

ORIGINAL ARTICLE

Title

Correlation of Glycated Albumin and Glycated Hemoglobin with Glycemic Control in Patients with Diabetic Chronic Kidney Disease on Hemodialysis

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*Received 21 December 2018, revised 8 March 2019, accepted 13 March 2019, published 1 April 2019***ABSTRACT**

Background and aims. Diabetes mellitus (DM) is the most common cause of end-stage renal disease (ESRD) worldwide and is the primary etiology of ESRD in Indonesia. It is estimated that there are 10 million patients with DM in Indonesia and about 25-40% of diabetics develop diabetic nephropathy (DN) within 25 years. Poor glycemic control is associated with increased mortality in a large observational study among diabetics on hemodialysis. Glycated hemoglobin, or known as HbA1c, was the currently recommended biomarker to monitor long-term glycemic control in diabetes mellitus guideline. However, it becomes underestimated in patients with DN on hemodialysis (DN-HD), because of 20-50% reduction of erythrocyte lifespan, clinical use of iron therapy, and effects of recombinant human erythropoietin. Glycated albumin (GA), ketoamine formed via a non-enzymatic glycation reaction of serum albumin, is free from interference by erythrocyte lifespan or erythropoietin therapy and subsequently can be used as an alternative biomarker to monitor glycemic control in DN-HD. As albumin has a half-life of only 14-21 days* compared to Hb 60-100 days in well ESKD patients, thus GA may provide a better reflection of recent diabetic control than HbA1c. The aim of this study was to analyze the correlation between GA and HbA1c with glycemic control in DN-HD.

Methods The study was an analytical observational study with a cross-sectional design. The subjects were consecutive patients with DN-HD who visited Hemodialysis Unit at Mohammad Hoesin General Hospital Palembang during August-November 2014. The glycemic control index was determined by the average value of 2 times a week pre-HD

random blood glucose for 4 weeks (aRBG).

Results. The subjects were 25 patients with an average age of 56.16±7.49 years old. The average value of GA was 26.94±7.74%. GA was strongly correlated with aRBG with $r=0.776$; $p=0.000$. After correcting for age, sex, and BMI, the correlations became significantly very strong ($r=0.809$, $p<0.001$). The simple linear regression for the relationship between GA and aRBG was $aRBG=4.62 \times GA + 42.74$ ($R^2=0.602$, $P<0.001$), estimating that a 1% increase of GA was associated with 4.62mg/dL increase of aRBG. After correcting for age, sex, & BMI, the correlations between HbA1c and aRBG were significant ($r=0.852$, $p<0.001$).

Conclusion. GA was strongly correlated with glycemic control in patients with DN-HD and HbA1c was correlated better.

Keywords. *Glycated albumin*, HbA1c, glycemic control, DN-HD.

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INTRODUCTION

The incidence of diabetes mellitus (DM) is exponentially increased. There are 422 million diabetics worldwide nowadays and it is estimated the number would be 629 million

diabetics in 2045^{1,2}. According to the International Diabetes Federation (IDF) data in 2017, Indonesia is ranked sixth of the world's nations for people living with DM. It is estimated that there are 10.3 million diabetics in Indonesia and it is predicted to increase to be 16.7 million in 2045². As the consequence for increasing number of diabetics, the incidence of the DM complication, including diabetic nephropathy (DN), becomes a serious public health concern. The previous study estimated that 25-40% diabetics will develop DN within 25 years³. DN is currently the primary cause for end-stage renal disease (ESRD) worldwide⁴, and is the major etiology for ESRD in Indonesia, according to Indonesian Renal Registry 2015⁵.

Previous studies show that poor glycemic control can increase the incidence of cardiovascular complication which becomes the major cause of mortality in patients with DN⁶. American Diabetes Association (ADA) 2017 recommends two suggested assessments for glycemic control which are self-monitoring blood glucose (SMBG) and hemoglobin A1c (HbA1c)⁷. HbA1c is widely used as the biomarker for glycemic control and prognostic modality for long-term DM complication because of its nature that reflects average plasma glucose concentration for 2-3 months. In diabetic nephropathy patients undergoing hemodialysis (DN-HD), the measurement of HbA1c is considered unreliable to quantify long-term glycemic control⁸. The condition is due to the 20-50% reduction of erythrocyte lifespan, clinical use of iron therapy, effects of recombinant human erythropoietin, uremic conditions, and needs to recurrent blood transfusion in DN-HD^{9,10}. Iron therapy and erythropoietin use will be followed by the reduction of HbA1c value without any glycemic status changes.

