Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 10s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Difference In Clinical & Biochemical Profile In Patients Of Long Standing Diabetes Having Diabetic Retinopathy & Patients Who Do Not Have Diabetic Retinopathy With Special Reference To Serum Bilirubin

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Cite this paper as: Dr. Jay Mehta, Dr. Sunidhi Gautam, Dr. Tirtha Patel, Dr. Gunjan Kabra, Dr. Nikhil Gore, Dr. Hasmukh D Ahir, Dr. Punit Singh, (2025) Difference In Clinical & Biochemical Profile In Patients Of Long Standing Diabetes Having Diabetic Retinopathy & Patients Who Do Not Have Diabetic Retinopathy With Special Reference To Serum Bilirubin. *Journal of Neonatal Surgery*, 14 (10s), 304-309.

ABSTRACT

e nanosized-based carrier systems which comprise solid lipid matrix combined with liquid lipids and surfactants. The aim of Diabetic retinopathy (DR) is a common complication of long-standing diabetes mellitus (DM) and is a leading cause of vision loss worldwide. Mounting evidence suggests that the presence of DR may be associated with alterations in various clinical and biochemical parameters, including serum bilirubin levels. This paper aims to explore the differences in the clinical and biochemical profiles of patients with long-standing DM, with and without DR, with a specific focus on serum bilirubin.

Purpose: To study the association between serum bilirubin concentration and different grades of diabetic retinopathy in patients with type-2 diabetes mellitus

Settings and Design: Cross sectional (observational) study

Materials and Methods: A cross-sectional (observational) study was conducted among patients with duration of diabetes more than or equal to 3 years. Seventy-six eligible patients were undergone complete ophthalmic evaluation along with detailed Ocular and medical history followed by examination and measurements as described above. Diabetic gradings were done according to International Clinical Disease Severity Scale. All patients were grouped as without and with diabetic retinopathy changes using Early Treatment of Diabetic Retinopathy Study (ETDRS) classification. All patients were investigated to assess their glycaemic control (RBS and HbA1c) and serum bilirubin levels (Diazo method). Findings were recorded in a pre-designed proforma and analysed for relationship of biochemical parameters with various stages of diabetic retinopathy

Results: The mean age of the study participants was 59.72 years. Among 7.9% had a duration of diabetes of more than ten years. 55.3% of the study participants had a duration of diabetes less than five years. In the present study, the mean total bilirubin was 0.58 mg/dl among diabetic patients. The mean values of direct and indirect bilirubin were 0.34 mg/dl (SD - 0.14mg/dl) and 0.24 mg/dl (SD- 0.07 mg/dl), respectively.

Conclusion: The proportion of diabetic retinopathy was significantly higher with long duration of diabetes. The mean values of total bilirubin, direct bilirubin and indirect bilirubin were significantly higher among the patients with no diabetic retinopathy compare to patients having diabetic retinopathy. Independent of conventional risk variables, low blood bilirubin concentrations were significantl related with an elevated risk of DR. Serum bilirubin may be used as a biomarker to identify persons at risk for DR.

Keywords: *TYPE 2 DIABETES, BILIRUBIN, RETINOPATHY, HBA1C*

1. INTRODUCTION

Diabetes mellitus (DM) is a growing global health concern, particularly in countries like India, where the prevalence of overweight/obesity and unhealthy lifestyles contribute significantly to its burden. With approximately 77 million people diagnosed with diabetes in India in 2019, projected to rise to over 134 million by 2045, the impact on public health and healthcare systems is substantial. Type 2 diabetes, the predominant form, presents a risk for both microvascular and macrovascular complications, leading to early morbidity and mortality and imposing a heavy financial burden on healthcare infrastructure.[1]

Diabetic retinopathy (DR), a microvascular complication of diabetes, has emerged as a leading cause of visual impairment worldwide, particularly affecting individuals of working age. Chronic hyperglycemia precipitates the gradual dysfunction of retinal blood vessels, ultimately leading to impaired vision or blindness if left untreated. Despite its devastating consequences, DR often goes undiagnosed in its early stages, highlighting the urgent need for improved screening and management strategies.

