



Research Article

Serum Fibulin-5, VEGF-C, and selenium-binding protein-1 levels across stages of diabetic retinopathy: An observational study on pathophysiological associations

 Muhammed Selman Arslan¹,  Muzaffer Katar¹,  Ender Sener²

¹Department of Medical Biochemistry, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

²Department of Ophthalmology, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

Abstract

Objectives: Diabetic retinopathy (DR) is a major microvascular complication of diabetes characterized by vascular instability and oxidative stress. This study aimed to evaluate the serum levels of Fibulin-5, Selenium-Binding Protein-1 (SBP-1), and Vascular Endothelial Growth Factor-C (VEGF-C) across different clinical stages of DR and to investigate their independent pathophysiological associations.

Methods: This cross-sectional study included 179 participants categorized into four groups: healthy controls (n=45), diabetes mellitus (DM) without retinopathy (n=45), non-proliferative DR (NPDR) (n=45), and proliferative DR (PDR) (n=44). Serum levels were measured using ELISA. The strength of clinical associations was evaluated via ROC analysis, and independent relationships were assessed using multivariable logistic regression models adjusting for age and HbA1c.

Results: Serum Fibulin-5 and SBP-1 levels were significantly elevated in the NPDR group compared to all other groups ($p < 0.001$ for both). In multivariable regression, both Fibulin-5 (OR: 3.13, $p = 0.0004$) and SBP-1 (OR: 1.63, $p = 0.004$) maintained a strong, independent association with the NPDR stage, distinct from systemic glycemic control. VEGF-C levels did not show significant differences among the groups ($p = 0.310$).

Conclusion: The stage-specific dramatic elevations of Fibulin-5 and SBP-1 in NPDR suggest a systemic reflection of a compensatory mechanism against early retinal microvascular injury and oxidative stress, which appears to diminish in the advanced PDR stage. These findings provide novel observational insights into the systemic dynamics of extracellular matrix remodeling and redox stress in DR pathogenesis.

Keywords: Diabetic retinopathy, Fibulin-5, ROC analysis, SBP-1, VEGF-C

How to cite this article: Arslan MS, Katar M, Sener E. Serum Fibulin-5, VEGF-C, and selenium-binding protein-1 levels across stages of diabetic retinopathy: An observational study on pathophysiological associations. Int J Med Biochem 2026;9(2):111–116.

Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus and remains one of the leading causes of vision loss worldwide [1]. The global prevalence of DR is increasing in parallel with the rise in diabetes, posing a significant public health problem. The International Diabetes Federation has estimated that the number of DM patients worldwide will increase from 463 million in 2019 to 700 million by 2045 [2]. Similarly, it is estimated that the global prevalence of DR will rise significantly, reaching approximately 160.5 million by 2045 [3].

DR is classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [4]. NPDR, the early stage, is characterized by microaneurysms, hemorrhages, and exudates. Over time, it may progress to PDR, which involves pathological neovascularization and carries a high risk of severe vision loss. The pathophysiology involves hyperglycemia-induced endothelial dysfunction, oxidative stress, inflammation, and extracellular matrix (ECM) remodeling [5, 6].

Address for correspondence: Muhammed Selman Arslan, MD. Department of Medical Biochemistry, Tokat Gaziosmanpasa University Faculty of Medicine, Tokat, Türkiye

Phone: +90 551 976 86 24 **E-mail:** selmanarsslan@gmail.com **ORCID:** 0009-0007-0994-7603

Submitted: December 11, 2025 **Revised:** April 03, 2026 **Accepted:** April 07, 2026 **Available Online:** April 15, 2026

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



While anti-VEGF therapies have transformed management, DR is a multifactorial disease [7]. Evaluating circulating molecules that reflect ECM remodeling and angiogenesis could offer mechanistic insights into disease progression. Fibulin-5 (FBLN5) is an integrin-binding ECM glycoprotein involved in vascular remodeling and elastic fiber assembly, potentially acting as an endogenous anti-angiogenic factor by restricting endothelial cell proliferation [8, 9]. Alongside ECM stability, the redox balance in the ischemic retina is a critical component of the pathophysiological response. Selenium-Binding Protein 1 (SBP-1), recently characterized as a methanethiol oxidase, plays a pivotal role in modulating redox signaling by producing hydrogen sulfide (H₂S), a protective gasotransmitter, and neutralizing reactive oxygen species (ROS) [10]. However, the systemic fluctuations of SBP-1 across DR stages remain poorly understood. VEGF-C, a regulator of lymphangiogenesis, has been less studied in DR compared to VEGF-A but is thought to support endothelial survival under hyperglycemic stress [11].

