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Original Article

Biochemistry Section

Serum Retinol-binding Protein 3 as a Potential Biomarker for Diabetic Retinopathy Severity: A Cross-sectional Study

KINJAL P PATEL[1], CHIRAG K PANDYA[2], BHARGAV J PATEL[3], SANDIP S SENDHAV[4], PRASAD KHODKE[5]

ABSTRACT

Introduction: Diabetic Retinopathy (DR) is one of the leading causes of visual impairment worldwide. Its progression is influenced by complex metabolic, inflammatory and neurodegenerative mechanisms. Retinol-binding Protein 3 (RBP3), a retina-specific glycoprotein essential for the visual cycle, has recently gained attention due to its potential neuroprotective and anti-inflammatory roles. Reduced RBP3 levels may contribute to retinal dysfunction, making it a possible biomarker for DR risk stratification.

Aim: To assess serum RBP3 levels among Type 2 Diabetes Mellitus (T2DM) patients and determine its association with the severity of DR, glycaemic control and systemic inflammation.

Materials and Methods: A hospital-based cross-sectional study was conducted at Nootan Medical College and Research Centre, Visnagar, Gujarat, India, from January 2023 to February 2024, in collaboration with the Departments of Biochemistry, Ophthalmology, and Medicine. A total of 100 T2DM patients (aged 45-65 years) were enrolled. Detailed retinal examinations were performed to classify DR severity. Serum RBP3 levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA). Glycated Haemoglobin (HbA1c) and high-sensitivity C-Reactive Protein (hs-CRP) were evaluated as indicators of glycaemic status and systemic inflammation. Statistical analysis was performed using MedCalc software, with p-value <0.05 considered significant.

Results: The study included 100 patients with T2DM presenting with vision problems, with a mean age of 55.04±4.47 years (range: 45-65 years); 55% were female, and 45% were male. DR was present in 87% of participants, with mild non proliferative DR being the most common stage. Serum RBP3 levels showed a strong inverse correlation with DR severity (p-value <0.0001). Significant negative correlations were observed between RBP3 and HbA1c (r=–0.9136, p-value <0.0001) and between RBP3 and hs-CRP (r=–0.9654, p-value <0.0001).

Conclusion: Serum RBP3 levels show a significant inverse association with the severity of DR, hyperglycaemia, and inflammation. These findings indicate that lower serum RBP3 levels are associated with more advanced retinopathy, poorer glycaemic control, and heightened systemic inflammation. RBP3 may serve as a promising biomarker for early detection and risk assessment in DR. Larger, longitudinal studies with predictive analysis are required to establish its diagnostic and therapeutic relevance.

Keywords: Diabetes mellitus, Inflammation, Vision disorders

INTRODUCTION

The DR is one of the most prevalent microvascular complications of diabetes mellitus and remains a leading cause of vision loss among working-age adults worldwide [1,2]. With the global rise in diabetes prevalence, the incidence of DR has also increased steadily. A meta-analysis by Yau JW et al. reported that approximately one-third of individuals with diabetes show signs of retinopathy, with about 10% experiencing vision-threatening stages [3].

The pathogenesis of DR is multifactorial, involving hyperglycaemia-induced oxidative stress, formation of Advanced Glycation End Products (AGEs), chronic low-grade inflammation, and neurovascular dysfunction [4,5]. These molecular and cellular insults contribute to endothelial damage, pericyte loss, and disruption of the blood-retinal barrier, ultimately leading to retinal ischemia and neovascularisation [6]. Recent studies also emphasise that neuronal and glial alterations in the retina may occur before detectable vascular damage, suggesting that DR should be recognised as both a neurodegenerative and vasculopathic disorder [4,5,7].

Although well-known systemic risk factors such as poor HbA1c, hypertension, and duration of diabetes are linked to DR progression, they are often insufficient to accurately predict disease onset or severity. Consequently, there is a growing need for reliable, retina-specific biomarkers that can facilitate early detection, risk stratification, and therapeutic monitoring of DR [8].

