The predictive power of microalbuminuria in diagnosing diabetic retinopathy in adults with Type II diabetes mellitus

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Abstract
Introduction: Diabetes Mellitus is one of the most common metabolic disorders, resulting in hyperglycemia and is associated with micro and macro vascular complications. Diabetic retinopathy (DR) is a widely accepted cause of blindness in adults. The duration of diabetes, glycemic control and microalbuminuria (MA) have been implicated in the onset and progression of DR.

Materials and Methods: The aim of our study is to correlate FBS, PPBS, HbA1c and microalbuminuria with diabetic retinopathy and to find out MA as the predictor of DR in T2DM patients. Our study included, 50 T2DM patients with DR, 50 T2DM patients without DR and 50 controls of both sex in the age group of 40 – 60 years. Fasting blood sugar (FBS) and post prandial blood sugar (PPBS) were estimated by Glucose Oxidase method, glycated hemoglobin (HbA1c) by Ion Exchange Resin Method and urine samples were assayed for Microalbumin by Immunoturbidimetric assay and DR was diagnosed using Fundoscopy.

Results: In our study, levels of urinary microalbumin, FBS, PPBS and HbA1c in T2DM patients with DR is increased than T2DM patients without DR than the control group, which is highly significant (p <0.001). HbA1c and Microalbuminuria in T2DM are positively correlated. All the parameters (FBS, PPBS, HbA1c and microalbuminuria) in group A cases are positively correlated with grades of Diabetic Retinopathy.

Conclusion: Microalbuminuria and diabetic retinopathy are closely associated in T2DM patients and is a reliable marker which can predict the risk for the development of DR. All patients with MA should undergo regular retinal evaluation.

Keywords: Type II diabetes mellitus (T2DM), Microalbuminuria (MA), Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Glycated Hemoglobin (HbA1c), Diabetic Retinopathy (DR).

Introduction

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. The world prevalence of diabetes among adults (aged 20 – 79 years) was 6.4%, affecting 285 million adults in 2010, and will increase to 7.7%, 439 million adults by 2030.¹ India has the largest number of diabetic patients in the world estimated to be approximately 51 million in the year 2010 and in 2030, it will raise to 87 million.²

Diabetes mellitus affects generalized minor and major blood vessels. The diabetic patients are at increased risk of developing specific complications such as retinopathy, which leads to blindness, renal failure, nephropathy, neuropathy and atherosclerosis resulting in stroke, gangrene and coronary disease.

In contrast to western countries where the largest increase in the number of diabetic patients are elderly population aged >64 years, the majority part of the increase in Asia will occur among the population aged 45-64 years. These patients have longer disease duration and thus are associated with a higher risk of long term complications, including diabetic retinopathy. DR increases the chance of losing sight about 25 times higher than normal individuals.³ Major precipitating factors of DR are: duration and type of diabetes, age of onset, hyperglycemia, poor glycemic control (HbA1c level), hypertension, dyslipidemia, variation in hormonal levels, genetics, smoking and microalbuminuria.

Increased blood sugar initiates the development of microvascular complications in DM. There is a direct relation between the degree of glycemic control and the incidence and progression of retinopathy.⁴ Most adverse effects of glucose are mediated indirectly through Advanced Glycation End products. Altered glomerular endothelial permeability in kidneys is a result of disruption of the integrity of the endothelial barriers, allows excessive amount of albumin to escape into the glomerular ultrafiltrate. When the tubular reabsorptive capacity for albumin from the ultrafiltrate exceeds the threshold, it appears in urine.⁵

Microalbuminuria

When 30 to 300 mg of albumin is excreted per day in urine. Albumin molecule is relatively small and it is often the first protein to enter the urine after the kidney is damaged.⁶

There is also an increased incidence of microalbuminuria in India (27% – 63%) when compared to the west (5% - 23%).⁷ 15 – 20 % of diabetic patients have microalbuminuria. Diabetics with microalbuminuria are more prone for kidney, cardiac and ocular disorders as well.⁸
The magnitude of damage caused by the microvascular complications of diabetes, stresses the need for sensitive markers of screening for retinopathy. This study highlights the association between FBS, PPBS, HbA1c and microalbuminuria in the onset, progression and severity of DR.