Inflammation plays a crucial role in the pathogenesis of DR, as evidenced by elevated levels of pro-inflammatory cytokines and chemokines observed in the vitreous, serum, and ocular tissues of diabetic individuals. Alongside chronic hyperglycemia, factors such as oxidative stress, dysregulation of nitric oxide synthase, and the formation of advanced glycation end products contribute to retinal vascular abnormalities characteristic of DR.[2]

Nearly 5% of the 37 million blind people worldwide are blind due to diabetic retinopathy resulting from vascular abnormalities in the retina[3]

Proliferative type (17 million) and cystoid/macular oedema (21 million) are the two kinds of sightthreatening DR (STDR) that affect 38 million people worldwide.[4]

The length of the illness is the strongest indicator of diabetic retinopathy. It has been established that as diabetes is present for more extended periods, the risk of retinal problems increases. After 20 years of diabetes, over 99 percent of persons with type 1 diabetes and 60 percent of those with type 2 diabetes acquire diabetic retinopathy. According to studies conducted in India, 18 and 34 per cent of individuals with recognized diabetes have DR (of any severity).8 It has been revealed that better control of the known risk factors, such as hypertension, blood glucose,and lipids,as well as early detection and treatment of STDR,can minimize the risk of blindness from DR.[5],[6],[7]

Diabetes-related retinopathy results in permanent vision loss. Fortunately, with better diabetes management and continued diabetic retinopathy treatment, the disease's progression and vision loss can be slowed down by 90%. Diabetic retinopathy is one of the diseases given priority under the VISION 2020 project, which aims to eradicate preventable blindness worldwide. The World Health Organization (WHO) has reinvigorated all of its member nations to set up various prevention initiatives to prevent and control the blindness caused by diabetic retinopathy to prevent this preventable cause of blindness. In people with type 2 diabetes mellitus, bilirubin has an endogenous protective impact on the retinal vasculature.[8]

Several studies have examined the antioxidant role of serum bilirubin and its association with the microvascular complications of diabetes, but its role in retinopathy needs to be further observed.[9],[10] Urinary albumin excretion is inversely related to and independently determined by serum bilirubin levels. If the protective action of serum bilirubin against diabetic retinopathy is proven, it will play a significant role in managing diabetic retinopathy,[11] which is an avoidable condition. Evidence suggests that low bilirubin levels have been linked to coronary artery disease and peripheral artery disorders.[12] Therefore, higher serum bilirubin levels may protect people with diabetes from developing diabetic retinopathy.

This paper aims to review and analyze the differential clinical and biochemical profiles of patients with long-standing diabetes, with and without DR, with a particular focus on serum bilirubin levels. By synthesizing existing evidence, we seek to elucidate the potential role of serum bilirubin as a biomarker and therapeutic target in the management of DR. Understanding these differences could aid in risk stratification, early detection, and personalized intervention strategies, ultimately improving outcomes and reducing the burden of this sight-threatening complication among individuals with long-standing diabetes

2. MATERIALS AND METHODS

Study setting: The study was conducted in the Department of Ophthalmology of Dhiraj hospital, Piparia, Waghodia, Vadodara, Gujarat

Study type**:** It was a cross sectional (observational) study

- Study duration: The study was conducted for one and half year of duration.
- Study participants**:** Patients who visited to the study setting were evaluated for the eligibility criteria
- Sample size: 75

- Sampling technique: All eligible participants were acquired purposively in the present study
- **Inclusion criteria:** Patients of more than 18 year of age with either sex
  ⇒ Patients with duration of diabetes more than or equal to 3 year
  ⇒ Willing to participate in study

- **Exclusion criteria**: Individuals with uncertain diabetic duration
  .⇒ Pregnant women.
  ⇒ Patient with Hypertension
  ⇒ Patients who had Hazy media like Corneal opacity, Uveitis.
  ⇒ Patients with Pre-existing Retinal diseases/dystrophies.
  ⇒ Patients who had factors that retard progression of DR-High myopia, advanced POAG.
  ⇒ Patients with factors that accelerate the progression of DR –Severe anemia,
  ⇒ renal failure Patients with chronic liver disease and disease which affect bilirubin level
  ⇒ Patients who had cancer treatment in last 5 year
  ⇒ Patients who were not willing to participate in study

Data collection procedure:

After getting permission from the Institutional Ethics Committee (IEC), data collection procedure was started. Data was collected as per performa (Annexure-I). Before enrolment of the study participants informed consent form were getting signed from them. Patients coming to the Out Patient Department (OPD) were undergone complete ophthalmic evaluation along with detailed Ocular and medical history followed by examination and measurements as described above. Diabetic gradings were done according to International Clinical Disease Severity Scale. All patients were grouped as without and with diabetic retinopathy changes using Early Treatment of Diabetic Retinopathy Study (ETDRS) classification. All patients were undergoing investigations to assess their glycaemic control (RBS and HbA1c) and serum bilirubin levels (Diazo method). Findings were recorded in a pre-designed proforma and analyzed for relationship of biochemical parameters with various stages of diabetic retinopathy.

