

# Relationship Between Glycosylated Hemoglobin and Risk of Microalbuminuria in Patients with Type 2 Diabetes Mellitus

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## ABSTRACT

Nephropathy is a common complication of Diabetes Mellitus that could lead to End Stage Kidney Disease (ESKD). Microalbuminuria is important as an 'early marker' of renal disease as it represents a time when renal biopsy shows no or minimal changes. Glycosylated Hemoglobin (HbA1c) represents the average glucose concentration over the period of 2-3 months and is accepted as a useful index of mean blood glucose.

The purpose of the study was to study the relationship between HbA1c and urinary microalbumin in patients of type 2 diabetes mellitus. A prospective study was conducted on 200 known diabetics. Detailed history was taken and thorough physical examination of all the patients was done followed by HbA1c estimation by Bio Rad D10 HPLC machine and microalbumin by Nyco Card Microalbumin test kit. Statistical analysis was done using Karl Pearson's correlation using SPSS software version 19. 56.5% of the cases were males and 43.5% females. 43.5% cases were positive for microalbumin, of which 47% had duration of diabetes between 5 to 10 years ( $p < 0.05$ ). 35% cases had HbA1c in the range of 8.1-10% of which 67% had microalbuminuria ( $p < 0.05$ ). Microalbuminuria showed a significant correlation with HbA1c and duration of diabetes, thus serving as an invaluable tool in monitoring of glycaemic status and screening for diabetic nephropathy.

**KEY WORDS:** diabetes, diabetic nephropathy, glycosylated haemoglobin (HbA1c), urinary microalbumin.

## INTRODUCTION:

Diabetes mellitus (DM) is one of the most common chronic diseases in most countries.<sup>[1]</sup> Diabetic nephropathy (DN) is one of the most common complications, and an important cause of renal failure.<sup>[2]</sup> Microalbuminuria is the earliest clinically detectable stage of diabetic kidney disease at which appropriate interventions can retard, or even reverse, the progress of nephropathy.<sup>[3]</sup>

Glycosylated haemoglobin (GHb) is a useful index of mean glycaemia during the preceding 120 days.<sup>[4]</sup> It is also a predictor of complications as measures reducing HbA1c correspondingly reduce the risk of complications.<sup>[5]</sup>

The present study was done to evaluate the relationship between duration of diabetes, degree of

hyperglycemia and the incidence of microalbuminuria in patients with diabetes mellitus. This correlation can have important implications in deciding how strictly the blood sugar levels of diabetic patients need to be controlled for optimum health and prevention of complications like diabetic nephropathy.

## MATERIALS AND METHODS:

A prospective study, including randomly selected 200 known type 2 diabetic patients attending both outpatient and inpatient departments was conducted from August 2011 to June 2013. A detailed history was taken and thorough physical examination of all the patients was done, followed by HbA1c estimation and tests for proteinuria (both microalbumin and macroalbumin).

Blood samples were taken in EDTA vacutainers for HbA1c. It was tested on the BIO RAD D10 dual programme HPLC machine by cation exchange chromatographic technique.

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For protein estimation, random urine sample was taken. All samples were tested for presence of albumin by URITRACE 10 PA reagent strips. (Based on the principle of protein error of Ph indicator). Albumin negative samples were then tested for microalbumin by the NYCO CARD microalbumin test kit following the principle of sandwich format immunometric assay.

Statistical analysis was done by applying Karl Pearson's correlation using Statistical Programme for Social Sciences (SPSS) version 19. p value of <0.05 was considered statistically significant.

