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Comparison of glycated albumin and glycated Hemoglobin in type 2 diabetic patients with end-stage of renal disease

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Abstract

Background: Various analytes are used to assess glycemic control in laboratory medicine. Glucose measurements show current glucose levels, but sample stability can be influenced by diet and stress. Hemoglobin A1c (HbA1c) is the best marker for long-term control but can be affected by elevated urea levels. This study compared glycated albumin (GA) and HbA1c in diabetic patients undergoing hemodialysis.

Methods: A comparative cross-sectional study was conducted with a sample size of 280 volunteers. Among these, there were 115 diabetic patients with end-stage renal disease (ESRD), 95 diabetic patients without ESRD, and 75 non-diabetic patients with ESRD. Laboratory measurements included HbA1c, GA, urea, and creatinine, assessed using standard laboratory techniques. Data analysis was carried out using SPSS statistical software.

Results: Levels of HbA1c were lower in diabetic patients with ESRD compared to diabetic patients without ESRD. In contrast, GA levels were higher in diabetics with ESRD. A significant negative association was observed between HbA1c levels and urea levels. However, creatinine levels were not associated with either HbA1c or GA.

Conclusion: The estimation of glycated hemoglobin levels can be affected by high blood urea. Therefore, GA may be a better glycemic indicator for diabetic patients with ESRD.

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Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by the inability to maintain blood glucose levels (1). DM is the primary cause of chronic kidney disease (CKD) and a strong risk factor for end-stage renal disease (ESRD) and cardiovascular disease (2). The progression to ESRD is marked by a significant decrease in the glomerular filtration rate. Patients may present with various symptoms related to the underlying disorder, including oliguria, edema, and azotemia (3). Supportive renal dialysis may be required to sustain patients until the inflammation subsides (4). The estimation of blood glucose is no longer widely used as a monitoring test due to a lack of sample stability. In addition, glucose concentrations are influenced by multiple factors, including diet and psychological stress, and only reflect the glucose level at the time of collection (5). Fructosamine is the generic name for plasma protein ketoamines (6). This term refers to the ketoamine rearrangement product formed by the interaction of glucose with the E-amino group on lysine residues of albumin (7). Measurements of fructosamine can serve as an index of average blood glucose concentration over an intermediate period (8). Since all glycated serum proteins are considered fructosamine and albumin is the most abundant serum protein, fructosamine measurement is predominantly a measure of glycated albumin (GA) (9). Glycosylated hemoglobin refers to a hemoglobin compound formed when glucose reacts with the amino group of hemoglobin (10). The glucose molecule attaches non-enzymatically to hemoglobin, forming a ketoamine. The rate of this reaction is directly proportional to plasma glucose concentrations (11). Given that the average lifespan of a red blood cell is approximately 120 days, the glycosylated hemoglobin level at any point reflects the average blood glucose level over the previous 2 to 3 months (12).

Some factors may affect HbA1c levels, preventing them from accurately reflecting real glycemic control (13). These factors include variants of hemoglobin that may shorten the lifespan of erythrocytes and the presence of interfering substances, such as certain drugs (14). To manage anemia, a common complication of CKD, patients are treated with erythropoietin and iron, which stimulate the production of new erythrocytes. As a result, HbA1c levels may be lower than expected. Furthermore, the presence of uremia, common in patients with CKD, can interfere with HbA1c measurements performed using methods in some clinical laboratories in Sudan. This interference is directly related to the carbamylation of hemoglobin (15). Therefore, alternative tests for monitoring glycemia have been proposed for glycemic control in CKD patients (8). Based on this, the aim of this research is to estimate GA concentration and HbA1c levels in diabetic Sudanese patients with ESRD.

Methods

This cross-sectional comparative study was conducted to estimate GA concentrations and HbA1c levels in diabetic Sudanese patients with ESRD from March to June 2021. A total of 285 volunteers were included in the study, divided into three groups:

1. **DM with ESRD:** 115 DM patients with ESRD who were undergoing dialysis, with a mean age of 48 years.
2. **DM without ESRD:** 95 DM patients without ESRD, matched with the first group in terms of gender and age.
3. **ESRD without DM:** 75 non-diabetic patients with ESRD.

The exclusion criteria eliminated any patients with types of anemia that could affect HbA1c levels.

