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Study of the Effect of Glycated Albumin Compared to Glycated Hemoglobin as An Indicator of Blood Glucose in Haemodialysis Patients Suffering from Diabetes Mellitus

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ABSTRACT

Background: The prognosis of individuals with diabetes mellitus (DM) and chronic renal disease who get regular hemodialysis (HD) is improved by strict glycemic management. Glycated haemoglobin (HbA1c) may not be a useful test for glycemic management in certain patients.

Objective: We aimed to assess the efficacy of glycated albumin (GA) versus HbA1c, as a glycemic control indicator, in diabetic patients on HD.

Patients and methods: In between 2016 and 2017; a total of 75 subjects were included in the study. Participants were divided into 3 groups: *Group 1*; diabetic patients on HD (n=50), *Group 2*; diabetics with normal renal function (n=10) and *Group 3*; control group (n=15). Through history and clinical evaluation was performed. GA and HbA1c were done in all groups.

Results: diabetic patients on HD had significantly higher GA, while HbA1c was significantly higher in those diabetic patients with normal renal function. GA had 87.1% sensitivity and 72.73% specificity at a cutoff point >31% for prediction of uncontrolled DM in those patients on regular HD while HbA1c had 72% sensitivity and 73% specificity at a cutoff point >6.7%. GA had 67% sensitivity and 85% specificity at a cutoff point >27% for prediction of uncontrolled DM in those patients with normal renal function, while HbA1c had 67% sensitivity and 71% specificity at a cutoff point >7.9%.

Conclusion: Glycated albumin could be used as an indicator for glycaemic control in patients on regular HD. Future studies are warranted to confirm such findings.

Keywords: Glycated albumin, Glycated hemoglobin, End stage renal disease, Haemodialysis, Diabetes mellitus.

INTRODUCTION

The most frequent reason for starting dialysis is diabetes mellitus (DM), which accounts for approximately 45% of patients in some countries. Diabetes also contributes to cardiovascular events by causing neuropathy, retinopathy, and atherosclerosis. Strict glycemic management has been shown to improve the outlook for diabetic patients receiving hemodialysis (HD) for chronic renal disease [(1-3)].

Glycated albumin (GA), glycated hemoglobin, and other indicators are helpful for assessing long-term blood glucose management (HbA1c). Due to the rise of immature erythrocytes caused by blood loss during HD and the use of the erythropoiesis-stimulating drug ESA for renal anemia, studies have shown that HbA1c tends to be lower in patients receiving HD compared to those who have residual kidney function [(4)]. However, because serum GA is unaffected by variations in erythrocyte survival time, it was proposed that it may serve as a substitute test for glycemic control in people with type 2 DM [(5)].

The development of significant DM consequences such as arterial stiffness, peripheral vascular calcification, nephropathy, neuropathy, retinopathy, and Alzheimer's disease is highly influenced by glycated albumin, as opposed to HbA1c. This is due to the fact that GA is an AGE (advanced glycation end product) precursor [(6)].

The current study aimed to evaluate the efficacy of GA versus HbA1c, as a glycemic control indicator, in diabetic patients on HD.

PATIENTS AND METHODS

A total of 75 subjects were included in this comparative study conducted at Outpatients Clinic of Internal Medicine Department at Assuit University in the period between 2016 and 2017.

Participants

The study enrolled the following groups: ***Group 1*** included 50 diabetic patients with end stage renal disease with estimated glomerular filtration rate (eGFR) <15 ml/min and on regular HD. ***Group 2*** included 10 diabetic patients with normal renal function with eGFR >90 ml/min. ***Group 3*** included 15 apparently healthy age and sex matched volunteers as control.

Exclusion criteria included: diabetic nephropathy stages 3, 4 presented with marked proteinuria, nephrotic syndrome, hyperthyroidism or glucocorticoid therapy due to increased albumin metabolism, liver cirrhosis or hypothyroidism due to decreased albumin metabolism, malignancy, malnutrition due to affected glycated albumin, gastrectomy due to marked postprandial hyperglycemia and abnormal hemoglobin (variant hemoglobin) due to abnormal HbA1c values.

