ORIGINAL RESEARCH

Inverse Correlation between Serum Bilirubin Levels and Diabetic Retinopathy in Type 2 Diabetes Mellitus: A cross-sectional study

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ABSTRACT

Background: Diabetic retinopathy (DR) is a major microvascular complication of Type 2 Diabetes Mellitus (T2DM), influenced by oxidative stress and inflammation. Emerging evidence suggests that serum bilirubin, a natural antioxidant, may play a protective role in vascular integrity.

Aim: To evaluate the inverse association between serum bilirubin levels and the presence and severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus.

Material and Methods: This hospital-based, cross-sectional observational study included 120 T2DM patients aged ≥40 years. All participants underwent serum bilirubin testing, HbA1c measurement, and dilated fundus examination. DR was graded as No DR (NDR), Non-Proliferative DR (NPDR), or Proliferative DR (PDR) based on ETDRS classification. Statistical analysis included ANOVA, Pearson's correlation, and logistic regression to identify independent predictors of DR.

Results: Of the 120 participants, 48 (40%) had NDR, 52 (43.33%) had NPDR, and 20 (16.67%) had PDR. Serum total bilirubin levels were highest in the NDR group (0.89 ± 0.21 mg/dL) and lowest in the PDR group (0.66 ± 0.18 mg/dL), with significant differences ($p < 0.001$). Bilirubin levels negatively correlated with HbA1c ($r = -0.35$, $p < 0.001$), diabetes duration ($r = -0.29$, $p = 0.002$), and presence of DR ($r = -0.41$, $p < 0.001$). Logistic regression confirmed serum bilirubin as an independent protective factor against DR (AOR = 0.42, $p = 0.001$).

Conclusion: An inverse association exists between serum bilirubin levels and diabetic retinopathy severity in T2DM patients. Lower bilirubin levels independently predict higher risk of DR, highlighting its potential as a non-invasive biomarker for microvascular risk stratification.

Keywords: Type 2 Diabetes Mellitus, Diabetic Retinopathy, Serum Bilirubin, Oxidative Stress, Risk Factors

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes mellitus and represents a leading cause of vision impairment and blindness among working-age adults worldwide. The global burden of diabetes continues to increase at an alarming rate, with corresponding growth in diabetes-associated complications, particularly those affecting the retina. DR results from chronic hyperglycaemia-induced damage to the retinal microvasculature, characterized by increased vascular permeability, capillary occlusion, ischemia, and, eventually, neovascularization. Despite significant advances in glycaemic management and retinal therapies, the identification of novel biomarkers and protective factors remains a critical area of

interest in mitigating the progression and severity of DR. Recent evidence has brought attention to bilirubin, a product of heme catabolism, for its potential antioxidative, anti-inflammatory, and vasoprotective properties. Traditionally regarded as merely a waste product, bilirubin is now increasingly being recognized as a potent endogenous cytoprotective molecule. Unconjugated bilirubin, in particular, appears to exert favourable effects on vascular function by attenuating oxidative stress and inflammation—both key contributors to endothelial dysfunction in diabetes[1]. In experimental diabetic models, upregulation of the heme oxygenase-1 (HO-1) pathway has demonstrated vascular protection and improved glycaemic outcomes, partly through the actions of bilirubin.[1]

In clinical settings, inverse relationships between serum bilirubin levels and metabolic indices such as glycatedhaemoglobin (HbA1c) have been observed among individuals with Type 2 diabetes mellitus (T2DM).[2] These findings raise the possibility that bilirubin levels may not only reflect the oxidative status of the body but may also influence the progression of diabetic complications. The enzymatic degradation of heme by HO-1 produces biliverdin, carbon monoxide, and ferrous iron, with biliverdin subsequently being reduced to bilirubin. This process appears to play a compensatory role in countering the redox imbalance associated with diabetes and insulin resistance.[3]