## RESULTS:

The study included patients in the age group ranging from 30-80 years with mean age of 52.2 years. Maximum cases (37%) were in the age group of 41-50 years, followed by 23.5% cases in the age group of 51-60 years. Majority of cases, 75, (37.5%) had duration of diabetes upto 5 years followed by 70 (35%) cases with duration of 5- 10 years. Out of the total cases, 67 (33.5%) were normoalbuminurics. 133 showed proteinuria, of which 87 (43.5%) were microalbuminurics and 46 (23%) were macroalbuminurics. Among microalbuminuric patients, 60 (68.97%) were males and 27 (31.03%) were females. 119/200 patients (59.5%) were hypertensive. Among the microalbuminurics, 57 (65.5%) were both diabetic and hypertensive. These findings were statistically significant (p value < 0.05) of the total microalbuminuric cases, 52/87 (59.7%) were smokers. A positive correlation was observed. (p value <0.05). Duration of diabetes was upto 5 years in 46/67 (68.6%) cases without proteinuria. Majority of microalbuminuric 41/87 (47.13%) and macroalbuminuric cases 15/46 (32.6%) had duration between 5-10 years. In the patients with duration of diabetes between 11-15 years, 17/87 (19.5%) were microalbuminurics and 13/46 (28.2%) were macroalbuminurics. A significant correlation was observed between duration of diabetes and the development of micro and subsequently macroalbuminuria (p value <0.05). Most of the patients, 70, (35%) had HbA1c in the range of 8.1-10% of the total cases, 37 (18.5%) showed good glycaemic control (HbA1c upto 7%). Out of these, 33 (89.2%) showed no proteinuria. However, in two cases microalbuminuria was present. 163 (81.5%) cases showed poor glycaemic control. Maximum number of patients without any proteinuria, 33/67 (49.2%) showed HbA1c upto 7.0%. Amongst the microalbuminuric

patients, maximum 47/87 (54.02%) had HbA1c in the range of 8.1-10%. Maximum macroalbumin positive patients 16/46 (34.7%) had HbA1c in the range of 10.1-12%. A positive correlation was seen between degree of glycaemic control and development of proteinuria (p value <0.05).

## DISCUSSION:

The first detectable sign of kidney damage is the appearance of microalbuminuria.<sup>[6]</sup> This allows early intervention with the goal of delaying the onset of overt diabetic nephropathy.<sup>[7]</sup> To maximize prevention of microalbuminuria development, blood pressure should be maintained at less than 130/80 mm Hg, and HbA1c should be kept below 7%.<sup>[5]</sup> The level of glycaemic control also plays an important role in the transition from normoalbuminuria to microalbuminuria to macroalbuminuria.<sup>[8]</sup>

Hence, two important recommendations for the follow-up of diabetics include monitoring of glycaemic status by HbA1c and screening for nephropathy with urine microalbumin to assess disease progression and to detect potential progression towards end organ damage.<sup>[9]</sup>

The age range of patients in our study was 30-80 years with the mean age of 52.2 years. Similar mean age was observed in various other studies by Chowta NK et al, Kanakmani J et al, Maskari FA et al.<sup>[8,10,11]</sup> Although the exact reason why the residents of developing countries, especially Asian, are more prone to diabetes at a younger age remains speculative, there is growing evidence to support the concept of the 'Asian Indian Phenotype'. The term refers to the peculiar metabolic features of Asians characterized by a propensity to excess visceral adiposity, elevated serum triglycerides and an increased ethnic susceptibility to diabetes.<sup>[1,6]</sup>

Microalbuminuria is a useful predictor of renal failure in diabetics. The causal risk factors for microalbumin are poor glycaemic control and raised blood pressure. Duration of diabetes, male sex and smoking as additional risk factors for microalbuminuria.<sup>[12]</sup>

In our study, 33.5% cases were normoalbuminurics, 66.5% were proteinurics, of which 43.5% had microalbuminuria and 23% albuminuria. Similar results were obtained in many other studies by Jha P et al, Al Sheikh et al, Muraliswaran P et al etc.<sup>[5,12,13]</sup> High microalbumin levels can be due to irregular

**Table 1:** Demographic Profile according to status of proteinuria

	NORMOALBUMINURIA	MICROALBUMINURIA	MACROALBUMINURIA
No. of PATIENTS	67(33.5%)	87(43.5%)	46(23%)
MEAN AGE	47.3 years	52.8 years	59.6 years
MEAN DURATION	4.59 years	8.6 years	12.68 years
MALES	33 (49.25%)	60(68.97%)	22(47.82%)
FEMALES	34(50.24%)	27(31.03%)	24(52.18%)
SMOKERS	22(32.83%)	52(59.77%)	22(47.82%)
HYPERTENSIVES	22(32.83%)	57(65.52%)	41(89.13%)
MEAN A1c	7.37%	9.76%	11.10%

