ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 6, Issue – 1, February – 2021 , Page No. : 01 - 06

Mannose Binding Lectin as a Predictor of Diabetic Retinopathy in Indian Patients with Diabetes

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Citation this Article: Dr. Shreyans Jain, Dr Dhiraj Saini, Dr R.P Agrawal, Dr J.K Meel, Dr B.L Meena, "Mannose Binding Lectin as a Predictor of Diabetic Retinopathy in Indian Patients with Diabetes", IJMSIR- February - 2021, Vol – 6, Issue - 1, P. No. 01 – 06.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Diabetic retinopathy is leading cause of blindness and vision impairment in working age population around the world. A reliable screening biomarker of diabetic retinopathy would be of tremendous benefit in detecting population in need of further assessment and treatment. Therefore, this study was conducted to find out association between MBL and diabetic retinopathy.

Methodology: This was an observational study conducted on 200 diabetic patients during 12 months period. Serum MBL level was measured by enzyme linked immune sorbent assay. Retinopathy was graded from digital retinal photography, taken with non mydriaticautofundus camera and classified according to Early Treatment Diabetic Retinopathy Study (ETDRS). Correlation of MBL, hsCRP, duration of disease, HbA1c, other predictors with diabetic retinopathy was assessed by Pearson correlation coefficient. Statistical analysis was performed using SPSS version 17.0.

Results: Serum MBL levels were significantly higher in diabetic patients with retinopathy as compared tothose without retinopathy ($p<0.001$).Mean MBL level showed highly significant correlation with severity of retinopathy ($p<0.001$). On applying Pearson Correlation, maximum association of diabetic retinopathy was seen with MBL ($r=0.783$) followed by hsCRP ($r=0.441$), HbA1c ($r=0.346$) and duration of diabetes ($r=0.184$).

Conclusion: Our study concluded that MBL is novel independent marker of diabetic retinopathy in Indian population, suggesting a possible role of MBL in pathogenesis of diabetic retinopathy.

Keywords: Diabetic retinopathy, MBL, Mydriatic Auto fundus

Introduction

India is home to over 74 million diabetics, and the number is estimated to exceed 123 million by 2040[1]. Increasing longevity, changing lifestyle and dietary habits contribute to increasing prevalence of diabetes mellitus (DM) in India and all over the world[2]. Largest increase in the disease burden (among all non-communicable diseases) between the year 1996 and 2016 was noted for DM at 80%[3]. Diabetes and its complications are now an area of focus for prevention of mortality and morbidity. Absence of acute symptoms

and lack of awareness are the main barriers for detection of DM and its complications[4,5]. Prevalence of DM in India has been reported to be between 10.2% and 36% in various population-based surveys[6-9]. However, there was a variation in the age group included and the methodology used in these surveys. A multistate survey to establish prevalence of DM published in 2010 reported age-specific prevalence of DM.

Diabetic retinopathy is one of the leading causes of visual impairment in industrialized countries in the working age group and one of the frequent causes of blindness in developing countries like India. According to World Health Organization; diabetic retinopathy is 4.8% of the 37 million cases of blindness throughout the world[10].

Mannose-binding lectin (MBL) is synthesized by hepatocytes and belongs to the family of C-type lectins[11]. Its carbohydrate recognition domains bind in a calcium dependent manner to patterns of carbohydrate residues found on microorganisms. MBL exerts an important role in the innate immune system, and several studies have indicated that low levels of MBL might affect the outcome of infectious diseases, critical illness, and kidney graft survival[12-14].

Material and Methods

The study was approved by the institutional review board and informed consent was obtained by all patients prior to study entry.