Statistical Analysis:

Epi info CDC 7 version was used to enter and analyse data. Mean and standard deviation was used to represent continuous variables. Proportions were used for categorical variables. The t-test was used to evaluate the relationship between continuous variables. The chi-square test was used to evaluate the relationship between categorical variables. Statistical significance was defined as a p-value less than 0.05.

3. RESULTS

Table 1 - Association between Diabetic retinopathy grade & duration of diabetes among study participants (n=76)

Grading of DR	**Duration of diabetes**		**Total**
	<5 years	**5-10 years**	**>10 years**	
NO DR	27 (64.3%)	4 (14.3%)	0 (0%)	31
NPDR	15 (35.7%)	21 (75%)	0 (0%)	36
PDR	0 (0%)	3 (10.7%)	6 (100%)	9
Total	42	28	6	76

Chi-square-65.79, p-value <0.05

As per Table 1, the proportion of proliferative diabetic retinopathy was significantly higher in patients with more than ten years of diabetes. Non-proliferative diabetic retinopathy was significantly higher among patients with a duration of diabetes of 5-10 years.

Table2 - Association of total bilirubin with diabetic retinopathy grading

Grading of DR	Total Bilirubin (<0.3 mg/dl)	Total Bilirubin (0.3-0.6 mg/dl)	Total Bilirubin (>0.6 mg/dl)	Total Patient
No DR	00 (0%)	13 (41.9%)	18 (58.1%)	31 (40.8%)
Mild NPDR	00 (0%)	15 (100%)	00 (0%)	15 (19.7%)
Moderate NPDR	00 (0%)	09 (60%)	06 (40%)	15 (19.7%)
Severe NPDR	00 (0%)	06 (100%)	00 (0%)	06 (7.9%)
PDR	03 (33.33%)	06 (66.7%)	00 (0%)	09 (11.9)
Total Patient	03 (3.9)	49 (64.5)	24 (31.6)	76

As shown in Table2, around 67% of the patients with proliferative diabetic retinopathy had a total bilirubin value of 0.3-0.6 mg/dl. Among all patients with Mild NPDR and Severe NPDR, the total bilirubin value is 0.3-0.6 mg/dl. Among 60% of the patients with Moderate NPDR had total bilirubin 0.3-0.6 mg/dl, while 40% had more than 0.6 mg/dl.

Table 3: Serum Bilirubin associated with different DR grades among study participants

Grading of DR	Total Bilirubin	Direct Bilirubin	Indirect Bilirubin
No (n=31)	0.69 ± 0.19	0.43 ± 0.14	0.27 ± 0.06
Mild NPDR (n=15)	0.46 ± 0.08	0.24 ± 0.05	0.22 ± 0.04
Moderate NPDR (n=15)	0.6 ± 0.21	0.34 ± 0.14	0.26 ± 0.10
Severe NPDR (n=6)	0.45 ±0.05	0.25 ± 0.05	0.2 ± 0.0
PDR (n=9)	0.43 ± 0.18	0.23 ± 0.1	0.2 ± 0.1
p-value	<0.001	<0.001	0.03

As shown in Table 3, the mean value of total bilirubin, direct bilirubin and indirect bilirubin was significantly high among the patients with no diabetic retinopathy

4. DISCUSSION

Diabetes Mellitus is a metabolic disorder primarily defined by hyperglycemia resulting from varied interactions between genetic and environmental variables

A major microvascular complication of type 2 diabetes that can lead to blindness is diabetic retinopathy (DR).67

Several clinical investigations examining potential correlations between blood bilirubin and the risk of diabetes (and its consequences) have been published since the revelation of bilirubin's positive function as a physiologic antioxidant.68, 69

The present study was conducted to find the association between serum bilirubin concentration and different grades of diabetic retinopathy in patients with type-2 diabetes mellitus. The research comprised 76 people who had diabetes. In the current research, the prevalence of diabetic retinopathy was 59.2%. Non-proliferative and proliferative DR represented 47.4% and 11.8%, respectively. In the research by **John J et al.,62** 38.2% of the 110 individuals with diabetes mellitus showed diabetic retinopathy, whereas 68.2% did not. Seven individuals with retinopathic alterations

had proliferative disease/PDR, whereas the remainder had non-proliferative retinopathy of different severity.

