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Original Research Article

Role of HbA1c and Microalbumin as an Early Risk Marker of Diabetic Nephropathy

Prithvi Bahadur Shah[1], Arun Acharya[1], Sabina Shrestha[2], Sujan Shrestha[2]

[1]Department of Biochemistry, Norvic International Hospital, Kathmandu, Nepal
[2]Department of Pathology, Norvic International Hospital, Kathmandu, Nepal

Corresponding Author: Prithvi Bahadur Shah

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ABSTRACT

Aim: The aim of this study was to correlate glycosylated hemoglobin and urinary microalbumin and to compare urinary microalbumin level between different groups as an early risk marker of Diabetic nephropathy.
Methods: The study was conducted among six hundred individuals attending Out-patient department at Norvic International Hospital, Kathmandu, Nepal. Glycosylated hemoglobin was estimated using NycoCard Boronate affinity assay and urinary microalbumin level was estimated using NycoCard solid phase, sandwich-format Immunometric assay.
Results: Statistically significant differences were observed in mean value of glycosylated hemoglobin and urinary microalbumin in different groups i.e. Normal control, Poor control, and Bad Control. Mean value were (5.96 ± 0.38) (8.45 ± 5.24) (p=0.024); (7.5 ± 0.75) (25.81 ± 33.24) (p=0.002); (10.5 ± 1.24) (35.01 ± 46.36) (p= 0.000), respectively. After applying ANOVA in different groups of urinary microalbumin, mean differences were noted and were statistically significant ($p<0.05$).
Conclusion: This study suggests aggravating glycemic control triggers excretion of high urinary microalbumin.

Keywords: Glycosylated hemoglobin, urinary microalbumin, Diabetic Nephropathy, Glycemic control

INTRODUCTION

Diabetes mellitus is one of the common metabolic disorders characterized by chronic hyperglycemia and disturbances in carbohydrate, fat, and protein metabolism due to absolute or relative deficiency of insulin secretion or its action. People with diabetes mellitus are at an increased risk of chronic complications which affect many organ systems. Chronic complications of diabetes mellitus include microvascular complications (Nephropathy, Retinopathy, and Neuropathy) and macrovascular complications (coronary artery disease and cerebral vascular disease). [1]

Diabetes mellitus is among the leading causes of kidney failure [2] and screening for early signs of diabetes-related kidney disease (nephropathy) can prove to be cost effective for developing countries. [3] Diabetic Nephropathy is a common consequence of long standing diabetes mellitus. [4] The patho-physiologic basis for elevated urinary albumin excretion entails the binding of glucose to proteins resulting in excessive protein glycosylation with the buildup of advanced glycosylated end products (AGE's). This leads to deposition of AGE's on the glomerulus resulting in renal and glomerular hypertrophy, mesangial matrix accumulation and

thickening of glomerulus basement membrane. This abnormality permits the leakage of low molecular weight proteins (albumin). [5] This is the stage of microalbuminuria (Incipient Nephropathy) which could be reversible with good glycemic control. [6] According to a study by Tobe et al. reduction of HbA1c level by 1 % (i.e. 7.5% to 6.5%) also significantly decreases microalbumin level, even to normal. [7] Increased level of microalbuminuria is associated with increased risk of progressive kidney disease leading towards end stage renal disease (ESRD) and cardiovascular morbidity and mortality in diabetic patients as reported in an earlier study. [6]

Glycosylated hemoglobin reflects average plasma glucose over the period of 8-12 weeks. [8] Estimation of glycosylated hemoglobin can be performed at any time of the day and does not require any special preparations. This property has made it the preferred test for assessing glycemic control in people with diabetes mellitus. [9] Similarly, estimation of microalbumin in urine has been the gold standard for monitoring diabetic nephropathy progression. [10]

Therefore, this study was an effort to correlate HbA1c and urinary microalbumin levels and comparing the mean difference in microalbumin level based on severity of hyperglycemia.

