRACT

Aims and Objectives: The aim of this study was to determine the role of hyperhomocysteinemia in the progression of diabetic retinopathy and to determine the association of hyperhomocysteinemia with various grades of diabetic retinopathy.

Diabetic retinopathy is the most common ocular complication of Diabetes mellitus. Various studies have shown that mild elevations of homocysteine in plasma are associated with an increased risk of vaso-occlusive disease, thrombosis, and stroke.

Materials and Methods: A total of 97 patients who were diagnosed with diabetic retinopathy from October 2018 to September 2019 were included in our study. Written informed consent was taken from all the participants. Best corrected visual acuity (BCVA), anterior segment examination using slit lamp biomicroscopy examination(SLE), fundoscopy using indirect ophthalmoscope and using 90D lens on slit lamp was done in all patients. Serum homocysteine was assessed in all. The data was analysed using SPSS version 17.0. Results were expressed as mean, frequency and percentage.

Results: Out of 97 patients, mean serum homocysteine seen in mild non proliferative diabetic retinopathy, moderate non proliferative diabetic retinopathy, severe non proliferative diabetic retinopathy and proliferative diabetic retinopathy was 13.8 ± 0.33, 14.6 ± 0.44, 14.64 ± 0.41 and 15.78 ± 1.33 respectively.

Conclusion: In our study we found serum homocysteine levels was elevated in proliferative diabetic retinopathy when compared to non-proliferative diabetic retinopathy.

1. Introduction

India being known as the diabetic capital of the World, regular monitoring and good glycemic control is important. Diabetes mellitus is a group of metabolic disorders characterized by high blood sugars levels over a prolonged time.[1] Type 2 Diabetes mellitus is a metabolic disease characterized by elevation of blood glucose concentrations, lipid abnormalities, and vascular complications.

Diabetes is a major cause of both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular diseases and nontraumatic lower extremity amputations), affecting, therefore, nearly every other organ in the body. Chronic exposure to elevate glucose and fatty acid concentrations can result in damage to different types of cells by various mechanisms (glucolipotoxicity).[2–4] The diabetic retinopathy (DR) is a neurovascular complication of diabetes mellitus and it is the leading cause of vision loss among working adults worldwide. DR is a multifactorial progressive diseaseof the retina where the pathogenesis of

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https://doi.org/10.18231/j.ijceo.2024.028

the disease is extremely complex involving different cells, molecules, and factors.[5] Hyperglycemia, hyperlipidemia, dysregulated hormones levels, and growth factors induce a cascade of biochemical and physiological changes leading to the neurovascular damage in the retina through oxidative stress, inflammation, and apoptosis.[6]

Diabetic retinopathy is the most common ocular complication of diabetes mellitus.[7] Control of these complications depends on proper management and retinal status monitoring and regular check of blood glucose levels. If left untreated it may be sight-threatening. Homocysteine is a sulfur containing amino acid derived from the methionine metabolism.[8] Hyperhomocysteinemia (>15micromol/L) makes a person more prone for endothelial injury finally leading onto inflammation of blood vessels. Homocysteine has been associated with extracellular matrix changes. Diabetic retinopathy being a neurovascular complication of diabetes, is a leading cause for vision loss among working adults worldwide.[9] Numerous factors play a role in progression of diabetic retinopathy. Hyperhomocysteinemia has been postulated as a potential risk factor in the development and progression of diabetic retinopathy. Several studies indicate that mild elevations of homocysteine in plasma are associated with an increased risk for vaso-occlusive disease, thrombosis, and stroke.[9] High levels of plasma homocysteine is seen in type 2 diabetes mellitus patients as well as in pre diabetic individuals with insulin resistance are toxic to the vascular endothelium due to the formation of free radicals which in turn cause direct endothelial injury and exposing the underlying vascular matrix and smooth muscle, thus promoting hypercoagulability state and finally thrombosis.[8] Several studies indicate that mild elevations of homocysteine in plasma are associated with an increased risk for occlusive vascular disease, thrombosis, and stroke.[10,11] There are few studies on the relationship between plasma homocysteine and diabetic retinopathy and hence this study was undertaken.

2. Aims and Objectives

To determine the role of hyperhomocysteinemia in the progression diabetic retinopathy. To determine the association of hyperhomocysteinemia with various grades of diabetic retinopathy.