- Blood samples were taken from a peripheral vein at the time of admission. Hematology and biochemistry was determined by routine techniques using an automated analyser.
- MBL (Mannose-Binding Lectin) Human ELISA Kit is an *in vitro* enzyme-linked immunosorbent assay for the quantitative measurement of Human MBL in sera, plasma and cell culture supernatants. This assay employs an antibody specific for Human MBL coated on a 96-well plate.
- Glycated haemoglobin (HbA_1c) by ion exchange method.
- hs-CRP

Diagnostic Criteria For Diabetes Mellitus

1. Diagnostic criteria for Diabetes Mellitus (DM)
   - Fasting glucose level ≥126 mg/dl
   - Two hour plasma glucose level ≥200 mg/dl during an oral glucose tolerance test
   - Random blood sugar ≥200mg/dl plus symptoms of diabetes
   - $HbA_1c \geq 6.5$
2. **Assessment Of Diabetic Retinopathy**: Participants underwent a retinal photography. Retinopathy was graded from the digital retinal photographs, taken with Non Mydriatic Auto Fundus Camera AFC 230/210 (for 7 visual fields) at Diabetic Care and Research Centre, PBM Hospital, Bikaner.
3. All findings and the diagnosis of diabetic retinopathy were confirmed by the same ophthalmologist and classified according to early treatment diabetic retinopathy study classification of diabetic retinopathy (ETDRS).

- Non proliferative diabetic retinopathy (NPDR)

1. No DR
2. Very mild NPDR
   - Microaneurysms only
3. Mild NPDR
   - Any or all of microaneurysms, retinal haemorrhages, exudates, cotton wool spots, up to the level of moderate NPDR. NO intraretinalmicrovascular anomalies (IRMA) or significant beading

4. Moderate NPDR
- Severe retinal haemorrhages (more than ETDRS standard photograph 2A: about 20 medium large per quadrant) in 1-3 quadrants or mild IRMA
- Significant venous beading can be present in no more than 1 quadrant
- Cotton wool spots commonly present

5. Severe NPDR
- The 4-2-1 rule; one or more of
- Severe haemorrhages in all 4 quadrants
- Significant venous beading in 2 or more quadrants
- Moderate IRMA in 1 or more quadrants

6. Very severe NPDR
- Two or more of the criteria for severe NPDR

- Proliferative diabetic retinopathy (PDR)

1. Mild-moderate PDR
- New vessels on the disc (NVD) or new vessels elsewhere (NVE), but extent insufficient to meet the high risk criteria

2. High risk PDR
- New vessels on the disc (NVD) greater than ETDRS standard photograph 10A (about 1/3rd disc area)
- Any NVD with vitreous haemorrhage
- NVE greater than ½ disc area with vitreous haemorrhage

3. Advanced diabetic eye disease
- Rubeosisiridis, tractional retinal detachment, neovascular glaucoma, vitreous haemorrhage

Statistical Analysis

Results were express as percentages for categorical variables and as medians (interquartile ranges [IQRs]) for the continuous variables. χ^2test as appropriate, correlations among continuous variables were assessed by the Spearman rank correlation coefficient. Different statistical methods will be used to investigate whether MBL allows predicting of DR in diabetes. First, the relation of MBL with the two points was investigated with the use of logistic regression models. For multivariate analysis, we included confounders, known risk factors, and other predictors as assessed in univariate analysis. All statistical analyses were performed with SPSS 17.0 software. All testing was two-tailed, and P values of <0.05 considered to indicate statistical significance depending on the number of statistical variables.

Results

In present study, out of total 200 cases, 41 cases had their hs-CRP <1 and out of them no case had retinopathy, 134 cases had their hs-CRP between 1-3 and out of them 22.4% cases had retinopathy while 25 cases had their hs-CRP >3 and out of them 64% cases had retinopathy. Mean hs-CRP in retinopathy absent patients was 1.68±0.92 while in retinopathy positive cases it was 2.96±1.56 (p<0.001). Mean FBS in retinopathy absent patients was 173.48±64.57 mg/dl while in retinopathy positive cases it was 184.78±42.04mg/dl (p>0.05). Mean MBL in retinopathy absent patients was 2417.70±371.51 while in retinopathy positive cases it was 3574.57±442.12 (p<0.001). Mean HbA1C in retinopathy absent patients was 8.61±1.5 gm% while in retinopathy positive cases it was 10.19±2.57 gm% (p<0.001). In present study, 154 cases had normal findings while 13 cases had very mild NPDR and out of them 6 and 7 cases belonged to MBL group 2001-3000 and >3000 respectively, Mild NPDR was present in 10 cases, moderate NPDR was present in 7 cases, Severe NPDR was present in 8 cases, very severe NPDR was present in 5 cases and PDR was present in 3 cases and they all belonged to MBL group >3000 (p<0.001). Mean hs-CRP in MBL

