

Usefulness of Estimation of Glycated Albumin and Glycosylated Haemoglobin in Indian Diabetic Chronic Kidney Disease Patients

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Abstract

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BACKGROUND: It is unclear whether the glycated hemoglobin (HbA1c) assay accurately reflects glycemic control in patients with chronic kidney disease (CKD).

AIM: To evaluate the usefulness of glycated albumin (GA) in diabetic CKD population with reference to glycemic control in comparison to HbA1c.

MATERIALS AND METHODS: Totally 194 Diabetic CKD (Male: 126, Female: 68) patients who attended a private nephrology clinic, were taken for the study. The age ranged between 18 to 87 years. Blood samples were collected in fasting state in all the patients and all biochemical estimations were done using fully automated analyzer.

RESULTS: The mean estimated GFR levels were 82.47, 44.32, 24.13 and 10 ml/min/1.73 m² in Group I, II, III & IV respectively. The GA levels were significantly increased when the eGFR levels have been decreased. Also the GA: HbA1c ratio differed significantly when compared between the groups I & II, I & III and group I & IV of CKD patients.

CONCLUSION: GA estimation is a useful marker in assessment of short term glycemic control in stage III & IV (< 30 ml/min/1.73m²) diabetic CKD patients. GA: HbA1c ratio if routinely done may also become a useful marker in Diabetic CKD population in future.

Introduction

Glycosylated hemoglobin (HbA1c) is most often used as an intermediate indicator for blood glucose control in diabetics, and the Diabetes Control and Complications Trial (DCCT) [1], United Kingdom Prospective Diabetes Study (UKPDS) [2] and Kumamoto Study [3] have greatly valued HbA1c as an indicator for blood glucose control. However, HbA1c levels are influenced by other factors in addition to blood glucose. Of these other factors, the life span of erythrocytes is particularly important. The HbA1c assay provides falsely low readings in diabetic patients with end-stage renal disease (ESRD) [4–6]. This phenomenon likely relates to the shortened red blood cell survival observed in ESRD, with reduced time available for glucose and hemoglobin to chemically interact [7]. In contrast, the glycated albumin (GA) assay appears to more accurately

reflect recent glycemic control in diabetic patients with ESRD who are on dialysis [4–6]. The GA assay mainly reflects serum glucose control over the preceding 17-day period (maximum 60 days), relative to the HbA1c assay which predominantly reflects glycemic control over the preceding 30 days (maximum 120 days).

It is unclear whether the HbA1c assay accurately reflects glycemic control in patients with moderate and advanced stages of chronic kidney disease (CKD), particularly those with stages 3,4 and stage 5 CKD [8]. This is an important concern since HbA1c has recently been recommended as a screening test for diabetes mellitus, the number of patients with CKD far exceeds those with ESRD and improved glucose control reduces progression of CKD, benefits diabetic retinal disease [9-11] and possibly benefits atherosclerosis as well [12].

As on date, no studies have been conducted to establish the correlation between glucose and glycemic control markers so as to predict the most accurately representing biomarker in Indian patients with CKD stages 3, 4 and 5. Hence, the present study undertaken to determine whether GA is a better biomarker than HbA1c for glycemic control in Indian patients with CKD stages 3, 4 and 5.