The RBP3, also known as Interphotoreceptor Retinoid-binding Protein (IRBP), is a large glycoprotein synthesised by photoreceptors and secreted into the interphotoreceptor matrix, where it plays an essential role in the visual cycle and retinoid transport between photoreceptors and the Retinal Pigment Epithelium (RPE) [9]. Mutations or reductions in RBP3 expression have been associated with retinal degeneration and photoreceptor dysfunction, underscoring its neuroprotective importance [10].

Recent investigations suggest that RBP3 may act as a protective factor in DR. In a landmark study, Yokomizo H et al., found that diabetic individuals resistant to DR exhibited significantly higher retinal and vitreous RBP3 levels than those who developed retinopathy [11]. Moreover, RBP3 was shown to bind to Glucose Transporter 1 (GLUT1) in retinal endothelial and Müller cells, reducing glucose uptake and thereby mitigating hyperglycaemia-induced oxidative and inflammatory stress [11]. Similarly, Fickweiler W et al., demonstrated that higher vitreous RBP3 concentrations correlated with reduced levels of inflammatory cytokines and Vascular Endothelial Growth Factor (VEGF), and with slower DR progression [12].

Experimental studies have also demonstrated that downregulation of RBP3 occurs early in the course of diabetic retinal disease and

may contribute to enhanced VEGF signalling and neuronal apoptosis [13,14]. Collectively, these findings suggest that RBP3 exerts anti-inflammatory, antioxidative, and neuroprotective effects within the diabetic retina. While previous research has mainly focused on intra-ocular RBP3 levels (in-vitreous or aqueous humour) in DR, data on circulating or serum RBP3 concentrations remain limited [4,10,12]. Therefore, investigating serum RBP3 levels could offer a minimally invasive and clinically feasible biomarker for early identification, risk stratification, and monitoring of DR progression. Given the complex interplay between metabolic control, inflammation, and retinal neurovascular integrity, assessing serum RBP3 alongside established markers such as HbA1c and hs-CRP may provide novel insights into the pathophysiological links between systemic and retinal compartments in diabetes. Hence, the present study aimed to evaluate the relationship between serum RBP3 levels and DR severity, and to explore its potential utility as a biomarker in DR.

MATERIALS AND METHODS

A hospital-based cross-sectional study was conducted at Nootan Medical College and Research Centre, Visnagar, Gujarat, India, from January 2023 to February 2024, in collaboration with the Departments of Biochemistry, Ophthalmology, and Medicine. Before study initiation, ethical clearance was obtained from the Institutional Ethics Committee (Ref: IEC/NMCRC/APPROVAL/10/2023). Written informed consent was obtained from all participants. Patient confidentiality was strictly maintained throughout the study.

Sample size calculation: The sample size was calculated to detect a moderate correlation (r=0.30) between serum RBP3 levels and DR severity, with a power of 80% and a significance level of 5% (α=0.05). Using the standard formula for correlation studies: $n = \{(Z\alpha + Z\beta)/C\}^2 + 3$,

where $C = 0.5 \times \ln\{(1+r)/(1-r)\}$,

with r=0.30 [15],

the estimated minimum sample size was 85. To account for attrition and incomplete data, a total of 100 patients were planned for recruitment.

Inclusion criteria: Diagnosed cases of T2DM, aged between 45 and 65 years, patients presenting with visual complaints, and those willing to provide informed consent.

Exclusion criteria: It included individuals with non diabetic causes of retinopathy, such as hypertensive retinopathy or Age-related Macular Degeneration (AMD), the presence of ocular conditions that could interfere with retinal assessment, pregnant or lactating women, and those with serious systemic illnesses or cognitive impairments.

Study Procedure

Eligible patients from the Medicine Outpatient Department (OPD) were enrolled consecutively after screening. Diabetes mellitus was confirmed using American Diabetes Association (ADA) criteria [16]. Each participant underwent a comprehensive ocular examination. After pharmacological dilation of pupils, a trained ophthalmologist performed indirect ophthalmoscopy to evaluate the fundus. The severity of DR was classified using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system [17]. This systematic grading provided a standardised assessment for correlation with biochemical parameters.

