



Study of Relationship between HbA1c and Microalbuminuria of Diabetic Patients

Suman Kanti Chowdhury^{1*}, Shibani Datta², Muhammad Tanvir Mohith³, Soumitra Roy⁴,
Md. Jalal Hossain⁵, Nahida Zafrin⁶, Mahmudur Rahman⁷, Abdullah Md Abu Ayub Ansary⁸

¹Assistant Professor, Department of Medicine, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh.

Email ID: sumandmck55@gmail.com,

Orcid ID: 0000-0003-0906-2120.

²MD Thesis Part Student, Department of Paediatrics, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh.

Email ID: sdaky13@gmail.com

Orcid ID: 0000-0002-9713-8967.

³Assistant Professor, Department of Medicine, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh.

Email ID: drmohithtanvir@gmail.com

Orcid ID: 0000-0002-8458-2308.

⁴Assistant Professor, Department of Medicine, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh.

Email ID: dr.soumitra68@gmail.com

Orcid ID: 0000-0003-2186-9445.

⁵Assistant Professor, Department of Medicine, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh. Email ID: Jalalh1709@gmail.com,

Orcid ID: 0000-0002-9289-7606.

⁶Assistant Professor, Department of Medicine, Sylhet M A G Osmani Medical College, Sylhet, Bangladesh. Email ID: zafrin76@gmail.com,

Orcid ID: 0000-0001-7200-8616.

⁷Medical Officer, 250 Bed District Sadar Hospital, Sunamganj, Bangladesh,

Email ID: mahmudurocky6747@gmail.com ,

Orcid ID: 0000-0001-5082-3214.

⁸Junior Consultant (Surgery), OSD, DGHS, Dhaka, Bangladesh.

Email ID: ansary.mmc@gmail.com,

Orcid ID: 0000-0003-0011-302

*Corresponding author

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Abstract

Background: Globally, as of 2010, an estimated 285 million people had diabetes, with type 2 making up about 90% of the cases. Its incidence is estimated to almost double, by 2030. Diabetic nephropathy is a consequence of long standing diabetes. The prevalence of microalbuminuria predicts progression to diabetic nephropathy. Measurement of glycated hemoglobin (HbA1c) has become the preferred method of diagnosis as well as assessing long-term glycaemic control. The present study was conducted to determine the magnitude and prevalence of microalbuminuria in relation to HbA1c in a group of diabetic patients admitted in Comilla Medical College Hospital of Bangladesh. **Objectives:** The relationship between HbA1c and microalbuminuria of diabetic patients was assessed in a hospital-based cross-sectional study in a tertiary level hospital. **Material & Methods:** A hospital-based cross-sectional descriptive study was carried out in department of Medicine, Comilla Medical College Hospital from 1st July, 2011 to 30th June, 2012. One hundred known admitted diabetic patients with age 25–84 years were included in this study. **Results:** Microalbuminuria had a significant correlation with HbA1c ($p < 0.05$) ($r = 0.24$). Increasing HbA1c was associated with increasing microalbuminuria above optimal cut-off points of HbA1c 7%. The prevalence of microalbuminuria was 33.33 % at HbA1c (6.1–6.9)%, whereas it was 75% at HbA1c (7.1–7.9)%. Microalbuminuria was 38.74 ± 9.76 mg/gm ($p < 0.05$) at HbA1c $< 7\%$, whereas it was 65.86 ± 21.29 mg/gm ($p < 0.05$) at HbA1c $\geq 7\%$. **Conclusions:** The present study found an early onset of microalbuminuria in the selected community which could be due to poor glycaemic control (high HbA1c $\geq 7\%$) after excluding other causes of microalbuminuria. Screening for microalbuminuria and HbA1c test should be done in both newly and already diagnosed diabetic patients as an early marker of renal dysfunction and glycaemic control.

Keywords:- HbA1c & Microalbuminuria, ACR, Diabetes mellitus, Diabetic nephropathy.



