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# The correlation of folic acid and homocysteine serum with vascular density and retinal non-perfusion area in diabetic retinopathy

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## Abstract

**Background :** Diabetic Retinopathy (DR) is the most common microvascular complication of Diabetes Mellitus (DM). Homocysteine has been studied as a biomarker in DR, while folic acid exhibits anti-proliferative effects in DR.
**Objective :** To analyze the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area in healthy individuals and patients with diabetic retinopathy.
**Methods :** This is an observational study with a cross-sectional design, conducted in Dr. Kariadi Hospital and GAKI laboratory in Semarang in January 2023. This study included 60 samples: 15 healthy individuals, 15 patients with DM but no DR, 15 patients with Non-Proliferative Diabetic Retinopathy (NPDR), and 15 patients with Proliferative Diabetic Retinopathy (PDR). Patients were examined for serum folic acid and homocysteine using blood laboratory tests, vessel density and retinal non-perfusion areas using optical coherence tomography angiography (OCTA).
**Results :** There was a negative correlation with weak strength between folic acid levels and retinal non-perfusion area of the retina in all samples (Folic acid levels vs retinal non-perfusion area, p = 0.009, Spearman correlation = -0.335). There was a positive correlation with weak strength between folic acid levels and vascular density in all samples (Folic acid levels vs vascular density, p = 0.009, Spearman correlation = 0.337). There was a positive correlation with moderate strength between homocysteine levels and retinal non-perfusion area in all samples (Homocysteine levels vs non–perfusion area of the retina, p = 0.001, Spearman correlation = 0.426). There was a positive correlation with moderate strength between homocysteine levels and vascular density in all samples (Homocysteine levels vs vascular density, p = 0.001, Spearman correlation = -0.414).
**Conclusion :** There was a correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion areas.

**Keywords:** Folic acid, Homocysteine, Vascular density, retinal non-perfusion area, Diabetic Retinopathy

## Introduction

Diabetic retinopathy (DR), a major microvascular complication of Diabetes Mellitus (DM), poses a significant risk of sight-threatening retinal damage. It is one of the leading causes of blindness in adults.[1–5] According to The Early Treatment Diabetic Retinopathy Study (ETDRS), DR is categorized into Non-proliferative (NPDR) and Proliferative (PDR) types, diagnosed through vascular abnormalities in the retina.[6] Often undetected, the study on the prevalence of DR in Indonesia reports that among Indonesian adults

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with type 2 diabetes in urban and rural areas, around 1 in 4 adults with diabetes suffers from vision-threatening DR.[5] It was reported in 2020 on the global prevalence of DR study that the number of adults worldwide with DR and vision-threatening DR was estimated at 103.12 million and 28.54 million respectively. These numbers were projected to increase to 160.50 million and 44.82 million, respectively. [4] This highlights the urgent need for effective DR screening, prevention and therapy methods.

In Diabetes Mellitus, Hyperglycemia initiates alternate pathways for metabolizing glucose. These pathways lead to the release of cytokines and growth factors, resulting in vascular endothelial impairment, increased vascular permeability, and microvascular occlusion. This occlusion subsequently causes retinal ischemia.[7,8] Retinal non-perfusion areas are quantitative biomarkers to characterize ischemia in DR.[7,9] Inflammatory cytokines and growth factors released in response to hyperglycemia can exacerbate endothelial damage and pericyte loss. .[7,10] Endothelial cell damage can result in capillary dropout, a key feature leading to reduced vascular density without pericyte support. Capillaries become destabilized and may collapse, leading to a decrease in vascular density.[11,12] Optical coherence tomography angiography (OCTA) allows visualization of retinal capillaries and measures retinal non-perfusion areas.[9]

