ANATOL J FAMILY MED
The Anatolian Journal of Family Medicine

Review

DOI: 10.5505/anatoljfm.2021.16056
Anatol J Family Med 2021;4(1):2–6

# A Review of Homocysteine as a Diagnostic Tool for Diabetic Retinopathy

Aleeza Fatima,[1] Mohammed Channa,[1] Kalina Trifonova,[2] Kiril Slaveykov[3]

[1]Department of Ophthalmology, Faculty of Human Medicine, Medical Faculty Trakia University, Stara Zagora, Bulgaria
[2]Department of Ophthalmology and Otorhinolaryngology, Medical Faculty Trakia University, Stara Zagora, Bulgaria
[3]Department of Internal Diseases and General Medicine, Medical Faculty Trakia University, Stara Zagora, Bulgaria

## ABSTRACT

The aim of this systematic review is to identify plasma homocysteine (Hcy) as a screening and diagnostic indicator for assessing diabetic retinopathy (DR) risk in patients with type 2 diabetes mellitus. Following PRISMA guidelines, data was gathered from publications between 2000–2019 from the Springer, JAMA, Lancet, and PubMed databases, as well as from diabetes-specific journals. Observational, experimental, and multi-ethnic studies, meta-analyses, systematic reviews were included and studies that did not measure plasma Hcy, or included only patients with type 1 diabetes were excluded. The collected results were pooled and analysed for this systematic review. The majority of studies suggested an affirmative relationship exists between hyperhomocysteinemia (HHcy) and DR, whereas some studies showed only limited clinical significance. HHcy is considered a pivotal risk factor for macular edema progression in patients with DR. Serum Hcy levels could be used to assess microvascular risksforthe development and progression of DR.

**Keywords:** Diabetic retinopathy, diabetes mellitus, hyperhomocysteinemia, homocysteine

**Please cite this article as:** Fatima A, Channa M, Trifonova K, Slaveykov K. A Review of Homocysteine as a Diagnostic Tool for Diabetic Retinopathy. Anatol J Family Med 2021;4(1):2–6.

**Address for correspondence:** Dr. Aleeza Fatima. Department of Ophthalmology, Faculty of Human Medicine, Medical Faculty Trakia University, Stara Zagora, Bulgaria

**Phone:** +447398000610

**E-mail:** aleezaf9@gmail.com

**Received Date:** 07.11.2020
**Accepted Date:** 25.01.2021
**Published online:** 10.03.2021



## INTRODUCTION

Globally, 93 million people have been diagnosed with diabetic retinopathy (DR). Predictive data suggests that figure will increase to 430 million individuals by 2030, indicating the potentially large burden of DR and the importance of determining modifiable risk factors.[1,2]

DR damages retinal pericytes, causing proliferative (PDR) and non-proliferative (NDR) retinopathy.[3] NDR manifests as microaneurysms and hard exudate.[4] PDR is associated with ischemia, vascular endothelial growth factors, and neo-vascularization.[5]

Homocysteine (Hcy) in healthy individuals is converted into other amino acids or back to methionine; in patients with diabetes mellitus (DM), this pathway is disrupted, causing hyperhomocysteinemia (HHcy), which accelerates cell injury and damages retinal capillaries.[6-8] Mild HHcy caused by a mutation in the methylenetetrahydrofolate reductase gene is linked with DR.[9]

## METHOD

PRISMA guidelines were followed to examine articles, research papers, meta-analyses, and systematic reviews relevant to this research. Keywords used to narrow the search included the following: "homocysteine," "diabetic retinopathy," "diabetes mellitus," and "hyperhomocyste-

inemia." Electronic research was identified from databases such as PubMed, MBASE, Lancet, JAMA, and Springer and the journals Diabetes and Metabolism, Diagnostic Pathology, Diabetes Care, Diabetologia, and the Pakistan Journal of Ophthalmology, to name a few.

The selected data was assembled from 12 studies in Table 1.[10-21] Exclusion criteria included studies with patients with Type 1 DM or studies that observed the relationships between "diabetes and homocysteine" but did not include "retinopathy" or that examined "diabetes and diabetic retinopathy" but did not measure plasma Hcy levels. Further exclusions involved studies that included the macrovascular pathology of plasma Hcy levels.