INTRODUCTION

Diabetes mellitus (DM) has long been recognized as a major public health problem for its adverse health impact on individuals and for its economic burden on the health care system and the society at large.^[1] The International Diabetes Federation (IDF) in 2005 confirmed that diabetes is one of the most common non-communicable diseases globally and constitutes a major cause of death in most developed countries as well as many developing and newly industrialized countries.^[2] The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025.^[3] Patients with Type 2 diabetes often have a long asymptomatic period of hyperglycemia and many have complications at the time of diagnosis.^[4] Diabetic Nephropathy is a common consequence of longstanding diabetes mellitus. It is characterized by the presence of large amounts of urinary proteins, mostly albumin.^[5] Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycaemia.^[5] The laboratory test for early detection of diabetic nephropathy is the measurement of microalbumin in urine (microalbuminuria).^[6] There are many conditions causing microalbuminuria but hypertension and diabetes are the two biggest risk factors, besides old age and weight gain.^[7] Microalbuminuria predicts progression to diabetic nephropathy and cardiovascular diseases.^[8] Increased level of microalbuminuria is associated with increased risk of progressive kidney disease leading towards ESRD and cardiovascular morbidity and mortality in diabetic patients as reported in an earlier study.^[9] It is therefore most reliable as an

indicator of incipient diabetic nephropathy within the first 10 years of type 1 diabetes, when majority of the patients with microalbuminuria will progress to overt nephropathy within further 10 years.^[10] It is also a potentially useful marker of an increased risk of macrovascular disease.^[10] According to the American Diabetes Association (ADA), microalbuminuria, defined as urinary albumin excretion rate of 20 - 200 mcg/min on a timed specimen or 30 - 300 mg/gm in urinary ACR (albumin to creatinine ratio) from a spot collection (preferred method) without an alternative clinical explanation (such as urinary tract infection, heart failure or exercise in the past 48 hours) or urinary protein excretion rate of 30-300mg/day in a 24 hr collection.^[5,11,12] 24 hour collection of urine for quantitative assessment of urinary albumin excretion rate is currently considered the gold standard measurement of microalbuminuria.^[13] While many experts now support the use of random or first morning tests for urinary albumin to creatinine ratio as a convenient and accurate approach to screening patients.^[14] It must be measured on at least two of three measurements over a 2 to 3 month period.^[15] A repeat test should be done 3 to 6 months after the first positive test for microalbuminuria.^[16] Lastly, the test is inaccurate in a person with too much or too little muscle mass. This is due to the variation in creatinine level which is produced by the muscle.^[17] Some Individual level of microalbumin: a) 24h urine collection: 30 - 300 mg/24h,^[18] b) Short-time urine collection: 20 - 200 µg/min,^[18] c) Spot urine albumin sample: 30 - 300 mg/l of urine or µg/gm of urine,^[19] d) Spot urine albumin/creatinine ratio: i) Women: 3.5 - 25 or 35 mg/mmol or 30-400 mg/gm,^[19] ii) Men: 2.5 or 3.5 - 25 or 35 mg/mmol or 30 - 300



mg/gm.^[19] Current recommendations of the American Diabetes Association (ADA) are to screen for micro- albuminuria once a child is 10 years old and has Type 1 diabetes for 5 years and to screen children with Type 2 diabetes at diagnosis and annually thereafter.^[20] HbA1c is a measure of erythrocyte hemoglobin glycation, since erythrocytes have about 120 days life span, HbA1c reflects mean glycaemic value for the previous 3 months (weighted to the most recent months).^[21] Blood samples for HbA1c can be drawn whether or not the patient is fasting, as it does not reflect the patterns of glycaemia, the effects of food or exercise.^[22,23] Increased blood pressure, poor glycaemic control and smoking are some risk factors for microalbuminuria.^[10] Glycated hemoglobin (HbA1c) has proved to be a good indicator of long term glycaemic control and reflect the mean glucose value (MGV). A linear relationship with HbA1c, microalbuminuria and the incidence of diabetic nephropathy is known to exist.^[24] Significant predictors of microalbuminuria included HbA1c, creatinine, and the presence of hypertension.^[25] The present study was carried out in Comilla Medical College Hospital to assess the prevalence of microalbuminuria with relation to HbA1c. Microalbuminuria and HbA1c were measured as a marker of renal damage and glycaemic control respectively.