The pathophysiology of DR is strongly linked to oxidative stress, which disrupts the blood-retinal barrier and accelerates the loss of pericytes and endothelial cells. The excessive generation of reactive oxygen species (ROS) contributes to mitochondrial dysfunction, capillary basement membrane thickening, and upregulation of pro-angiogenic factors such as vascular endothelial growth factor (VEGF).[4] Numerous studies have reported increased lipid peroxidation and depletion of endogenous antioxidants such as vitamins C and E in patients with DR.[5] Bilirubin, by virtue of its lipophilic antioxidant capacity, may counteract oxidative lipid damage and thereby limit the progression of retinal microangiopathy.

Hyperglycaemia-induced formation of advanced glycation end products (AGEs), activation of protein kinase C, and polyol pathway flux are other known mechanisms contributing to DR pathogenesis. These overlapping metabolic disturbances converge on a common endpoint of oxidative stress and inflammation.[6] Within this framework, bilirubin's role as an antioxidant gains relevance, as it has been shown to scavenge peroxyl radicals and inhibit low-density lipoprotein (LDL) oxidation.[7] The potential of bilirubin to stabilize vascular endothelium, reduce leukocyte adhesion, and suppress NADPH oxidase activity further supports its protective role in the diabetic milieu.[8]

Epidemiological studies have demonstrated that individuals with higher serum total bilirubin levels have a lower risk of developing T2DM and its complications, including cardiovascular disease and nephropathy.[9] In diabetic cohorts, a consistent negative correlation has been reported between bilirubin levels and arterial stiffness, carotid intima-media thickness, and other surrogate markers of vascular dysfunction.[10] These observations support the hypothesis that bilirubin could serve as an independent protective biomarker in the stratification of microvascular risk, including the likelihood of DR.

AIM AND OBJECTIVES

Aim:

To investigate the association between serum bilirubin levels and the presence and severity of diabetic retinopathy (DR) in patients with Type 2 Diabetes Mellitus (T2DM).

Objectives:

1. To compare serum total, direct, and indirect bilirubin levels among T2DM patients with and without diabetic retinopathy.
2. To assess the correlation between serum bilirubin levels and the severity of diabetic retinopathy (e.g., non-proliferative vs. proliferative stages).
3. To evaluate the relationship between serum bilirubin levels and glycemic control indicators, such as HbA1c, in T2DM patients.
4. To determine whether serum bilirubin levels serve as an independent protective factor against the development and progression of diabetic retinopathy, after adjusting for other risk factors like duration of diabetes and blood pressure.

MATERIALS AND METHODS

Study Design

- Type: Hospital-based, observational, cross-sectional study.
- Nature: Analytical; aims to find an inverse association between serum bilirubin levels and diabetic retinopathy.

Study Place

The study was conducted in the Department of Ophthalmology in collaboration with Department

of Biochemistry, Major SD Singh Medical college, farrukhabad Uttar Pradesh, India.

Study Duration

The study was carried out over a period of six months, from November 2014 to April 2015 after receiving Institutional Ethics Committee approval.

Study Population

- Sample Size: 120 patients.
- Sampling Technique: Consecutive sampling.
- Source: Patients with Type 2 Diabetes Mellitus attending the outpatient and inpatient departments.

Inclusion Criteria

Adults aged ≥ 40 years.

Confirmed diagnosis of T2DM for at least one year.

Recent fasting serum bilirubin report (within the past month).

Willingness for dilated fundus examination.

Ability to give informed consent.

Exclusion Criteria

Type 1 or gestational diabetes.

Chronic liver disease, haemolyticanaemia, or other bilirubin metabolism disorders.

Ocular pathologies unrelated to DR (e.g., glaucoma, uveitis).

History of ocular trauma or intraocular surgery in the past six months.

Ethical Considerations

Approval: Obtained from the Institutional Ethics Committee (IEC).

Consent: Written informed consent obtained after explaining the study's purpose and procedures.

