# Correlation of Serum Bilirubin Levels in Type 2 Diabetes Mellitus Patients with and without Diabetic Retinopathy

Johncy John[1], Gajaraj Tulsidas Naik[2], Suria C. Rashmi[3], Sheetal Vaijanath Zille[4], Swetha Sampangi Iyer[5], Meghana Neeralagi[6], Asma M.K.[7]

[1, 2, 3, 4, 5, 6, 7] Department of Ophthalmology, Mysore Medical College and Research Institute, Mysore, Karnataka, India.

**ABSTRACT**

**BACKGROUND**

Diabetic retinopathy is becoming one of the common blinding disease in the world affecting people in both developing and developed countries.Basic mechanism thought to be of advanced glycation end products and othertoxic mediators causingtissue destruction and pathological process. Antioxidants have a major role in preventing this pathological process. Among various antioxidants some of the common blood products have thought to have a role. One among them is serum bilirubin. This study is done to know the correlation of diabetic retinopathy and serum bilirubin levels and thus know its importance in future in preventing progression of this blinding disease.

**METHODS**

A cross sectional study was done among OPD patients with type 2 diabetes for a period of one year. Inclusion criteria were diagnosed cases of type 2 diabetes for more than 1 year and age above 40 years. Exclusion criteria included all systemic diseases/drugs affecting liver function tests, confounding factors affecting serum bilirubin levels, extremely poor glycemic control and subjects in whom fundus was not visible due to media opacities excluding causes linked with diabetic retinopathy. After taking consent, detailed history and ophthalmic evaluation, venous blood was drawn and sent for serum bilirubin analysis. Diabetic retinopathy was classified according to ETDRS classification. Statistical study was done after compiling data.

**RESULTS**

Among the study subjects – 38.2% were diabetics. Common age group was 51 to 60 years with incidence of diabeties more in males 64.3%. Among diabetic retinopathy noted– mild NPDR was 31%, moderate NPDR was 35.7%, severe NPDR was 11.9%, very severe NPDR was 4.8% and PDR was 16.6 % respectively. The mean serum total bilirubin levels in non DR was 0.597 ± 0.17, mild NPDR was 0.4 ± 0. 15, moderate NPDR was 0.36 ±0.12, severe NPDR was 0.36±0.17, very severe NPDR was 0.35±0.07, low risk PDR was 0.3±0.10 and high risk PDR was 0.32±0.15 respectively.

**CONCLUSIONS**

This study concluded that severity of diabetic retinopathy was inversely proportional to the total, direct and indirect serum bilirubin levels.

**KEY WORDS**

Diabetic Retinopathy, Serum Bilirubin, Diabetes Mellitus, ETDRS

*Corresponding Author:*
*Dr. Johncy John,*
*Department of Ophthalmology,*
*Mysore Medical College and Research Institute, Mysore, Karnataka, India.*
*E-mail: johncyponnattil@gmail.com*

*DOI: 10.14260/jemds/2021/810*

*How to Cite This Article:*
*John J, Naik GT, Rashmi SC, et al. Correlation of serum bilirubin levels in type 2 diabetes mellitus patients with and without diabetic retinopathy. J Evolution Med Dent Sci 2021;10(45):4013-4018, DOI: 10.14260/jemds/2021/810*

*Submission 02-11-2021,*
*Peer Review 06-12-2021,*
*Acceptance 13-12-2021,*
*Published 31-12-2021.*

## BACKGROUND

India known as diabetic capital of world has a high prevalence of type 2 diabetes mellitus, which is projected to affect about 69.9 million Indians by the year 2025.[1] With limited access to quality health care, the population is prone to develop microvascular complications such as neuropathy, nephropathy, retinopathy and macrovascular complications like cardiovascular diseases. Diabetic retinopathy (DR) is a common microvascular complication, which is one of the leading causes of adult visual impairment and blindness.[2] Though all risk factors such as hyperglycemia, dyslipidemia, hypertension, and duration of diabetes are associated with development and progression of diabetic retinopathy,[3] the altered milieu of oxidants and antioxidants in the sera of patients with type 2 diabetes are additional contributors. Oxidative stress has been implicated in the pathogenesis of microvasular and macrovasular complications of diabetes.[4] Hyperglycemia generates oxidative stress and is associated with the free radical mediated lipid peroxidation. In diabetes mellitus, the glucolipotoxicity leads to endothelial dysfunction and micro and macrovasularcomplication.[5]