Following the ocular examination, venous blood samples were collected from all participants using three types of vacutainers: plain tubes for serum-based assays, Ethylenediaminetetraacetic Acid (EDTA) tubes for plasma analysis, and sodium fluoride tubes for glucose estimation. All samples were centrifuged promptly to separate serum or plasma, and aliquots were stored under appropriate temperature-controlled conditions until biochemical analysis.

Serum RBP3 concentrations were determined using a commercially available ELISA kit in accordance with the manufacturer's protocol [18]. Systemic biochemical markers were also evaluated. The hs-CRP, an indicator of systemic inflammation, was measured using a turbidimetric immunoassay method. HbA1c, a marker of long-term glycaemic control, was quantified using High-performance Liquid Chromatography (HPLC). All laboratory analyses were conducted following Standard Operating Procedures (SOPs) and quality control measures to ensure accuracy and reproducibility of results.

STATISTICAL ANALYSIS

All data were entered into Microsoft Excel and analysed using MedCalc software (version 23.3.5). Descriptive statistics, including means, standard deviations, and percentages, were used to summarise demographic and clinical variables. Correlation between study parameters was assessed using Pearson's and Spearman's correlation coefficients, depending on data distribution. Group comparisons were performed using an Independent sample t-test and F-tests to evaluate variance equality. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study consisted of 100 patients diagnosed with T2DM and presenting with vision problems. The mean age of the participants was 55.04±4.47 years (range: 45-65 years), indicating a relatively homogeneous age distribution. The study included 55 female and 45 male participants.

A total of 87 participants exhibited some form of DR, with mild Non Proliferative Diabetic Retinopathy (NPDR) being the most prevalent stage [Table/Fig-1].

Retinopathy grade	Number of patients (n)
No retinopathy (Grade 0)	13
Mild non proliferative DR	49
Moderate non proliferative DR	13
Severe non proliferative DR	15
Proliferative DR (PDR)	10

[Table/Fig-1]: The severity of Diabetic Retinopathy (DR) was classified into different grades based on retinal examination findings (N=100).

As DR severity increases from grade 0 to grade 4, mean RBP3 concentrations decrease consistently. The ranked values of RBP3 show a perfect inverse correlation with DR grade (ρ=-1.00), and the (p-value <0.0001) [Table/Fig-2].

DR Grade	Description	RBP3 (Mean±SD) ng/mL	Rank (RBP3)
0	No retinopathy	2.46±0.12	5
1	Mild NPDR	1.41±0.14	4
2	Moderate NPDR	0.38±0.09	3
3	Severe NPDR	0.10±0.05	2
4	Proliferative DR	0.03±0.02	1

[Table/Fig-2]: Spearman's correlation analysis: RBP3 vs DR Grade.
Spearman's correlation coefficient (ρ): -1.00 p-value:<0.001 (statistically significant); DR: Diabetic Retinopathy; NPDR: Non Proliferative Diabetic Retinopathy; RBP3: Retinol Binding Protein 3; ρ: Spearman's rank correlation coefficient; p: p-value (statistical significance).

The variance of HbA1c (10.0333) was considerably higher than that of serum RBP3 (0.7245), suggesting greater variability in glycaemic control compared to RBP3 levels. Similarly, hs-CRP demonstrated a variance of 2.776, which was also higher than that of RBP3, indicating wider fluctuations in systemic inflammatory status [Table/Fig-3].

Although the F-test indicated unequal variances among the compared parameters, the independent sample t-test assuming equal variances was still appropriate in this context because all groups had identical sample sizes (n=100 for each comparison).

When sample sizes are equal, the standard t-test is well-established to be highly robust to violations of homogeneity of variance, producing results almost identical to Welch's t-test. To confirm the reliability of the current study findings, Welch's unequal-variance t-test was performed additionally, which yielded the same direction of effect and similarly significant p-values< 0.0001 [Table/Fig-4].

