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Association between Proliferative Diabetic Retinopathy and Serum Bile Acid Level in Patients with Type 2 Diabetes Mellitus

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Abstract

Diabetic Retinopathy (DR) is a microvascular complication of diabetes mellitus that affects the eye. Symptoms range from being asymptomatic to having mild visual disturbances to complete loss of vision. Cholic acid and chendeoxycholic acid (CDCA) are the primary bile acids which are synthesised in the liver cells. In humans the ocular function mainly relies on CYP27A1 and CYP46A1 of which CYP27A1 is the principal hydroxylase that causes the major chunk of cholesterol elimination by the bile acids which are synthesised by the hydroxylation of cholesterol through the process of enzyme catalysis. The present cross-sectional study was conducted to determine the association between proliferative diabetic retinopathy and serum bile acid level in patients with Type 2 diabetes mellitus. A total of 100 patients visited the medicine and ophthalmology OPD as well as those who were admitted in the department of General medicine and department of ophthalmology of ASCOMS Hospital Jammu were included in the study and categorised into two groups-patients living with T2DM without any ophthalmological complications and Patients suffering from T2DM along with diabetic retinopathy. Groups were compared for their Bile acid levels. The result findings revealed that the bilirubin and bile acid are the protective factors of diabetic retinopathy and the oxidative stress was lesser among patients with diabetic

retinopathy. There was significant difference between bilirubin and bile acids in two groups. It was concluded that bile acid decreases the risk of diabetic retinopathy.

Keywords: Type 2 diabetes mellitus, Diabetic retinopathy, Complications, Bilirubin and Bile acid.

Introduction

Diabetes mellitus (DM) is a major lifestyle medical problem which is occurring throughout the world it can cause a variety of long term systemic complications that can have a major impact on the quality of life of an individual.

DM can lead to various vascular and non-vascular complications which are similar to both type I and type II variants. Vascular complications are further divided into microvascular namely retinopathy, neuropathy, neuropathy and macro-vascular including coronary heart disease peripheral vascular disease a cerebrovascular disorders.

Diabetic Retinopathy (DR) is a microvascular complication of diabetes mellitus that affects the eye. Symptoms range from being asymptomatic to having mild visual disturbances to complete loss of vision.

DR can be classified as Non Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR). NPDR generally appears late in the first decade or early in the second decade of diabetes. NPDR can have milder changes to a more extensive disease presenting as intra-retinal microvascular abnormalities, venous vessel caliber changes, micro-aneurysms, micro-haemorrhages. It can even lead to diabetic macular oedema, neovascular glaucoma and ultimately resulting in Retinal Detachment (RD). The appearance of on or within 1DD of optic disc (NVD) and new vessel formation elsewhere in the fundus (NVE) is the gold standard of PDR.

Cholic acid and chendeoxycholic acid (CDCA) are the primary bile acids which are synthesised in the liver cells. Cholesterol is the component responsible for their synthesis, glycine or taurine for their conjugation and finally they get secreted in the bile canaliculi. Secondary bile acids namely deoxycholate and lithocholate are produced as the bacterial metabolites of primary bile acids in the colon.

Primary and secondary bile acids are either taurine or glycine conjugated to form primary and secondary conjugated bile acids. A stereoisomer of CDCA called ursodeoxycholic acid (UDCA) is a secondary bile acid which is found in a very low concentration. In humans the ocular function mainly relies on CYP27A1 and CYP46A1 of which CYP27A1 is the principal hydroxylase that causes the major chunk of cholesterol elimination by the bile acids which are synthesised by the hydroxylation of cholesterol through the process of enzyme catalysis. CYP46A1 is expressed mainly in the neural retina and helps in maintaining the retinal cholesterol homeostasis and retinal immune response. CYP27A1 and CYP46A1, their combined deficiency may lead to cataracts, glaucoma, neurodegenerative disorders and premature retinal degeneration due to the accumulation of lipids and new vessel formation. This leads to a belief that the bile acids have a protective role in various diseases affecting the retina as well as the CNS.

Thus, the present study was conducted to determine the association between proliferative diabetic retinopathy and serum bile acid level in patients with Type 2 diabetes mellitus.

Aims and objectives

To assess the relationship between the serum bile acid levels and the proliferative retinopathy in patients

diagnosed with Type II DM according to the WHO diagnostic criteria in the year 2019.

Material and methods

This prospective cross-sectional study was conducted at Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, over the period of six months (March 2022 to August 2022).

