ORIGINAL ARTICLE

Relation of microalbuminuria to glycosylated hemoglobin and duration of type 2 diabetes

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Abstract

Background: Nephropathy is one of the complications of type 2 diabetes mellitus that could lead to end-stage renal disease. Persistent microalbuminuria is the best predictor of high risk of developing diabetic nephropathy. The relation between HbA_{1c} and microalbuminuria with the duration of diabetes is not clear.

Objectives: To determine microalbuminuria levels in type 2 diabetics and to correlate changes in microalbuminuria levels to glycosylated hemoglobin level and duration of diabetes.

Materials and Methods: Study was conducted at Medical College, Kolkata. Fifty both male and female type 2 diabetics of age groups 30-60 years, without any complications were taken as cases and 50 healthy (male and female) subjects of comparable age were taken as controls. Cases with anemia, any other diseases or person using drugs that could affect HbA_{1c} levels and microalbuminuria were excluded from the study. Fasting and postprandial blood glucose, HbA_{1c} serum urea and serum creatinine were analyzed. Urine was analyzed for microalbuminuria. The Statistical Software SPSS 15.0 were used for the analysis of the data.

Results: Urinary microalbumin, HbA_{1c} levels were significantly higher in the cases. Microalbumin levels were linearly correlated to the duration of diabetes and HbA_{1c}.

Conclusions: Impaired glycemic control is associated with significant elevations in urinary microalbumin levels. Furthermore, there is an increased urinary microalbumin levels with increased duration of diabetes, which suggests that the detection of increased urinary microalbumin levels at the initial stage can avert, reduce the clinical and economic burden of diabetic complications in future.

Key words: HbA_{1c}, microalbuminuria, type 2 diabetes mellitus

Date of Acceptance: 22-Apr-2012

Introduction

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in several countries.[1] It is also the cause of chronic hemodialysis and renal transplantation. Several studies have suggested that detection of early changes in renal function via microalbuminuria tests prevent further progression of the disease.[2-5] Microalbuminuria is common (prevalence rates of 10-48%) and is a well-established risk factor for macrovascular diseases in type 2 diabetics. Microalbuminuria defined as urinary albumin excretion rate of 20-200 μg/min or urinary protein excretion rate of 30-300 μg/min predicts future development of overt nephropathy.[6] As microalbuminuria can be reversed and the future development of overt diabetic nephropathy significantly reduced, screening for microalbuminuria and timely therapeutic intervention has become standard of care worldwide. Microalbuminuria is also considered to be a predictor for cardiovascular disease both among diabetic and non-diabetic subjects,[7,8] and is one of the

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Access this article online	
Quick Response Code:	Website: www.njcponline.com
	DOI: ***
	PMID: *******

components of the metabolic syndrome (insulin resistance syndrome).[4,9] Microalbuminuria (MAU) represents the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease.[10] However, it is not clear whether MAU represents an independent predictor or rather a marker of organ damage, since mechanisms linking MAU with end-organ damage have not been fully explained.[11] HbA_{1c} is a blood glucose control marker in diabetic patients. Glycosylated hemoglobin (HbA_{1c}) results from post-translation changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. Glycosylation of hemoglobin takes place under physiological condition by a reaction between glucose and N-terminal valine of beta chain of molecules.[12] Higher levels of HbA_{1C} were associated with increased risk for development of microangiopathy in diabetic. This may be due to the fact that HbA_{1c} has special affinity for oxygen thereby causing tissue anoxia and plays a role in causation of micro and macroangiopathy.[13] Several studies have shown a positive correlation between microalbuminuria and HbA_{1c}.[14-17] However, this has not been established. These findings become an important and an interesting aspect for a detailed study.

Materials and Methods

Study was conducted at Medical College, Kolkata. Usual permission from ethical committee and consent from subjects and controls were taken before commencing the study. Fifty both male and female type 2 diabetics of age groups 30-60 years, without any complications were taken as cases and 50 healthy (male and female) subjects of comparable age were taken as controls. Cases with anemia, any other diseases or person using drugs that could affect HbA_{1c} levels and microalbuminuria were excluded from the study. 0.5 ml of venous sample was collected from the subjects. The samples were centrifuged, separated and stored at 4°C until analysis. The blood samples were analyzed for HbA_{1c} (immuno-inhibition method),[18] fasting blood glucose and postprandial blood glucose (GOD-POD),[19] serum urea (urease method)[20] and serum creatinine (Jaffe's Kinetic).[21] Urine sample was analyzed for microalbumin (immunoturbidimetric method).[22]

Statistical analysis

Student's *t* test has been used to find the significance of study parameters on continuous scale between two groups and to test the homogeneity samples based on age (or continuous parameters) and Chi-square test to test the homogeneity of samples based on parameters on categorical scale between two groups. Pearson correlation between duration and microalbumin is computed to find the relationship. The Statistical Software SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs and tables.

