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Research Article

TO STUDY GLYCATED HEMOGLOBIN LEVEL AMONG DIABETES PATIENTS WITH CHRONIC KIDNEY DISEASE NOT ON HEMODIALYSIS

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ABSTRACT

The prevalence of Diabetes Mellitus (DM) has been increasing worldwide including India, both in rural and urban dwellers. Studies have shown prevalence rate of DM to be 2-4% in rural and 4-11% among urban dwellers. In parallel with increase in diabetes a dramatic increase in prevalence of diabetic nephropathy (DN) has been noted which is the single most common cause of End Stage Renal Disease. Glycated hemoglobin (HbA_1c) is currently accepted as the most diagnostic and prognostic biomarker of glycemic control in subjects with diabetes. However, in diabetic patients with CKD, HbA_1c may not be the most informative biomarker of glycemic index. Therefore objective of the study was to assess whether HbA_1c is a reliable indicator of diabetic status in CKD patients in the advancing stage. 120 diabetic subjects with CKD, who were not on maintenance hemodialysis, were included in the study. They were divided into 4 groups depending on eGFR: Group I (n=30, eGFR≥60ml/min/1.73m^2), Group II (n=30, eGFR:60-30ml/min/1.73m^2), Group III (n=30, eGFR: 30-15ml/min/1.73m^2), Group IV (n=30, eGFR :< 15ml/min/1.73m^2). Their blood samples were used to measure Glucose, HbA_1c, Serum creatinine and Hemoglobin. eGFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula using electronic abstraction. Analysis was done using SPSS 15. Kruskal-Wallis test was used for analysis. A significant correlation (p value of 0.00) was found between HbA_1c and eGFR. Also significant change is seen in hemoglobin with change in eGFR. Significantly lower HbA_1c values were seen in diabetic patients with advancing stage of CKD who were not on maintenance hemodialysis.
Key words: Chronic Kidney disease, Diabetes mellitus, Glycated hemoglobin, eGFR, Hemodialysis.

INTRODUCTION

Global incidence of diabetes mellitus (DM) is rising exponentially. In India, DM is gaining momentum. [1] Studies have shown prevalence rate of DM to be 2-4% in rural and 4-11% among urban dwellers.[2]India will become the "diabetes capital of world" by year 2025 as declared by WHO.[2] The number of diabetic persons is expected to increase from 3.1 million in year 2000 to 7.9 million by 2030. Chronic Kidney disease (CKD) is the major complication for individuals with diabetes. Therefore with increasing prevalence of diabetes, prevalence of CKD continues to rise.

Studies have shown that intensive glycemic control reduces the development of CKD in patients with type 2 diabetes.[3] Glycated hemoglobin (HbA_1c) is currently accepted as the most informative biomarker of glycemic control in subjects with diabetes and is highly prognostic for long term diabetic related complications.[1] HbA_1c represents the average of blood glucose concentration during preceding 3 months. HbA_1c of 6.5% was associated with 21% reduction in both new onset and worsening of nephropathy.[3]However its reliability is questioned in patients with diabetes and CKD. CKD may have significant impact on HbA_1c concentration and values may be falsely low or high. HbA_1c is also affected by factors like RBC lifespan, blood transfusions, hemolytic anemia, chronic malaria, etc. In patients with CKD on hemodialysis, RBC lifespan is reduced by 20-50% leading to reduced value forHbA_1c. Fewer studies are done to determine whether this applies to CKD patients not on

hemodialysis. Therefore, aim of this study was to assess whether HbA_1c is a reliable indicator for diabetes in CKD patients who are not on maintenance hemodialysis.