A total of 100 patients visited the medicine and ophthalmology OPD as well as those who were admitted in the department of General medicine and department of ophthalmology of ASCOMS Hospital Jammu were included in the study.

Patients were categorised into two groups-patients living with T2DM without any ophthalmological complications and Patients suffering from T2DM along with diabetic retinopathy. Groups were compared for their Bile acid levels.

Inclusion criteria

1. T2DM patients.
2. Patients falling in the age group of 18-69 years.
3. Both male and female.
4. Diagnosed with T2DM for the duration of more than 10 years.
5. Clinical diagnosis was made according to the WHO criteria 2019 (6) HbA1C </= 10%.
6. PDR according to Abbreviated Early Treatment Diabetic Retinopathy Study (ETDRS) classification of diabetic retinopathy.
7. No Diabetic retinopathy changes on examination and investigations.

Exclusion criteria

1. T1DM, Pregnancy, Any systemic disorder such as renal insufficiency or cardiovascular diseases or liver diseases, recent infection, inflammatory disorder, autoimmune disorder, COVID 19, diabetic maculopathy, any other posterior segment pathologies, optic nerve pathologies, ocular media is hazy where fundus difficult to visualise and malignancy.
2. Already a participant in another interventional study.
3. Smoker.
4. Any ongoing steroid or other hormonal treatment or have taken with in a period of last three months of the start of the study.
5. Any eye procedure done for any cause. Ongoing drug therapy for any ophthalmological condition.
6. Patients suffering from cataract or glaucoma corneal opacity and vitreous haemorrhage. HbA1C more than 10%.
7. NPDR according to Abbreviated Early Treatment Diabetic Retinopathy Study (ETDRS) classification of diabetic retinopathy.

A detailed history was collected and all patients were examined. Patients examined were conscious cooperative and well oriented to time place and person. The vitals were noted including the blood pressure, pulse rate, Oxygen saturation, Temperature and fasting blood sugar levels (FBS). The height, weight was noted and Body Mass Index (BMI) calculated. The waist and hip circumference was measured and waist to hip ratio (WHR) calculated. Dry mucous membrane and reduced skin turgor was checked. Signs of infection were noted such as boils, abscess, fungal infections or any necrotic areas particularly in the lower limb region. Signs of insulin resistance like Acanthosis Nigricans were checked. Signs suggestive of dyslipidemia including xanthelasmata and xanthoma were noted. Necrobiosis lipoidica, a yellow indurated or ulcerated area

surrounded by a red margin indicating collagen degeneration was also looked. Skin was examined for any discolouration- yellow coloured indicating hepatic condition or blueish discolouration called cyanosis. Any collection of fluid or any kind of swelling was noted. Eyes were examined for pallor and icterus. The CVS and the peripheral vascular systems were examined with a particular emphasis to the arterial pulses in the feet. The CNS examination was done where both the sensory and the motor components were covered. The higher motor function abilities were also tested. Reflexes were checked.

For all the patients visual acuity, torch light examination, slit lamp examination, gonioscopy, applanation tonometry, fundoscopy and OCT 3D macula.

Blood samples were collected and tested for the fasting blood sugar (FBS) after the patients had fasted for more than 8 hours (overnight fasting). HbA1C levels were checked to assess the glycemic burden. Biochemical investigations included (1) LFT's- total protein, serum albumin, serum globulin, plasma alanine aminotransferase (ALT), plasma aspartate aminotransferase (AST), Alkaline phosphatase (ALP), plasma gamma glutamyl transferase (GGT). (2) RFT's- Serum urea, creatinine, uric acid, (3) Electrolytes- serum calcium, phosphate, sodium, potassium.(4) lipid profile- serum cholesterol, HDL, LDL, serum triglyceride. Haematological investigations included haemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), platelet count, ESR levels. Thyroid function test were done to screen for the commonly associated hypothyroidism Urine Routine examination included (1) physical characteristics- color, appearance, pH, specific gravity (2) chemical characteristics- albumin, glucose, ketones, bilirubin, urobilinogen (3) microscopic- pus cells, red blood cells, epithelial cells, casts, crystals, parasites. Urine albumin: creatinine ratio (UACR) was calculated to assess for early signs of diabetic nephropathy. Pancreatic antibodies (anti-GAD and islet cell) were also estimated to confirm a diagnosis of diabetes of autoimmune origin.

Data was tabulated, organised, analysed and interpreted in both descriptive and inferential statistics by using statistical package for social science software (SPSS), version 20. Categorical variables were expressed as number and percentage.