All participants were subjected to the following:

1. Full history taking which include: type of diabetes, duration of illness, complications, type and dose of treatment.

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2. The diagnosis of diabetes was based on a history of diabetes or on the American Diabetes Association (ADA) criteria. Information collected from participants included demographic data, height, weight.
3. Information on duration and weekly doses of erythropoietin, which had not been changed during the three months before determination of GA and HbA1c, was also obtained.
4. Blood samples for hemoglobin, HbA1c levels and biochemical parameters including serum albumin, serum urea and creatinine and self-monitoring of capillary blood glucose
5. Serum level of glycated albumin by enzyme linked immune assay (ELISA) kit.

Blood sampling

Under strict aseptic conditions, five milliliters (5 ml) of venous blood were taken from each of the patients and controls. In a standard vacutainer tube, 3 ml were collected and allowed to clot for 10 to 20 minutes. Centrifugation was used to separate the serum for 20 minutes at 2000–3000 rpm. For the quick assessment of serum albumin, urea, creatinine, and eGFR, the separated was utilised. A portion of the serum was kept at -20^{o}C for GA evaluation. For the Hb and HbA1c test, the remaining 2 ml were collected into an EDTA vacutainer.

For three days in a row, two-point daily self-monitoring of capillary blood glucose (SMBG) was carried out. Using an ELISA test provided by EIA ab, the serum level of glycosylated albumin was measured.

Ethical consent:

An approval of the study was obtained from Institutional Review Board, Faculty of Medicine, Assiut University. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All statistical analyses were performed using SPSS version 20 (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). While nominal data was reported as number and frequency, continuous data was expressed as mean and standard deviation (SD) or median and interquartile range.

The study's nominal data were compared between groups using the Chi-square test, while the means of two groups were compared using the student's t-test and more than two groups were compared using the ANOVA test. In the current investigation, Person's correlation was utilized to assess the relationships between HbA1c and glycated albumin and other factors. In order to evaluate the diagnostic precision of HbA1c and glycated albumin in predicting uncontrolled DM in individuals receiving regular dialysis, ROC curve was utilized. *P* value was significant if $\leq$0.05.

RESULTS

Demographic and baseline laboratory data of the studied groups (Table 1):

Mean age of those patients on HD (52.28 ± 7.52 years) was significantly higher than those diabetics with normal kidney function (43.30 ± 10.49 years) and control group (48.46 ± 9.11 years) (*P*< 0.001). The current study showed that diabetic patients on HD had significantly higher GA and random blood sugar in comparison to the healthy control group and diabetic patient with normal renal function. It was noticed HbA1c was significantly higher in those diabetic patients with normal renal function in comparison to other groups. Other demographic and laboratory are summarized at table 1.

Table (1): Demographic and baseline laboratory data of studied groups

Variable	GI (n= 50)	GII (n= 10)	GIII (n= 15)	*P-value*
Age (years)	52.28 ± 7.52	43.30 ± 10.49	48.46 ± 9.11	< 0.001
Sex				
Male	30 (60%)	5 (50%)	10 (66.7%)	
Female	20 (40%)	5 (50%)	5 (33.3%)	0.71
BMI (kg/m^2)	29.04 ± 3.69	27.50 ± 3.84	26.67 ± 2.95	0.06
Duration (years)	14.34 ± 2.89	5.04 ± 1.21	--	0.03
Hemoglobin (g/dl)	9.11 ± 0.95	11.55 ± 0.74	11.70 ± 0.63	< 0.001
Albumin (g/dl)	4.07 ± 0.51	4.79 ± 0.32	4.45 ± 0.52	0.87
Urea (mg/dl)	132.66 ± 31.51	32.60 ± 6.39	29.93 ± 5.44	< 0.001
Creatinine (mg/dl)	6.31 ± 1.10	1.02 ± 0.22	1.01 ± 0.13	< 0.001
eGFR (ml/min/1.73 m^2)	9.80 ± 2.35	85.70 ± 3.88	93.33 ± 4.65	< 0.001
HbA1c (%)	7.01 ± 1.04	8.31 ± 0.98	5.29 ± 0.47	< 0.001
Glycated albumin (%)	40.49 ± 8.70	37.3 ± 6.70	24.10 ± 3.07	< 0.001
RBS (mg/dl)	365.18 ± 9.80	314.90 ± 7.31	122.1 ± 8.65	< 0.001

Data was expressed inform of mean (SD), frequency (percentage). *P* value was significant if $\leq$0.05. **BM*I,*** body mass index, eGFR, estimated glomerular filtration rate, HbA1c; glycated hemoglobin; RBS: random blood sugar, **GI**, diabetics patients on hemodialysis; **GII**, diabetic patients with normal kidney function; **GIII**, control subjects

Correlation analysis between HbA1c and different variables in the Current Study (Table 2):

In both groups of diabetes HbA1c had positive significant correlation with glycated albumin, random blood sugar and hemoglobin level. In case of control group, HbA1c had positive significant correlation with random blood sugar. All other correlations were insignificant.