Folic acid, also known as vitamin B9, is an essential water-soluble vitamin for human health. It is a synthetic form of folate, a naturally occurring B vitamin found in certain foods.[13] The research conducted by Zhenglin Wang et al.[14] showed that folic acid could suppress the proliferation of retinal vascular endothelial cells (RVECs) by 33.33%. Therefore, these findings suggested that folic acid has an inhibitory effect on the proliferation and migration of endothelial or vascular smooth muscle cells (VSMC).[14] Research by Vviviek Dave, et al.[15] showed that Folic acid plays a protective role against retinal thinning in the early stages of DR in mice genetic model of type 2 diabetes mellitus obesity. These findings suggested that Folic acid may serve as a potential therapeutic agent against DR through potential suppression of angiogenesis, inflammation, and oxidative stress.[15] Homocysteine has been investigated as a biomarker as well as a risk factor for vascular disease. Homocysteine is involved in oxidation-reduction reactions and induces oxidative stress.[16] Xunwen Le et al.[17] conducted a meta-analysis study summarized studies involving a total of 2.184 diabetic patients and found elevated homocysteine levels associated with an increased risk of DR in patients with Diabetes Mellitus.[17] Several studies have shown an association between folic acid and homocysteine with vascular disease, especially in DR with various underlying mechanisms. Meanwhile, research into how folic acid and homocysteine serum affect vascular density and retinal non-perfusion areas has never been studied.[13–17] Given the accessibility and cost-effectiveness of serum folic acid and homocysteine testing, as well as folic acid supplementation or dietary interventions, these factors hold promise as potential therapeutic or preventive agents in DR management. They may also serve as preliminary diagnostic tools for DR identification. This study aims to determine the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area.

## Methods

This study was an observational study with a cross-sectional design. Sample size uses measures for unpaired numerical, analytical comparisons. The sample size was determined based on statistical calculations by setting a confidence level of 95% and a power test of 95%; thus, the results of the formula for calculating the minimum sample used were 60 samples. The total sample of this study was 60 patients. The samples were 15 healthy patients, 15 diabetes mellitus patients without diabetic retinopathy (DM), 15 patients with non-proliferative type diabetic retinopathy (NPDR), and 15 patients with proliferative type diabetic retinopathy (PDR) who came to the Merpati eye clinic of Dr. Kariadi Hospital Semarang.

This study was conducted in Dr. Kariadi Hospital and GAKI laboratory in Semarang in January 2023. Patients were examined for serum folic acid and homocysteine using blood laboratory tests. Vessel density and retinal non-perfusion areas were examined using optical coherence tomography angiography (OCTA). Optical Coherence Tomography (OCT) is a non-invasive imaging technology that can detect loss of retinal nerve tissue by qualitatively assessing the retinal layers and quantitatively measuring the thickness of the retinal tissue with high resolution.[18] Optical Coherence Tomography Angiography (OCT-A) can non-invasively map ocular blood flow circulation to the capillary stage, relate perfusion to neuronal damage, describe microvascular and neuronal connections in DM, and find one of the predictive markers for diabetic retinopathy. [19,20] From the results of the OCTA scan image, a trained ophthalmologist assesses the distribution and pattern of blood vessels. This assessment can help identify areas of abnormal or reduced blood flow. Vascular density is obtained from the proportion of the scan area occupied by blood vessels. This is represented as a percentage. The ophthalmologist also manually examines the OCTA images to identify and confirm areas of non-perfusion. These areas may appear as dark or empty spaces in the blood vessel tissue.

Inclusion criteria were patients with a history of DM, funduscopy examination found with diabetic retinopathy or without diabetic retinopathy by ETDRS, and for healthy patients there was no history of DM or signs of DR. The exclusion criteria for this study were patients who had undergone lasers, anti-VEGF injections, and vitrectomy surgery. Analysis was carried out to determine the differences in folic acid levels, homocysteine serum levels, vascular density, retinal non-perfusion area between groups, and the correlation between folic acid and homocysteine with vascular density and non-perfusion area of the retina in all samples. The data in this study were analyzed using SPSS 26. For comparing all groups, the One-Way ANOVA test or the Kruskal-Wallis test was used, while the comparison between two groups was conducted using the Mann-Whitney test. The One Way ANOVA test was used to compare more than two groups, and in this study, it was used for comparing four groups. Following a significant ANOVA result, the Games-Howell test served as a post-hoc analysis to identify the specific groups that differ. The correlation test was used to determine the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area in all samples.

