Research Square

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Predictors of Retinal Vascular Density Changes in Gestational Diabetes: A Clinical and Metabolic Analysis

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Abstract

Background

Gestational diabetes mellitus (GDM) is associated with microvascular complications that may manifest even in the absence of clinical retinopathy. Optical coherence tomography angiography (OCTA) enables non-invasive assessment of retinal microvascular structure; however, the relationship between retinal vascular density and clinical-metabolic parameters in GDM remains insufficiently characterized. This study aimed to evaluate the independent predictors of retinal vascular density changes in pregnant women with GDM using OCTA.

Methods

This prospective study included 44 pregnant women diagnosed with GDM between 24 and 28 gestational weeks via a 75-gram oral glucose tolerance test at Başakşehir Çam and Sakura City Hospital. Macular microvascular parameters were assessed using swept-source OCTA (Topcon DRI OCT Triton) at 30–34 gestational weeks, concurrently with HbA1c measurement. Glycemic control status was determined by adherence to home blood glucose monitoring (fasting < 95 mg/dL, 1-hour postprandial < 140 mg/dL; ≥80% compliance defined as controlled). Physical activity and dietary adherence were also recorded. Hierarchical linear regression analysis with 1000-iteration bootstrap resampling was performed to identify independent predictors of superficial and deep foveal and parafoveal vascular density.

Results

Mean age was 33.1 ± 5.0 years, and median BMI was 30.63 [5.86] kg/m². Twenty-nine patients (65.9%) were glycemically controlled. Controlled patients demonstrated significantly higher vascular density across all retinal regions compared to uncontrolled patients (superficial foveal VD: 20.41 vs. 15.84%, p = 0.001; deep foveal VD: 15.66 vs. 13.11%, p = 0.006; superficial parafoveal VD: 44.64 vs. 41.44%, p = 0.001; deep parafoveal VD: 45.54 vs. 43.44%, p = 0.001). Hierarchical regression revealed that the addition of glycemic control, physical activity, and dietary adherence significantly improved the model's explanatory power ($\Delta R^2 = 0.342$, p = 0.001). Glycemic control was an independent predictor across all retinal regions. Physical activity emerged as the strongest independent predictor in the deep foveal capillary plexus (β = 0.452, 95% CI: 1.534–5.896, p = 0.001); whereas dietary adherence showed no independent effect in any region.

Conclusion

Retinal microvascular density in GDM is independently associated with glycemic control and physical activity, with the deep capillary plexus demonstrating the greatest metabolic sensitivity. These findings suggest that OCTA may serve as a valuable tool for detecting subclinical microvascular changes in GDM, and that lifestyle factors — particularly physical activity — play a role beyond glycemic regulation alone.

Introduction

Gestational diabetes mellitus represents glucose intolerance that arises or is first diagnosed during pregnancy, constituting a prevalent health concern with substantial short- and long-term impacts on both mother and offspring [1]. Characterized by progressive insulin resistance and pancreatic beta-cell dysfunction, GDM is increasingly recognized as a clinically significant risk factor for early-onset microvascular injury [2].

Retinopathy is seen as among the earliest and most clinically relevant complications resulting from diabetes mellitus in terms of microvascular diseases. OCTA allows the imaging of microvasculature structure in the retina with very high resolution. It has become an important tool to detect preclinical changes in the vascular system before retinopathy[3].

Despite growing clinical interest, studies evaluating retinal microvascular changes specifically in GDM remain scarce, and the relationship between OCTA-derived parameters and key metabolic determinants of the condition has yet to be adequately characterized. Glycemic control, dietary adherence, physical activity compliance, and HbA1c levels constitute the primary monitoring parameters in the clinical follow-up of GDM [4]. However, whether these variables independently influence retinal microvascular density has not been established.

The present study, therefore, aimed to evaluate the independent predictors of retinal vascular density changes in pregnant women with GDM, using OCTA-based quantification of both the superficial and deep capillary plexuses.