**Materials and Methods**

Patients who attended OPD and are admitted in the wards of Medicine department in Navodaya Medical College Hospital and Research Centre for type II diabetes mellitus were chosen randomly and screened for the study. Detailed history and clinical investigations were recorded in the pretested proforma. The study was carried out in the department of biochemistry, Navodaya Medical College over a period of six months from December 2016 to May 2017.

150 cases were studied, out of which 50 were T2DM with DR, 50 were T2DM without DR and 50 were controls (without T2DM) of both sex within the age group of 40 to 60 years.

Patients with T1DM, T2DM with overt proteinuria i.e., > 300 mg/day and haematuria, hypertension were not included in the study.

**Results**

**Table 1: Overall parameters in our study**

|                | FBS (mg/dl) Mean ±SD | PPBS (mg/dl) Mean ±SD | HbA1c Mean ±SD | microalbuminuria (mg/day) Mean ±SD |
|----------------|----------------------|-----------------------|----------------|----------------------------------|
| T2DM with DR   | 193.88±37.92         | 274.68±56.01          | 10.2580±1.46   | 225.54 ±53.11                    |
| T2DM without DR| 156.42±22.79         | 213.40±39.07          | 8.5880±1.31    | 33.60±46.60                      |
| Controls       | 91.76±11.70          | 111.78±6.55           | 5.1480±.31     | 23.74±14.64                      |
| p-value        | .000 (< 0.001)*      | .000 (< 0.001)*       | .000 (< 0.001)*| .000 (< 0.001)*                  |

*highly significant.

**Bar diagram 1: Type II diabetes mellitus duration in cases**

**Table 2: Association between Diabetes Duration and Grades of Diabetic Retinopathy**

| Duration of Diabetes mellitus | Grade 1 DR | Grade 2 DR | Grade 3 DR | Grade 4 DR |
|-------------------------------|------------|------------|------------|------------|
| 1 to 5 years                  | 7 (14%)    | 8 (16%)    | 2 (4%)     | 0          |
| 6 to 10 years                 | 1 (2%)     | 2 (2%)     | 9 (18%)    | 5 (10%)    |
| >10 years                     | 0          | 0          | 4 (8%)     | 12 (24%)   |

FBS was estimated by Glucose Oxidase method, Glycated hemoglobin (in EDTA tubes) by Ion Exchange Resin Method. Random midstream urine samples (10 ml) were collected in a sterile container without preservative and assayed for microalbumin by Immunoturbidimetric assay. Again blood sample was collected 2 hours after meal for estimating PPBS and DR was diagnosed by ophthalmologist by ophthalmic examination using direct and indirect ophthalmoscopy.

The study divided the participants into five groups based on the grades of DR. DR is classified based on Fundoscopy into five grades: group 1: no DR (grade 0: no diabetic retinopathy), group 2: mild NPDR (grade 1: mild non proliferative diabetic retinopathy), group 3: moderate NPDR (grade 2), group 4: severe NPDR (grade 3) and group 5:PDR (grade 4: proliferative diabetic retinopathy).

**Statistical Analysis**

The statistical analysis was done using SPSS v16.0 software. ANOVA (One way analysis of variance) with Post Hoc test (multiple comparison), Chi square test for duration of T2DM and Pearson’s correlation coefficient for evaluating the relationship between HbA1c levels and microalbumin levels. P-value of < 0.05 and < 0.001 was considered significant and highly significant respectively.
Table 3: Correlation of HbA1c and Microalbuminuria

| Microalbuminuria (mg/day) | HbA1c | p-value |
|---------------------------|-------|---------|
|                           | .803  | .000 (< 0.001)* |