Bilirubin is a cytoprotectant with antioxidant and anti-inflammatory properties on the microvasculature.[6] Studies in diabetic rats shown that bilirubin accelerated wound healing.[7] Bilirubin has some protective effects according to many studies.[8] Retina is a source of free radical production, and various retinal changes happen because of oxidative stress in humans with metabolic conditions like type 2 diabetes mellitus.[9] Bilirubin has an endogenous protective effect on the retinal vasculature in patients with type 2 diabetes mellitus.[10] Serum bilirubin concentration has been shown to be inversely related to and an independent determinant of urinary albumin excretion.[11] CAD and peripheral artery diseases were associated with low bilirubin levels.[11] Thus, increased levels of serum bilirubin may be protective against diabetic retinopathy amongst persons with diabetes.[12]

Hence, this study is undertaken to know the role of bilirubin levels in diabetic retinopathy.

## METHODS

The study was conducted for a duration of one year from December 2015 to December 2016. An cross sectional comparative study was conducted in the department of ophthalmology after obtaining ethical clearance.

### Inclusion Criteria

1. Diagnosed cases of type 2 diabetes mellitus.
2. Duration of diabetes for 1 year and above.
3. Patients with age more than 40 years.

### Exclusion Criteria

Patients with history of chronic alcohol consumption, history of pre-existing hepatobiliary abnormalities or any other acute disease affecting hepatic functions within past 6 months, patients with blood levels of SGOT or SGPT greater than three times the normal level, intake of hepatotoxic drugs in past 6 months (antitubercular drugs, antiepileptic drugs etc), patients who were on anti-diabetic drugs like thiazolidinedione (piaglitazone) and alpha 1 glucosidase inhibitor (acarbose), patients with haemolytic anemia and other haemolytic conditions, patients in whom proper evaluation of fundus cannot be done (patients with cataract, corneal opacity etc), patients with extremely poor glycemic control.

The study was conducted after obtaining informed consent from the patients. A detailed history was taken from all patients regarding age, gender, duration of type 2 diabetes mellitus, history of alcohol intake, hepatobiliary disorders, hypertension, or cardiovascular diseases and history of drug use. Fasting blood glucose, postprandial blood glucose levels were obtained in all cases. Venous blood was drawn from the patients on the day of examination and serum total bilirubin, direct and indirect bilirubin, SGOT, SGPT and HbA1C levels were estimated.All patients underwent a detailed ophthalmic evaluation. A detailed fundus examination was done through dilated pupils with slit lamp biomicroscope using +78D/90D, indirect and direct ophthalmoscopy. Subjects were classified as cases without diabetic retinopathy and those with diabetic retinopathy. Cases with retinopathic changes were again classified into non proliferative diabetic retinopathy (mild, moderate, severe and very severe NPDR) and proliferative retinopathy (low risk PDR and high risk PDR), according to ETDRS classification.

### Sample Size

110 according to below formula

$S = Z2pq/d2$

Where p (prevalence) =10.5%,[13] level of significance = 5%, and absolute allowable error = 6%, using estimator set up technique for proportion, the inflated sample size was 110. Sampling was purposive sampling.

### Statistical Analysis

Statistical analysis included descriptive statistics, inferential statistics, chi square test and cramers V test. SPSS software version 16.0 used.

## RESULTS

110 patients were included in the study for a study duration of 1 year. Depending on diabetic retinopathic changes, they were divided into two groups - Patients with diabetic retinopathy (DR) and those without disease (NO DR). Diabetic retinopathy of varying grades were present in 42 patients (38.2%). 68 patients (61.8%) had no retinopathic changes. In the present study 42 patients had retinopathic changes. 35 patients showed varying severity of non proliferative DR and 7 patients showed proliferative disease/PDR.

Age of the patients ranged between 45- 80 years. Most of them belonged to the age group 51-60 years. Mean age of DR group was 60.76 ± 5.26 years and that of the NO DR group was 59.88 ± 7.18 years. p value = 0.29

Among 110 subjects, 57 were males and 53 were females. The DR group comprised 27 males and 15 females. The other group comprised 30 males and 38 females.