Methods

Ethics Approval and Study Design

This prospective study was conducted at Başakşehir Çam and Sakura City Hospital. The study protocol was approved by the institutional ethics committee (Ethics Committee No. 275-2025) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Participant Selection and Exclusion Criteria

Pregnant women who attended the internal medicine outpatient clinic on at least two occasions at two-week intervals and who performed regular home blood glucose monitoring for a minimum of five days —

including fasting and one-hour postprandial measurements — were eligible for inclusion. To ensure the reliability of the study and the accuracy of OCTA measurements, patients meeting any of the following criteria were excluded:

- Systemic hypertension or albuminuria [5],
- Cataract or other ocular media opacities capable of reducing image quality or interfering with OCTA acquisition [6],
- Anemia is defined as a hemoglobin level below 10 g/dL, as it can confound retinal oxygenation and vascular density measurements [7].
- A confirmed diagnosis of diabetes mellitus before pregnancy [5].

GDM Diagnosis and Clinical Follow-up

The diagnosis of GDM was established by a 75-gram oral glucose tolerance test administered between 24 and 28 weeks of gestation [1]. Following diagnosis, all patients received dietary counseling in accordance with the medical nutrition therapy protocols recommended by Cheong et al. [8]. Adherence to the prescribed food groups and meal pattern was assessed at each outpatient visit, and patients were classified as adherent or non-adherent accordingly.

With respect to physical activity, short postprandial walks of 10–15 minutes following main meals were recommended to all patients, primarily to attenuate postprandial glucose excursions. Patients who completed at least 10–15 minutes of postprandial walking on a minimum of five days per week were classified as physically active [9]. Glycemic control was assessed based on home blood glucose monitoring data. Target thresholds were defined as a fasting glucose level below 95 mg/dL and a one-hour postprandial glucose level below 140 mg/dL [4,10]. Patients who met these targets on more than 80% of recorded measurements were classified as having controlled glycemia [10,11].

Laboratory and Ophthalmic Measurements

HbA1c measurements, reflecting each patient's metabolic control status, and OCTA imaging to assess retinal microvascular structure were performed between 30 and 34 weeks of gestation concurrently. Macular microvascular parameters were evaluated using a swept-source optical coherence tomography angiography device (Topcon DRI OCT Triton; Topcon Corporation, Tokyo, Japan). A fovea-centered 3 × 3 mm scanning protocol was applied in all participants. The analysis included only images with a signal strength index≥7 and free of motion or segmentation artifacts.

Segmentation of the superficial capillary plexus was performed using the device's automated segmentation software, whereas boundaries for the deep capillary plexus were defined manually by the investigators. To assess the reliability of deep capillary plexus segmentation, two investigators independently re-analyzed 15 randomly selected images; interobserver agreement was found to be good

(ICC = 0.81)[12]. Deep capillary plexus boundaries were delineated within a depth range of 70–150 μm from the retinal surface, using the internal limiting membrane as the reference plane.

Vascular density values for both the superficial and deep capillary plexuses were calculated within the foveal and parafoveal regions as defined by the Early Treatment Diabetic Retinopathy Study grid [13].

Statistical Analysis

Statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA). Sample size was determined a priori using G*Power software (version 3.1.9.7). Power analysis indicated that a minimum sample of 43 participants was required to detect a large effect size ($f^2 = 0.35$) in a multiple linear regression model with five predictors, at a significance level of $\alpha = 0.05$ and a power of $1 - \beta = 0.80$. The enrollment of 44 patients exceeded this threshold, confirming adequate statistical power for the planned analyses.

Normality of continuous variables was assessed using the Shapiro-Wilk test, along with visual inspection of histograms and Q-Q plots. Normally distributed variables are presented as mean ± standard deviation (Mean ± SD), while non-normally distributed variables are reported as median and interquartile range (Median [IQR]). Categorical variables are expressed as frequencies and percentages (n, %).

Between-group comparisons of continuous variables were performed using the Mann-Whitney U test, given the non-normal distribution of the data. To identify independent predictors of retinal vascular density in patients with GDM and to determine the contribution of metabolic parameters beyond demographic covariates, hierarchical linear regression analysis was conducted using the enter method. Multicollinearity was assessed by inspecting variance inflation factor (VIF) values, with all values remaining below the accepted threshold of 10 [5,14]. To evaluate the internal validity and stability of the regression coefficients, 1000-iteration bootstrap resampling was applied, and bias-corrected and accelerated (BCa) 95% confidence intervals were computed. Statistical significance was set at $p < 0.05$ throughout.

Results

Of the 55 pregnant women enrolled in the study, 11 were excluded due to unsatisfactory OCTA images or lack of home blood glucose control; thus, 44 pregnant women with GDM were included in the analysis. Since it was not expected to be possible to exclude the effects of inter-eye correlation, a random selection of one eye from each woman was made.