Despite advances in understanding local ocular changes, there is a lack of comprehensive studies evaluating the systemic reflection of concurrent ECM stabilization and redox modulation during the progression of DR. Therefore, the primary purpose of this cross-sectional study was to simultaneously quantify the serum levels of Fibulin-5, SBP-1, and VEGF-C across different clinical stages of DR. We aimed to determine the independent associations of these circulating molecules with disease stages, hypothesizing that systemic variations reflect a stage-specific pathophysiological response to retinal ischemia and oxidative stress.

Materials and Methods

Study design and participants

This cross-sectional study included 179 participants recruited at a single tertiary center. Participants were categorized into four groups: healthy controls (n=45), type 2 diabetes mellitus without retinopathy (n=45), non-proliferative DR (n=45), and proliferative DR (n=44). Diabetic retinopathy staging was performed according to the international clinical diabetic retinopathy disease severity scale [4]. Inclusion criteria were age >18 years. Exclusion criteria included other ocular pathologies, systemic inflammatory diseases, active malignancy, and significant renal impairment (to prevent confounding effects on the renal clearance of the measured molecules). This study was approved by the Tokat Gaziosmanpaşa University (Date: 13.12.2024, Decision no: 24-MOBAEK-036) and conducted in accordance with the Declaration of Helsinki.

Clinical and laboratory assessment

Demographic data (age, sex) and systemic comorbidities were recorded. Venous blood samples were obtained after an overnight fast (at least 8 hours). Blood was collected into serum separator tubes (SST) and EDTA tubes. Samples were centrifuged at 3500 rpm for 10 minutes to separate the serum. Serum aliquots were stored at -80°C until analysis to prevent protein degradation.

Routine biochemical parameters were analyzed using the Roche Cobas 6000 series c501 autoanalyzer (Roche Diagnostics, Mannheim, Germany). Fasting plasma glucose was measured using the hexokinase method, and serum creatinine was measured using the Jaffe colorimetric assay. HbA1c levels were determined using an immunoturbidimetric inhibition immunoassay.

Serum assays

Serum Fibulin-5, SBP-1, and VEGF-C concentrations were measured using commercially available quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits strictly following the manufacturers' instructions (Reed Biotech Ltd., Catalog Nos: RE1713H for Fibulin-5, ESD0133H for SBP-1, and RE1931H for VEGF-C).

- VEGF-C ELISA kit sensitivity: 65.63 pg/mL; Detection Range: 109.38–7000 pg/mL.
- Fibulin-5 ELISA kit sensitivity: 1.88 ng/mL; Detection Range: 3.13–200 ng/mL.
- SBP-1 ELISA kit was utilized according to the manufacturer's standard protocols, and optical densities were measured spectrophotometrically at 450 nm.

Statistical analysis

Statistical analyses were performed using MedCalc (version 20.009). The conformity of continuous variables to a normal distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as median (interquartile range, IQR). Group comparisons were conducted using the Kruskal-Wallis test with Bonferroni-corrected post-hoc pairwise Mann-Whitney U tests. To evaluate the strength of the clinical associations, Receiver Operating Characteristic (ROC) curve analysis was utilized. To assess the independent association of these molecules with DR presence, multivariate binary logistic regression analysis was performed, adjusting for potential confounders such as HbA1c and age. Due to the right-skewed nature of the data, concentrations were normalized using a Log₁₀ transformation prior to regression analysis. A two-sided p-value <0.05 was considered statistically significant.

Results

Participant characteristics

Age and sex distribution were comparable among the groups, as determined by the Kruskal-Wallis and Chi-square tests (p=0.280 and p=0.824, respectively) (Table 1). As expected, fasting glucose and HbA1c were significantly higher in the diabetic groups compared to the controls (p<0.001). The clinical, demographic, and biochemical characteristics of the study population are summarized in Table 2.