3. Materials and Methods

A hospital-based comparative study was conducted at our tertiary care centre over a period of one year from October 2018 to September 2019. A hospital based comparative cross-sectional study involved patients with type 2 diabetes mellitus visiting Ophthalmology Out patient clinic with diabetic retinopathy. A total of 97 patients; out of which 59 were Males and 38 Females were involved in this study. Data regarding demographic profile and risk factors were documented. The Ethical Clearance was obtained from Institutional Ethics Committee. Informed written consent was taken by all patients. Routine ophthalmic evaluation involving best corrected visual acuity, anterior segment examination using slit lamp biomicroscopy, Intraocular pressure and fundus examination was done in all. Along with that, general physical examination, systemic evaluation of blood sugars and control level were assessed in all patients. Assessment of diabetic retinopathy was done with indirect ophthalmoscope using 20D lens and slit lamp biomicroscope with 90D lens. Diabetic retinopathy was classified into different categories; No diabetic retinopathy, mild non proliferative diabetic retinopathy, moderate non proliferative diabetic retinopathy, severe non proliferative diabetic retinopathy, proliferative diabetic retinopathy based on Early Treatment Diabetic Retinopathy Study. Patients with history of liver disease, pregnant or postpartum women**,** patients with hazy ocular media in one or both eyes precluding adequate visualization of the fundus. Patients with retinal vessel occlusion, retinal vasculitis, retinal degenerations or vitreous hemorrhage associated with ocular trauma, which may have resulted in ambiguity in the diagnosis and grading of diabetic retinopathy, patients on drugs (Methotrexate, Trimethoprim, Cholestyramine, Metformin, H2 receptor antagonists and Proton pump inhibition, Niacin, Theophylline, Fibrates, Diuretics, Cyclosporin A) were excluded from our study. Serum homocysteine was assessed in all patients. The data was entered in Microsoft EXCEL software and statistical analysis was performed with the help of SPSS version 17.0 by using descriptive statistics like mean, frequency and percentage.

4. Results

A total of 97 patients were examined. Out of 97, 59 were males and 38 were females. Mean age was 65.12±9.28 years (age group of 54-79 yrs). The mean duration of diabetes was 17.627± 9.29 years in PDR patients which was longer than the patients of NPDR and the no DR patients (14.27±6.27). Out of 194 eyes, 38 eyes (19.58%) had Proliferative diabetic retinopathy (PDR) and non proliferative diabetic retinopathy (NPDR) was seen in 156(80.41%) (Table 1). Out of 156 cases of NPDR, mild, moderate and severe NPDR was seen in 66(42.30%), 59 (37.82%) and 31 eyes (19.87%) respectively (Table 2). Mean serum homocysteine seen in mild NPDR, Moderate NPDR, severe NPDR and PDR was 13.8 ± 0.33, 14.6 ± 0.44, 14.64 ± 0.41 and 15.78 ± 1.33 respectively (Tables 1 and 2).

5. Discussion

Homocysteine is an emerging risk factor for cardiovascular and nondiabetic ocular vaso-occlusive diseases.[7]

Table 1: Shows number of eyes with PDR and NPDR and serum homocysteine levels in each group

	Proliferative DR	Non-Proliferative DR
No of eyes (n=194)	38 (19.58%)	156 (80.41%)
Serum homocysteine (mean value)	15.78 ± 1.33	14.43 ± 0.38

Table 2: Shows number of eyes in mild, moderate and severe NPDR and homocysteine levels in each group

Non- Proliferative DR	Mild	Moderate	Severe
Out of 156 eyes	66 (42.30%)	59 (37.82%)	31(19.87%)
Serum homocysteine (mean value)	13.8 ± 0.33	14.6 ± 0.44	14.64 ± 0.41

Homocysteine may be a good biomarker for increased risk of diabetes complications, since nephropathy, retinopathy, and cardiovascular disease have all been linked to higher homocysteine levels.[7] Homocysteine is toxic to the vascular endothelium and therefore induces thrombosis and thus may play a role in aggravating the hypoxic state such as that seen in diabetic retinopathy by further closure of the capillary bed. An increase in plasma and in vitreous concentration of homocysteine in proliferative diabetic retinopathy has been shown.[7,10–12]