The average age in the sample studied was 33.1 ± 5.0 years, and the median BMI was 30.63 [5.86] kg/m². The median HbA1c level in pregnant women was 5.5% [0.67]. 37 patients (84.1%) used insulin, whereas other patients did not use any medications. Using home blood glucose monitoring, 29 (65.9%) patients had adequate glycometabolic control, whereas 15 (34.1%) were uncontrolled. Regarding

lifestyle adherence, 36 patients (81.8%) adhered to dietary recommendations, but only 13 patients (29.5%) had sufficient physical activity.

Regarding OCTA findings, the mean superficial foveal vascular density was 19.3 ± 4.6%, and the mean deep foveal vascular density was 15.1 ± 3.8%. The mean superficial parafoveal vascular density was 43.6 ± 1.9%, and the mean deep parafoveal vascular density was 44.6 ± 2.2%.

Statistically significant differences were observed between glycemically controlled and uncontrolled GDM groups across all retinal vascular density parameters, including superficial foveal, deep foveal, superficial parafoveal, and deep parafoveal vascular density (Table 1).

Table 1: Baseline characteristics and OCTA metrics according to glycemic control status in patients with gestational diabetes

Variables	Controlled Group (n=29) Median [IQR]	Uncontrolled Group (n=15) Median [IQR]	p-value
Age (years)	34 [6]	31 [9]	0.243
BMI (kg/m^2)	32.18 [6.80]	30.17 [5.29]	0.366
HbA1c (%)	5.4 [0.3]	6.1 [1.0]	**0.001**
OCTA Parameters			
Superficial Foveal VD (%)	20.41 [5.93]	15.84 [4.16]	**0.001**
Superficial Parafoveal VD (%)	44.64 [2.38]	41.44 [2.70]	**0.001**
Deep Foveal VD (%)	15.66 [5.29]	13.11 [5.74]	**0.006**
Deep Parafoveal VD (%)	45.54 [2.16]	43.44 [3.48]	**0.001**

BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; HbA1c: Glycated Hemoglobin; IQR: Interquartile Range; OCTA: Optical Coherence Tomography Angiography; VD: Vascular Density. Data are presented as median [IQR]. Group comparisons were performed using the Mann–Whitney U test. Statistically significant p-values ($p < 0.05$) are shown in bold.

Comparison of retinal vascular density parameters according to insulin treatment status revealed no statistically significant differences between groups. Superficial foveal, superficial parafoveal, deep foveal, and deep parafoveal vascular density values were similar between patients receiving insulin therapy and those not receiving insulin (p = 0.343, p = 0.228, p = 1.000, and p = 0.053, respectively).

Patients adherent to the specialized diet demonstrated significantly higher superficial foveal vascular density (p = 0.014) and deep parafoveal vascular density (p = 0.045) compared to non-adherent patients,

while differences in deep foveal (p = 0.055) and superficial parafoveal vascular density (p = 0.092) did not reach statistical significance (Figure 1).

Physically active patients exhibited significantly higher vascular density in the superficial foveal (p = 0.014), superficial parafoveal (p = 0.002), and deep parafoveal (p = 0.038) regions compared to inactive patients, whereas the difference in deep foveal vascular density did not reach statistical significance (p = 0.055) (Figure 2).

Analysis of Predictors of Retinal Vascular Density

Hierarchical linear regression was used to assess factors contributing to changes in the microvasculature of the retina through a two-step process based on the enter approach. At the first step, the covariates included were the age of mothers and their BMIs. Neither of the covariates had any significant effect on vessel density. Also, the model predicted just 3% of the variance (p = 0.536).

At the next stage, when added to the existing model, the variables of glycemic control status, physical activity, and dieting significantly improved the explanatory value of the model ($\Delta R^2 = 0.342$, $p < 0.001$).

The results obtained from layer-specific analysis showed that each layer displayed unique predictive models. For instance, the regression model formulated for the deep foveal capillary plexus was found to have the best predictive performance, which was evidenced by an R-squared value of 0.438. This layer was found to be the most metabolically responsive, while physical activity was shown to be the most influential predictor variable (β = 0.452; 95% CI: 1.534–5.896, p = 0.001).