Study Procedure

Clinical and Laboratory Assessment

- Demographics: Age, gender, duration of T2DM, BMI, BP, medications.
- Blood Sampling: Fasting venous blood collected under aseptic precautions.
- Biochemical Tests:
  - Serum bilirubin (total, direct, indirect): Measured using the diazo method via automated analyzer.
  - HbA1c: Measured using high-performance liquid chromatography (HPLC).
  - Other Tests: Fasting blood glucose, liver and renal function parameters.

Ophthalmologic Assessment

- Visual Acuity: Best-corrected visual acuity (BCVA).
- Anterior Segment Evaluation: Slit-lamp biomicroscopy.
- IOP Measurement: Goldmannapplanation tonometry.
- Posterior Segment: After pupil dilation—indirect ophthalmoscopy and slit-lamp biomicroscopy with a 90D lens.
- Imaging: Fundus photography with a non-mydriatic fundus camera (where applicable).
- Classification of DR: Based on ETDRS criteria into:
  - No Diabetic Retinopathy (NDR)
  - Non-Proliferative Diabetic Retinopathy (NPDR)
  - Proliferative Diabetic Retinopathy (PDR)

Outcome Measures

- Primary Outcome: Association between serum bilirubin levels and the presence/severity of diabetic retinopathy.
- Secondary Measures: Correlation with HbA1c, duration of diabetes, and other clinical factors.

Statistical Analysis

- Software Used: SPSS version 25.0.
- Descriptive Statistics: For demographic and clinical profiles.
- Inferential Statistics:

Independent t-test – Comparing bilirubin levels between DR vs. non-DR groups.

ANOVA – Comparing bilirubin levels across NDR, NPDR, and PDR groups.

Pearson's Correlation Coefficient – To assess linear association.

Significance Level: p-value < 0.05 considered statistically significant.

RESULTS

Table 1: Demographic, Clinical and Laboratory Parameters of Study Participants

Parameter	Mean ± SD / n (%)
Age (years)	57.3 ± 9.2
Gender	
Male	68 (56.67%)
Female	52 (43.63%)
Duration of Diabetes (years)	8.5 ± 4.6

Body Mass Index (BMI, kg/m²)	26.2 ± 3.1
Systolic Blood Pressure (mmHg)	138.4 ± 12.6
Diastolic Blood Pressure (mmHg)	84.9 ± 9.5
Fasting Blood Glucose (mg/dL)	152.6 ± 37.8
HbA1c (%)	8.1 ± 1.2
Total Bilirubin (mg/dL)	0.78 ± 0.22
Direct Bilirubin (mg/dL)	0.24 ± 0.09
Indirect Bilirubin (mg/dL)	0.54 ± 0.18

Table 1 showsthe study included 120 patients with a mean age of 57.3 ± 9.2 years. The sample comprised 68 males (56.67%) and 52 females (43.63%). The average duration of diabetes among participants was 8.5 ± 4.6 years, reflecting a moderately long-standing diabetic population. The mean body mass index (BMI) was 26.2 ± 3.1 kg/m², suggesting that most patients fell within the overweight category. Mean systolic and diastolic blood pressures were 138.4 ± 12.6 mmHg and 84.9 ± 9.5 mmHg, respectively, indicating suboptimal blood pressure control in several cases. Glycaemic control was poor overall, as reflected by a mean fasting blood glucose of 152.6 ± 37.8 mg/dL and an average HbA1c of 8.1 ± 1.2%. The mean total serum bilirubin was 0.78 ± 0.22 mg/dL, with direct and indirect bilirubin levels averaging 0.24 ± 0.09 mg/dL and 0.54 ± 0.18 mg/dL, respectively.