This research was approved by the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University / Dr. Kariadi Central General Hospital Semarang no.1349/EC/KEPK-RSDK/2022 and research permit number: DP.02.01/I.II/10484/2022.

## Results

This study analyzed a total of 60 samples: 15 from healthy patients (without DM), 15 samples of patients with Diabetes mellitus (DM) without DR, 15 samples of DM patients with non-proliferative diabetic retinopathy (NPDR), and 15 samples of DM patients with proliferative diabetic retinopathy (PDR).

**Table 1.** Sample characteristics

| **Age (years)** | | |
|---|---|---|
| Mean | 46.63 ± 11.88 | |
| Median | 50.00 | |
| Modus | 52 | |
| minimum | 23 | |
| maximum | 67 | |
| **Gender** | **Frequency** | **Percentage** |
| Female | 39 | 65 % |
| Male | 21 | 35 % |
| Total | 60 | 100 % |

Patients' average age was 46.63 ± 11.88 years. Patients' sex were predominately female (65%) while men were only 21%.

**Table 2**. The comparison of each variable in all sample groups

| Variable | Groups | Mean ± SD | p |
|---|---|---|---|
| **Folic Acid (ng/ml)** | Healthy patients (n=15) | 5.62 ± 2.25 | 0.055 |
| | DM (n=15) | 6.05 ± 3.83 | |
| | NPDR (n=15) | 4.74 ± 0.56 | |
| | PDR (n=15) | 4.72 ± 0.59 | |
| **Homocystein Serum (µmol/L)** | Healthy patients (n=15) | 4.38 ± 2.22 | 0.008* |
| | DM (n=15) | 7.28 ± 3.24 | |
| | NPDR (n=15) | 7.50 ± 3.63 | |
| | PDR (n=15) | 8.50 ± 3.85 | |
| **Vascular Density ($mm/mm^2$)** | Healthy patients (n=15) | 18.82 ± 0.42 | 0.000* |
| | DM (n=15) | 17.37 ± 0.59 | |
| | NPDR (n=15) | 15.85 ± 0.51 | |
| | PDR (n=15) | 13.33 ± 1.36 | |
| **Retinal non-perfusion areas (%)** | Healthy patients (n=15) | 53.41 ± 0.94 | 0.000* |
| | DM (n=15) | 57.30 ± 1.18 | |
| | NPDR (n=15) | 60.29 ± 1.07 | |
| | PDR (n=15) | 67.29 ± 3.91 | |

Note : * significant ($p < 0.05$)

The folic acid difference test was performed using the Kruskal Wallis test because the folic acid level data was abnormally distributed based on the normality test. There are no significant differences in folic acid levels between all the case groups ($p = 0.055$). One-Way Anova test was done to analyze serum homocysteine levels, vascular density, and retinal non-perfusion area because the data was normally distributed. From the results of the Homocysteine difference test, Homocysteine based on the case group showed significant differences ($p = 0.008$). The results of the vascular density and retinal non-perfusion area difference test based on case groups also showed significant differences ($p<0.01$).

Post hoc Games-Howell test was conducted to determine the difference in homocysteine serum, vascular density, and retinal non-perfusion area between groups. Meanwhile, folic acid levels did not proceed to the post hoc test because there was no significant difference in the difference test between all groups. In the Games-Howell Post hoc test, significant differences were found in serum homocysteine levels between healthy groups with DM groups ($p=0.041$), NPDR (0.043) and PDR groups (0.008). There were significant differences between the entire group in vascular density and retinal non-perfusion areas.