MATERIALS AND METHODS

SUBJECTS SELECTION

The study was conducted among six hundred individuals attending Out-patient department at Norvic International Hospital, Kathmandu, Nepal. Out of six hundred, two hundred individuals were non diabetic (normal control) and four hundred individuals were known case of type 2 diabetes mellitus.

SAMPLE COLLECTION AND ESTIMATION

Blood samples were collected in EDTA (ethylene-diamine tetra acetic acid) vacutainer for HbA1c. It was estimated using NycoCard Boronate affinity assay. Similarly, morning urine samples were taken in a sterile container for micro albumin estimation using NycoCard solid phase, sandwich-format Immunometric assay.

INCLUSION CRITERIA

Individuals above 35 years of age were taken, out of which two hundred individual were known case of non-diabetic (Normal Control) and four hundred individuals were known case of diabetes mellitus.

EXCLUSION CRITERIA

Patients taking oral hypoglycemic drugs, chronic illness, diabetic nephropathy and pregnant females were excluded from the study.

STATISTICAL ANALYSIS

Statistical analyses were done by using Statistical Programme for Social Sciences (SPSS) version 16. Karl Pearson correlations were applied to correlate glycosylated hemoglobin with microalbumin and ANOVA was applied to compare mean differences in microalbumin level between three different groups. Statistical Significance was considered for all tests at ($p< 0.05$). Significance level represented as;

(*) less significant ($p<0.05$),
(**) significant ($p<0.01$) and
(***) highly significant ($p<0.001$)

RESULT

1. Tabular representations showing correlation of glycosylated hemoglobin level with urinary microalbumin level in different study groups; Normal Control, Poor Control, and Bad Control.

Table 1.1: Correlation of glycosylated hemoglobin with urinary microalbumin level in Normal Control using Karl Pearson's correlation.

Parameters	Mean ± SD	r- value	p-value
Glycosylated Hemoglobin	5.96 ± 0.38	0.16	0.024*
Microalbumin	8.45 ± 5.24		

P < 0.001 *** P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in mean value of

glycosylated hemoglobin (5.96 ± 0.38) and urinary microalbumin level (8.45 ± 5.24) in normal control. (p=0.024). After applying Pearson's correlation coefficient it was found to have positive correlation between Glycosylated hemoglobin and urinary microalbumin level (r = 0.16).

Table 1.2: Correlation of glycosylated hemoglobin with urinary microalbumin level in Poor Control using Karl Pearson's correlation.

Parameters	Mean ± SD	r- value	p-value
Glycosylated Hemoglobin	7.5 ± 0.75	0.22	0.002**
Microalbumin	25.81 ± 33.24		

P < 0.001 *** P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in mean value of glycosylated hemoglobin (7.5 ± 0.75) and urinary microalbumin level (25.81 ± 33.24) in Poor control. (p=0.002). After applying Pearson's correlation coefficient it was found to have positive correlation between Glycosylated hemoglobin and urinary microalbumin level (r = 0.22).

Table 1.3: Correlation of glycosylated hemoglobin with urinary microalbumin level in Bad Control using Karl Pearson's correlation.

Parameters	Mean ± SD	r-value	p-value
Glycosylated Hemoglobin	10.5 ± 1.24	0.397	0.000***
Microalbumin	35.01 ± 46.36		

P < 0.001 *** P < 0.01 ** P < 0.05 * NS = Non significant

Statistically significant differences were observed in mean value of glycosylated hemoglobin (10.5 ± 1.24) and urinary microalbumin level (35.01 ± 46.36) in Poor control. (p=0.000). After applying Pearson's correlation coefficient it was found to have positive correlation between Glycosylated hemoglobin and urinary microalbumin level (r = 0.397).

2. **Comparative study of urinary microalbumin level using ANOVA in different study groups; Normal control, Poor control, and Bad control.**

Samples		Mean Difference	p-value
Normal Control	Poor Control	-17.36	0.000
	Bad Control	-26.56	0.000
Poor Control	Normal Control	17.36	0.000
	Bad Control	-9.20	0.015
Bad Control	Normal Control	26.56	0.000
	Poor Control	9.20	0.015

Statistically significant differences in mean value of urinary microalbumin level were observed between three different groups after applying ANOVA, the results of mean difference and significance level is tabulated above. Mean differences were statistically significant at p <0.05.