Table (2): Correlation of HbA1c with different variables in different groups

Variable	Diabetics with hemodialysis	Diabetics with normal renal function	Control group
Age (years)	0.11 (0.83)	0.15 (0.19)	-0.16 (0.33)
RBS (mg/dl)	0.11 (0.00)	0.15 (0.00)	0.12 (0.03)
Hemoglobin (g/dl)	0.78 (0.00)	0.33 (0.01)	0.11 (0.09)
Serum albumin (%)	-0.05 (0.63)	-0.13 (0.25)	-0.32 (0.33)
Urea (mg/dl)	0.11 (0.13)	0.50 (0.01)	0.40 (0.12)
Creatinine (mg/dl)	0.17 (0.13)	0.70 (0.13)	0.36 (0.18)
Body mass index (kg/m^2)	0.01 (0.38)	0.30 (0.22)	0.11 (0.69)
Duration (years)	0.11(0.23)	0.56 (0.14)	0.39 (0.09)
eGFR (ml/min/1.73 m^2)	-0.18 (0.09)	-0.52 (0.12)	0.11 (0.09)
Glycated albumin (%)	0.45 (0.01)	0.64 (0.03)	0.32 (0.07)

Data was expressed in from of r (strength of correlation), *P* (significance of correlation). eGFR, estimated glomerular filtration rate, HbA1c; glycated hemoglobin; RBS: random blood sugar

Correlation analysis between GA and different variables in the current study (Table 3):

In both groups of diabetes glycated albumin had positive significant correlation with glycated hemoglobin and random blood sugar. In case of control group, glycated albumin had positive significant correlation with random blood sugar. All other correlations were insignificant.

Table (3): Correlation of glycated albumin with different variables in different groups

Variable	Diabetics with hemodialysis	Diabetics with normal renal function	Control group
Age (years)	0. 06 (0.65)	0.16 (0.35)	-0.16 (0.55)
RBS (mg/dl)	**0.75 (0.00)**	**0.87 (0.00)**	**0.80 (0.00)**
Serum albumin (%)	-0.10 (0.48)	0.50 (0.25)	-0.14 (0.16)
Urea (mg/dl)	0.02 (0.88)	0.16 (0.64)	0.19 (0.70)
Creatinine (mg/dl)	-0.08 (0.57)	0.34 (0.33)	-0.35 (0.16)
Body mass index (kg/m^2)	0.08 (0.56)	-0.18 (0.38)	-0.09 (0.69)
Duration (years)	0.11 (0.44)	0.51 (0.22)	0.26 (0.34)
eGFR (ml/min/1.73 m^2)	-0.08 (0.19)	-0.15 (0.42)	-0.02 (0.19)
HbA1c (%)	**0.45 (0.01)**	**0.64 (0.03)**	0.32 (0.07)

Data was expressed in from of r (strength of correlation), *P* (significance of correlation). eGFR, estimated glomerular filtration rate, HbA1c; glycated hemoglobin; RBS: random blood sugar.

Accuracy of HbA1c and GA in prediction of uncontrolled DM:
In diabetic patients with regular hemodialysis (Table 4, figure 1)

GA had 87.1% sensitivity and 72.73% specificity at a cutoff point >31% for prediction of uncontrolled DM in those patients on regular hemodialysis while HbA1c had 72% sensitivity and 73% specificity at a cutoff point >6.7%.

Table (4): Accuracy of HbA1c and GA in prediction of uncontrolled DM in patients on hemodialysis.