Comparison	Sample size (A vs B)	Mean (A vs B)	Variance (A vs B)	p-value (F-test)
HbA1c vs RBP3	100 vs 100	8.56 vs 1.12	10.0333 vs 0.7245	< 0.001 (unequal variances)
hsCRPvs RBP3	100 vs 100	3.45 vs 1.12	2.776 vs 0.7245	< 0.001 (unequal variances)
HbA1c vshsCRP	100 vs 100	8.56 vs 3.45	10.0333 vs 2.776	< 0.001 (unequal variances)

[Table/Fig-3]: Assessment of variance equality among the study parameters. Each of these comparisons showed a p-value <0.0001, suggesting statistically significant differences in mean values.

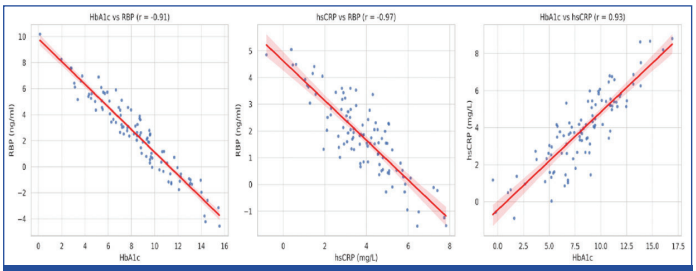
Comparison	Mean difference	t-value	95% CI of difference in means	p-value
HbA1c vs RBP3	-7.22	-22.014	-7.8674 to -6.5738	< 0.0001 (significant)
hsCRPvs RBP3	-2.82	-15.074	-3.1892 to -2.4513	< 0.0001 (significant)
HbA1c vshsCRP	-5.11	-12.295	-5.1061 to -3.6945	< 0.0001 (significant)

[Table/Fig-4]: Comparison of mean values between HbA1c, RBP3 and hsCRP.

There was a strong inverse correlation between RBP3 and both HbA1c and hsCRP, indicating that lower RBP3 levels were associated with higher glycaemic levels and increased inflammation. Conversely, HbA1c and hsCRP show a strong positive correlation, suggesting that poor glycaemic control is linked with elevated inflammatory markers [Table/Fig-5,6].

Comparison	Pearson's r	95% CI for r	p-value
HbA1c vs RBP3	-0.9136	-0.9411 to -0.8740	< 0.0001 (strong inverse correlation)
hsCRP vs RBP3	-0.9654	-0.9766 to -0.9489	< 0.0001 (strong inverse correlation)
HbA1c vs hsCRP	0.9302	0.8979 to 0.9526	< 0.0001 (strong positive correlation)

[Table/Fig-5]: Correlation between RBP3 and clinical biomarkers.



[Table/Fig-6]: Correlation scatter plots.

DISCUSSION

The present study demonstrated a significant inverse association between serum RBP3 levels and the severity of DR, highlighting the potential of RBP3 as a systemic biomarker for retinal health. This aligns with the findings of Yokomizo H et al., who reported higher retinal and vitreous RBP3 levels in diabetic individuals resistant to DR, suggesting a protective role of RBP3 against hyperglycaemia-induced oxidative stress and inflammation [11]. Similarly, Fickweiler W et al., observed that elevated vitreous RBP3 concentrations were associated with lower levels of inflammatory cytokines and VEGF, as well as slower progression of DR, supporting the concept that RBP3 may modulate both neurovascular and inflammatory pathways [12].

While previous studies predominantly assessed intraocular RBP3 levels in retinal or vitreous samples [9,11-13], serum-based measurements are minimally invasive and more practical for routine clinical use. The current study's findings extend these observations by demonstrating that circulating RBP3 may reflect retinal pathology in a clinically feasible manner.

However, García-Ramírez M et al., showed that IRBP (RBP3) downregulation occurs early in DR, even before vascular changes are evident, indicating that serum RBP3 may be more reflective of established disease rather than preclinical changes [13]. This distinction is important when considering serum RBP3 as a biomarker for early detection versus disease monitoring.

The study also found significant correlations between serum RBP3 and systemic markers such as HbA1c and hsCRP. These findings are consistent with the established role of chronic hyperglycaemia and low-grade inflammation in DR pathogenesis [5,16]. Tang J and Kern TS emphasised the role of inflammation in DR [5], while Thomas RL et al., and Yau JW et al., highlighted the importance of metabolic control and disease duration as predictors of DR risk [2,3]. By showing that serum RBP3 inversely correlates with these markers, the current study suggests a mechanistic link whereby RBP3 may mitigate glucose- and inflammation-induced retinal damage.