Serum molecular levels

Median serum Fibulin-5 levels showed a statistically significant difference across the study groups (p<0.001). Post-hoc analy-

Table 1. Comparison of gender parameter between study groups

| Gender | Control (n=45) | DM (n=45) | NPDR (n=45) | PDR (n=44) |
|---------------|----------------|-----------|-------------|------------|
| Male, n (%) | 18 (40.0) | 14 (37.8) | 17 (37.8) | 17 (38.6) |
| Female, n (%) | 27 (60.0) | 31 (62.2) | 28 (62.2) | 27 (61.4) |

Data are presented as n (%) for categorical variables. There was no statistically significant difference between the groups according to the Chi-square test ($p=0.824$). DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; n: Participant number.

Table 2. Comparison of demographic and biochemical parameters between study groups

| Parameter | Control (n=45) | DM (n=45) | NPDR (n=45) | PDR (n=44) | p* |
|-------------------------|----------------|-------------|-------------|-------------|--------|
| Age (years) | 66 (13) | 65 (13) | 63 (8) | 60 (11) | 0.280 |
| Fibulin-5 (ng/mL) | 9.3 (5.2) | 9.9 (6.2) | 24.3 (34.2) | 8.8 (7.7) | <0.001 |
| VEGF-C (pg/mL) | 2362 (1647) | 2235 (1479) | 2854 (1647) | 2075 (2674) | 0.310 |
| Fasting Glucose (mg/dL) | 99 (16) | 124 (51) | 144 (114) | 239 (138) | <0.001 |
| Creatinine (mg/dL) | 0.83 (0.27) | 0.82 (0.35) | 0.91 (0.28) | 0.88 (0.37) | 0.608 |
| HbA1c (%) | 5.7 (0.4) | 6.8 (2.0) | 8.1 (3.5) | 8.8 (2.9) | <0.001 |

*: Overall p-values were derived from the Kruskal-Wallis test. DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; VEGF-C: Vascular endothelial growth factor-C; HbA1c: Glycated hemoglobin; IQR: Interquartile range. Data are presented as median (IQR).

Table 3. SBP-1 levels across the study groups

| Study groups | n | Median (pg/mL) | IQR (25%–75%) | Min-Max | Overall p-value* | Significant differences (Post-Hoc)** |
|--------------|----|----------------|-----------------|-----------------|------------------|---|
| Control | 45 | 1643.31 | 922.45–2885.23 | 215.58–10225.23 | <0.0001 | None |
| DM | 45 | 1498.34 | 867.10–2489.70 | 211.68–14489.24 | | None |
| NPDR | 45 | 5207.66 | 1857.51–7150.51 | 156.06–35886.01 | | > DM ($p<0.0001$) > Control ($p<0.0001$) |
| PDR | 44 | 2673.87 | 584.49–8341.09 | 62.83–21256.38 | | None |

*: Overall p-value was derived from the Kruskal-Wallis test; **: Post-hoc pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction. DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; SBP-1: Selenium-binding protein-1; IQR: Interquartile range.

sis revealed that serum Fibulin-5 was significantly higher in the NPDR group (Median: 24.3 ng/mL) compared to healthy controls (9.3 ng/mL), diabetic patients without retinopathy (9.9 ng/mL), and patients with PDR (8.8 ng/mL) (Fig. 1). Similarly, serum SBP-1 levels exhibited a highly significant variance across the groups ($p<0.001$). SBP-1 concentrations peaked in the NPDR group (Median: 5207.66 pg/mL), which was significantly higher than both the control (1643.31 pg/mL) and DM without retinopathy (1498.34 pg/mL) groups. In the PDR group, SBP-1 levels declined to a median of 2673.87 pg/mL, losing statistical significance compared to the controls. Detailed variance analyses of SBP-1 levels across the study groups are provided in Table 3. In contrast, serum VEGF-C levels did not demonstrate significant differences among the groups ($p=0.310$).

Clinical association analysis (ROC)

To assess the discriminative association of the molecules in distinguishing NPDR from diabetic patients without retinopathy, a ROC curve analysis was performed. Fibulin-5 demonstrated a significant association with an Area Under the Curve (AUC) of 0.793 (95% CI: 0.700–0.886). At a cut-off value of >16.99 ng/mL, Fibulin-5 exhibited a sensitivity of 64.4% and a specificity of 86.6%. SBP-1 also showed a robust association profile with an