MATERIALS AND METHODS:

This cross-sectional study was conducted on 120 diabetic subjects with CKD who were not on maintenance hemodialysis. Subjects attending nephrology OPD in Sri Ramachandra Hospital were included in the study. Subjects with blood glucose concentration between 140-200mg/dL were included in the study. Informed consent was obtained from all subjects. Their blood samples were used to measure HbA_1c, Serum creatinine, Hemoglobin and eGFR. Subjects were divided into 4 groups depending on the severity of kidney disease. Severity of kidney disease was calculated using estimated glomerular filtration rate (eGFR). Group I consisted of 30 subjects with eGFR :>60ml/min/1.73m^2, Group II consisted of 30 subjects with eGFR: 60-30ml/min/1.73m^2, Group III consisted of 30 subjects with eGFR: 30-15ml/min/1.73m^2, and, Group IV consisted of 30 subjects with eGFR :<15 ml/min/1.73m^2. Renal transplant patients and severely ill patients were not included in the study. Glucose, hemoglobin, HbA_1c, and creatinine were measured by Hexokinase method, photometric method, High Performance Liquid Chromatography method (HPLC), and Jaffe's method respectively. eGFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula using electronic abstraction and values are expressed in ml/min/1.73m^2.Ethicalclearance was obtained before start of the study.

Statistical Analysis was done using SPSS 15. Kruskal-Wallis test was used for analysis. Statistical significance is tested by assuming mean ranks in the test. P values < 0.05 were considered significant.

RESULTS:

A significant correlation (p value of 0.00) was found between HbA_1c and eGFR as shown in Table 1. To eliminate the effects of changes in glycemic control on HbA_1c, subjects with postprandial blood glucose concentration between 140-200mg/dL were included in the study. Also significant change in hemoglobin was seen with change in eGFR (P= 0.00) as shown in Table 2.

Table 1: Comparison of HbA_1c between the groups.

Groups with eGFR (ml/min/ 1.73m^2)	**Mean HbA1c± SD**	**P value**
Group I (>60)	**8.4 ± 2.09**	**0.000**
Group II (60-30)	**8.0 ± 1.45**	
Group III (30-15)	**7.9 ± 0.95**	
Group IV(<15)	**6.3 ± 0.20**	

Table 2: Comparison of Hemoglobin between the groups.

Groups with eGFR ($ml/min/1.73m^2$)	Mean Hb± SD	P value
Group I (>60)	12.3± 2.3	0.000
Group II (60-30)	10.0± 1.4	
Group III (30-15)	10.6± 1.6	
Group IV(<15)	9.9± 1.1	