Materials and Methods

Patients

Totally 194 CKD (Male: 126, Female: 68) patients who attended a private nephrology OPD clinic were taken for the study. The age ranged between 18 and 87 years. The duration of diabetes mellitus was 6-20 years. The patients were categorized into four groups according to GFR estimation by MDRD formula, Group I > 60 ml/min/1.73 m² (n: 46) (CKD stage 2), Group II 30-59 ml/min/1.73 m² (n: 62) (CKD stage 3), Group III 16-29 ml/min/1.73 m² (n: 46) (CKD stage 4) & Group IV >15 ml/min/1.73 m² (n: 40) (CKD stage 5). Subjects who received pancreas transplants, history of suggestive hypoglycemia, recent hospitalization, presence of sepsis, those with ESRD currently receiving any form of dialysis therapy were excluded. All the patients included in the study were on self-monitoring of glucose at home, done thrice in a week, as fasting, 2hr post lunch and pre dinner. In the present study, we have taken into account the average blood glucose in the previous one month period for those who have completed one month of self-monitoring. Measurement of GA and HbA1c levels were determined in all study subjects. Informed and written consent were obtained from all the patients. Estimated GFR was calculated using the 4-variable MDRD equation. Statistical analysis was done by using Medcalc statistical software.

GA and HbA1c Assays

Serum albumin concentrations were measured using the bromocresol purple (BCP) assay (modified BCP method using the Lucica (GA-L kit; Asahi Kasei Pharma Corp., Tokyo, Japan). GA was measured using the Lucica GA-L kit (Asahi Kasei Pharma Corp.) on serum samples. This kit uses an enzymatic method that converts GA to glycated amino

acids. The glycated amino acids are then oxidized with formation of hydrogen peroxide, which is coupled to a dye yielding a purple-blue color. The GA and HbA1c analysis were performed on the automated 'Biosystems A15' instrument (Biosystems, USA) and HbA1C by Bio RadD10. To measure the percent of GA, the conversion formula supplied with the Lucica GA-L assay kit was applied to all study subjects; the formula used to calculate percent of GA is $[(GA \text{ concentration}/\text{albumin})/1.14 \times 100] + 2.9$. The blood glucose estimation done by glucose oxidase method [13] and serum creatinine by alkaline picrate method [14]. GA to HbA1C ratio accurately compares the two parameters, more than individual comparison.

Results

Blood samples were collected from 194 diabetic patients with various stages of GFR. The clinical characteristics of the four groups are summarized in the table. The mean estimated GFR levels were 82.47, 44.32, 24.13 and 10 ml/min/1.73 m² in Group I, II, III & IV respectively. Mean age & sex in various groups as Group I (49.13± 12.64) (N: 46 M:30 F:16), Group II (58.92 ± 7.55) (N: 62 M:38 F:24), Group III (57.26 ± 10.06) (N: 46 M:28 F: 18)and Group IV (54.9 ± 9.16) (N: 40 M: 32 F: 8). The mean blood urea of groups I,II,III and IV were 24.17± 5.64,56.21 ± 18.72, 80.30 ± 22.56 and 109.25 ± 54.05 respectively. The mean ± SD of serum creatinine levels were 0.96 ± 0.17, 2.90±0.19, 3.66±0.54 and 5.10±1.73 in group I, II, III and IV respectively. The average total protein (Albumin, globulin) of group I,II , III and IV were 7.29 (3.60, 3.69), 6.57 (3.12, 3.45), 6.87 (3.17, 3.70) and 6.54 (3.1, 3.44) respectively.

Mean (SD) HbA1c (%) and GA (%) concentrations were 9.96 (3.63) and 27.84 (13.51) in group I, 9.68 (1.43) and 38.76 (6.73) in group II, 8.46 (1.96) and 43.28 (14.46) in group III & 8.63 (1.89) and 49.84 (8.77) in group IV. GA: HbA1c ratios for all the groups were studied. This ratio helps to compare the two parameters among the various groups. The GA: HbA1c ratio differed significantly when compared between groups I &II, I &III and I & IV of CKD patients ($P = <0.0001$, $P = <0.0001$ & $P = <0.0001$ respectively).

Table 1: Clinical characteristics among four groups.