In study subjects, diabetic age ranged from 1- 25 years. Mean diabetic age of DR and NO DR group was 7.55 ± 5.02 and 4.96 ± 4.46 years respectively. 23.8% of patients in DR group were on OHA+INSULIN, whereas in NO DR group only 7.4 % were on OHA+INSULIN.

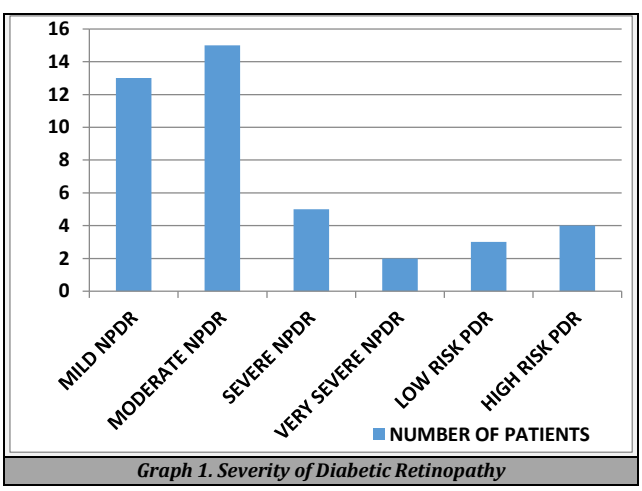
Percentage of patients with co-morbid conditions was high in DR group (p = 0.004). Hypertension was present in 45.2% of patients in DR group and in 35.2% of patients without DR. Hypercholesterolemia was present in 19% and 4.40% of patients in DR group and NO DR group respectively.

Mean values of FBS and PPBS were significantly higher in patients with DR. Mean values of FBS and PPBS in patients with DR were 198.40 ± 57.76mg/dl, 274.24 ± 59.08mg/dl respectively (p = 0.001 and 0.002 respectively). In patients without DR mean values of FBS and PPBS were 161.45± 50.97mg/dl and 236.82 ± 59.52mg/dl respectively.

Mean value of HbA1c was significantly higher in patients with DR. Mean value of HBA1c in patients with DR was 9.97 ± 1.39 and in those without DR the value was 8.70 ± 1.5. (p= 0.000).

| Grade of Severity of Diabetic Retinopathy | Number of Patients | Percentage |
|---|---|---|
| Mild NPDR | 13 | 31.0% |
| Moderately severe NPDR | 15 | 35.7% |
| Severe NPDR | 5 | 11.9% |
| Very severe NPDR | 2 | 4.8% |
| Low risk PDR | 3 | 7.1% |
| High risk PDR | 4 | 9.5% |
| **Total** | 42 | 100% |

*Table 1. Distribution of Severity of Diabetic Retinopathy*




*Graph 1. Severity of Diabetic Retinopathy*

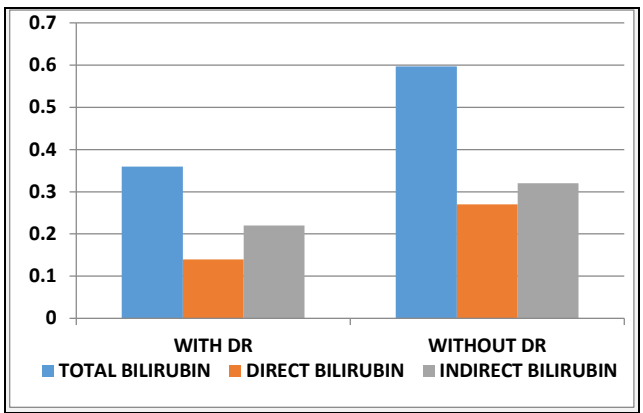
| Group | Total Bilirubin (mg/dl) | Direct Bilirubin (mg/dl) | Indirect Bilirubin(mg/dl) |
|---|---|---|---|
| Patients with DR | 0.36 ± 0.13 | 0.14 ± 0.06 | 0.22 ± 0.095 |
| Patients without DR | 0.597 ± 0.17 | 0.27 ± 0.099 | 0.32 ± 0.11 |