group ≤2000 was 1.28±0.49, in MBL group 2001-3000 it was 1.85±1.08 and in >3000 MBL group it was 2.60±1.49 (p<0.001). In our study, parameters like MBL, HbA1c, duration of diabetes, hs-CRP and systolic BP had significant association with diabetic retinopathy (p<0.05). However it was maximum with MBL followed by hs-CRP and HbA1c while least correlation was found with systolic BP and duration of diabetes.

Discussion

Diabetic retinopathy is well recognized sight threatening microvascular complication of diabetes. According to WHO statistics amongst the blind population worldwide, 5% of them belong to diabetic retinopathy[15]. However with appropriate medical and ophthalmological care it can be prevented in 90% of case. Nonetheless, diabetic retinopathy remains the prime reason of vision loss in developing countries. The exact mechanism by which diabetes causes retinopathy remains unclear.

This study was conducted in tertiary care hospital, Bikaner (North West Rajasthan) to find out the prevalence of diabetic retinopathy and also to assess the correlation between serum MBL level and diabetic retinopathy.

In our study serum MBL levels were significantly higher in patients with diabetic retinopathy as compared to patients with no diabetic retinopathy (3574.57±442.12µg/l vs. 2417.70±371.51 µg/l respectively: p<0.001), difference was found to be statistically highly significant. Man et al also investigated serum MBL level in patients with type 2 diabetes with and without retinopathy and observed serum MBL levels were significantly higher in patients with diabetic retinopathy as compared to those without diabetic retinopathy [3456(IQR 3128-3800)µg/l and 2432(IQR-2100-2670)] µg/l, respectively : p<0.001)

In our study, elevated MBL levels paralleled with the severity of diabetic retinopathy. MBL level in patients with very mild and mild diabetic retinopathy was 3363.04±342.48, in moderate to severe diabetic retinopathy it was 3649.33±370.65 and in very severe and proliferative diabetic retinopathy it was 4042.50±188.89. Similarly Genget al[16] in their study reported that there is correlation between elevated MBL level and the severity of diabetic retinopathy. These data suggests that there is possible role of MBL in pathogenesis of diabetic retinopathy. It needs to be investigated whether MBL level is a cause of diabetic retinopathy or merely a marker of it.

In present study we found that prevalence amongst patient with good glycemic control (HbA1c ≤7%) was only 6.5% as compared to 93.5% in those having poor control (HbA1c >7%). Mean HBA1c in patients with diabetic retinopathy was 10.19±2.57 while in patients without diabetic retinopathy was 8.61±1.50 and difference was found to be statistically highly significant. Similar to results of present study, Manaviet al[17] found significant association between HbA1C and diabetic retinopathy. Yun et al[18] studied the association between diabetic retinopathy and HbA1c and concluded that diabetic retinopathy was significantly more in patients having higher levels of HbA1c (odds ratio=3.46). Alabdulwahhab[19] in his study reported that patients with poor glycemic control have 1.99 times more chance to develop diabetic retinopathy. These data confirms physiological relationship between hyperglycemia and diabetic retinopathy.

In our study, parameters like MBL, HbA1c, duration of diabetes, hs-CRP and systolic BP had significant association with diabetic retinopathy (p<0.05).

However it was maximum with MBL followed by hs-CRP and HbA1c while least correlation was found with systolic BP and duration of diabetes.

Conclusion

The present study demonstrated that serum MBL level is an independent risk factor for diabetic retinopathy in Indian population, suggesting a possible role of MBL in the pathogenesis of diabetic retinopathy. We suggest that further studies should be carried to investigate whether specific inhibition of MBL and complement system in high-risk patients might be a therapeutic option for reducing the risk of developing diabetic retinopathy.

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