Control of these complications depends on proper management and retinal status monitoring and regular check of blood glucose levels. If left untreated it may be sight-threatening.[12–15] Folate / vitamin B12 / vitamin B6 deficiency, renal failure, hyperproliferative disorders and hypothyroidism are associated with increased serum homocysteine levels.[15–17] Hyperhomocysteinemia could therefore, be a potentially modifiable risk factor for diabetic retinopathy. Dietary supplementation could be achieved at a very affordable cost, thereby saving the patient not only from the burden of morbidity caused by the disease, but also from the economic impact. This is especially relevant in India, where there is a high prevalence of diabetes as well as vitamin B12 deficiency. In our study, mean plasma homocysteine levels in Proliferative Diabetic Retinopathy was 15.78± 1.33 and in Non Proliferative Diabetic Retinopathy was 14.43±0.38. The result of is consistent with study done by Brazionis et al wherein a higher mean plasma homocysteine was seen in patients with retinopathy when compared to patients without any retinopathy changes(p=0.001).[7] M Goldstein et al., dealing with a possible correlation between hyperhomocyteinemia and diabetes melitus.[8] A study done by Giulia Malaguarnera et al showed higher plasma levels of homocysteine in diabetics with proliferative diabetic retinopathy(15.86 ± 1.34) compared to both Nonproliferative diabetic retinopathy (14.56±0.64) similar to our study.[9] A study done by Giulia Malaguarnera et al showed higher plasma levels of homocysteine in diabetics with proliferative diabetic retinopathy compared to both Nonproliferative diabetic retinopathy and without retinopathy.[9] DNAmethylation is an important aspect in both DNA repairand gene stability. There is growing evidence that histone modification and DNA methylation plays an important role in the development of diabetic retinopathy. It has been suggested that the inactivation of DNA repair pathways, which leads to increased mutation rate and chromosomal instability, can initiate and accelerate the proliferative process. Further evidence suggested that the proliferation rate of cells would cause an elevation of circulating homocysteine or an increase in the concentration of cells would deplete folate and inactivate the methionine synthase catalyzed remethylation reaction. This potential link between the microvascular changes that occur in diabetic retinopathy and hyperhomocysteinemia may be useful as a predictor for diabetic retinopathy.[9] Diabetic retinopathy is one of the microvascular complications of diabetes which may not have symptoms in the early stages. Control of these complications depends on proper management and monitoring of retinal status and blood glucose levels after the early detection of retinopathy but may progress to a sight-threatening stage if left untreated. Homocysteine and diabetes increase oxidative stress and reduce nitric oxide formation and may cause endothelial dysfunction. Homocysteine enhances smooth muscle proliferation and affects the extracellular matrix. Thus elevated homocysteine levelmay act as a pathogenetic link or an instrument through which various risk factors may exert their deleterious effect on the promotion of diabetic retinopathy.[9] It is important to search for modificable risk factors in patients with diabetes mellitus type 2. The aminoacid homocysteine may be such a risk factor. This potential link between the microvascular changes that occur in diabetic retinopathy and hyperhomocysteinemia may be useful as a predictor for retinopathy. Diabetic retinopathy is one of the microvascular complications of diabetes which may not have symptoms in the early stages. Control of these complications depends on proper management and monitoring of retinal status and blood glucose levels after the early detection of retinopathy but may progress to a sight-threatening stage if left untreated. Homocysteine and diabetes increase oxidative stress and reduce nitric oxide formation and may cause endothelial dysfunction. Homocysteine enhances smooth muscle proliferation and affects the extracellular matrix. Thus elevated homocysteine level may act as a pathogenetic link through which various risk factors may exert their deleterious effect on the promotion of diabetic retinopathy.[6] Although type 2 diabetes mellitus is definitely associated with premature atherosclerosis and

microvascular complications, only a handful of studies have dealt between hyperhomocysteinemia and macro- or microangiopathic complications. The significance of hyperhomocysteinemia in type 2 diabetes has been further complicated by the multiple ways of considering impaired renal function and vitamin status.

6. Conclusion

In our study we found homocyteine levels were elevated in patients with proliferative diabetic retinoapthy as compared to non-proliferative diabetic retinopathy. Also, the higher concentration of hyperhomocysteine in diabetic patients may play a role in accelerating the microvascular retinal changes. Therefore, contribute to the progression of diabetic retinopathy. India being the diabetic capital of the world, close monitoring of diabetic patients and good blood sugar regulation is important for prevention of diabetic retinopathy. Thus, understanding and characterizing the homocysteine role in the pathogenesis of diabetic retinopathy could help in identifying novel target to combat this blinding disease which is the major cause of blindness among adult population, the working population in a developing country like India.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Pooja H V, Lakshmi M S. Role of hyperhomocysteinemia in the progression of diabetic retinopathy. *Indian J Clin Exp Ophthalmol* 2024;10(1):160-163.