Indices	Glycated albumin	Glycosylated hemoglobin
Sensitivity	87.1%	72%
Specificity	72.73%	73%
PPV	92%	90%
NPV	62%	42%
Cutoff point (%)	> 31%	> 6.7
AUC	0.91	0.76
***P* value**	< 0.001	< 0.001

P value was significant if < 0.05. **PPV**, positive predictive value; **NPV**, negative predictive value; **AUC**, area under the curve; GA: glycated albumin; HbA1c: glycated hemoglobin; AUC: area under the curve

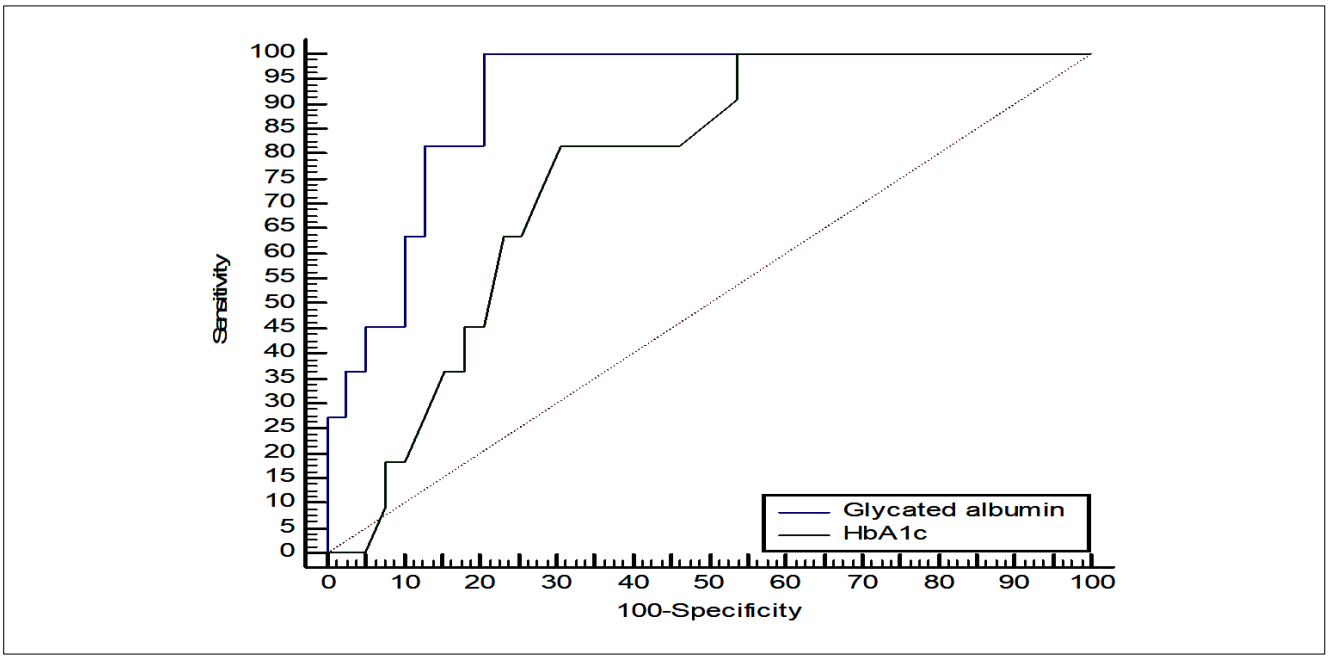

Figure (1): Diagnostic accuracy of HbA1c and glycated albumin in prediction of uncontrolled diabetes mellitus in patients on hemodialysis.

In diabetic patients with normal renal function (Table 5, figure 2)

GA had 67% sensitivity and 85% specificity at a cutoff point >27% for prediction of uncontrolled DM in those patients with normal renal function while HbA1c had 67% sensitivity and 71% specificity at a cutoff point >7.9%.

Table (5): Accuracy of HbA1c and GA in prediction of uncontrolled DM in case of normal renal function

Indices	Glycated albumin	Glycosylated hemoglobin
Sensitivity	67%	67%
Specificity	85%	71%
PPV	67%	60%
NPV	85%	100%
Cutoff point (%)	> 27%	> 7.9
AUC	0.71	0.91
***P* value**	< 0.001	< 0.001

P value was significant if < 0.05. **PPV**, positive predictive value; **NPV**, negative predictive value; **AUC**, area under the curve; GA: glycated albumin; HbA1c: glycated hemoglobin; AUC: area under the curve.