Table 2: Distribution of Patients According to Diabetic Retinopathy Status

Diabetic Retinopathy Grade	Number of Patients (n)	Percentage (%)
No Diabetic Retinopathy (NDR)	48	40.0%
Non-Proliferative DR (NPDR)	52	43.33%
Proliferative DR (PDR)	20	16.67%
Total	**120**	**100%**

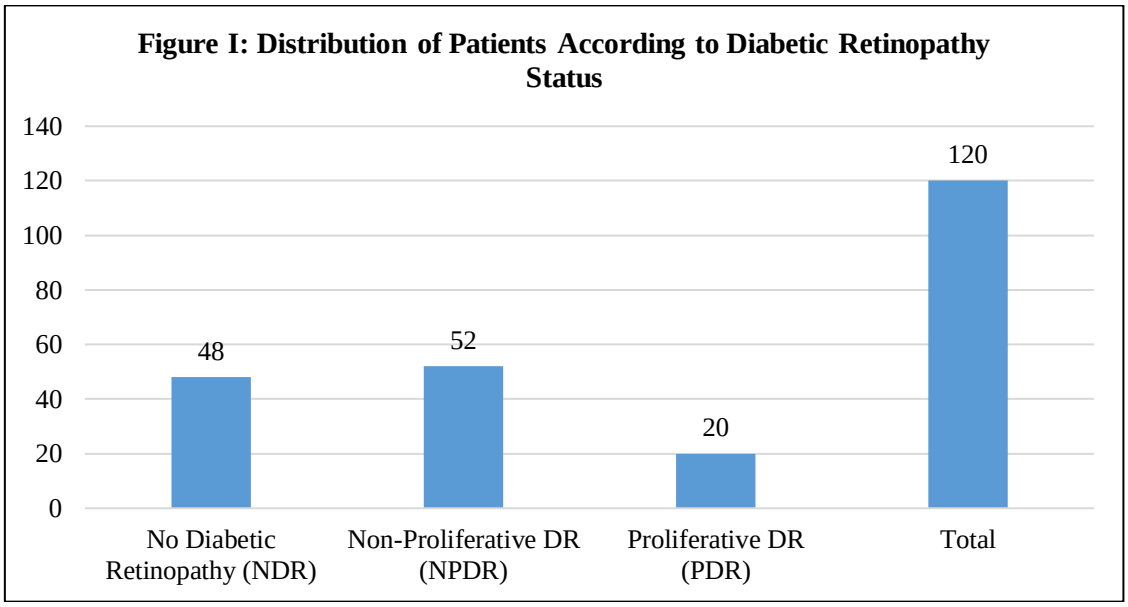

Table 2 and figure I, shows thatbased on ETDRS grading, 48 patients (40%) had no signs of diabetic retinopathy (NDR), while 52 patients (43.33%) presented with non-proliferative diabetic retinopathy (NPDR), and 20 patients (16.67%) had proliferative diabetic retinopathy (PDR). This distribution highlights that nearly 60% of the study population exhibited some form of retinal microvascular damage, underlining the high prevalence of DR among long-standing Type 2 diabetic individuals.

Table 3: Comparison of Mean Serum Bilirubin Levels According to DR Status

Group	Total Bilirubin (mg/dL) Mean ± SD	Direct Bilirubin (mg/dL) Mean ± SD	Indirect Bilirubin (mg/dL) Mean ± SD

NDR	0.89 ± 0.21	0.28 ± 0.10	0.61 ± 0.18
NPDR	0.73 ± 0.20	0.23 ± 0.08	0.50 ± 0.17
PDR	0.66 ± 0.18	0.21 ± 0.07	0.45 ± 0.15
p-value	**< 0.001**	**< 0.01**	**< 0.01**

Table 3 showsa statistically significant inverse trend was observed between bilirubin levels and severity of diabetic retinopathy. Patients with no DR (NDR) had the highest mean total bilirubin level of 0.89 ± 0.21 mg/dL, followed by those with NPDR (0.73 ± 0.20 mg/dL) and PDR (0.66 ± 0.18 mg/dL). Similar patterns were seen for both direct and indirect bilirubin. The differences were statistically significant, with a p-value < 0.001 for total bilirubin and < 0.01 for both direct and indirect components. This suggests that lower bilirubin levels are significantly associated with greater retinal vascular damage and DR severity.