Conversely, glycemia became the critical factor in the determination of capillary density in the superficial parafoveal capillary network (p = 0.001) with no significant independent impact of exercise in this particular retinal area. Adherence to diet was not a significant predictor of vascular density in any of the four retinal areas considered, implying that the effect of dietary compliance on microvascular structure in the retina occurs indirectly via glycemic control (Table 2).

Table 2. Comprehensive summary of independent predictors of retinal vascular density across capillary layers in patients with gestational diabetes mellitus.

Region	Layer	Glycemic Control β (p)	Physical Activity β (p)	Diet Intervention β (p)	Model R2
Fovea	Superficial	0.461 (**0.003**)	0.307 (**0.033**)	0.030 (0.842)	0.372
	Deep	0.437 (**0.003**)	0.452 (**0.001**)	0.055 (0.697)	0.438
Parafovea	Superficial	0.534 (**0.001**)	0.212 (0.131)	0.039 (0.792)	0.384
	Deep	0.418 (**0.008**)	0.284 (0.056)	0.021 (0.894)	0.322

β: standardized regression coefficient; R^2: coefficient of determination; VD: Vascular Density. All models were adjusted for maternal age and body mass index in the first step of hierarchical regression analysis. Bootstrap resampling (1000 iterations) was applied to assess model stability; bias-corrected and accelerated (BCa) 95% confidence intervals for glycemic control and physical activity excluded zero across all significant models. Statistically significant p-values ($p < 0.05$) are shown in bold.

There was no presence of multicollinearity in the regression model, as the variance inflation factor for each variable remained less than 1.350. Bootstrapping indicated that the results of the study are reliable, as physical activity and glycemic control were statistically significant with their 95% confidence interval not including zero.

As a further measure to test the reliability of the model, a sensitivity analysis was performed wherein age and body mass index were left out of the regression model. The model continued to be statistically significant and demonstrated almost similar explanatory power ($R^2 = 0.348$, adjusted $R^2 = 0.300$, $p < 0.001$).

Discussion

This study investigated the association between the microvascular architecture of the retina and metabolic status/clinical features in women with GDM by OCTA, indicating that glycemic regulation plays an important role in influencing regional variations in retinal microvascular density. Taken together, our observations indicate that GDM can lead to microvascular changes even in the early stages, which may be more than a simple metabolic disorder.

The patients with good glycemic control had significantly increased vascular density in both superficial and deep capillary plexuses, highlighting the susceptibility of retinal microvascular architecture to the effects of metabolism. Our results coincide with previous studies using optical coherence tomography angiography demonstrating a decreased vascular density and microvascular perfusion in women with GDM [5,14,15], Therefore, we can conclude that even short-term exposure of retinal vessels to hyperglycemia due to GDM exerts its detrimental effect on retinal microcirculation. In addition, our results are in accordance with the literature data on subclinical changes of microvasculature visualized by OCTA before the clinical diagnosis of diabetes [16].

The influence of glycemic control on retinal microvascular structure may be attributed to hyperglycemia-induced endothelial dysfunction, increased oxidative stress, and impaired capillary perfusion[17]. These mechanisms, well-established in the pathogenesis of diabetic retinopathy, are thought to be activated at an early stage even in shorter-duration metabolic disturbances such as GDM. The reduction in retinal vascular density has been proposed to correlate with disease progression, and OCTA has been suggested as a potential early biomarker for monitoring microvascular deterioration [18,19]. In this context, the present study provides further support for the notion that microvascular changes in GDM are detectable at an early stage, preceding the onset of clinically evident retinopathy.

Even though there was a significant prevalence rate of the usage of insulin among the participants of the research, no statistical relationship could be established between the two. This indicates that the changes observed in the retinal microvessels have nothing to do with the method of treatment chosen but rather with metabolic conditions. [14].

One interesting outcome of the study is the conclusion about physical activity being an independent determinant of vessel density of the deep foveal capillary plexus. This is because physical activity not only affects metabolism but seems to have direct effects on microvasculature health. Physical activity has been associated with improvements in endothelial functions, increase in nitric oxide bioavailability, and increased microvascular perfusion [20]. The restriction of this relationship to the deep capillary plexus follows suit since the deep capillary plexus is more metabolically sensitive than the superficial capillary plexus. Thus, the importance of physical activity in the management of GDM becomes more important than previously thought, as physical activity does not only help in controlling GDM but also in maintaining microvasculature integrity. Additionally, the consistent results of the study following the sensitivity analysis conducted without taking age and BMI into consideration confirm that the main outcomes are reliable and valid.