MATERIAL AND METHODS

This cross-sectional descriptive study was carried out in Comilla Medical College Hospital from 1st July, 2011 to 30th June, 2012. One hundred known diabetic patients (58 males and 42 females) with age range 25–84 years were included in this study. Patient complaints of symptoms suggesting diabetes with FBS \geq 7

mmol/L or RBS \geq 11.1 mmol/L or HbA1c \geq 6.5% & also known diabetic patients were included in this study. Prior to initiation of this study, the research protocol was approved by Bangladesh College of Physicians and Surgeons (BCPS). The aims and objectives of study were explained to the patients in easily understandable local language and then informed consent was taken from each case. It was assured that all were informed and records were kept confidential and the procedure will be helpful for both the physician and the patients in making rational approach of the case management. Data were collected by semi structured questionnaire by the investigator as soon as possible after the admission of the patient & were by face to face interview. Information was collected by taking medical history and clinical examination and subsequent laboratory investigations. Proper permission was taken from the concerned departments. Their informed written consent was taken in a consent form before collecting data. Fasting & two hours after breakfast venous blood and morning urine samples were collected for analysis of FBS, two hours postprandial glucose, creatinine, HbA1c and microalbuminuria. Those diabetic patients who are hypertensive & who had other causes of microalbuminuria like recent (24 hrs) vigorous exercise, fever, heart failure, urinary tract infection, prostatitis, menstruation etc. have not been included in the study. Purposive non-probability sampling technique was used for data collection. A structured questionnaire regarding the demographic data such as age, sex, duration of diabetes, height and body weight were measured. Blood pressure, smoking habit, family history of diabetes, renal disease and hypertension were recorded for

each patient. The body mass index (BMI) was calculated as weight (Kg) divided by height (m) squared.^[26] Venous blood was collected into two test tubes; with no anticoagulant for serum creatinine, and with Ethylene Diamine Tetra Acetic Acid (EDTA) for HbA1c. Morning urine sample was collected in a container (without preservative) for analysis of creatinine and microalbumin. HbA1c was estimated by Boronate affinity chromatography (HPLC) which separates total glycosylated hemoglobin by binding to solid-phase dihydroxyborate¹³ using Nycocard Immunoassay kit (USA). Serum creatinine was analysed by alkaline picrate, Jaffe's Method (Biocon Kit). Microalbumin was estimated by Sandwich Format Immunometric Assay method. After collection, all data were checked for inadequacy, irrelevancy and inconsistency. All data were recorded systemically in preformed data collection form and quantitative data were expressed as mean and standard deviation and qualitative data as frequency distribution and percentage. All statistical analysis was done by using SPSS version 13.0. Pearson's correlation

co-efficient test was applied to observe association of microalbuminuria with HbA1c. All p values <0.05 considered as statistically significant (95% confidence limit).

RESULTS

Among 100 known case of diabetes mellitus, 29 patients had HbA1c < 7 %, other 71 patients had HbA1c ≥ 7 %. Among 100 known case of diabetes mellitus, 47 patients had micro-albuminuria. The prevalence of micro-albuminuria was 33.33% with HbA1c 6.1-6.9 %, whereas it was 75% with HbA1c 7.0-7.9 % & 52.54 % with HbA1c ≥ 8.0 %. The micro-albuminuria of those participants with HbA1c level < 7%, was 38.74 ± 9.76 (mg/gm) (mean ± SD). On the other hand, it was 65.87 ± 21.29 (mg/gm) with HbA1c ≥ 7%. (p<0.05) Micro-albuminuria in diabetic patients has shown a significant correlation with HbA1c. (r=0.24) (p<0.05) Pearson's correlation co-efficient test was applied to observe association of micro-albuminuria with HbA1c.

Table 1: Distribution of the study participants' age by HbA1c cut-off points.

Age (years)	HbA1c <7% (n=29)	HbA1c ≥ 7% (n=71)
25-34	1(3.4)	3(4.2)
35-44	5(17.2)	17(23.9)
45-54	5(17.2)	22(30.9)
55-64	10(34.5)	16(22.54)
65-74	4(13.8)	10(14.1)
75-84	4(13.8)	3(4.2)

Table 2: Distribution of microalbuminuria with the study participants' age.

Age (years)	Risk group (n=100)	Prevalence of microalbuminuria(%) n=47
25-34	4	2(50)
35-44	22	11(50)
45-54	27	10(37.03)

55-64	26	13(50)
65-74	14	7(50)
75-84	7	4(57.14)

Table 3: Association between HbA1c and prevalence of microalbuminuria.