Fig 1: Mean Value of HbA1c

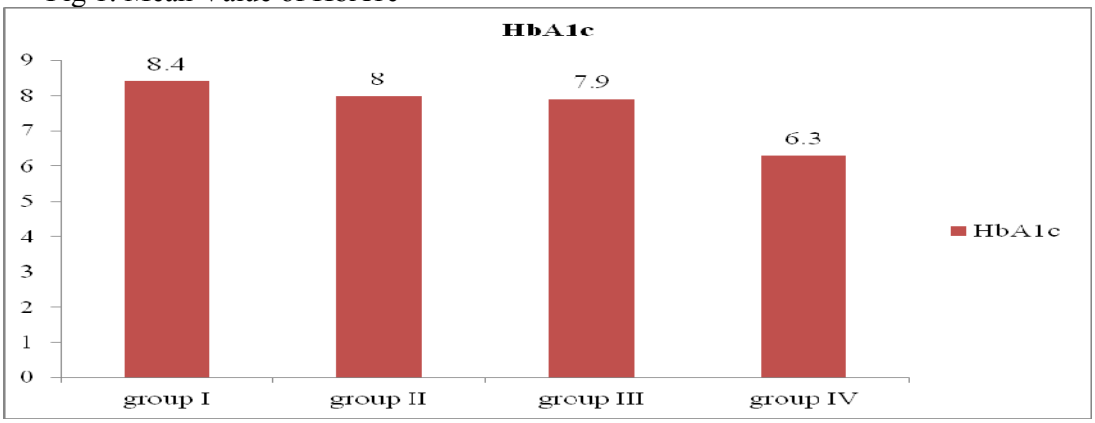
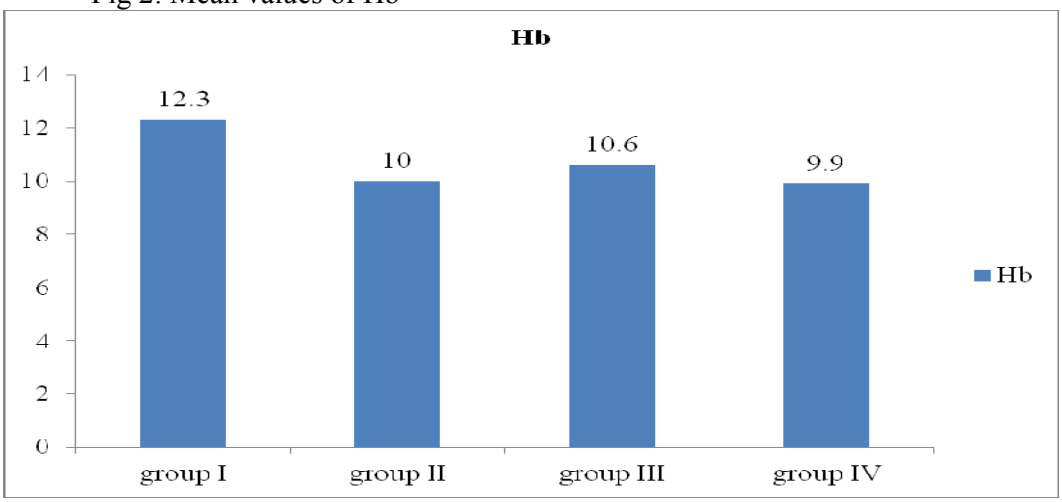


Fig 2: Mean values of Hb



DISCUSSION:

Diabetes is a major health problem among CKD patients and is the leading cause of end stage renal disease (ESRD). National kidney foundation has defined chronic kidney disease (CKD) as either kidney damage or glomerular filtration rate (GFR) below 60 ml/min/1.73m^2 for three or more months with or without evidence of kidney damage, irrespective of the cause.[4] Improved glycemic control slows the progression of CKD. HbA_1c is a good indicator of glycemic control in initial stages but, its reliability in advancing stage is questioned.

This study showed that HbA_1c values were significantly reduced in group 4 subjects compared to group 3 subjects (Table1). To eliminate influence of differences in glycemic control among four groups on HbA_1c, only patients with postprandial glucose between 140-200mg/dL were included. Therefore lower HbA_1c in group 4 were not due to differences of severity of diabetes. Low HbA_1c in advanced stages of CKD is due to reduced lifespan of erythrocytes. This leads to shorter exposure of erythrocytes to chemically bond with glucose.[12]

Subjects in group 2 (with eGFR 60-30ml/min/1.73m^2) have relatively preserved kidney function. In these subjects not much change is required in hyperglycemia treatment. Subjects in group 3 and group 4 (eGFR 30-15ml/min/1.73m^2 and <15ml/min/1.73m^{2}respectively) have reduced kidney function leading to altered glucose metabolism and pharmacokinetics placing them at risk of both hyperglycemia and hypoglycemia.[13] Falsely increased HbA_1c is due to carbamylation of erythrocytes interfering with HbA_1c. Falsely decreased HbA_1c is due to increased erythrocyte turnover (reduced lifespan) or because of erythropoietin use.[13]

Thus HbA_1c performs well with milder CKD compared to severe forms of CKD. The lack of reliability of HbA_1c in patients with diabetes and renal disease has led to further research in this area. Serum Glycated albumin (GA) is now under investigation and researchers have hypothesized it to be an alternative marker for glycemic control in patients with diabetes, including those with ESRD.[6] This points to use of alternative methods for measuring glycemic control such as capillary glucose testing and continuous glucose monitoring and therapy should not be based on the HbA1c value alone.[8] Kenji Shima et al similarly found that diabetic patients with CKD not on hemodialysis had significantly lower values of HbA_1c compared with diabetic patients without renal dysfunction.[14] Fredriek E Vos et al in their study found that HbA_1c significantly underestimates glycemic control in patients with stages 4 and 5 of CKD.[1]