In the present study, the mean total bilirubin was 0.58 mg/dl among diabetic patients. The mean values of direct and indirect bilirubin were 0.34 mg/dl (SD -0.14mg/dl) and 0.24 mg/dl (SD- 0.07 mg/dl), respectively. According to **Ndisang JF et al.,72** this may be partially explained by elevated blood bilirubin decreasing oxidative stress and preventing glycosylation of haemoglobin. In addition, activation of the heme oxygenase system and increased bilirubin/biliverdin synthesis have improved insulin production and sensitivity in diabetic rats. Consequently, it is possible to conclude that bilirubin improves glycemic control through its effects on insulin. Additional research is required to clarify the mechanism behind this

connection accurately. According to **Cheriyath et al.,54** bilirubin may significantly function in Glycemic regulation. Increased heme oxygenase-1expression is responsible for converting haemoglobin to bilirubin, related to improved insulin sensitivity and glucose metabolism.

In this research, the mean value of total bilirubin, direct bilirubin and indirect bilirubin was significantly high among the patients with no diabetic retinopathy. In the research conducted by **John J. and colleagues,62** the mean levels of total, direct, and indirect bilirubin were 0.36 mg/dl, 0.14 mg/dl, and 0.221 mg/dl, respectively, in the DR group. In the absence of retinopathy, total, direct, and indirect bilirubin mean levels were 0.59, 0.27, and 0.32 mg/dl, respectively. In a statistical sense, the group with diabetic retinopathy had lower mean values.

According to **Obrosova IG et al.,73** excessive generation of free radicals and the resulting oxidative stress contribute considerably to the progression of DR.

According to **Baranano DE et al.,74** bilirubin may protect cells against a 10,000-fold excess of hydrogen peroxide as a powerful antioxidant and cytoprotective agent. Thus, a decreased blood bilirubin content is predicted to be related to higher oxidative stress and, consequently, a quicker development of DR.

In light of these physiologic actions of bilirubin, it may be hypothesized that bilirubin might effectively inhibit or obstruct the pathways leading to the formation of diabetic retinopathy and so serve as a possible biomarker for diabetic retinopathy risk

5. SUMMARY & CONCLUSION

The following inferences can be drawn from the present study-

- In the present cross sectional and observational study 76 patients with diabetes with or without diabetic retinopathy were evaluated in association with serum bilirubin level.
- The mean age of the patients was 59.72 years (SD 8.37 years). Most participants (43.4%) were in the age group of 61-70 years.
- The proportion of males and females in the present study was 59.2% and 40.8%, respectively.
- The prevalence of diabetic retinopathy in the present study was 59.2%. The proportion of non-proliferative DR and proliferative DR was 47.4% and 11.8%, respectively.
- 55.3% of the study participants had a duration of diabetes less than five years, while 36.8% had a duration of diabetes between 5 to 10 years. Among 7.9% had a duration of diabetes of more than ten years.
- The patients having diabetes of less than 10 years of duration had only mild to moderate NPDR while those having duration more than 10 years had PDR. This is because severity of diabetic retinopathy increases with diabetic age.
- The mean HBA1C value for patients without diabetic retinopathy was lowest (7.85%) which was higher (9.31%) in patients with NPDR and highest (11.31%) in patients having PDR. This shows direct relationship of severity of diabetic retinopathy to HBA1C level.

Summary & Conclusion 68

- In the present study, the mean total bilirubin was 0.58 mg/dl among diabetic patients. The mean values of direct and indirect bilirubin were 0.34 mg/dl (SD -0.14mg/dl) and 0.24 mg/dl (SD- 0.07 mg/dl), respectively.
- Maximum 49 (64.5%) of the patients with diabetes had total serum bilirubin between 0.3-0.6 mg/dl out of which majority 28 (57.1%) had either no diabetic retinopathy or mild diabetic retinopathy. 24 (31.6%) patients had total serum bilirubin value more than 0.6 mg/dl out of which majority 18 (75%) had no diabetic retinopathy. Only 3 (3.9%) patients had total bilirubin value is less than 0.3 mg/dl and all had PDR (most severe grade of diabetic retinopathy). In all patients with PDR total bilirubin value less than 0.6 mg/dl and 3 had value less than 0.3 mg/dl.
- To summarize in present study the mean value of total bilirubin, direct bilirubin and indirect bilirubin was significantly high among the patients with no diabetic retinopathy compared to those who had diabetic retinopathy.
- This shows protective action of bilirubin against severity of diabetic retinopathy.

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