HbA1c (%)	Risk group (n=100)	Prevalence of Microalbuminuria (%) (n=47)
≤6.0	8	0(0)
6.1-6.9	21	7(33.33)
7.0-7.9	12	9(75)
≥8.0	59	31(52.54)

Table 4: Microalbuminuria of study participants by HbA1c cut-off points.

HbA1c(%)	Microalbuminuria (mg/gm)	p value*
<7 (n=29)	38.74 ± 9.76	<0.05*
≥ 7(n=71)	65.87 ± 21.29	<0.05*

Table 5: Correlation of microalbuminuria with HbA1c (n=100).

Microalbuminuria mg/gm (57.99 ± 18.01)	Pearson Correlation, r	1	0.24
	p- value		<0.05*
	n	100	100
HbA1c (%) (8.68 ± 2.26)	Pearson Correlation, r	0.24	1
	Sig. (2-tailed)	0	
	n	100	100

*highly significant

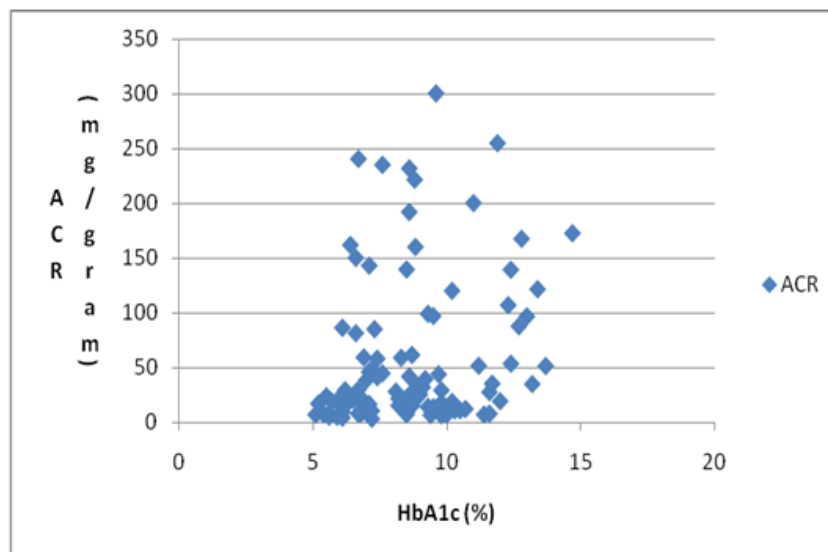


Figure 1: Relationship between HbA1c & microalbuminuria

DISCUSSION

From the hundred known diabetic patients studied, 58% were males and 42% were females with 64% having a family history of diabetes. Only 47% patients have micro- albuminuria, 25% were male & 22% were female. Fasting & two hours after breakfast plasma glucose of those participants with HbA1c < 7 were 7.13 ± 1.1 mmol/l & 8.37 ± 1.9 mmol/l respectively ($p < 0.001$). Those whom had HbA1c ≥ 7 , their FBS & two hours after breakfast plasma glucose were 11.1 ± 3.1 mmol/l & 14.48 ± 5.8 mmol/l respectively ($p < 0.001$). Serum creatinine of those with HbA1c < 7 were 0.96 ± 0.14 mg/dl ($p < 0.005$), whereas it was 1.15 ± 0.41 mg/dl with HbA1c $\geq 7\%$ ($p < 0.005$). Microalbuminuria of those patients with HbA1c < 7 were 38.74 ± 9.76 mg/gm ($p < 0.05$), whereas it was 65.87 ± 21.29 mg/gm with HbA1c ≥ 7 ($p < 0.05$). Micro-albuminuria in diabetic patients has shown a significant correlation with HbA1c ($p < 0.05$) ($r = 0.24$) [Table 5]. Here, Pearson's correlation co-efficient, r was 0.24, which is statistically significant.^[25,26,27,28] The prevalence of micro-albuminuria was 0% with HbA1c < 6%, whereas, it were 33.33% with HbA1c 6.1 - 6.9%, 75% with HbA1c 7.0 - 7.9%, 52.54% with HbA1c $\geq 8\%$. The present study was conducted on a group of 100 admitted diabetic patients in Comilla Medical College Hospital. 64% had family history of diabetes showing that Type 2 diabetes has a strong genetic component and parental history of diabetes is significantly associated with micro- albuminuria.^[29,30,31,32] Blood glucose is a continuous variable, rising and falling about 10-folds in people with diabetes.^[33] Earlier studies have reported glycosylated hemoglobin to be used as a diagnostic test for Type 2 Diabetes instead of