Table 4: Correlation Between Serum Total Bilirubin and Diabetic Parameters

Parameter	Correlation Coefficient (r)	p-value
Duration of Diabetes	-0.29	0.002
HbA1c (%)	-0.35	< 0.001
Systolic BP	-0.18	0.042
Presence of DR	-0.41	< 0.001

Table 4 shows thePearson correlation analysis revealed a significant inverse correlation between serum total bilirubin and duration of diabetes (r = -0.29, p = 0.002), HbA1c levels (r = -0.35, p < 0.001), systolic blood pressure (r = -0.18, p = 0.042), and presence of diabetic retinopathy (r = -0.41, p < 0.001). These findings reinforce the hypothesis that higher serum bilirubin levels may be protective against the metabolic and vascular stressors contributing to DR development. The strongest negative correlation was observed between bilirubin and the presence of DR, further supporting the potential anti-oxidative and anti-inflammatory role of bilirubin in diabetic microangiopathy.

Table 5: Logistic Regression Analysis for Predictors of Diabetic Retinopathy

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Serum Total Bilirubin	0.42	0.28 – 0.76	0.001
HbA1c (%)	1.52	1.17 – 1.96	0.003
Duration of Diabetes	1.35	1.11 – 1.64	0.005
Systolic BP	1.08	1.01 – 1.15	0.026

Table 5 shows the multivariate logistic regression analysis identified serum total bilirubin as an independent protective factor against diabetic retinopathy, with an adjusted odds ratio (AOR) of 0.42 (95% CI: 0.28–0.76, p = 0.001). Conversely, poor glycaemic control (HbA1c ≥ 8%) showed a significantly increased risk for DR with an AOR of 1.52 (95% CI: 1.17–1.96, p = 0.003). Similarly, longer duration of diabetes (AOR = 1.35, p = 0.005) and elevated systolic blood pressure (AOR = 1.08, p = 0.026) were also significant risk factors. These results confirm that while traditional risk factors like chronic hyperglycaemia and hypertension contribute to DR, low bilirubin levels independently increase the risk, highlighting its potential utility as a biomarker for retinopathy risk stratification.

DISCUSSION

The current study included 120 patients with a mean age of 57.3 ± 9.2 years, among whom 56.67% were males and 43.63% females. The average diabetes duration was 8.5 ± 4.6 years, with poor glycaemic control reflected by a mean HbA1c of 8.1 ± 1.2%. Additionally, patients had elevated fasting blood glucose levels (152.6 ± 37.8 mg/dL) and borderline hypertensive systolic (138.4 ± 12.6 mmHg) and diastolic pressures (84.9 ± 9.5 mmHg). These clinical features suggest a high-risk profile for the development of diabetic complications. Similar demographic trends were noted by Joshi et al. (2008), who highlighted the burden of uncontrolled diabetes in Indian populations due to poor awareness and care infrastructure.[11]

Regarding diabetic retinopathy (DR) status, 60% of participants had some form of DR, with 43.33% having non-proliferative DR and 16.67% with proliferative DR. This prevalence aligns with the global data reported by Yau et al. (2012), who estimated the worldwide DR prevalence in diabetic individuals at approximately 35% but noted higher rates in populations with longer disease duration and poor control.[12] Our findings support the notion that DR prevalence escalates with disease chronicity and insufficient metabolic control, consistent with the pathophysiological insights provided by Cheung et al. (2010) regarding retinal capillary damage and ischemia.[13]