The study was approved by the Scientific and Ethical Committee of the Clinical Chemistry Department, Faculty of Medical Laboratory Science, Al-Neelain University (IRB Serial No: NU-IRB-17-10-10). Verbal consent was obtained from the participants, ensuring their acceptance to participate in the study and reassuring them of confidentiality. Before specimen collection, donors were informed that their samples would be used for research purposes.

Data was collected using a structured interview questionnaire designed to gather and maintain all relevant information pertaining to each case examined.

A volume of approximately 5.0 ml of venous blood was obtained from each participant. The collection was performed under aseptic conditions, with 2.5 ml transferred into sterile EDTA tubes for the measurement of HbA1c, while the remaining 2.5 ml was placed in sterile plain tubes to facilitate serum extraction for the assessment of GA. The GA levels were determined using the enzyme-linked immunosorbent assay (ELISA) method provided by CUSABIO (USA, Catalog Number CSB-E09599h). This assay employs a competitive inhibition enzyme immunoassay technique. The microtiter plate provided in this kit is pre-coated with GA. Standards or samples are added to the appropriate microtiter plate wells, along with a Horseradish Peroxidase (HRP)-conjugated antibody preparation specific for GA. A competitive inhibition reaction occurs between the pre-coated GA and the GA in the samples. A substrate solution is then added to the wells, resulting in color development inversely proportional to the amount of GA in the samples. The reaction is stopped, and the intensity of the developed color is measured.

The assessment of HbA1c was conducted using a sandwich ELISA method, employing the Double Antibody kit from Fine Test Company (China, Catalogue No.: ER1030). This kit operates on the principle of sandwich ELISA technology, wherein a capture antibody is pre-coated onto 96-well plates, and a biotin-conjugated antibody functions as the detection antibody. The standards, test samples, and biotin-conjugated detection antibody were sequentially added to the wells and then washed with a wash buffer. HRP-Streptavidin was added, and unbound conjugates were removed through additional washes with the wash buffer. Tetramethylbenzidine substrate was used to visualize the HRP enzymatic reaction. Tetramethylbenzidine was catalyzed by HRP to produce a blue-colored product, which turned yellow upon the addition of an acidic stop solution. The intensity of the yellow color is proportional to the target amount of HbA1c captured in the plate. The optical density absorbance was measured at 450 nm using a microplate reader, and the target concentration was calculated accordingly.

The precision and accuracy of all methods used in this study were verified using a commercially prepared control sample before applying the test samples.

Data obtained from this study were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.

Results

The demographic and clinical characteristics of the study population are summarized in Table 1, which compares diabetic patients with ESRD (DM with ESRD) to those without ESRD (DM without ESRD). The analysis included 115 patients in the DM with ESRD group and 95 patients in the DM without ESRD group. The mean age was 46 years for the DM with ESRD group and 49 years for the DM without ESRD group (p = 0.45), with similar percentages of females: 41% in the DM with ESRD group and 42% in the DM without ESRD group (p = 0.52). The duration of diabetes was slightly longer among patients with ESRD (21 years) compared to those without ESRD (19 years), though the difference was not statistically significant (p = 0.24). For patients with ESRD, the mean duration of ESRD was 7.2 years.

A comparison of various biochemical parameters between patients with DM and those with ESRD who do not have DM is presented in Table 2. The DM group had a higher fasting blood glucose (FBG) level (185 ± 7.5 mg/dl) than the ESRD group (79.1 ± 5.6 mg/dl; p = 0.0001). HbA1c was also significantly elevated in the DM group (7.1 ± 1.2%) compared to the ESRD group (3.1 ± 0.70%; p = 0.0001), as was GA, with levels of 15.5 ± 1.8% in DM patients versus 10.9 ± 2.16% in ESRD patients without DM (p = 0.001).

A separate group of 75 ESRD patients without DM was also included for comparison. Across the three groups (DM with ESRD, DM without ESRD, and ESRD without DM), the mean ages and gender distributions were matched, with no significant differences observed in age or percentage of females.

The correlations among serum creatinine, blood urea, and FBG with HbA1c and GA are outlined in Table 3, reflecting the findings from the study participants. A significant inverse correlation was noted between HbA1c and both serum creatinine (r = -0.65, p = 0.002) and blood urea (r = -0.75, p = 0.001). Conversely, FBG had a positive correlation with HbA1c (r = 0.57, p = 0.002). In contrast, GA showed no significant correlation with serum creatinine or blood urea but did exhibit a significant positive correlation with FBG (r = 0.63, p = 0.001). These findings suggest distinct relationships between these biomarkers and glycemic indices, indicating that HbA1c and GA may reflect different aspects of glucose metabolism and renal function.