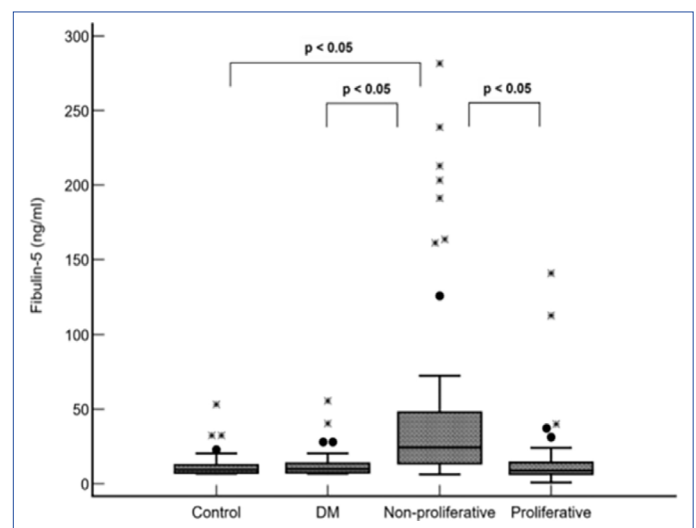


Figure 1. Box-plot diagrams illustrating the serum distributions of Fibulin-5 across the study groups. The central horizontal line represents the median, while the boxes indicate the interquartile ranges (IQR). Whiskers represent the data range excluding outliers.

DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; IQR: Interquartile range.

Table 4. AUC and optimal cut-off values for Fibulin-5, SBP-1 and VEGF-C

| Biomarker | AUC | Optimal Cut-off | Sensitivity (%) | Specificity (%) |
|-----------|-------|-----------------|-----------------|-----------------|
| Fibulin-5 | 0.793 | >16.99 ng/mL | 64.44 | 86.67 |
| SBP-1 | 0.757 | >2725.56 pg/mL | 71.11 | 80.00 |
| VEGF-C | 0.591 | >2853.89 pg/mL | 51.11 | 71.11 |

Optimal cut-off values were determined by maximizing the Youden Index in the Receiver Operating Characteristic (ROC) curve analysis to discriminate the non-proliferative diabetic retinopathy (NPDR) stage from diabetic patients without retinopathy. AUC: Area under the curve; SBP-1: Selenium-binding protein-1; VEGF-C: Vascular endothelial growth factor-C.

Table 5. Multivariable logistic regression analysis for independent associations with the NPDR stage

| Model and independent variables | Coefficient (β) | OR | 95% CI | p |
|---------------------------------|-------------------------|------|------------|---------------|
| Model 1: SBP-1 | | | | |
| SBP-1 (Per 2-fold increase) | 0.487 | 1.63 | 1.16–2.29 | 0.004 |
| HbA1c (%) | 0.626 | 1.87 | 1.29–2.71 | 0.001 |
| Creatinine (mg/dL) | 1.079 | 2.94 | 0.41–21.16 | 0.283 |
| Age (years) | 0.012 | 1.01 | 0.94–1.09 | 0.744 |
| Model 2: Fibulin-5 | | | | |
| Fibulin-5 (Per 2-fold increase) | 1.141 | 3.13 | 1.65–5.94 | 0.0004 |
| HbA1c (%) | 0.611 | 1.84 | 1.26–2.69 | 0.001 |
| Creatinine (mg/dL) | 0.963 | 2.62 | 0.33–20.66 | 0.360 |
| Age (years) | -0.009 | 0.99 | 0.91–1.07 | 0.823 |
| Model 3: VEGF-C | | | | |
| VEGF-C (Per 2-fold increase) | 0.101 | 1.11 | 0.62–1.99 | 0.735 |
| HbA1c (%) | 0.737 | 2.09 | 1.43–3.05 | 0.0001 |
| Creatinine (mg/dL) | 1.163 | 3.20 | 0.53–19.28 | 0.204 |
| Age (years) | 0.010 | 1.01 | 0.94–1.09 | 0.772 |

Dependent variable: Presence of NPDR vs. DM without Retinopathy. Biomarker concentrations were Log10 transformed and scaled to reflect the likelihood associated with a 2-fold increase in circulating levels. NPDR: Non-proliferative diabetic retinopathy; OR: Odds ratio; CI: Confidence interval; HbA1c: Glycated hemoglobin; FBLN-5: Fibulin-5; SBP-1: Selenium-binding protein-1; VEGF-C: Vascular endothelial growth factor-C.