*Table 2. Mean Values of Total, Direct and Indirect Bilirubin Levels*

Mean values of total, direct and indirect bilirubin levels in DR group were 0.36 mg/dl, 0.14mg/dl and 0.221mg/dl respectively. In the group without retinopathy, mean values of total, direct and indirect bilirubin levels were 0.597 mg/dl, 0.27mg/dl and 0.32mg/dl respectively. Mean values were statistically lower in the group with diabetic retinopathy. (p value =0.00)

As the blood level of total bilirubin decreases, percentage of patients having diabetic retinopathy increases. In the group of patients with total bilirubin level 0.71- 0.90 mg/dl, percentage of patients having diabetic retinopathy was nil, while in the group with total bilirubin less than 0.30mg/dl, 45.2% had retinopathy. Prevalence of diabetic retinopathy increased from 0.00% to 92.90% as direct bilirubin level decreased from 0.5mg/dl to 0.1-0.2mg/dl. (p value= 0.000).

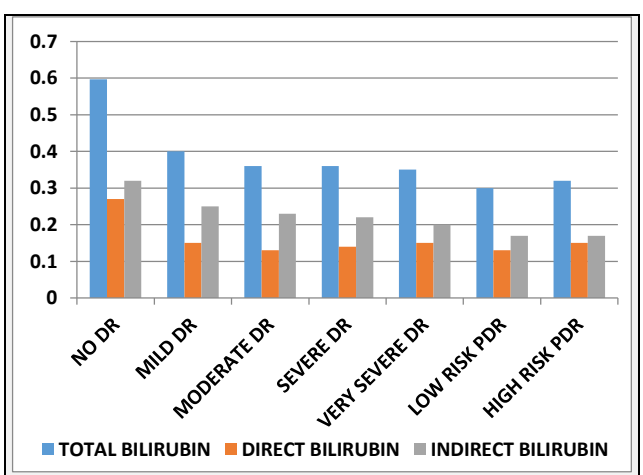
Prevalence of diabetic retinopathy in persons with highest indirect bilirubin levels (>0.4mg/dl) was 0.00% compared with the prevalence of 9.1%, 31.00% and 59.50% in those with lower levels, 0.3-0.4mg/dl, 0.2-0.3mg/dl, and 0.1-0.2mg/dl respectively. (p = 0.007).




*Graph 2. Mean Values of Total, Direct and Indirect Bilirubin Levels in Patients with and without Diabetes*

| Severity of DR | Mean Value of Total Bilirubin(mg/dl) | Mean Value of Direct Bilirubin(mg/dl) | Mean Value of Indirect Bilirubin (mg/dl) |
|---|---|---|---|
| No diabetic retinopathy | 0.597 ± 0.17 | 0.27±0.099 | 0.32±0.12 |
| Mild NPDR | 0.4 ± 0. 15 | 0.15±0.078 | 0.25±.0967 |
| Moderately severe NPDR | 0.36 ±0.12 | 0.13±0.046 | 0.23±0.097 |
| Severe NPDR | 0.36±0.17 | 0.14±0.089 | 0.22 ±0.11 |
| Very severe NPDR | 0.35±0.07 | 0.15±0.07 | 0.20 ±.14 |
| Low risk PDR | 0.3±0.10 | 0.13±0.057 | 0.17 ±0.06 |
| High risk PDR | 0.32±0.15 | 0.15±0.05 | 0.17 ±.095 |

*Table 3. Severity of Diabetic Retinopathy and Mean Value of Total, Direct and Indirect Bilirubin*




*Graph 3. Severity of Diabetic Retinopathy and Mean Value of Total, Direct and Indirect Bilirubin*

Mean value of total bilirubin in patients with mild, moderate, severe, very severe NPDR and PDR were 0.4mg/dl, 0.36mg/dl, 0.35mg/dl and 0.3mgldl respectively. Severity of diabetic retinopathy was more in patients with lower total bilirubin levels. Levels of total bilirubin were significantly lower in patients with late stages of retinopathy as compared to those without retinopathy. (p value= 0.000).