In the absence of an independent association between dietary adherence and retinal vascular density, it can be concluded that diet-induced effects operate through glycaemic regulation, not microvasculature. This conclusion is supported by strong scientific evidence regarding the relationship between diet and glycaemia in patients suffering from GDM [10]. In terms of clinical significance, it may be concluded that the impact of diet on retinal microvascularity is indirect, and glycaemic control serves as the main mediator.

Differential sensitivity between retinal layers is yet another clinically significant finding of the current study. Increased sensitivity of the deep capillary plexus to disturbances in metabolism can be explained by its increased rate of oxygen utilization and reduced ability for autoregulation compared with the superficial plexus [21,22]. This finding corroborates the extensive literature data on the role of the deep capillary plexus as the location of early pathological lesions in patients with diabetic retinopathy [23]. In this regard, OCTA examination of each retinal layer is a highly clinically relevant finding in identifying early microvascular damage preceding retinopath

Among the important clinical aspects of the current study, it should be noted that the changes in microvasculature in GDM patients occur not only because of glycemic status but may also depend on various lifestyles [24,25]. Given the non-invasive nature of OCTA, it can serve as a convenient method to investigate the emergence of microvascular changes in this type of patients. It will also allow for further research into the connection between GDM and cardiometabolic risks in the future.

Limitations of the current study need to be considered. To begin with, the relatively small sample size as well as the single center design of this study might limit the generalizability of the results obtained. Next, the measurement of capillary blood glucose levels, although feasible in the outpatient population, is known to have certain limitations when it comes to the identification of all forms of fluctuations in

glycemia during pregnancy. Continuous glucose monitoring devices would provide a more detailed description of glycaemic load experienced. In addition, physical activity data were derived solely from patient self-report, introducing the potential for recall bias and social desirability bias. Lastly, the cross-sectional nature of the study limits its ability to draw causality relationships between the identified risk factors and microvascular retinal density changes.

Conclusion

The present investigation shows that the retinal microvascular density of pregnant women with GDM is independently related to both glycemic regulation and physical exercise, with deep capillary plexus density being particularly sensitive to changes in metabolism. The regional and layer-specific association suggests the ability of OCTA to serve as an effective, non-invasive diagnostic tool for early detection of microvascular changes in GDM patients prior to clinical signs of retinopathy. Independent impact of physical exercise on deep foveal capillary density implies that lifestyle has a direct influence on microvasculature beyond that caused by glycemic regulation. Large prospective investigations are needed to confirm this effect and to determine whether lifestyle improvement will lead to beneficial changes in retinal microvasculature in this cohort of patients.

Declarations

Competing interests

The authors declare that they have no competing interests.

AI-Assisted Writing Disclosure

During the preparation of this manuscript, the authors used an artificial intelligence-based language tool (Claude, Anthropic) to assist with English language editing, phrasing, and academic writing style. All scientific content, data interpretation, and conclusions were generated solely by the authors. The authors take full responsibility for the integrity and accuracy of the published work.

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Consent to publish

Not applicable.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the institutional ethics committee of Başakşehir Çam and Sakura City Hospital (Ethics Committee No. 275-

2025). Written informed consent was obtained from all participants before enrollment.

Author contributions

A.D.K., C.G., and M.Ö.T. contributed to the conception and design of the study. A.D.K., S.E., and K.D. were responsible for data collection and patient follow-up. C.G. and H.Ö. performed the statistical analyses and contributed to data interpretation. M.Ö.T. and S.A.Ö. conducted the literature review. A.D.K. and C.G. drafted the manuscript. All authors critically revised the manuscript, provided intellectual input, and approved the final version.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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Figures