One of the key findings of this study is the inverse association between serum bilirubin levels and DR severity. Patients without DR had significantly higher mean total bilirubin levels (0.89 ± 0.21 mg/dL) compared to those with NPDR (0.73 ± 0.20 mg/dL) and PDR (0.66 ± 0.18 mg/dL), with $p < 0.001$. This gradient was also reflected in both direct and indirect bilirubin levels. Similar inverse associations have been reported in various studies.These findings align with previous studies suggesting that bilirubin, known for its antioxidant and anti-inflammatory properties, may play a protective role against the development and progression of DR. Bilirubin can scavenge reactive oxygen species and inhibit lipid peroxidation, thereby mitigating oxidative stress—a key factor in the pathogenesis of DR.[14]

The Hisayama Study, a population-based study in Japan, reported that higher serum bilirubin levels were associated with a lower prevalence of DR, independent of other risk factors.[15] Similarly, a study by Sekioka et al. found that serum total bilirubin concentration was negatively associated with the increasing severity of retinopathy in T2DM patients.[16]

In our correlation analysis, serum total bilirubin showed a statistically significant inverse correlation with duration of diabetes ($r = –0.29$, $p = 0.002$), HbA1c ($r = –0.35$, $p < 0.001$), systolic blood pressure ($r = –0.18$, $p = 0.042$), and DR presence ($r = –0.41$, $p < 0.001$). These findings indicate that lower bilirubin levels are closely tied to both systemic metabolic derangements and retinal vascular pathology. Dave et al. (2015) similarly reported that patients with DR had significantly lower bilirubin and higher levels of malondialdehyde (MDA), a lipid peroxidation marker, confirming bilirubin's antioxidant role in neutralizing free radicals and preventing endothelial dysfunction.[17]

The logistic regression analysis further reinforced our findings. Serum total bilirubin emerged as an independent protective factor against DR with an adjusted odds ratio (AOR) of 0.42 (95% CI: 0.28–0.76, $p = 0.001$), even after adjusting for confounders such as HbA1c, blood pressure, and diabetes duration. In contrast, HbA1c ≥ 8% (AOR = 1.52, $p = 0.003$), longer diabetes duration (AOR = 1.35, $p = 0.005$), and elevated systolic blood pressure (AOR = 1.08, $p = 0.026$) significantly increased the odds of DR. These observations are in line with Sreelekshmi et al.[18], who also found bilirubin to be an independent inverse predictor of DR, and with experimental evidence from Obrosova et al.[19] andKowluru et al.[20] showing that antioxidants can suppress retinal vascular endothelial growth factor (VEGF) and oxidative stress.

From a mechanistic perspective, bilirubin acts via the hemeoxygenase pathway, reducing oxidative injury by scavenging reactive oxygen species (ROS). Baranano et al. (2002) emphasized the cytoprotective role of biliverdinreductase and bilirubin in oxidative environments.[21] Moreover, Ryu et al. (2014) suggested that higher bilirubin levels confer systemic vascular protection beyond the retina, as seen in lower incidences of chronic kidney disease among individuals with elevated bilirubin.[22]

LIMITATIONS OF THE STUDY

- Cross-sectional Design: Limits the ability to infer causality between bilirubin levels and DR progression.
- Single-centre Study: Limits generalizability to broader populations.
- Sample Size: Moderate; may limit power to detect small differences.
- Selection Bias: Consecutive sampling from hospital attendees may not reflect the general T2DM population.
- Uncontrolled Confounders: Possible influence from unmeasured variables like nutritional status, antioxidant intake, or subclinical hepatic dysfunction.
- No Longitudinal Follow-up: Does not evaluate progression or regression of DR over time.
- Reliance on Fundus Photography: Limited documentation where fundus imaging was not feasible or done.

CONCLUSION

This study demonstrates a significant inverse association between serum bilirubin levels and

the presence and severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus. Lower bilirubin levels were independently associated with increased risk of retinopathy, even after adjusting for glycaemic control, diabetes duration, and blood pressure. These findings suggest that serum bilirubin may serve as a protective antioxidant biomarker and a potential predictor for diabetic microvascular complications.

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