Table 1. A comparison of DM patients with ESRD and DM patients without ESRD

Variable	DM with ESRD (N =115)	DM without ESRD (N =95)	P-value
Age (Mean±SD)	46±2.5	49±1.9	0.45
Female (%)	41	42	0.52
Duration of DM (Mean±SD)	21±2.3	19±1.9	0.24
Duration of ESRD (Mean±SD)	7.2±2.2	-	-
Fasting Blood Glucose (Mean±SD mg/dl)	230±5.6	185±7.5	0.045
HbA1C (%)	7.1±1.2	8.2±2.3	0.035
Glycated Albumin (%)	17.2±1.5	15.5±1.8	0.025
Blood Urea (Mean±SD mg/dl)	215±11.5	37±1.2	0.001
Serum Creatinine (Mean±SD mg/dl)	7.5±1.2	1.1±0.4	0.001

Table 2. A comparison between DM patients without ESRD and patients with ESRD

Variable	DM without ESRD (N =95)	ESRD patients without DM (N =75)	P-value
Age (Mean±SD)	49±1.9	48±2.0	0.5
Female (%)	42	40	0.6
Duration of DM (Mean±SD)	19±1.9	-	-
Duration of ESRD (Mean±SD)	-	7.4±1.4	-
FBG (Mean±SD mg/dl)	185±7.5	79.1±5.6	0.0001
HbA1C (%)	7.1±1.2	3.1±0.70	0.0001
Glycated Albumin (%)	15.5±1.8	10.9±2.16	0.001
Blood Urea (Mean±SD mg/dl)	37±1.2	237±22.4	0.0001
Serum Creatinine (Mean±SD mg/dl)	1.1±0.4	8.7±0.74	0.0001

Table 3. Correlation Of Serum Creatinine, Blood Urea, and Fasting Blood Glucose with HbA1c and glycated albumin

Biochemical parameter	HbA1c (r, p-value)	Glycated Albumin (r, p-value)
Serum Creatinine	r = -0.65, p = 0.002	r = 0.11, p = 0.34
Blood Urea	r = -0.750, p = 0.001	r = 0.13, p = 0.43
Fasting Blood Glucose	r = 0.57, p = 0.002	r = 0.63, p = 0.001

This table presents the correlation coefficients (r) and p-values for serum creatinine, blood urea, and fasting blood glucose with HbA1c and glycated albumin. Negative r-values indicate an inverse relationship, while positive r-values indicate a direct relationship. Statistical significance is noted for correlations with p-values less than 0.05.

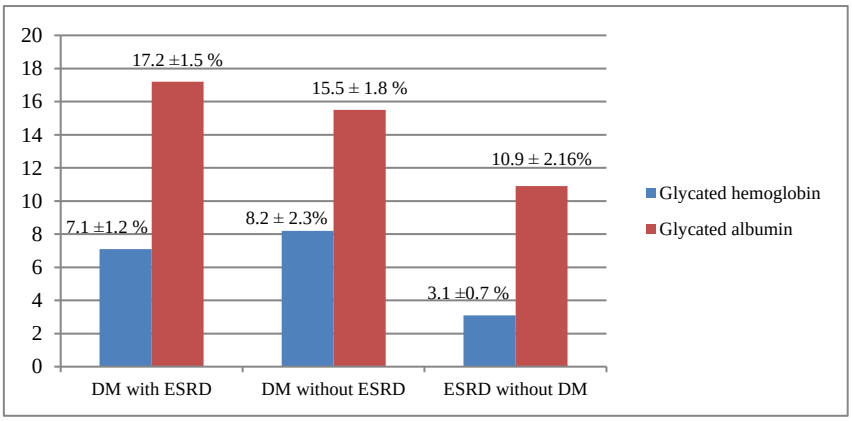

Figure 1. DM with ESRD: Diabetes mellitus patients with end-stage renal disease, DM without ESRD: Diabetes without end-stage renal disease, ESRD without DM: End-stage renal disease patients without diabetes

Discussion

A good determination of glycemic control is crucial in the diabetic population (16), as improved glycemic control reduces complications in patients with type 1 and type 2 DM. Diabetic patients on regular dialysis are at high risk of cardiovascular complications (17). The deterioration of kidney function occurs gradually, and in its early stages, it may present asymptomatically because the kidney maintains GFR despite progressive destruction of nephrons (18). Diabetic patients on dialysis continue to have poor survival compared to those with other causes of ESRD (19). This may be due to the poor glycemic control caused by using HbA1c as a glycemic indicator. Several studies have demonstrated that HbA1c is lower in patients with ESRD compared to DM patients with normal renal function, due to many factors, including RBC lifespan and interferences with the estimation method (20,21).