*highly significant

Table 4: correlation of T2DM (FBS, PPBS and HbA1c), Microalbuminuria and Grades of DR

| DR             | Grade 1 DR | Grade 2 DR | Grade 3 DR | Grade 4 DR | p-value |
|----------------|------------|------------|------------|------------|---------|
| FBS (mg/dl)    | 161.25±26.03 | 169.90±18.28 | 196.36±30.22 | 219.78±37.91 | .000 (< 0.001)* |
| PPBS (mg/dl)   | 231.00±36.29 | 229.70±23.08 | 270.43±26.48 | 322.39±56.30 | .000 (< 0.001)* |
| HbA1c          | 8.88±.92   | 9.08±.64   | 9.92±.68   | 11.77±.99   | .000 (< 0.001)* |
| Microalbuminuria (mg/day) | 141.62±10.04 | 179.60±14.40 | 238.14±15.77 | 278.56±11.26 | .000 (< 0.001)* |

*highly significant.

Discussion

There is an increase in FBS, PPBS and HbA1c values in T2DM patients with DR than T2DM without DR than the control group (<0.001). Our findings are comparable with the previous studies, who have found that there was a significant association between glycemic control with the severity of DR.8

Hyperglycemia is a very potent predictor of proliferative DR. The risk of DR increases stepwise with increasing degrees of hyperglycemia.4 Every 1% rise in HbA1c levels in T2DM results in 37% increase in the microvascular complications.9 Hyperglycemia leads to glycation of virtually all proteins, resulting in the formation advanced glycation end products (AGE). These AGEs induce cross linking of collagen and other extracellular matrix proteins in many tissues including arterial vessel walls.10 Hyperglycemia induced vascular injury leads to increased glucose flux through the polyol pathway, resulting in cellular damage, thereby resulting in the various micro and macro vascular complications.4

An increase in urinary microalbumin levels (p < 0.001) in T2DM patients with DR than T2DM without DR and the control group. But the increase is not significant among T2DM patients without DR when compared to controls (p > 0.05). High levels of MA may be an indicator of proliferative DR. Possible reason for this is MA is strongly related to the degree of hyperglycemia, which leads to the formation of advanced glycation end products. These AGEs result in various microvascular complications.4 Boelte MC et al, concluded that patients with proliferative retinopathy more often presented renal involvement, including urinary albumin excretion within the microalbuminuria range.11 Numerous studies have reported that MA might be an independent risk factor for DR in type 1 and type II DM.12 Patients with MA were 2.6 times more likely to suffer from severe retinopathy. MA and diabetic retinopathy share common determinants. Both are said to be due to generalized vascular dysfunction.10

The duration of type II diabetes mellitus in patients with retinopathy was significantly higher when compared to the diabetic patients without retinopathy (p < 0.001). 24% of our T2DM patients (with more than 10 years duration of DM) with DR showed proliferative diabetic retinopathy. The risk of Diabetic Retinopathy increases by 1.89 times for every 5-year increase in the duration of diabetes mellitus.13 K. G Santosh et al., have shown that glycosylated hemoglobin, MA and the duration of diabetes mellitus were independently related to DR.14

In our research study, HbA1c and MA in diabetic patients with DR were positively correlated, which was similar to the findings reported by some previous study.15-18 In another study, there was no significant association of MA with HbA1c, but there was a strong association with fasting blood glucose, which was similar to an earlier study.19 Poor glycemic control (HbA1c) is a risk factor of MA.20

Our research study showed an increase in urinary microalbumin levels leads to the development and progression of DR. There is an association between microalbuminuria and Diabetic Retinopathy in type II diabetic patients and is a reliable marker of retinopathy.12 there is a significant statistical correlation between the prevalence of MA and the presence of diabetic retinopathy.21-23

Conclusion

Microalbuminuria and diabetic retinopathy are closely associated in patients with T2DM. It may be a marker for the risk of onset and progression of proliferative retinopathy. Despite major advances in the treatment of DR, affected subjects must be identified as early as possible by aggressively targeting the risk factors and by regularly screening the affected individuals since early diagnosis (retinal evaluation, biochemical parameters like HbA1c and MA), prompt treatment, prudent diet, exercise and life style modification can reduce retinopathy. Good control of blood sugar levels reduces the chance of
Microalbuminuria and Diabetic Retinopathy in patients with T2DM.

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