The observed variance in serum RBP3 relative to HbA1c and hsCRP supports its potential reliability as a biomarker. While HbA1c showed greater variability, serum RBP3 appeared more stable, suggesting it could complement traditional risk factors in predicting DR severity. These findings resonate with studies by Sasongko MB et al., who proposed novel serum biomarkers outperforming traditional markers for DR risk stratification [15].

Supporting the need for improved diagnostic and prognostic tools, Jenkins AJ et al., (2015) highlighted that although numerous systemic and ocular biomarkers have been associated with the development and progression of DR, no single biomarker has yet proven sufficient for routine clinical application, underscoring the continued search for reliable molecular indicators [19]. More recently, Dai L et al., (2024) demonstrated that advanced deep-learning systems can accurately predict the time to progression of DR, outperforming conventional clinical predictors and offering new possibilities for individualised screening and management [20]. Together, these studies reinforce the growing emphasis on standardised grading, biomarker discovery, and technological innovation in enhancing early detection and personalised care for DR.

Limitation(s)

The present study has several limitations that must be acknowledged. Recruitment from a single centre may limit the generalisability of the findings to broader and more diverse populations. The cross-sectional design prevents inference about causality or temporal relationships between serum RBP3 levels and the progression of DR. Although serum RBP3 was evaluated, more direct insights into retinal pathophysiology might have been obtained by measuring intraocular (vitreous or retinal) levels, which were not assessed. Potential confounding factors such as medication use, glycaemic variability, and co-existing comorbidities were not fully controlled and may have influenced the results independently of DR severity. While a perfect inverse correlation (Spearman's ρ=-1.00) between RBP3 levels and DR severity was observed, such results are uncommon in biological systems and may reflect the ordinal nature of grading or sample homogeneity. Additionally, the current study did not establish predictive metrics such as diagnostic cut-off values or odds ratios, which limits immediate clinical applicability. Future prospective studies with larger, more diverse populations are warranted to validate these findings and to establish optimal serum RBP3 thresholds using Receiver Operating Characteristic (ROC) curve analysis and regression-based predictive modelling.

CONCLUSION(S)

The present study demonstrates a strong negative correlation between serum RBP3 levels and the severity of DR, indicating that reduced RBP3 may be closely linked with disease progression which suggests that RBP3 has potential utility as a reliable biomarker for early detection and risk stratification in DR. The findings also support the possibility that RBP3 plays a protective role in retinal physiology, aligning with previous evidence from experimental studies. By identifying the correlation, the current study strengthens the rationale for incorporating RBP3 into clinical assessments of patients with diabetes. The present study results highlight the need for further research to elucidate the mechanistic pathways through which RBP3 influences retinal health and to explore its potential as a therapeutic target. Overall, the study provides valuable insight that may contribute to improved monitoring and management strategies for preventing vision loss in diabetic individuals.

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PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Biochemistry, Nootan Medical College and Research Centre, Sankalchand Patel University (SPU), Visnagar, Gujarat, India.
2. Associate Professor, Department of Biochemistry, Nootan Medical College and Research Centre, Sankalchand Patel University (SPU), Visnagar, Gujarat, India.
3. Assistant Professor, Department of Ophthalmology, G.M.E.R.S. Medical College, Vadnagar, Gujarat, India.
4. Professor, Department of Biochemistry, Nootan Medical College and Research Centre, Sankalchand Patel University (SPU), Visnagar, Gujarat, India.
5. Assistant Professor, Department of Biochemistry, Nootan Medical College and Research Centre, Sankalchand Patel University (SPU), Visnagar, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Kinjal P Patel,
5-Gayatri Nagar Society, Part-1, B/H-Rajkamal Petrol Pump, Near Mahashakti Ground, Mehsana-384002, Gujarat, India.
E-mail: drkinjal1687@gmail.com

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