Mean value of direct bilirubin level in patients without retinopthy was 0.27mg/dl. In patients with mild NPDR, mean direct bilirubin level was 0.15mg/dl and in PDR mean value of direct bilirubin was 0.13mg/dl. (p value= 0.000).

Severity of diabetic retinopathy was more in patients with lower levels of indirect bilirubin. Mean value of indirect bilirubin in patients with mild NPDR was 0.25mg/dl. Mean value of indirect bilirubin in patients with moderate, severe, very severe NPDR and PDR were 0.23mg/dl, 0.22mg/dl, 0.20mg/dl and 0.17mg/dl respectively. (p value= 0.001).

## DISCUSSION

Of the 110 patients with diabetes mellitus, 38.2% had diabetic retinopathy and 68.2% patients had no retinopathy. Among those with retinopathic changes, 7 patients had proliferative disease/PDR and the rest had varying severity of non-proliferative retinopathy.

According to National Health and Nutrition Examination Surveys III (NHANES III),[13] prevalence of diabetic retinopathy among persons with diabetes aged 40 years or older was 28.5%. The Chennai Urban Rural Epidemiology Study (CURES)[14] reported the prevalence of DR in urban Chennai to be 17.6% in diabetic population. In SankaraNethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study 2 (SN-DREAMS 2), the prevalence of diabetic retinopathy in the population with diabetes mellitus was estimated as 18.0%. Prevalence of DR was found to be higher in the current study compared to previous studies. Limited number of subjects and increased number of uncontrolled diabetics might have contributed to the increased prevalence of DR in the present study.

In the present study, age of the patients ranged from 45 – 80 years. Most of them belonged to the age group of 51-60 years. Mean age of DR group was 60.76 ± 5.26 years and group without diabetic retinopathy, was 59.87 ± 7years. Several epidemiologic studies like CURES Eye study[14] and The United Kingdom Prospective Diabetes Study (UKPDS)[15] had showed significant correlation between age and DR . But present study did not find any significant correlation between increasing age and DR (p = 0.29).

Present study had near equal sex distribution with slight male predominance. Among 110 subjects, 57 were males and 53 were females. Prevalence of DR was more in males. 64.3% (27) of males had DR, while only 35.7% (15) of females had DR. Sex distribution in the present study was statistically significant (p=0.04). Similar male preponderance was seen in epidemiological studies like CURES Eye study,[14] UKPDS study[15] and The Andra Pradesh Eye Disease study (APEDS).[16]

In the present study, duration of diabetes since diagnosis (diabetic age) ranged from 1 – 25 years. Mean diabetic age of the patients without retinopathy was 4.96± 4.48 years. While those having retinopathy had a longer mean diabetic age (7.55± 5.02 years). The association of longer diabetic age with higher risk of DR was statistically significant with p=0.006. It is in accordance with previous studies like The Diabetes Control and Complications Trial (DCCT),[17] CURES Eye study, UKPDS study and APED study. The CURES Eye study had found that for every five year increase in diabetic age, the risk for DR increased by 1.89 times.

Poor control of diabetes is an important risk factor for diabetic retinopathy. Tight glycemic control, can prevent or delay the development and progression of diabetic retinopathy. Raised HbA1c is associated with an increased risk of developing proliferative disease.[18] Most of the patients in the present study had poor glycemic control. Mean values of FBS, PPBS and HbA1c in patients with DR were 198.40 ± 57.76mg/dl, 274.24 ± 59.08mg/dl and 9.97 ± 1.39 respectively (p = 0.001, 0.002 and 0.000 respectively). In patients without DR (NO DR group) mean values of FBS, PPBS and HBA1c were 161.45± 50.97 mg/dl, 236.82 ± 59.52 mg/dl and 8.70 ± 1.5 mg/dl respectively.

In the present study, 76.1% (p = 0.004) of patients with diabetic retinopathy had other co-morbid conditions like hypertension (45.2%), hypercholesterolemia (19.00%), ischemic heart Disease (4.8%) and diabetic nephropathy (7.1%). Association between these co-morbid conditions and DR was statistically significant with p = 0.004. ETDR study[19] showed that patients with higher levels of total cholesterol were at increased risk of developing DR compared with those having normal levels.