AUC of 0.757, yielding a sensitivity of 71.1% and a specificity of 80.0% at a cut-off of >2725.56 pg/mL. The ROC curves are shown in Figure 2 for Fibulin-5 and Figure 3 for SBP-1. Detailed diagnostic metrics and optimal cut-off values are presented in Table 4.

Multivariate logistic regression analysis

To evaluate whether the molecules are independently associated with the NPDR stage, we performed a multivariate binary logistic regression analysis adjusting for age, creatinine, and HbA1c. The analysis revealed that normalized serum Fibulin-5 maintained a strong independent association with NPDR. Every 2-fold increase in circulating Fibulin-5 levels was associated with a 3.13-fold increased likelihood of NPDR presence (Odds Ratio: 3.13, 95% CI: 1.65–5.94, $p=0.0004$). Parallel to this, SBP-1 was also identified as an independent correlate, with a 2-fold increase raising the likelihood of NPDR by 1.63 times (OR: 1.63, 95% CI: 1.16–2.29, $p=0.004$). This indicates that the variations of Fibulin-5 and SBP-1 are not solely driven by systemic glycemic status or renal function (Table 5). VEGF-C lost all statistical significance when adjusted for HbA1c ($p=0.735$).

Discussion

In this study, we observed that serum Fibulin-5 and SBP-1 concentrations are significantly elevated in patients with non-pro-

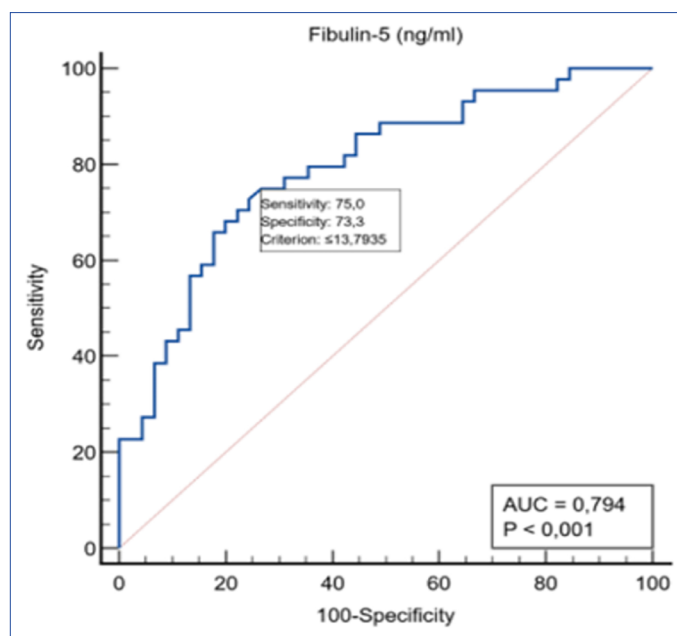


Figure 2. Receiver operating characteristic (ROC) curves demonstrating the discriminative association of Fibulin-5 for detecting the non-proliferative diabetic retinopathy (NPDR) stage.

AUC: Area under the curve; CI: Confidence interval.

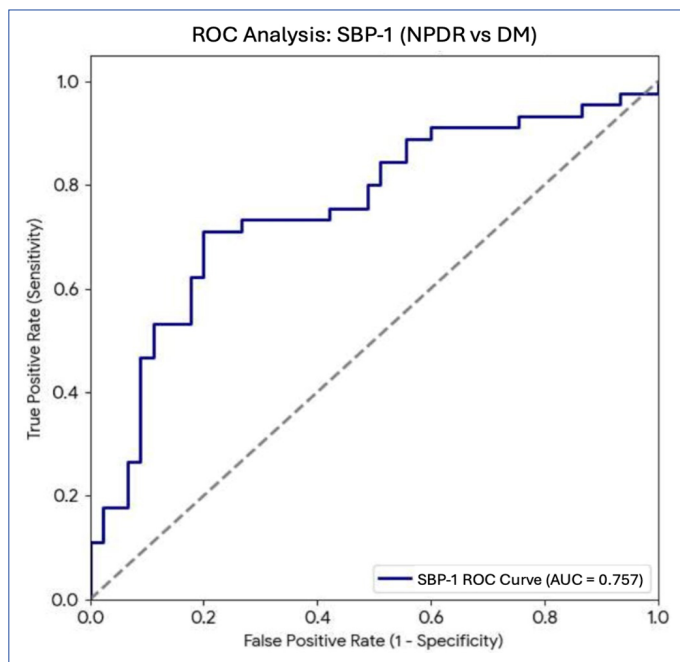


Figure 3. Receiver operating characteristic (ROC) curves demonstrating the discriminative association of SBP-1 for detecting the non-proliferative diabetic retinopathy (NPDR) stage.