Results

Mean levels of biochemical parameters are represented in Table 1. Levels of Fasting Blood Glucose (FBG), Post-prandial Blood Glucose (PPBG), Glycosylated Hemoglobin (HbA_{1c}), Microalbumin, Serum Urea and Serum Creatinine were found to be higher in cases compared with controls and found to be statistically significant ($P < 0.001$). Microalbumin levels in relation to duration of type 2 diabetes were represented in Table 2. Microalbumin levels (g/day) were found to be highest i.e., 0.449 ± 0.160 g/ day in diabetic subjects with duration of diabetes more than four years, statistically significant ($P < 0.001$). The correlation graph of microalbumin levels to duration of diabetes is depicted in Graph 1. The correlation graphs of microalbumin levels to HbA_{1c} in controls and cases are depicted in Graphs 2 ($r = 0.451$; $P = 0.046$) and 3 ($r = 0.609$; $P = 0.004$), respectively Graph 3.

Discussion

FBG, PPBG values are higher in type 2 diabetics and are statistically significant ($P < 0.001$). Serum urea and serum creatinine were found to be higher in type 2 diabetics compared with controls and is statistically significant in cases ($P < 0.001$). Measurement of HbA_{1c} is used in the long-term monitoring of DM. The level of HbA_{1c} has been widely accepted as an indicator of mean daily blood glucose concentration over the preceding 8–12 weeks. In the present study, levels of HbA_{1c} are higher in diabetics than in controls, and the elevations are of high statistical

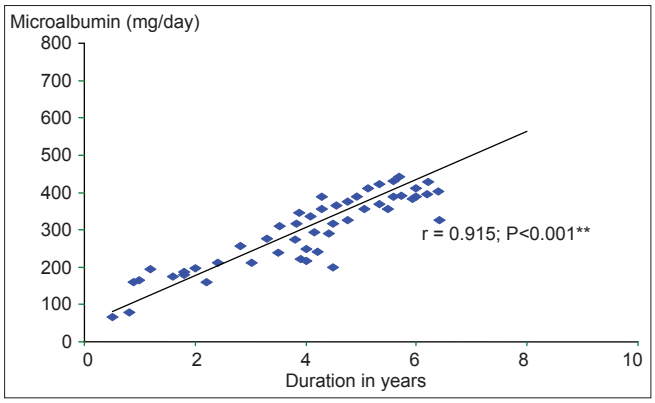
Table 1: Mean levels of biochemical parameters

Parameters	Controls	Cases	*P* value
FBG (mg/dl)	91.00±10.01	174.15±69.74	<0.001
PPBG (mg/dl)	119.40±21.16	221.75±74.12	<0.001
HbA_{1c} (%)	5.04±0.48	7.87±1.72	<0.001
Microalbumin (mg/day)	3.28±2.02	292.95±156.45	<0.001
Urea (mg/dl)	24.55±8.09	43±20.68	<0.001
Creatinine (mg/dl)	0.96±0.22	1.24±0.58	0.055

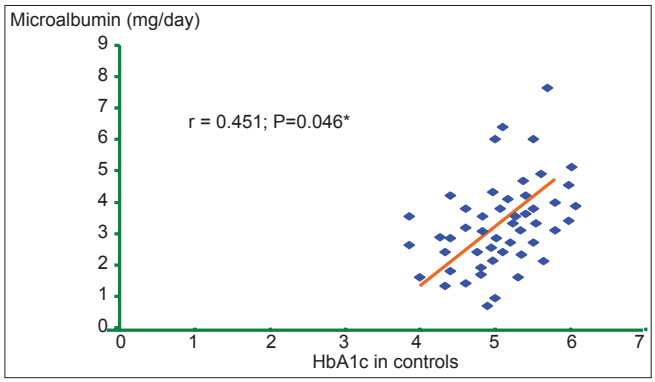
Table 2: Microalbumin in relation to duration of diabetes (in years)

Bio-chemical parameters Duration of diabetes (years)	Mean±SD	*P* value
Microalbumin (g/day)		
1-2	0.156±0.049	<0.001
2-4	0.228±0.016	
>4	0.449±0.160	