In the present study, mean values of total, direct and indirect bilirubin levels were significantly (p =0.000) lower in patients with diabetic retinopathy compared to those without retinopathy. Mean values of total, direct and indirect bilirubin levels in patients with DR were 0.36 ± 0.13mg/dl, 0.14 ± 0.06 mg/dl, and 0.22 ± 0.095mg/dl respectively. Mean values of total, direct and indirect bilirubin in patients without retinopathy were 0.597 ± 0.17mg/dl, 0.27 ± 0.099mg/dl and 0.32 ± 0.11mg/dl respectively. (p value = 0.000).

Bo Zhu, Xiaomei Wu et al. found that there was a negative association between bilirubin concentration and the risk of diabetic complications such as diabetic nephropathy, retinopathy and neuropathy.[20] Ho Chan Cho et al. assessed the relationship among diabetic retinopathy and total bilirubin levels and the study indicated bilirubin as a biomarker for increased risk of diabetic retinopathy.

In Indian population, only two studies assessed the correlation between bilirubin levels and DR. The study done by Apoorva Dave et al.[21] showed that all the three parameters – namely, total, direct and indirect bilirubin levels were lower in patients with retinopathy. Results of the current study were in concordance with the above study.[13] In South India, Divya Karuppannasamy et al. investigated the association between serum bilirubin concentration and DR in patients with type 2 diabetes mellitus. Total and direct bilirubin concentrations were found to be higher in patients without DR. These results were in concurrence with the present study.

In the present study, subjects were assigned to quartiles based on serum total bilirubin concentration (<0.3, 0.31-0.5, 0.51. 0.7 and above 0.70mg/dl). The prevalence of diabetic retinopathy was significantly lower among persons with higher bilirubin quartile compared to those with the lowest quartile (p=0.00).

In the group of patients with higher total bilirubin level (above 0.7 mg/dl), percentage of patients having diabetic retinopathy was zero, while in the group with lower total bilirubin level (<0.3mg/dl), 45.20% had retinopathy. Statistical significant, p = 0.000. This was in accordance with results of previous studies, which were done by Apoorva Dave et al.[21] Divya Karuppannasamy et al.[22] and the

Hisayamastudy.[12] The Hisayama study, conducted by Yasuda et al. found that after adjusting for factors known to be associated with diabetic retinopathy, the prevalence of diabetic retinopathy was significantly lower among persons with highest bilirubin quartile compared to those with lowest quartile. This study showed that elevated serum bilirubin levels may be protective against diabetic retinopathy among persons with diabetes independent of known risk factor.

In the present study, subjects were assigned into groups depending on the levels of direct and indirect bilirubin also. Result showed that the prevalence of DR was significantly higher in patients with lower levels of direct and indirect bilirubin. The indirect bilirubin levels was >0.4mg/dl in non DR compared with the prevalence of 9.1%, 31.00% and 59.50% in those with lower levels, 0.3-0.4mg/dl, 0.2-0.3mg/dl, and 0.1-0.2mg/dl respectively and this was statistically significant.

Most studies on serum bilirubin and DR had focused only on total bilirubin without separating the bilirubin types. Limited studies have shown a differentially protective effect of direct bilirubin on metabolic syndrome and chronic kidney disease.

Severity of diabetic retinopathy was more in patients with lower levels of total, direct and indirect bilirubin (p= 0.000, 0.000 and 0.001respectively). Levels of total, direct and indirect bilirubin were significantly lower in patients with late stages of retinopathy. The studies conducted by Apoorva Dave et al. and Divya Karuppannasamy et al. also found that the severity of diabetic retinopathy was inversely proportional to the total bilirubin levels. Further studies on the relation between bilirubin subtypes and severity of DR are needed.

### Limitations

- In this study, sample size was limited and the cross-sectional design of the study prevented determination of a temporal association or the cause-effect relationship between serum bilirubin levels and the development of retinopathy.
- We performed only a single measurement of serum bilirubin which might have been within subject variation.
- Test for anti-hepatitis C virus or USG on the hepatobiliary system, which may determine the bilirubin level, were not conducted.