Group	1 > 60 ml/min/1.73m ² (n= 46)	2 30 – 59 ml/min/1.73m ² (n= 62)	3 16 – 29 ml/min/1.73m ² (n= 46)	4 < 15 ml/min/1.73m ² (n= 40)	1&2 P Value	1&3 P Value	1&4 P Value
Age	49.13 ± 12.64	58.93 ± 7.56	57.26 ± 10.07	54.9 ± 9.16	<0.0001	0.0010	0.0190
S. Creatinine, mg/dl	0.965 ± 0.17	2.90 ± 0.19	3.66 ± 0.54	5.10 ± 1.73	<0.0001	<0.0001	<0.0001
B. Glucose, mg/dl	248.1 ± 100.9	284.9 ± 71.35	301 ± 96.72	398.9 ± 114.6	0.8475	0.0246	0.002
HbA1c	9.96 ± 3.63	9.68 ± 1.43	8.46 ± 1.96	8.63 ± 1.89	0.0130	0.0156	0.0402
GA %	27.84 ± 13.51	38.76 ± 6.73	43.28 ± 14.46	49.84 ± 8.77	<0.0001	<0.0001	<0.0001
GA: HbA1c %	2.79 ± 0.79	4 ± 1.18	5.11 ± 1.14	5.77 ± 0.69	<0.0001	<0.0001	<0.0001
Glucose/GA	8.91 ± 6.18	7.35 ± 2.96	6.95 ± 6.40	7.76 ± 2.38	0.0850	0.1386	0.2715
Glucose/HbA1c	24.90 ± 8.81	29.43 ± 7.61	35.57 ± 10.94	37.31 ± 11.19	0.0051	<0.0001	<0.0001
GFR	82.47 ± 14.46	44.32 ± 7.89	24.13 ± 3.74	10 ± 2.90	<0.0001	<0.0001	<0.0001

For group II, III and IV, HbA1c and estimated GFR levels were significantly decreased and the creatinine & blood glucose levels were increased significantly when compared with the group I. The GA levels were significantly increased when the eGFR have been decreased.

Discussion

To the best of our knowledge, there are no reports available in Indian population comparing glycosylated hemoglobin with glycosylated albumin in various stages of chronic kidney disease. The regular monitoring of the diabetes is highly warranted to all the diabetic patients, especially patients with chronic kidney disease to avoid the progression of CKD to ESRD. The HbA1c assay has marked limitations in diabetic patients with ESRD, with significant underestimation of recent glycemic control compared to blood glucose and the GA assay [4–6]. It is unclear whether the HbA1c assay accurately reflects glycemic control in patients with moderate and advanced stages of chronic kidney disease (CKD). In the present study it has been clearly observed that HbA1c is not an accurate marker in the moderate and severe stages of chronic kidney disease and the same be replaced by GA as an alternative marker and similar observation was noted in the previous study conducted on samples of New Zealand population [15].

The present analyses reiterate the earlier observations by demonstrating that the GA: HbA1c ratio differs among patients with stages 3, 4 or 5 CKD. This suggests that the HbA1c assay results are falsely reduced in stages 3, 4 & 5 CKD patients. It has been reported in earlier study [16] that HbA1c assay may be less accurate in diabetic subjects with advanced CKD. The present study also confirms that the estimation of HbA1c in diabetic CKD patients (stages 3, 4 & 5) may lead to underestimate the glycemic control.

GA/HbA1c ratio is significantly higher when blood glucose increased [17]. The present study also observed higher GA/HbA1c ratio when the blood glucose increased. In the present study it is observed that HbA1c does not accurately predict the glycemic control with worsening kidney function. It is found in the present study that GA is a better marker for glycemic control in severe kidney disease (CKD stages 3, 4 and 5) than in early phases of decreasing GFR.

Remarkably, GA is not only a marker for glycemic control in CKD but also has a biological impact in progression of the disease. Elevated levels of GA induce the metabolic disorders like retinopathy, nephropathy, neuropathy and coronary artery disease [18]. Therefore, whether the GA/HbA1c ratio reflects

insulin secretory function or elevated levels of GA persuade insulin secretory dysfunction needs more attention.