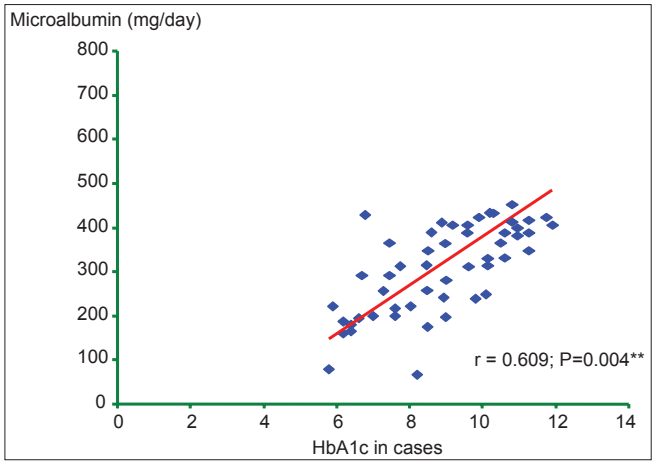
significance ($P < 0.001$). In this present study, it is found that diabetics with poor glycemic control had higher microalbumin levels compared with those of diabetics with good glycemic control, and this finding is in agreement with several other studies.[16,17,23,24] This study also highlights that there is a significant correlation between microalbumin levels and HbA_{1c} in cases. Studies have confirmed that there is an association of microalbumin levels with well-established risk factors such as age and poor glycemic control (HbA_{1c}). Similarly, the present study reveals that the diabetics' subjects having poor metabolic control are more prone to renal damage, and thus elevated microalbumin levels. Microalbumin levels are found to be higher in cases than in controls, and are found to be statistically significant ($P < 0.001$). The increased microalbumin levels in diabetic subjects may be due to an altered glomerular filtration barrier, at the podocyte level. Damage to the podocyte may be explained by the fact that there is an increase in the extracellular release of reactive oxygen species.



Graph 1: Correlation of microalbumin levels to duration of type 2 diabetes



Graph 2: Correlation of microalbumin levels to HbA_{1c} in controls



Graph 3: Correlation of Microalbumin levels to HbA_{1c} in cases

This study reveals that the mean value of microalbumin is more in males compared with females. This finding is in agreement with several other findings.[15,25,26] In the present study, no statistical correlation was found between the levels of microalbumin and between the ages of patients and is in agreement with previous studies.[27,28] In the present study, a good statistically significant correlation was found between the prevalence of microalbuminuria and duration of diabetes that was consistent with findings of past studies.[15,29-31] Our findings are in correlation with the findings of several other studies. Several studies on regression analysis and diabetes duration were identified as a strong predictor for the development of abnormal albuminuria in type 2 diabetes mellitus. Our study also shows that duration of diabetes is a strong predictor of increased microalbumin excretion. Previous studies in type 2 diabetics indicate that proteinuria and renal failure are common.[32] This signifies that as the duration of diabetes increases, the GFR (Glomerular Filtration Rate) decreases. Some studies have detected enlarged kidney in diabetics of less than 2 years of duration.[33-35]

Further studies on this aspect also gave the impression that enlarged kidney is not a common feature of type 2 diabetes mellitus.[36] The reasons for this apparent lack of enlarged kidney in type 2 diabetes mellitus could be two-fold; firstly, the onset of type 2 diabetes cannot be pinpointed with accuracy, as it may be preceded by a variable period of asymptomatic hyperglycemia of 5-7 years. During this period of asymptomatic hyperglycemia, the patient may have an enlarged kidney, which by the time of detection of diabetes may have regressed to the normal size or may even have contracted as a result of the ongoing destruction. Secondly, type 2 diabetes mellitus is the disease of the elderly, and age-related phenomenon might have a bearing on the kidney function. Generalized arteriosclerotic changes, decreased vascularity, concomitant hypertension or the presence of other non-diabetic renal diseases can also lead to a decrease in kidney function and size. The functional abnormality concomitant with enlarged kidney is hyper-filtration and intra-renal hypertension, which have been originally proposed to the off-key pathogenetic significance by a particular study.[37] So, it may be reported that proteinuria develops more frequently in subjects

with diabetes of long duration, poor glycemic control and albuminuria.

In type 2 diabetic patients, the duration of diabetes was the strongest predictor and elevated glycemic control (HbA_{1c}) as well predicted increased microalbumin excretion rate. So, it may be suggested that determination of microalbumin levels in urine is an easy method of screening diabetic patients, especially diabetic patients with long-term diabetes. It is further suggested screening for microalbuminuria in diabetic patients in order to reduce future kidney disease. From this study, it seems that if good glycemic control is maintained at early stages of diabetes, chances of microalbuminuria is less.

Despite its devastating consequences, microalbuminuria is still a largely unrecognized risk factor, and a large proportion of individuals with diabetes are not regularly screened. There are several limitations to this study that needs to be discussed. Firstly, this was a cross-sectional study and for this reason, it is not possible to establish a firm cause-effect relationship between the risk factors identified, their interaction and MAU. Secondly, although the measurements of urinary MAU were centralized, we obtained only one measurement of the microalbumin. Finally, the sample size (the number of cases) is so small that these results cannot be applied to the whole population of individuals suffering from type 2 diabetes mellitus. Despite its role as an independent predictor of renal and cardiovascular outcomes, the importance of monitoring microalbuminuria (MAU) and to act as a modifiable risk factor is still underestimated. Therefore, large-scale clinical trials to establish a relation between elevated microalbumin levels and type 2 diabetes mellitus are worth undertaking.

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How to cite this article: ???

Source of Support: Medical College, Kolkata, **Conflict of Interest:** None declared.