**Table 3.** The comparison of folic acid levels between patients without DR and with DR

| Group | Mean ± SD (ng/ml) | p |
|---|---|---|
| **Patients Without DR (n=30)** | 5.84 ± 3.10 | 0.011* |
| **Patiens With DR (n=30)** | 4.74 ± 0.57 | |

Because there was no significant difference in the Kruskal Wallis test, an analysis was carried out to determine the comparison of folic acid levels between patients without DR (healthy patients and DM patients without DR) (n=30) and the group of patients with DR (patients with

**Table 4.** Correlation test results of homocysteine and folic acid with retinal non-perfusion areas and vascular density in all samples

| | | Retinal non-perfusion areas | Vascular Density |
|---|---|---|---|
| **Homocystein Serum** | *r* | 0.426 | -0.414 |
| | *p* | 0.001* | 0.001* |
| **Folic Acid** | *r* | -0.335 | 0.337 |
| | *p* | 0.009* | 0.009* |

NPDR and PDR) (n=30). The Mann-Whitney test to determine the comparison of folic acid levels in patients with DR and without DR, obtained significant differences in the group of patients without DR and the group of patients with DR (p = 0.011)

The Spearman correlation test was also conducted to determine the correlation between folic acid and homocysteine serum with vascular density and non-perfusion area retina in all samples (n=60). The correlation value of homocysteine and the non-perfusion area was p = 0.001 with a Spearman correlation value of 0.426, showing a positive correlation with moderate correlation strength. In the correlation between homocysteine and vascular density, a value of p = 0.001 was obtained with a Spearman correlation value of -0.414, showing a negative correlation with moderate correlation strength. In the correlation between folic acid and non-perfusion areas, a value of p = 0.009 with a Spearman correlation value of -0.335 showed a negative correlation with weak correlation strength. In the correlation between folic acid and vascular density, a value of p = 0.009 was obtained with a Spearman correlation value of 0.337, showing a positive correlation with a weak correlation strength.

## Discussion

This study revealed significant correlations between folic acid and homocysteine levels with retinal conditions in all samples. A negative correlation with weak strength was found between folic acid levels and retinal non-perfusion area, suggesting that higher folic acid levels are associated with reduced non-perfusion area in the retina. Conversely, a significant but weak positive correlation was observed between folic acid levels and vascular density, indicating that higher folic acid levels are associated with increased vascular density in the retina. Previous research by Liu X et al.[21] on the palliative effects of folic acid on microvessels in the retina in diabetic retinopathy explained that the source of expression and the epigenetic profile within retinal microvascular endothelial cells, emphasizing the pharmacological mechanism of folic acid on DNA methylation and hydroxymethylation regulation within microvessel cells in DR.[21] Folic acid can downregulate a panel of genes associated with angiogenesis, inflammation, and oxidative stress.[15] In this study, a comparison of folic acid levels based on the 4 case groups (PDR, NPDR, DM no DR, and healthy patients) showed no significant difference. However, there was a significant difference in folic acid levels between patients without DR (healthy patients and DM patients without DR) compared with those with DR (Patients with NPDR and PDR). It was also found that the average folic acid levels of patients without DR were higher than those with DR. Therefore, it was found that folic acid was related to the incidence of DR but not related to the severity of DR. This aligns with the previous research conducted by Malaguarnera G et al. [22] , which found that diabetic patients with

Proliferative Diabetic Retinopathy (PDR) and Non-Proliferative Diabetic Retinopathy (NPDR) exhibited significant deficiencies in plasma folic acid and red blood cell folate compared to healthy subjects and diabetic subjects without retinopathy.[22] However, unlike this study, they also found a potential relationship between folic acid levels and the severity of DR. That research also found that the patients treated with metformin showed a significant decrease in folate. This has not been analyzed in this study and could possibly influence the results. Folate levels in the blood were also associated with age, sex, and severity of retinopathy in that study. [22] The findings of this study are also consistent with the research by Lei XW, et al.[23], which demonstrated that folic acid acts as a potential therapeutic agent targeting multiple signaling cascades in diabetic retinopathy. Consequently, a protective effect against early-stage retinal thinning in diabetic retinopathy was observed.[23]