AUC: Area under the curve; CI: Confidence interval.

liferative diabetic retinopathy (NPDR) compared to healthy controls, diabetic patients without retinopathy, and those with proliferative DR (PDR). Importantly, multivariate regression analysis confirmed that these elevations are independent of HbA1c levels, suggesting that they reflect localized pathophysiological mechanisms of extracellular matrix remodeling and redox stress rather than mere systemic hyperglycemia.

The most compelling finding of this study is the stage-specific biphasic trajectory—peaking at NPDR and subsiding at PDR—which points toward a novel "compensatory failure" mechanism in DR pathogenesis. Current literature highlights Fibulin-5 as a matricellular glycoprotein that restricts endothelial cell migration via integrin interactions, acting as an endogenous angiogenesis inhibitor [12]. The dramatic independent surge of Fibulin-5 during the NPDR stage likely reflects the vascular endothelium's physiological response to stabilize the basement membrane against escalating angiogenic stimuli. Recent proteomic analyses by Honoré et al. [13] have similarly identified Fibulin-5 alterations in DR, supporting its role as a dynamic correlate of vascular structural integrity. As the disease progresses to the PDR stage, the sharp decline in Fibulin-5 levels signifies the potential loss of this anti-angiogenic structural defense, coinciding with unrestrained pathological neovascularization.

A parallel compensatory mechanism is evident in the redox axis governed by SBP-1. Philipp et al. [10] recently characterized SBP-1 as a methanethiol oxidase that produces hydrogen sulfide (H₂S), an endogenous gasotransmitter known to confer microvascular vasodilation and activate antioxidant

pathways against reactive oxygen species. Animal models of early diabetic retinal neurodegeneration have shown that local retinal Selenbp1 gene expression is significantly upregulated [14]. Our detection of a massive systemic SBP-1 peak in the NPDR cohort aligns with this localized tissue response. The ischemic retina likely upregulates SBP-1 to balance the oxidative burden; this localized overproduction is then reflected in the systemic circulation due to blood-retinal barrier breakdown. The subsequent drop in SBP-1 during the advanced PDR stage provides clinical evidence of potential "cellular exhaustion," indicating that the local endothelial and glial cells synthesizing this enzyme may have succumbed to ischemia and apoptosis.

In contrast to Fibulin-5 and SBP-1, circulating VEGF-C levels did not differ significantly across diabetic retinopathy stages and lost all independent association in multivariable models. Although VEGF-C is involved in lymphangiogenesis and angiogenic signaling, systemic VEGF-C concentrations may not accurately reflect localized retinal angiogenic activity. This finding is consistent with previous reports indicating that intraocular levels of angiogenic mediators may be more relevant than serum measurements in the pathophysiology of diabetic retinopathy, or that systemic VEGF-C merely acts as a surrogate for chronic systemic inflammation rather than a specific ocular trigger [15].

Several limitations of this study should be acknowledged. The cross-sectional and single-center design fundamentally limits causal inference regarding the timeline of molecular fluctuations. Furthermore, specific clinical metadata such as the exact duration of diabetes and detailed antidiabetic medication histories were not uniformly available for all participants; thus, these variables could not be robustly included in our regression models. Consequently, we avoid proposing these molecules as definitive clinical biomarkers, but rather present them as systemic reflections of the underlying retinal pathophysiology. Additionally, the lack of paired vitreous samples restricts direct conclusions regarding local retinal production. Nevertheless, the clear stage-specific elevation of Fibulin-5 and SBP-1, along with their independence from glycemic control, highlights their relevance as circulating indicators of early microvascular remodeling and oxidative stress in diabetic retinopathy.

Conclusion

Serum Fibulin-5 and SBP-1 are significantly elevated in non-proliferative diabetic retinopathy and demonstrate a strong association with the disease stage, separate from systemic glycemic control. The sudden regression of these molecules in the proliferative stage suggests a phenomenon of cellular exhaustion and loss of compensatory vascular defense. While further longitudinal studies incorporating extended clinical metadata are required, these pathways provide valuable observational insights into the systemic dynamics of extracellular matrix remodeling and oxidative damage in early-stage diabetic retinopathy.