## DISCUSSION

Plasma total Hcy could be regarded as a helpful biomarker or an innovative risk factor for the mounting risk of DR

**Table 1.** Homocysteine levels in patients with diabetic retinopathy

| Study | Study base | Study subjects | Hcy levels (µmol/l) | Number of DR patients |
|---|---|---|---|---|
| Cho et al. 2011[10] | South Korea | 102 T2DM | 16.3±11.7 NDR | 5 PDR |
| | | | 19.2±8.4 T2DM | 62 NPDR |
| | | | | 35 NDR |
| Brazionis et al. 2007[11]* | Australia | 168 T2DM | 9.6 NDR | 48 DR |
| | | | 11.5 T2DM | 120 NDR |
| Hoogeveen et al. 2000[12]* | Netherlands | 454 (285 NGT, 169 IGT) | <9 NDR | 79 DR |
| | | 171 (65 KD, 106 NDD) | >16 T2DM | |
| Fotiou 2014[13] † | Greece | 140 T2DM | 11.1 NDR | 29 PDR |
| | | | 16.3 T2DM | 36 NPDR |
| | | | | 75 NDR |
| Abdella et al. 2002[14] † | Kuwait | 358 T2DM | 9.8 NDR | 90 NPDR |
| | | 10.5 T2DM | 55 PDR | 181 NDR |
| Looker et al. 2003[15] ‡ | USA (PI) | 396 T2DM | 9.89 PDR | 79 NPDR |
| | | 9.71 NPDR | 23 PDR | 279 NDR |
| Gupta et al. 2018[16] § | India | 78 T2DM | 17.71±8.16 NDM | 39 DR |
| | | | 17.98±6.26 T2DM | 39 NDR |
| Malaguarnera 2014[17] ‖ | Italy | 80 NDM | 7.8±6.4 NDM | 62 PDR |
| | | 175 T2DM | 12.1±6.8 NDR | 63 NPDR |
| | | | 18.2±5.6PDR | 50 NDR |
| | | | 14.4±6.7 NPDR | |
| Aydemir et al. 2008[18] § | Turkey | 12 NDM | 9.18±3.91 NDM | 20 PDR |
| | | 20 T2DM | 16.04±2.75 T2DM | |
| Ghayoor 2013[19] § | Pakistan | 77 NDM | <12 NDM | >12 T2DM |
| | | 77 T2DM | <12 NDR | 77 PDR |
| Goldstein et al. 2004[20] § | Israel | 156 NDM | 11.75±0.24 NDM | 46 PDR |
| | | 179 T2DM | 13.46±0.74 NDR | 71 NPDR |
| | | | 15.86±1.34 PDR | 62 NDR |
| | | | 14.56±0.64 NPDR | |
| Nguyen et al. 2009[21] ¶ | USA (AA/C/Ch/H) | 921 Total participants | 8.8 NDM | 643 NPDR |
| | | | 8.9 NDR** | |
| | | | 278 T2DM | |

AA:African American; C: Caucasian; Ch: Chinese; DR: Diabetic retinopathy; H: Hispanic; Hcy: Homocysteine; IGT: Impaired glucose tolerance; KD: Known diabetics; NDD: Newly diagnosed diabetics; NDM: Non-diabetic; NDR: No diabetic retinopathy; NGT: Normal glucose tolerance; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PI: Pima Indians; T2DM: Type 2 diabetes mellitus.

*Cross-sectional study; †Cohort study; ‡Longitudinal study; §Case control; ‖Randomized controlled trial; ¶Population-based study.

**Diabetes type not specified.

in individuals with Type 2 DM. Table 1 shows that HHcy is linked to an increased risk of DR in different populations. The studies collected for this review article were conducted in different parts of the world, the data also indicate that these results may apply to the general global population.