## CONCLUSIONS

- Mean values of total, direct and indirect bilirubin levels were significantly lower in patients with diabetic retinopathy compared to those without retinopathic changes.
- Levels of total, direct and indirect bilirubin were significantly lower in severe stages of DR. Severity of diabetic retinopathy was inversely proportional to the total, direct and indirect serum bilirubin levels

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

## REFERENCES

[1] Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance. In: Gan D, ed. Diabetes atlas. International Diabetes Federation. 3rd edn. Belgium: International Diabetes Federation 2006:15-103.
[2] Marozas LM, Fort PE. Diabetic retinopathy-update on prevention techniques, present therapies, and new leads. US Ophthalmic Rev 2014;7(1):54-8.
[3] Nguyen TT, Alibrahim E, Islam FMA, et al. Inflammatory, hemostatic and other novel biomarkers for diabetic retinopathy: the multi-ethnic study of atherosclerosis. Diabetes Care 2009;32(9):1704-9.
[4] Likidlilid A, Patchanans N, Peerapatdit T, et al. Lipid peroxidation and antioxidant enzyme activities in erythrocytes of type 2 diabetic patients. J Med Assoc Thai 2010;93(6):682-93.
[5] Sarah W, Gojka R, Anders G, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047-53.
[6] Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. Science 1987;235(4792):1043-6.
[7] Ram M, Singh V, Kumar D, et al. Antioxidant potential of bilirubin–accelerated wound healing in streptozotocin-induced diabetic rats. Naunyn Schmiedebergs Arch Pharmacol 2014;387(10):955-61.
[8] Abbasi A, Deetman PE, Corpeleijn E, et al. Bilirubin as potential causal factor in type 2 diabetes risk: a Mendelian randomization study. Diabetes 2015;64(4):1459-69.
[9] Moon JS, Chang WJ, Lee CH, et al. Relationship between serum bilirubin levels and coronary atherosclerosis in patients with type 2 diabetes. Korean Diabetes J 2008;32(4):338-45.
[10] Jung CH, Lee MJ, Kang YM, et al. Higher serum bilirubin level as a protective factor for the development of diabetes in healthy Korean men: a 4 year retrospective longitudinal study. Metabolism 2014;63(1):87-93.
[11] Fukui M, Tanaka M, Shiraishi E, et al. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. Kidney Int 2008;74(9):1197-201.
[12] Yasuda M, Kiyohara Y, Wang JJ, et al. High serum bilirubin levels and diabetic retinopathy: the Hisayama study. Ophthalmology 2011;118(7):1423-8.
[13] Nirmalan PK, Katz J, Robin AL, et al. Prevalence of vitreoretinal disorders in a rural population of southern India: the Aravind Comprehensive Eye Study. Arch Ophthalmol 2004;122(4):581-6.
[14] Rema M, Srivastava BK, Anitha B, et al. Association of serum lipids in diabetic retinopathy in urban South Indians - the Chennai Urban Rural Epidemiology Study (CURES) Eye Study-2. Diabeteic Medicine 2006;23(9):1029-36.
[15] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood – glucose control with sulphonylureas or insulin compared with conventional treatment 66 and

risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837-53.
[16] Krishnaiah S, Das T, Nirmalan PK, et al. Risk factors for diabetic retinopathy: findings from the Andra Pradesh eye disease study. Clin Ophthalmol 2007;1(4):475-82.
[17] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-86.
[18] Bowling B. Diabetic retinopathy. Chap- 13. In: Kanski` s cliniclal ophthalmology - a systemic approach. 8th edn. Elsevier 2016:520-38.
[19] Early treatment diabetic retinopathy study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991;98(5 Suppl):741-56.
[20] Zhu B, Wu X, Bi Y, et al. Effect of bilirubin concentration on the risk of diabetic complications: A meta-analysis of epidemiologic studies. Sci Rep 2017;7:41681.
[21] Dave A, Kalra P, Rakshitha Gowda BH, et al. Association of bilirubin and malondialdehyde levels with retinopathy in type 2 diabetes mellitus. Indian J Endocrinol Metab 2015;19(3):373-7.
[22] Divya K, Raghuram V, Lekha T, et al. Inverse association between serum bilirubin levels and retinopathy in patients with type 2 diabetes mellitus. J Clin Diagn Res 2017;11(2):NC09-12.