relying only on fasting blood glucose.^[33] In the present study as shown in [Table 5] microalbuminuria has a significant correlation with HbA1c ($p < 0.05$) ($r = 0.24$), similar to the study reported by Kassab.^[2] The complications of both Type 1 and 2 Diabetes do not develop or progress for 6-9 years when the average HbA1c level is kept at < 7%.^[34] The present study found an increase in HbA1c levels as indicated by a mean value of $8.68 \pm 2.26\%$. The population in the present study had an early onset of microalbuminuria, similar to that reported in an earlier study.^[35] Microalbuminuria is related to hyperglycemia and control of blood glucose level has been shown to prevent the development of nephropathy in Type 1 & 2 diabetes.^[36] The measurement of serum creatinine concentration is widely used clinically as an index of renal function.^[30] Serum creatinine concentration is widely affected by age, sex and body weight.^[30] Microalbuminuria and serum creatinine increase significantly in Type 2 diabetes as reported in an earlier study.^[30] Serum creatinine measurement is a convenient and inexpensive method of assessing renal function and a consistently elevated level indicates chronic kidney disease, but however some patients have a substantial decrease in glomerular filtration rate, while their serum creatinine concentration remains within the normal range and thus it is a poor screening test for mild kidney disease.^[37] A rapid decline in renal function can be predicted for patients having poor glycaemic control and micro- albuminuria.^[38,39] In adults, a diagnosis of microalbuminuria can precede Type 2 diabetes and is a component of the World Health Organization's definition of the metabolic syndrome.^[8] Minimizing microalbuminuria and having a tight glycaemic



control is an important treatment goal for patients with diabetes.^[40] HbA1c is an index of mean blood glucose in fasting and post-prandial state and is well established and widely used as a clinical measure of chronic glycaemia.^[41,42] Several studies indicate that HbA1c may show a glycaemic threshold with microvascular complications, suggesting it may additionally be useful as a diagnostic test for diabetes.^[43,44] In this hospital-based study of over 100 different aged individuals, we found a linear continuous relationship of HbA1c with microalbuminuria. We found no evidence for a threshold effect of HbA1c with microalbuminuria. It should be noted that the meta-analysis research group on the diagnosis of Diabetes using Glycated Hemoglobin levels has recommended an HbA1c cut-off point of $\geq 7.0\%$,^[45] which agrees well with our findings. The main strengths of our study are our precise estimation of microvascular endpoints collected using standardized protocols. In addition, HbA1c was measured according to internationally accepted standards. This is despite the many advantages to using HbA1c over other glycaemic measures such as less intra-individual variation,^[44] good ability to detect undiagnosed diabetes,^[46,47] and predict risk of developing microvascular complications both in type 1 and type 2 diabetes,^[48,49,50] and widespread acceptance as a common endpoint in clinical trials. However, high HbA1c levels were still positively associated with microvascular complications (e.g. those with an HbA1c level above 8% were fifty two times as likely to have microalbuminuria than those with an HbA1c below 6%). Despite the lack of an abrupt threshold, together with the

significant advantages of HbA1c over other glycaemic measures, for example, no requirement of fasting, less variability, consistent associations with micro- and macrovascular complications, and improved international standardization of measurement, our data support use of an HbA1c cut-off point between 6.6% and 7.0% in diagnosing diabetes.^[43,45,47,51] However, it will be important to examine the impact of using alternative tests of glycaemia or other diagnostic strategies, to identify those with microvascular complications. The public health impact of such strategies should also be carefully examined as the detection of these complications early will have an impact on healthcare resource use and the benefits of such early detection must be clearly delineated.

Limitations of the study

The study was conducted in a single hospital with small sample size. So, the results may not represent the whole community.

CONCLUSIONS

The screening for microalbuminuria is not yet consistently done in Bangladesh. Being a developing country; there is a dire need that microalbuminuria and HbA1c testing should be done in both, newly diagnosed as well as already diagnosed diabetic patients as an early marker of renal risk factor. Strict glycaemic control, having a healthy lifestyle, maintaining standard body weight is especially important for diabetic patients and for those with a family history of diabetes.^[5]

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