In a study conducted by Cho et al., which included 102 individuals with type 2 DM, the measurement of plasma Hcy in the group with DR had an average of 19.2 µmol/L and was higher than when compared with the average of 16.3 µmol/L for the group without DR; however, the difference was not statistically significant.[10] To examine the independent associations between the key risk factors and the presence of DR, Cho et al. performed a multiple logistic regression analysis that showed that Hcy is independently affiliated with DR (Odds ratio (OR)=1.1, 95% CI=1.0–1.1).[10]

A study by Huang et al. identified Hcy as an integral risk factor for developing DR in individuals with type 2 DM.[22] According to their study Hcy was associated with prolonged DM duration and the microvascular complications of DR. A study by Brazionis et al. of 168 patients with type 2 DM, also showed an elevated mean total plasma Hcy concentration in individuals with DM and DR versus those with DM and not DR.[11] A study based in the Netherlands by Hoogeveen et al. showed a positive predictive value of plasma levels of Hcy with an OR of 3.44 in patients with type 2 DM against 0.97 in patients without DM.[12] A study in Greece by Fotiou et al. working with patients with type 2 DM suggested that HHcy is a self-sufficient risk factor for the commencement and progression of DR.[13] On the contrary,in a study performed on 358 Kuwaiti patients with type 2 DM, multiple regression analyses showed no significant association between HHcy and DR.[14]

A systematic review and meta-analysis performed by Leiet al. attempted to explain the controversy with a few studies considering the relationship between Hcy levels and the progression of DR.[23] Data were produced from 2184 individuals with DM from 11 studies that were part of the meta-analysis. The collective OR proposed that an increase in Hcy levels within individuals with DM was correlated with the rise in the risk of DR. Lei et al. identified substantial heterogeneity in the studies, but the sensitivity analysis showed statistical significance.[12,23] Another meta-analysis of 31 studies involving 6394 participants found similar results.[24]

Some authors considered Hcy as a risk factor for the development of PDR. An older study of patients with type 2 DM conducted in Arizona from 1982 to 1985 showed the association of HHcy with the incidence of PDR.[15] Gupta et al. determined that the prevalence of HHcy, as well as the mean serum levels of Hcy, were elevated in the cases with PDR as compared to an NDR control group, although this dissimilarity was not statistically significant.[16] A study by Malaguarnera showed that higher plasma levels of Hcy have been found in a patient with DM with PDR in comparison to both NDR and those without DR.[17] Aydemir showed an elevated Hcy in the vitreous that was obtained during vitreoretinal surgery of patients with PDR, most likely ascribed to the breakdown of the blood–retina barrier.[18,25]

Different plasma Hcy concentrations were associated with the incidence or prevalence of DR and PDR in all studies. For example, in the Greek study, the threshold was found to be 13.7 µmol/L.[14] A high prevalence of DR was perceived in patients with type 2 DM who had fasting Hcy concentrations above 15 µmol/l.[12,26]

Some studies suggest the relatedness between Hcy levels and the development of macular edema in patients with type 2 DM. Mild to moderate elevation of Hcy may explain the role of vascular dysregulation and endothelial dysfunction in patients who had DR. The present study suggests that HHcy could be a significant risk factor for the development of macular edema.[27] Li et al. concluded that plasma total Hcy concentration is independently associated with the occurrence of macular edema in patients with type 2 DM.[28]

Some authors have argued that the decreased serum concentration of folic acid and vitamin B12, through raising serum Hcy concentrations, may also affect DR risk. According to the Greek study, folic acid is associated with decreased odds for DR. A threshold exists in serum vitamin B12 level (248.4 pg/mL) below which serum Hcy concentration significantly elevates with a decline in serum vitamin B12.[13] The data from an Indian study showed that higher Hcy levels were remarkably affiliated with lower vitamin B12 and folic acid but not with other B vitamins.[1] A study by Y. Sato et al. found that metformin-induced B12 decline in DM was related to the elevation of Hcy, and HHcy was independently associated with DR.[29]

## CONCLUSION

HHcy is positively associated with the increased risk of the development of DR and PDR. Further research is required to determine the threshold standard plasma Hcy concentration level that can lead to the prevalence or incidence of DR in patients with type 2 DM. Plasma Hcy concentration can be a pivotal indicator for assessing microvascular risk for the development and advancement of DR. Further research can help health care providers to use plasma Hcy as

a simple blood test to screen for DR and prevent visual impairment and blindness by taking timely measures. Treatment of individuals with an existing HHcy condition with folate and vitamin B12 also could reduce the risk of microvascular complications.

**Disclosures**

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Funding:** No funding was obtained for the entirety of this research.

**Authorship Contributions:** Concept – A.F., M.C.; Design – A.F., M.C.; Supervision – K.T., K.S.; Literature search – A.F., M.C.; Writing – A.F., M.C.; Critical Review – K.T., K.S.

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