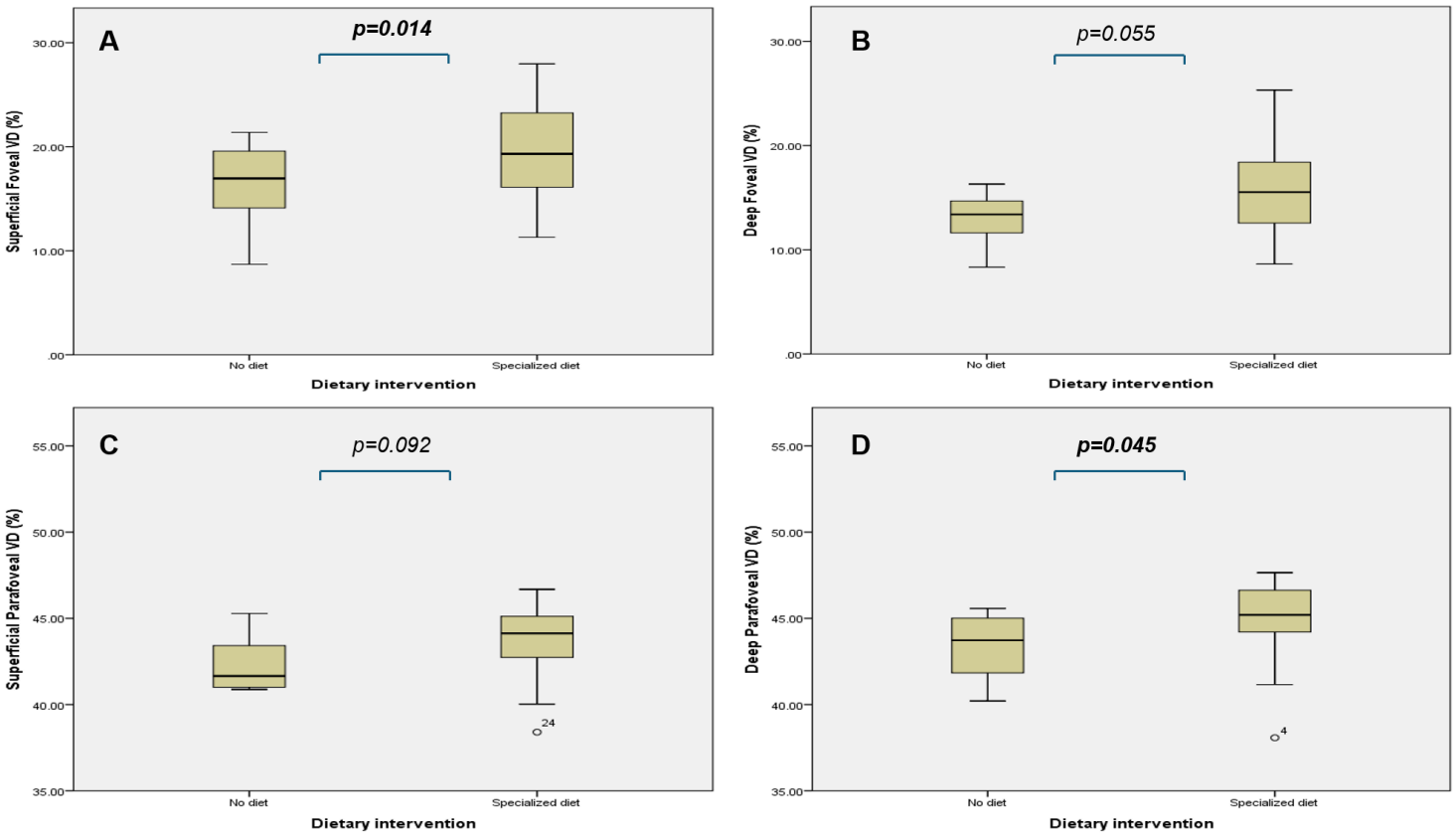


Figure 1

Comparison of retinal vascular density according to dietary intervention status in patients with gestational diabetes mellitus. Box plots illustrating the distribution of (A) superficial foveal vascular density, (B) deep foveal vascular density, (C) superficial parafoveal vascular density, and (D) deep parafoveal vascular density between patients with no dietary adherence and those following a specialized diet. Boxes represent the interquartile range (IQR); horizontal lines within boxes indicate the median; whiskers extend to the minimum and maximum values within 1.5 × IQR; open circles denote outliers. Group comparisons were performed using the Mann–Whitney U test. VD: Vascular Density. Statistically significant differences ($p < 0.05$) are indicated in bold italic.