DISCUSSION

Diabetes mellitus has become a major health problem in Nepal. According to World health organization (WHO), the percentage of diabetic patients has increased from 19.04% in 2002 to 25.9% in 2009 in Nepal. [11] Diabetes mellitus affects more than 436,000 people in Nepal, and this number is expected to rise to 1,328,000 by 2030. [12] Another study by WHO showed 3,224 deaths in Nepal in 2011 due to diabetes mellitus. [13] Diabetes mellitus has become a major risk factor for various microvascular complications such as nephropathy, neuropathy, and retinopathy. [14]

This study was conducted with the aim to correlate glycosylated hemoglobin (HbA1c) and urinary microalbumin level and to compare urinary microalbumin level between different groups as an early risk marker of nephropathy. For this purpose three different groups were defined based on aggravating glycemic control and were divided as follows:

1. Normal control (HbA1c < 6.5%)
2. Poor control group (HbA1c > 6.5% and < 9%)
3. Bad control group (HbA1c > 9%).

In this study mean value of glycosylated hemoglobin and urinary microalbumin in three different groups were (5.96 ± 0.38) (8.45 ± 5.24) (p=0.024); (7.5 ± 0.75) (25.81 ± 33.24) (p=0.002); (10.5 ± 1.24) (35.01 ± 46.36) (p= 0.000), respectively.

After applying Pearson correlation, it was found that there is a positive correlation between glycosylated hemoglobin and urinary microalbumin level in all these three groups. The r value of normal control was (r= 0.16), which is less statistically significant (p=0.0234).Similarly, when Pearson correlation was applied in Poor Control, positive correlation was found (r= 0.22), which is statistically significant (p=0.002). In third group when Pearson correlation was applied it also showed a positive correlation (r= 0.39), which is statistically highly significant as compared to other two groups (p=0.000). This is comparable to the study by Manjrekar et al. who has reported a gradual increase in microalbuminuria with increase in glycosylated hemoglobin. [15] Another study by Gupta et al. also reported a strong association of HbA1c level with urinary microalbuminuria excretion. [16]

For comparison of mean difference in urinary microalbumin level, ANOVA was applied. After applying ANOVA in different groups of urinary microalbumin, statistically significant differences were noted and were statistically significant ($p<0.05$). The mean difference in urinary microalbumin level of Normal control with Poor control and Bad control were -17.36 and -26.56 respectively. The mean difference in urinary microalbumin level of Poor control with Normal control and Bad control were 17.36 and -9.20 respectively. Similarly mean difference in urinary microalbumin level of Bad control with Normal control and Poor control were 26.56 and 9.20 respectively. From these findings, mean difference in urinary microalbumin level in different groups suggests aggravating glycemic control causes high excretion of urinary microalbumin. This is comparable to the study by Naveen et. al. where the elevated levels of microalbuminuria were seen in patients with poor glycemic control. [17] Also other studies have established the role of elevated levels of urinary microalbumin, which is an indicator of renal anomalies and diabetic nephropathy, is associated with poor glycemic control, evident by higher levels of glycosylated hemoglobin. [18]

Therefore this study suggests statistically significant positive correlation between glycosylated hemoglobin and urinary microalbumin level i.e. the increase in glycosylated hemoglobin level causes increased urinary microalbumin excretion. On the other hand, after applying ANOVA for comparison of mean value between different groups of urinary microalbumin level suggests high mean value of urinary microalbumin with aggravating glycemic control i.e. aggravating glycemic control causes high excretion of urinary microalbumin.

Findings of this study are limited as duration of diabetes and sex of the individuals were not considered. Hence, further studies need to be carried out for better interpretation of role of glycosylated hemoglobin in excretion of urinary microalbumin level in diabetes mellitus patients.

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