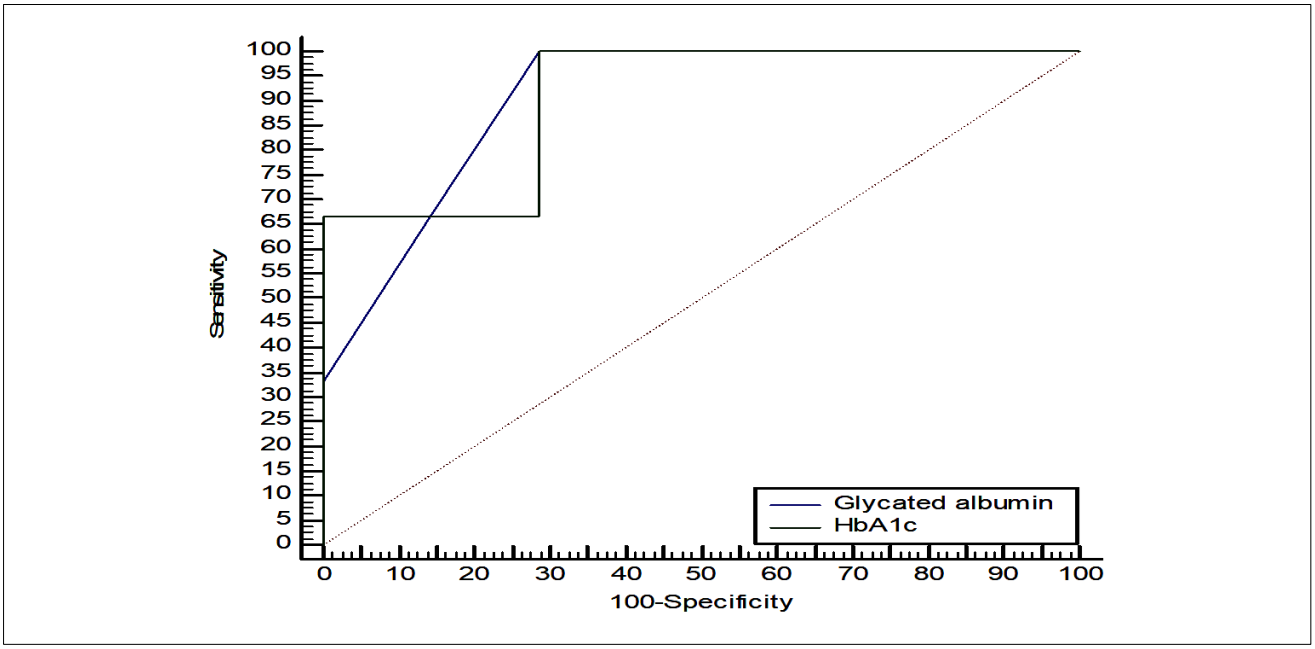

Figure (2): Diagnostic Accuracy of HbA1c and glycated albumin in prediction of uncontrolled diabetes mellitus in patients with normal renal function.

DISCUSSION

Low hemoglobin levels may result in decreased red blood cell survival and a shorter hemoglobin lifespan in dialysis patients who are getting high doses of erythropoietin; however, these effects may not be reversed by such high doses of erythropoietin. Contrarily, neither hemoglobin nor the levels of serum albumin or erythropoietin were linked to GA% [7].

This work was designed to assess role of GA as glycemic indicator in diabetic patients on regular hemodialysis. It included 75 subjects; were divided into three groups; ***Group I*** included 50 diabetic patients with end stage renal disease on regular dialysis, ***Group II*** included 10 diabetic patients with normal kidney function and ***Group III*** included 15 healthy subjects as control.

The current study showed that diabetic patients on hemodialysis had significantly higher GA and random blood sugar in comparison to the healthy control group and diabetic patient with normal renal function. It was noticed glycosylated hemoglobin was significantly higher in those diabetic patients with normal renal function in comparison to other groups.

The results of the current study demonstrated that determining GA added a more meaningful technique to evaluate glycemic control in HD patients with diabetes and that HbA1c significantly underestimates glycemic control in diabetic dialysis patients when compared to GA. According to **Sany *et al.* [8],** the significantly lower HbA1c value in relation to PG and GA in diabetic HD patients compared to diabetic patients with or without chronic kidney disease (CKD) may indicate that the measurement of HbA1c would lead to an underestimating of glycemic control in HD patients with diabetes.