The present study revealed that the mean HbA1c is higher in DM patients without ESRD compared to DM patients with ESRD. This might be related to decreased RBC lifespan in patients with ESRD due to many factors, such as uremia, continuous hemodialysis, and loss of blood during investigations and treatment (22).

The lower levels of HbA1c, due to the short lifespan of RBCs, affect the use of this test to assess glycemic control in these patients. The higher levels of % GA in patients with ESRD indicate that % GA may be a better indicator of glycemic control than HbA1c in hemodialysis patients. Inaba et al. reported the same finding in Japanese patients (23). Furthermore, the study conducted by Freedman et al. (24) concluded that HbA1c significantly underestimates glycemic control in peritoneal and hemodialysis patients relative to GA%.

In the present study, a negative association was observed between HbA1c and urea levels. This might be due to the formation of carbamylated hemoglobin (carbHb). CarbHb is reported to interfere with the measurement and interpretation of HbA1c in diabetic patients with ESRD (25) due to an increase in blood urea. It was previously reported that the use of the ion-exchange chromatography method in the estimation of HbA1c may cause false results due to interference from carbHb (22,26). This interference can be avoided by using newer ion-exchange chromatography assay methods, which show improved separation of the HbA1c fraction from other hemoglobin fractions and yield accurate results (26).

The results of the current study showed no association between creatinine and GA, while a significant association was observed with HbA1c. These results are in accordance with other studies (27,28).

This study is limited by three factors. Firstly, we did not use other methods for the estimation of HbA1c to compare the advanced method with the currently used one in Sudan. Secondly, there is no data available in the records regarding the history of blood transfusions for the patients included. Finally, as stated before, all glycemic monitoring methods currently in use have specific limitations. We suggest conducting large prospective studies to evaluate all monitoring tests and select the best one for monitoring diabetes in patients with ESRD.

Conclusion

Estimation of glycated hemoglobin using certain methods as an indicator of glycemic control among ESRD patients can be affected by elevated blood urea; therefore, GA can be a better alternative test.

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Ethical statement

The study received approval from the Scientific and Ethical Committee of the Clinical Chemistry Department, Faculty of Medical Laboratory Science, Al-Neelain University (IRB No: NU-IRB-17-10-10).

Conflicts of interest

No conflict of interest.