**Table 2:** Correlation of proteinuria with duration of diabetes.

DURATION OF DIABETES	NO		MICRO		MACRO	TOTAL	
	PROTEINURIA		ALBUMINURIA		ALBUMINURIA		
	CASES	%	CASES	%	CASES	%	
0-5	45	67.1	23	26.4	6	13.0	74
6-10	14	20.9	41	47.2	15	32.6	70
11-15	07	10.5	17	19.5	13	28.3	37
16-20	00	00	03	03.4	09	19.6	12
21-25	00	00	02	02.3	02	04.4	04
>25	01	1.5	01	01.2	01	02.1	03
TOTAL	67	100	87	100	46	100	200

**Table 3:** Status of Proteinuria according to HbA1c level.

HbA1c (%)	NO PROTEINURIA	MICRO ALBUMINURIA	MACRO ALBUMINURIA	TOTAL
UPTO 7.0	29	2	1	32
7.1-8.0	22	13	3	38
8.1-9.0	8	21	7	36
9.0-10.0	6	21	7	34
10.1-12.0	2	21	14	37
12.0-14.0	0	6	8	14
14.0-16.0	0	2	5	7
>16.0	0	1	1	2
Total	67	87	46	200

treatment and poor glycaemic control. The level of glycaemic control is a strong factor influencing the transition from normoalbuminuria to microalbuminuria.<sup>[8]</sup> A lower percentage of microalbumin was also seen in a number of studies by Chowta NK et al, Kanakmani J et al, Verghese A et al<sup>[8,10,14]</sup> while few studies by Maskari FA et al and Choo Kang E et al<sup>[11,15]</sup> showed a higher percentage of microalbuminuria. This variation can be due to difference in ethnic susceptibility to nephropathy.<sup>[16]</sup>

In the present study, maximum number of microalbumin positive patients (47.2%) had longer duration of diabetes (6-10 years) and higher HbA1c levels (8.1-10%) as compared to normoalbuminurics.

This is in accordance to other studies by Al Sheikh et al, Maiti A et al, Afkhami M et al.<sup>[12,17,18]</sup> This can be explained by the fact that higher HbA1c indicates persistent hyperglycaemia which leads to excessive protein glycosylation and subsequent deposition of these advanced glycated end products in the glomerulus. This results in glomerular hypertrophy and thickening of glomerular basement membrane, eventually leading to leakage of protein.<sup>[16]</sup> In contrast, in the study by Chowta N K et al<sup>[8]</sup> maximum number of microalbumin positive patients had duration of diabetes more than 15 years. This can again be due to variation in glycaemic controls of the cases studied. The causal risk factors for microalbumin are poor

glycaemic control and raised blood pressure.<sup>[15]</sup> Studies show that once microalbuminuria is present, it is most likely to progress to proteinuria in approximately 20-50% of the subjects and is accelerated by the presence of hypertension. Smoking has been described to be a major risk factor for the development of microalbuminuria. In our study, of the total microalbumin positive patients, 57(65.5%) were also hypertensive and 52 (59.7%) were smokers. This is in agreement with many earlier studies.<sup>[12,14,15,16,18]</sup>

Diabetes itself is not a high mortality condition, but is a major risk factor in other causes of death and has a high attributable burden of disability.<sup>[19]</sup> Diabetic nephropathy, a common sequelae of uncontrolled diabetes, greatly affects the quality of life and contributes to decreased life expectancy.<sup>[20]</sup>

Good glycaemic control is the key to preventing the onset of diabetic nephropathy. Duration of diabetes and level of glycaemic control has a significant contribution for the development of microalbuminuria by prolonged exposure to hyperglycaemia induced advanced glycosylation end products accumulation. The fact that presence of microalbumin can lead to adverse outcomes in diabetics, and the recognition that its risk factors and clinical course are amenable to treatment provide a genuine case for action.

## CONCLUSION:

Present study showed a positive correlation of microalbuminuria with duration of diabetes and level of glycaemic control (measured by HbA1c levels), which is in accordance with many previous reports. Also, presence of concomitant hypertension and smoking were important risk factors in early development of nephropathy. Therefore, regular screening for microalbuminuria in addition to continuous HbA1c estimation are important tools in the management of DM. Treatment of hypertension and aggressive lifestyle changes including measures to quit smoking should be given topmost priority.

The rising prevalence of diabetes can produce major constraints on health care budget. This urgently calls for not only good control of diabetes to prevent nephropathy but also to address the larger issue of primary prevention of diabetes, that is, reduction in the prevalence of diabetes itself by aggressive lifestyle modifications.

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