Meanwhile, there was a significant positive correlation with moderate strength between homocysteine levels and retinal non-perfusion areas, implying that higher homocysteine levels are associated with increased retinal non-perfusion area. Conversely, the study found a significant negative correlation of moderate strength between homocysteine levels and vascular density, suggesting that higher homocysteine levels are associated with lower vascular density in the retina. Homocysteine has been researched as a biomarker and risk factor for vascular disease, including vascular disease of the eye.[1] An increase in homocysteine is associated with increased oxidative stress. In the pathogenesis of diabetic retinopathy, oxidative stress and mitochondrial dysfunction initiate the development of the characteristic histopathology of DR.[1,24] High homocysteine can damage mitochondria, accelerate capillary cell apoptosis, and the progression of diabetic retinopathy. Inhibiting hyperhomocysteinemia in diabetic patients may help prevent the progression of DR.[24] Several studies have found that homocysteine is related to the severity of DR.[25,26] A study by Tawfik A et al.[27] showed an increase in homocysteine levels in the serum, vitreous, and retinas of diabetic patients and animal models of diabetes. Additionally, homocysteine was found to induce changes in the retinas of rats, which worsened under diabetic conditions. According to that study, homocysteine can be used as a biomarker in DR screening. Therapeutic targeting with homocysteine clearance could also be a future therapy for DR.[27] A meta-analysis by Lei X et al.[17] regarding the relationship between homocysteine levels and the risk of diabetic retinopathy also showed that increased homocysteine levels were associated with an increased risk of diabetic retinopathy, especially in patients with type 2 diabetes.[17] This is consistent with this study that found a significant difference in serum homocysteine levels across all groups ($p = 0.008$). Therefore, it is necessary to conduct serum homocysteine examinations in patients with diabetes mellitus to screen microvascular complications, particularly Diabetic Retinopathy.

Optical Coherence Tomography Angiography (OCTA) effectively visualizes retinal microvascular features, aiding in accurate Diabetic Retinopathy (DR) classification.[28] This study found significant differences in vascular density and retinal non-perfusion area across all groups. Previous research corroborated these findings, showing that DR patients have lower perfusion density, vessel length density, and fractal dimension compared to healthy eyes.[29] Further studies also noted marked differences in the avascular foveal area and vascular density between DR patients and healthy individuals, along with significant variations in retinal thickness and vessel density in different DR stages.[30]

This study has several limitations including the nature of the cross-sectional study, the low number of research samples, and other variables that could affect homocysteine and folic acid levels have not been specifically identified. Further research is needed on the role of folic acid and homocysteine in the severity of DR with other parameters and the influence of other substances that may affect the severity of DR. It is expected that this study can contribute to further research on examinations and therapies for DR.

## Conclusion

This study discovered significant correlations between folic acid and homocysteine levels with retinal conditions. Folic acid levels correlated with retinal non-perfusion area and vascular density in the retina. A notable difference was also found between patients without DR and those with DR, with higher average folic acid levels in patients without DR, suggesting a potential protective role against DR. Additionally, the study noted a correlation between homocysteine levels and retinal non perfusion area. There is also a correlation between homocysteine levels and vascular density. Serum homocysteine showed a significant difference in the severity of DR. This highlights homocysteine as a potential biomarker for DR severity and a target for therapeutic intervention. This study's findings suggest that regular monitoring of homocysteine serum and folic acid levels is useful in predicting the risk and progression of DR. Additionally, folic acid supplementation could potentially prevent or treat DR, though this warrants further investigation and confirmation through clinical trials. This research adds to the growing evidence of the importance of folic acid and homocysteine serum in DR and underscores the value of OCTA in the early detection and classification of DR.

## Conflict of interest

The authors declare that no conflict of interest with another person or institution.

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