In both groups of diabetes either with normal renal functions or with regular HD; glycosylated hemoglobin had insignificant correlation with different variables in the study but had significant moderate correlation with GA and strong correlation with random blood sugar.

In case of control group, HbA1c had insignificant correlations with different variables in the study with exception a weak correlation with random blood sugar. It was noticed that HbA1c had strong positive correlation with hemoglobin concentration in those patients on regular dialysis but it had weak correlation in those diabetic patients with normal kidney function.

Numerous researches have indicated that there are favorable correlations between hemoglobin concentration and HbA1c. However, **Inaba *et al.* [9]** observed that lower% GA was connected to increased serum albumin concentrations. Additionally, they stated that, with the exception of artificially elevated GA readings brought on by uremic toxin buildup, pre- and post-dialysis GA results were equivalent.

Sany *et al.* [8] found a negative connection between BMI and glycated albumin and explained this association by linking obesity-related inflammation to this negative association. The current study found a non-significant correlation between BMI and GA. Albumin is catabolized more quickly and its rate of production is slowed down by inflammation. Additionally, increased albumin turnover is caused by hyperinsulinemia in obese diabetes patients [10,11].

Peacock *et al.* [7] demonstrated HbA1c and GA relationships with recent random blood glucose measurements. Although there was a negative correlation between erythropoietin dosage and HbA1c, there was a positive correlation between HbA1c and hemoglobin concentration. It also demonstrated that there was no significant relationship between serum albumin, hemoglobin concentration, or erythropoietin dosage and GA.

In contrast, neither hemoglobin nor the amount of erythropoietin nor the quantity of serum albumin was related to % GA. As was already said, % GA is related to BMI, a variable for which adjustments can be made. Therefore, in HD patients, % GA may be a more accurate indication of long-term glycemia than HbA1c [12]. Additionally, compared to individuals without end stage renal disease (ESRD), people with ESRD had a weaker association between HbA1c and blood glucose. In the ESRD group, the GA/albumin ratio and blood glucose had associations that were equivalent to those in the non-ESRD group and were greater than those for HbA1c. Between the two patient groups, there was no discernible change in the GA/albumin ratio vs blood glucose [13].

Kuo *et al.* [14] reported that, among 128 patients with DM and stage 1–5 CKD, a decline in HbA1c was correlated with CKD stages, but this relationship disappeared after adjustment for hemoglobin. In addition, **Freedman *et al.* [15]** confirmed, in diabetic patients with stage 3–4 CKD, an inverse correlation between the eGFR and the glucose/HbA1c ratio, which indicated that HbA1c could be falsely low in lower eGFR. Accordingly, HbA1c levels appear to be falsely low in subjects with DM and advanced CKD.

The current study showed that GA had 87.1% sensitivity and 72.73% specificity at a cutoff point >31% for prediction of uncontrolled DM in those patients on regular hemodialysis while HbA1c had 72% sensitivity and 73% specificity at a cutoff point >6.7%. Also, It was noticed that glycated albumin had 67% sensitivity and 85% specificity at a cutoff point >27% for prediction of uncontrolled DM in those patients with normal renal function while HbA1c had 67% sensitivity and 71% specificity at a cutoff point >7.9%.

Finally, several published research revealed that while GA and HbA1c did not vary statistically significantly in the early stages of CKD, GA outperformed HbA1c in the latter stages of the disease. GA outperforms HbA1c in advanced CKD because HbA1c underrepresents and misrepresents patient glycemic status. The longevity of red blood cells, usage

of iron and/or erythropoietin treatment, uremia, and frequent blood transfusions are some factors that may contribute to the inaccuracy of HbA1c [16,17].

GA enables early detection of fast changes in total glucose so that immediate corrective action may be done. Furthermore, it has been demonstrated that elevated GA levels are linked to renal dysfunction, cardiovascular disease, and both the presence and severity of these conditions. Thus, in individuals with diabetes and nephropathy, GA may be a more accurate indicator of glycemic management as well as a predictor of developing vascular problems [18, 19].

In conclusion, GA provides a significantly better measure than HbA1c for the estimation of glycemic control in diabetic patients on HD, as HbA1c level is influenced by factors other than glucose. Also GA responds mush sooner to changes in glycemic control level, enabling us to evaluate the treatment regimen sooner, since it represents the time averaged PG level over 2-3 weeks.

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