Observation and Results

Around 100 patients with T2DM were examine of which 50 patients had the history of more than 10 years of diabetes with no retinopathic changes (NDR) and 50 patients had proliferative retinopathic changes (PDR) no significant differences in age, duration of disease, BMI, WHR, HbA1C, FBS were noted (p Value > 0.05). The level of bile acids and bilirubin in the NDR group was found to be significantly higher as compared to the PDR group. The levels of serum triglycerides, serum cholesterol, LDL cholesterol, SBP,DBP were found to be significantly lower than that in the PDR group (p Value < 0.05).

Table 1: Basic characteristics

Characteristics	NDR	PDR	P Value
Age (years)	50.2 ± 8.5	52.5 ± 9.1	0.708
Sex (M/F)	27/23	28/22	0.173
Duration (years)	9.4 ± 2.6	10.5 ± 1.7	0.146
BMI (kg/sq.m)	22.3 ± 1.8	25.6 ± 4.6	0.811
Weight height ratio	0.89 ±0.47	0.95 ±0.61	0.613
Systolic BP (mmHg)	132.15 ±14.37	142.31 ±18.12	0.04
Diastolic BP	79.25 ±8.72	86.38 ±7.23	0.118

(mmHg)			
FBS (mmol)	7.23±2.85	8.12±4.1	0.005
HbA1C (%)	7.13±2.21	9.1±1.95	0.014
S. Triglycerides (mmol/l	1.28±0.85	2.89±1.51	0.089
S. Cholesterol (mmol/l)	4.9 ± 1.65	6.9 ± 1.59	0.673
S. Chol LDL (mmol/l)	3.09 ± 0.89	3.78 ± 0.23	0.312
S. Chol HDL (mmol/l)	1.98±0.25	1.75±0.81	0.031
S. BIL Total (mg/dl)	0.59±0.21	0.37±0.21	0.003
S. BIL Conj (mg/dl)	0.17±0.12	0.31±0.25	0.027
S. BIL Non Conj (mg/dl)	0.31±0.21	0.19±0.14	0.015
TBA (µ mol/L)	4.27±2.15	3.57±2.65	0.102
Uric Acid (µ mol/L)	359.7 ± 100.2	418.5 ± 112.4	0.019

Table 2

Characteristics	Group A	Group B	Group C
Bile Acids	2.52±0.27	3.98±0.12	6.32±2.54
NDR	61	79	82
PDR	48	29	26
PDR Ratio (%)	41.34	26.79	23.01

Table 2 showed the comparison of patients with PDR with varying BA levels- on the basis of bile acid levels, cases were divided into three groups - Group A (low BA levels), Group B (middle level BA), Group C (high BA levels). The proportion of PDR in each group was compared. It was found that with the increase in the level of BA, the incidence of proliferative changes reduced gradually.

Table 3: Logistic Regression Analysis of PDR risk factors

Risk factors	B	SE	WALD	P	OR	95%CI
TBIL	-0.141	0.045	12.266	<0.001	0.789	0.789-0.816
TBA	-0.210	0.062	8.257	0.002	0.703	0.5784-0.812
LDL-C	0.370	0.124	11.152	<0.001	1.503	1.031-1.098
Constant	0.495	0623	0.628	0.289	-	-

Discussion

The diabetes mellitus is a global epidemic and the number of patients is increasing with the time. Along with this gradual increase of the disease, there is significant increase of associated microvascular complications i.e. diabetic retinopathy.

Bilirubin is a waste product of heme catabolism, but it plays an important role as a potential endogenous anti-oxidant. The various studies observed the negative association between serum bilirubin concentration and the risk of diabetes and with other associated complications of diabetes.

It was reported that increased expression of heme oxygenase, an enzyme used to break down the haemoglobin into bilirubin, is associated with enhanced insulin sensitivity and glucose metabolism, thus resulting in greater rates of rat model euglycemia.

The present study reported that the bilirubin and bile acid are the protective factors of diabetic retinopathy and the oxidative stress was lesser among patients with diabetic retinopathy. There was significant difference between bilirubin and bile acids in two groups.

The findings of the study are consistent with the study conducted by Karuppannasamy D et al., (2017) found

that the patients with low serum bilirubin level had more risk of developing diabetic retinopathy than patients with high serum bilirubin level.

Similarly, Cheriyath P et al., (2010) reported that patients with higher serum bilirubin level were significantly associated with decreased incidence of diabetes mellitus.

Conclusion

The present study concluded that there was significant association of diabetic retinopathy with bile acids or serum bilirubin. The bile acids or serum bilirubin serves as protective factors for the patients from diabetic neuropathy.

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