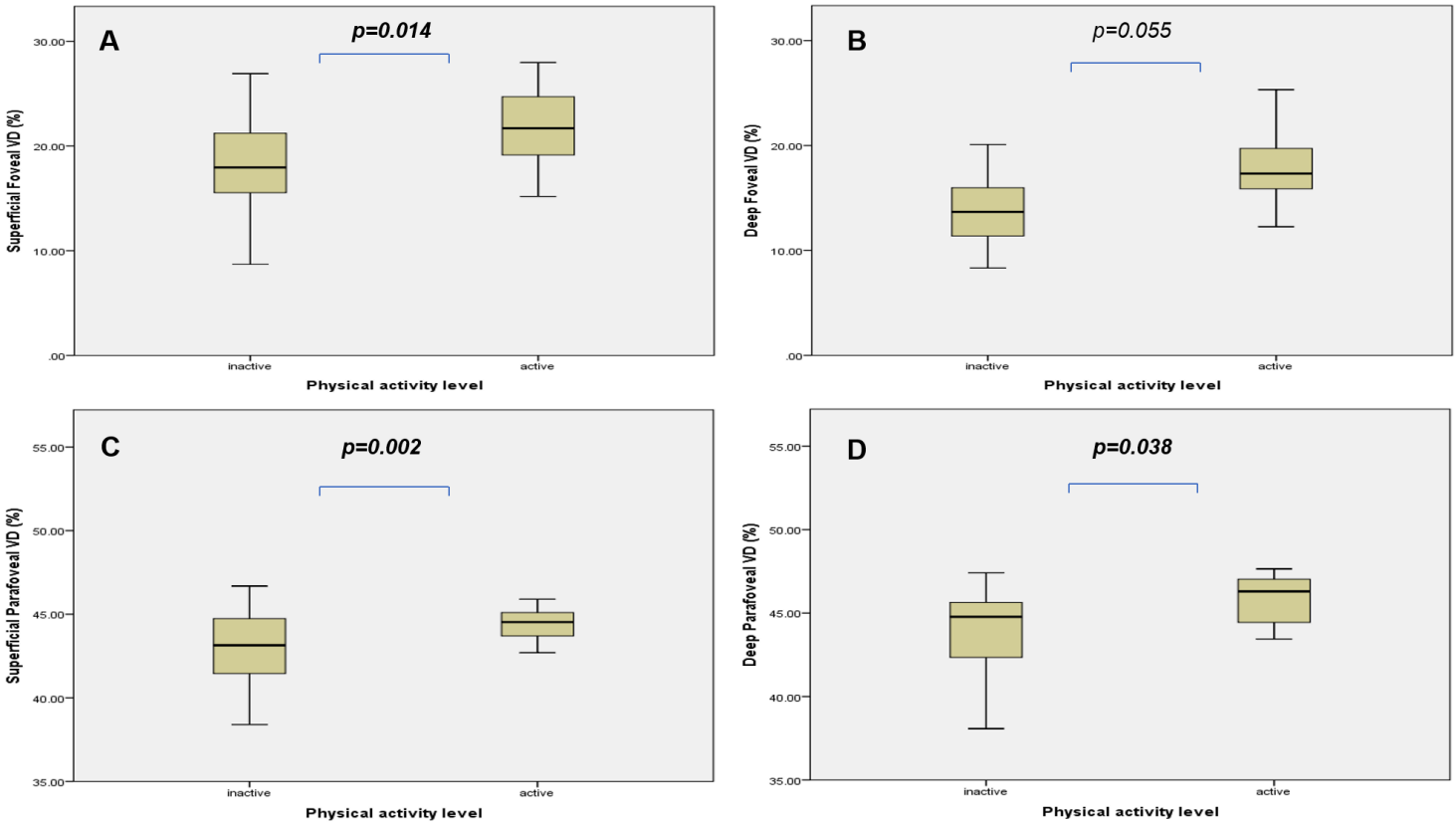


Figure 2

Comparison of retinal vascular density according to physical activity level in patients with gestational diabetes mellitus. Box plots illustrating the distribution of (A) superficial foveal vascular density, (B) deep foveal vascular density, (C) superficial parafoveal vascular density, and (D) deep parafoveal vascular density between physically inactive and active patients. Physical activity was defined as a minimum of 10–15 minutes of postprandial walking at least five days per week. Boxes represent the interquartile range (IQR); horizontal lines within boxes indicate the median; whiskers extend to the minimum and maximum values within 1.5 × IQR. Group comparisons were performed using the Mann–Whitney U test. VD: Vascular Density. Statistically significant differences ($p < 0.05$) are indicated in bold italic.