Commentary: Role of hyperhomocysteinemia in proliferative diabetic retinopathy: A case–control study

Hyperhomocysteinemia (HHcy) has been described as a risk factor for diabetic retinopathy (DR),[1] especially proliferative DR (PDR) in patients with both type 1 diabetes mellitus (DM)[2] and type 2 DM.[3] The study "Role of hyperhomocysteinemia in proliferative diabetic retinopathy: A case–control study" done by Gupta *et al*.[4] is well-appreciated. They have shown higher prevalence of HHcy and higher mean serum levels of homocysteine (Hcy) in the cases with PDR when compared with the controls with no retinopathy and also have given possible reasons for not getting statistically significant differences.

However, some points can be commented from the study by Gupta *et al*.[4] The small sample size in this study (39 cases and 39 controls) which involves a largely prevalent disease could have affected the results. In statistical analysis, paired *t*-test could have yielded better results. Considering the number of factors included in the analysis, a multiple logistic regression analysis would have yielded better results on covariance and confounding factors.

Some new perspectives can be explored from this article. Studies evaluating association of Hcy levels on DR in type 1 DM cases from India and comparison to those from outside India can further validate HHcy in DR cases, since geographical location has been mentioned to affect this association.[2] There is evidence suggesting that Hcy activates vascular inflammation through mediators, including vascular endothelial growth factor,[1] and the correlation of diabetic macular edema with HHcy has been mentioned.[5] The effects of folate and vitamin B-12 supplementation on the level of Hcy remains to be studied. HHcy in PDR can modulate dual enzymatic activity of paraoxonase (PON), that is, esterase activity (PON-AREase) and lactonase activity (PON-HCTLase) which can be evident from elevated levels of vitreous homocysteine thiolactone (HCTL) and PON-HCTLase activity in PDR.[6] This supports the association of HHcy with DR. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in remethylation of Hcy to methionine, and MTHFR gene polymorphism leads to impaired enzyme activity, resulting in HHcy and can contribute to the progression of DR.[1] Genetic studies involving MTHFR gene polymorphism can further validate this association.

Finally, association of HHcy with DR is an evolving topic. Future studies and discussion among peer group will enrich the collective academic knowledge and may help in future management of patients with DR.

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