Accuracy of the HbA_1c assay in dialysis patients is impacted by uremia. HbA_1c is also low in patients on peritoneal dialysis and CKD stage 5 who are not on maintenance hemodialysis. The HbA_1c levels are also theoretically suppressed by the resulting anemia associated with the shorter life span of erythrocytes.[6]

We also found significant change in haemoglobin concentrations (Table2) with change in eGFR. Haemoglobin was found to be significantly reduced in group 4 subjects compared to group 1 subjects. CKD is associated with erythropoietin (EPO) deficiency and normochromic normocytic anemia. EPO deficiency is because of transformation of peritubular fibroblasts into myofibroblasts. Therefore haemoglobin cannot be produced. In early stages of CKD, there is inverse relation between Hb and EPO release. Increase EPO compensates for decrease in Hb. As disease advances a direct relation is seen between Hb and EPO. Therefore in advanced stages of renal failure HbA_1c levels may not predict the glycemic status of individual.

Our study shows a moderate significant relationship between change in HbA_1c and hemoglobin concentration values; thus showing that change in Hb is not associated with change in HbA_1c. Our study is limited because of small sample size. However a significant

difference in HbA1c is seen with fall in eGFR. Further studies will be necessary with large sample size.

In summary, this study showed significantly lower values of HbA1c among diabetes with CKD not on maintenance hemodialysis. Therefore, HbA_1c should not be used alone for diagnosis of severity of diabetes in patients with ESRD.

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REFERENCES:

1. Frederiek E. Vos, John B. Schollum and Robert J. Walker. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. NDT Plus 20114: 368–375
2. Carl A. Burtis, Edward R Ashwood, David E Bruns. Tietz textbook of clinical chemistry and molecular diagnostics. Fourth Edition.2008. Pg: 1671- 1725
3. William t. Cefalu. A Critical Evaluation of Glycated Protein Parameters in Advanced Nephropathy: A matter of Life or Death. Diabetes care. Volume 35: 1621-1624.
4. Melissa L. Adams. Is HbA1c A Reliable Test In Patients With Diabetes And Renal Disease? 2009. Volume 22 - Issue 8
5. Freedman B.I., Shihabi Z.K.,Andries L, Cardona C.Y., Peacock T.P., Byers J.R., Russell G.B., Stratta R.J.,Bleyer A.J.2010. Relationship between Assays of Glycemia in Diabetic Subjects with Advanced Chronic Kidney Disease. Am J Nephrol; 31 : 375–379
6. Tom Moberly. Hba1c is unreliable in CKD patients on anaemia therapy.2010.
7. Frederiek E Vos, John B Schollum, Carolyn V Coulter, Patrick J Manning, Stephen B Duffull, Robert J Walker. Assessment of markers of glycaemic control in diabetic patients with chronic kidney disease using continuous glucose monitoring. Nephrology. 2011;17: 182-188.
8. InbaM, Okuno S, Kumeda Y.. Glycated albumin is a better glycemic indicator than Glycated hemoglobin values in hemodialysis patients with diabetes: Effect of anemia& erythropoietin injection. J Am SocNephrol. 2007;18: 896-903
9. Peacock T P, Shihabi Z K, Bleyer A J. Comparison of Glycated albumin and HbA_1c levels in diabetic subjects on hemodialysis. Kidney int. 2008; 73: 1062- 1068
10. Noah D.Lubowsky, Richard Siegel, and Anastassios G. Pittas. Management of Glycemia in Patients With Diabetes Mellitus and CKD. American Journal of Kidney Diseases. 2007;865-879