In conclusion, GA is a better marker for detecting short term glycemic control in Indian patients with CKD stages 4 & 5 (Group III & IV) and the assessment of glycemic control by HbA1c in those patients might lead to underestimation. The GA/HbA1c ratio has been directly proportional to the glucose levels in all stages of CKD. As the population studied in the present study is relatively small and large population studies are needed to confirm our results.

References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med.* 1993; 329 : 977-986.
2. UK Prospective Diabetes Group: Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998 ; 352 : 837-853.
3. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M : Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus-a randomized prospective 6-year study. *Diab Res Clin Pract.* 1995;28 : 103-117.
4. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, Okamura M, Okada S, Yamakawa T, Ishimura E, Nishizawa Y: Gly-cated albumin is a better glycemic indicator than glycosylated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. *J Am Soc Nephrol.* 2007;18:896–903.
5. Peacock TP, Shihabi ZK, Bleyer AJ, Dolbare EL, Byers JR, Knovich MA, Calles-Escandon J, Russell GB, Freedman BI: Comparison of glycosylated albumin and hemoglobin A(1c) levels in diabetic subjects on hemodialysis. *Kidney Int.* 2008; 73: 1062–1068.
6. Freedman BI, Shenoy RN, Planer JA, Clay KD, Shihabi ZK, Burkart JM, Cardona CY, Andries L, Peacock TP, Sabio H, Byers JR, Russell GB, Bleyer AJ: Comparison of glycosylated albumin and hemoglobin A1c concentrations in diabetic subjects on peritoneal and hemodialysis. *Perit Dial Int.* 2010; 30:72–79.
7. Viljoen M, de Oliveira AA, Milne FJ: Physical properties of the red blood cells in chronic renal failure. *Nephron.* 1991; 59:271–278.
8. Abe M, Matsumoto K: Glycosylated hemoglobin or glycosylated albumin for assessment of glycemic control in hemodialysis patients with diabetes? *Nat Clin Pract Nephrol.* 2008; 4:482–483.
9. American Diabetes Association: Standards of medical care in diabetes – 2009. *Diabetes Care.* 2009; 32(Suppl 1):S13–S61.
10. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000; 321: 405–412.

11. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR: Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003; 63:225–232.
12. Yamada S, Inaba M, Shidara K, Okada S, Emoto M, Ishimura E, Nishizawa Y: Association of glycated albumin, but not glycated hemoglobin, with peripheral vascular calcification in hemodialysis patients with type 2 diabetes. *Life Sci.* 2008; 83:516–519.
13. Trinder P. Determination of glucose in blood using glucose oxidase with alternate oxygen acceptor. *Ann Clin Biochem.* 1969;6:24.
14. Jaffe M. Über den Nieseschlag, Welchen pikrinsaure in normalen harn erzeugt und über eine neue reaktion des kreatinins. *Z Physiol Chem.* 1886; 10 : 391-400.
15. Frederik 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 disease using continuous glucose monitoring. *Nephrology.* 2012;17:182-188.
16. Barry I. Freedman, Zak K. Shihabi, Lilian Andries, Cesar Y. Cardona, Todd P. Peacock, Joyce R. Byers, Gregory B. Russell, Robert J. Stratta, Anthony J. Bleyer. Relationship between Assays of Glycemia in Diabetic Subjects with Advanced Chronic Kidney Disease. *Am J Nephrol.* 2010;31:375–379.
17. Takahashi S, Uchino H, Shimizu T, Kanazawa A, Tamura Y, Sakai K, Watada H, Hirose T, Kawamori R, Tanaka Y. Comparison of glycated albumin and glycated hemoglobin in type 2 diabetic patients: usefulness of GA for evaluation of short-term changes in glycemic control. *Endocrine Journal.* 2007;54 (1): 139-144.
18. Rondeau P, Bourdon E. The glycation of albumin: structural and functional impacts. *Biochimie.* 2011; 93:645-658.