Disclosures

Ethics Committee Approval: The study was approved by the Tokat Gaziosmanpaşa University Ethics Committee (no: 24-MOBAEK-036, date: 13/12/2024).

Informed Consent: Written informed consent was obtained.

Conflict of Interest Statement: None declared.

Funding: This study was supported by the Tokat Gaziosmanpaşa University Scientific Research Projects Commission (Grant Number: 2024/104).

Use of AI for Writing Assistance: None declared.

Authorship Contributions: Concept – M.S.A., M.K., E.S.; Design – M.S.A., M.K., E.S.; Supervision – M.S.A., M.K., E.S.; Resource – M.S.A., M.K., E.S.; Materials – M.S.A., M.K., E.S.; Data collection and/or processing – M.S.A., M.K., E.S.; Analysis and/or interpretation – M.S.A., M.K., E.S.; Literature review – M.S.A., M.K., E.S.; Writing – M.S.A., M.K., E.S.; Critical review – M.S.A., M.K., E.S.

Peer-review: Externally peer-reviewed.

References

1. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol* 2016;44(4):260–77. [\[Crossref\]](#)
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019;157:107843. [\[Crossref\]](#)
3. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology* 2021;128(11):1580–91. [\[Crossref\]](#)
4. Wilkinson CP, Ferris FL, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677–82. [\[Crossref\]](#)
5. Antonetti DA, Silva PS, Stitt AW. Current understanding of the molecular and cellular pathology of diabetic retinopathy. *Nat Rev Endocrinol* 2021;17(4):195–206. [\[Crossref\]](#)
6. Wei L, Sun X, Fan C, Li R, Zhou S, Yu H. The pathophysiological mechanisms underlying diabetic retinopathy. *Front Cell Dev Biol* 2022;10:963615. [\[Crossref\]](#)
7. Cheung N, Wong IY, Wong TY. Ocular anti-VEGF therapy for diabetic retinopathy: overview of clinical efficacy and evolving applications. *Diabetes Care* 2014;37(4):900–5. [\[Crossref\]](#)
8. Yanagisawa H, Schluterman MK, Brekken RA. Fibulin-5, an integrin-binding matricellular protein: its function in development and disease. *J Cell Commun Signal* 2009;3(3-4):337–47. [\[Crossref\]](#)
9. Sullivan KM, Bissonnette R, Yanagisawa H, Hussain SN, Davis EC. Fibulin-5 functions as an endogenous angiogenesis inhibitor. *Lab Invest* 2007;87(8):818–27. [\[Crossref\]](#)
10. Philipp TM, Gernoth L, Will A, Schwarz M, Ohse VA, Kipp AP, et al. Selenium-binding protein 1 (SELENBP1) is a copper-dependent thiol oxidase. *Redox Biol* 2023;65:102807. [\[Crossref\]](#)
11. Zhao B, Smith G, Cai J, Ma A, Boulton M. Vascular endothelial growth factor C promotes survival of retinal vascular endothelial cells via vascular endothelial growth factor receptor-2. *Br J Ophthalmol* 2007;91(4):538–45. [\[Crossref\]](#)
12. Albig AR, Schiemann WP. Fibulin-5 antagonizes vascular endothelial growth factor (VEGF) signaling and angiogenic sprouting by endothelial cells. *DNA Cell Biol* 2004;23(6):367–79. [\[Crossref\]](#)
13. Honoré B, Hajari JN, Pedersen TT, Ilginis T, Al-Abaiji HA, Lønkvist CS, et al. Proteomic analysis of diabetic retinopathy identifies potential plasma-protein biomarkers for diagnosis and prognosis. *Clin Chem Lab Med* 2024;62(6):1177–97. [\[Crossref\]](#)
14. Bogdanov P, Corraliza L, Villena JA, Carvalho AR, Garcia-Arumí J, Ramos D, et al. The db/db mouse: a useful model for the study of diabetic retinal neurodegeneration. *PLoS One* 2014;9(5):e97302. [\[Crossref\]](#)
15. Wakabayashi Y, Usui Y, Okunuki Y, Kezuka T, Takeuchi M, Goto H, Iwasaki T. Correlation of vascular endothelial growth factor with chemokines in the vitreous in diabetic retinopathy. *Retina* 2010;30(2):339–44. [\[Crossref\]](#)