Author contributions

AbdElkarim A. Abdrabo: Supervision, revision and data analysis. Israa Elgaily: Sample collection, laboratory analysis, writing, and revision.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014;37(Supplement-1):S81-S90. [View at Publisher] [DOI] [PMID] [Google Scholar]
2. Winocour PH. Diabetes and chronic kidney disease: an increasingly common multi-morbid disease in need of a paradigm shift in care. Diabetic Medicine, 2018;35(3):300-5. [View at Publisher] [DOI] [PMID] [Google Scholar]
3. Vaidya SR, Aeddula NR. Chronic Kidney Disease. 2024 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [View at Publisher] [PMID] [Google Scholar]
4. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. Nephrology Dialysis Transplantation. 2018;33(suppl-3):iii35-40. [View at Publisher] [DOI] [PMID] [Google Scholar]
5. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014;64(4):510-33. [View at Publisher] [DOI] [PMID] [Google Scholar]
6. Suo M, Wen D, Wang W, Zhang T. Comparative study on hemoglobin A1c, glycated albumin and glycosylated serum protein in aplastic anemia patients with Type 2 diabetes mellitus. Bioscience Reports. 2020;40(5):BSR20192300. [View at Publisher] [DOI] [PMID] [Google Scholar]
7. Neelofar K, Ahmad J. Amadori albumin in diabetic nephropathy. Indian journal of endocrinology and metabolism. 2015;19(1):39. [View at Publisher] [DOI] [PMID] [Google Scholar]
8. Selvin E, Sacks DB. Monitoring glycemic control in end-stage renal disease: what should be measured?. Clinical chemistry. 2017;63(2):447-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
9. Shimizu I, Kohzuma T, Koga M. A proposed glycemic control marker for the future: glycated albumin. J Lab Precis Med. 2019;4:23. [View at Publisher] [DOI] [Google Scholar]
10. Gillery P. A history of HbA1c through clinical chemistry and laboratory medicine. Clinical Chemistry and Laboratory Medicine (CCLM). 2013;51(1):65-74. [View at Publisher] [DOI] [PMID] [Google Scholar]
11. Leow MKS. Glycated hemoglobin (HbA1c): clinical applications of a mathematical concept. Acta Informatica Medica. 2016;24(4):233. [View at Publisher] [DOI] [PMID] [Google Scholar]
12. Haque KS, Siddiqui MR. Clinical significance of glycated hemoglobin (HbA1c). Anwer Khan Modern Medical College Journal. 2013;4(1):3-5. [DOI] [Google Scholar]
13. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomarker insights. 2016;11:BMI-S38440. [View at Publisher] [DOI] [PMID] [Google Scholar]
14. Parrinello CM, Selvin E. Beyond hba1c and glucose: The role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep. 2014;14:548. [View at Publisher] [DOI] [PMID] [Google Scholar]
15. Cohen MP, Hud E. Measurement of plasma glycoalbumin levels with a monoclonal antibody based ELISA. Journal of immunological methods. 1989;122(2):279-83. [View at Publisher] [DOI] [PMID] [Google Scholar]
16. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. Journal of Diabetes and its Complications. 2010;24(2):84-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
17. Drechsler C, Krane V, Ritz E, März W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation. 2009;120(24):2421-8. [View at Publisher] [DOI] [PMID] [Google Scholar]
18. Hashmi MF, Benjamin O, Lappin SL. End-Stage Renal Disease. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2023. [View at Publisher] [PMID] [Google Scholar]
19. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of diabetes in dialysis patients. In Seminars in dialysis. 2014;27(2):135-45. [View at Publisher] [DOI] [PMID] [Google Scholar]
20. Li Q, Ju Y, Jin T, Pang B, Deng J, Du T, Wang H. Haemoglobin A1c measurement in patients with chronic kidney disease. Clin Biochem. 2014;47(6):481-4. [View at Publisher] [DOI] [PMID] [Google Scholar]
21. Ly J, Marticorena R, Donnelly S. Red blood cell survival in chronic renal failure. Am J Kidney Dis. 2004;44(4):715-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
22. Yang X, Zhao B, Wang J, Wang L, Tao M, Lu J, et al. Red blood cell lifespan in long-term hemodialysis patients treated with roxadustat or recombinant human erythropoietin. Renal Failure. 2021;43(1):1428-36. [View at Publisher] [DOI] [PMID] [Google Scholar]
23. Inaba M, Okuno S, Kumeda Y et al. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. J Am Soc Nephrol. 2007;18:896-903. [View at Publisher] [DOI] [PMID] [Google Scholar]
24. Freedman BI, Shenoy RN, Planer JA, Clay KD, Shihabi ZK, Burkart JM, Cardona CY, Andries L, Peacock TP, Sabio H, Byers JR. Comparison of glycated albumin and hemoglobin A1c concentrations in diabetic subjects

on peritoneal and hemodialysis. Peritoneal Dialysis International. 2010;30(1):72-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
25. Little RR, Rohlfing CL, Tennill AL, Hanson SE, Connolly S, Higgins T, et al. Measurement of HbA(1c) in patients with chronic renal failure. Clin Chim Acta. 2013;418:73-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
26. Eckerbom S, Bergqvist Y, Jeppsson JO. Improved method for analysis of glycated haemoglobin by ion exchange chromatography. Annals of clinical biochemistry. 1994;31(4):355-60. [View at Publisher] [DOI] [PMID] [Google Scholar]
27. Chutani A, Pande S. Correlation of serum creatinine and urea with glycemic index and duration of diabetes in Type 1 and Type 2 diabetes mellitus: A comparative study. National Journal of Physiology, Pharmacy and Pharmacology. 2017;7(9):914-9. [View at Publisher] [DOI] [Google Scholar]
28. Herruer MH, van Kooten EA, Sluiter HE, Zuijderhoudt FM. Influence of uraemia on the determination of blood glycohaemoglobin by HPLC, electrophoresis and affinity chromatography. In diabetic and non-diabetic patients. Eur J Clin Chem Clin Biochem. 1994;32:361-4. [View at Publisher] [DOI] [PMID] [Google Scholar]

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