Glycated albumin (GA) is the ketoamine formed via a non-enzymatic glycation reaction of serum albumin¹¹. GA and HbA1c were both affected by inflammation, but GA is free from interference by erythrocyte lifespan or erythropoietin therapy which was common among patients with hemodialysis. GA has a serum half-life of approximately 20 days compared to HbA1c which has 120 days of serum half-life. The rapid change of GA as the response for glucose concentration changes offers a benefit for diabetics with fluctuated glucose concentration conditions such as postprandial hyperglycemia or abrupt glycemic status changes in short duration¹¹. GA is deemed to be used as a better biomarker to monitor glycemic control than HbA1c in patients with DN-HD who always have anemia. Previous studies show conflicting results. Peacock et al¹² and Sany et al¹³ concluded that HbA1c as the measurement for glycemic control is significantly underestimated compared to GA. The other studies which are done by Ichikawa et al¹⁴ and Inaba et al¹⁰ signified that HbA1c has stronger correlation compared to GA as glycemic control in DN-HD. The similar studies have been limited and there is no published study about GA and

HbA1c as glycemic control index in the Indonesian population. The aim of this study was to elaborate on the correlation between GA and glycemic control in patients with DN-HD. For the purpose of comparing, this study also aimed to identify the correlation between HbA1c and glycemic control in patients with DN-HD.

METHOD

The study was an analytical observational study with a cross-sectional design. The study was conducted in the hemodialysis unit of Mohammad Hoesin General Hospital on August-November 2014. The subjects were consecutively recruited based on the inclusion criteria. All subjects gave their written informed consent. The study was approved by the local Ethics Committee.

The subjects were the patients of DN-HD who were 18-60 years old. They were patients without any history of liver function abnormalities, hemoglobinopathy, and thyroid disease. Pre-HD random blood glucose was measured two times a week for four weeks in an aim to determine average random blood glucose, aRBG, as a measurement of glycemic control¹⁵. In the last measurement, the GA and HbA1c were also measured. The assessments of GA and HbA1c were conducted in Prodia Laboratory Palembang. *Lucica GA-L* kit was used to measure GA and *ADVIA 1650 automatic instrument* was used to analyze the measurement. HPLC-DCCT, a method which becomes a major reference method as used by the *National Glycohemoglobin Standardization Program* (NGSP), was used to assess HbA1c. HbA1c<7% indicated controlled DM7.

Statistical analysis was performed by *SPSS version 22.0 for Windows* (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as means±SD; skewed variables were expressed as medians and minimum-maximum range. Correlations between the GA, HbA1c, GA/HbA1c ratio, and aRBG were evaluated using Pearson correlation coefficient analysis. To examine the influence of confounding variables, multivariate analysis with multiple regression analysis was conducted. Statistical significance was indicated by a two-tailed P-value of <0.05.

RESULTS

The study recruited 25 patients with DN-HD whose characteristic was shown in table 1. The GA, HbA1c, and aRBG were shown in table 2. GA had a positive strong correlation with aRBG with $r=0.776$; $p=0.000$. After correcting for age, sex, and BMI, the correlations became significantly very strong ($r=0.809$, $p<0.001$). The simple linear regression for the relationship between GA and aRBG was $aRBG=4,62 \times GA+42.74$ ($Rsq=0.602$, $P<0.001$). It estimated that a 1%

Table 1. The characteristics of subjects

Characteristics	Value (n=25)
Gender	
Male	11
Female	14
Age (year)	56.16±7.49
Body mass index (kg/m ²)	21.10±2.16
Duration of diabetes (year)	9.98±6.35
Hemoglobin (g/dL)	7.92±1.19
Albumin (g/dL)	3.75±0.48

Table 2. GA, HbA1c, and aRBG in subjects

Characteristics	Value (n=25)
GA (%)	26.94±7.74
HbA1c (%)	6.7(5.3-11.4)
aRBG (mg/dL)	161.25(97.25-308.87)

increase of GA was associated with 4.62mg/dL increase of aRBG.

The correlation between HbA1c and aRBG was scored noted on $r=0.869$ and $p=0.000$. After correcting for age, sex, and BMI, the correlations remained significant ($r=0.852$, $p<0.001$). The relationship between GA and aRBG was $aRBG=30.96 \times HbA1c - 49.36$ ($Rsq=0.754$, $P<0.001$). The analysis estimated that a 1% increase of HbA1c was associated with 30.96mg/dL increase of aRBG. Meanwhile, the GA/HbA1c ratio was weakly correlated and statistically not significant ($Rsq=0.305$, $p=0.139$).

Table 3 and Table 4 presents the results of a multiple regression analysis of various clinical variables. In table 3, which included age, gender, body mass index, duration of diabetes in years, and GA, only GA was found significantly correlated with aRBG.

Table 3. Multivariate regression analysis of glycated albumin and average random blood glucose

Clinical Variable	B	SE(B)	T	Partial Rsq	P
Age (years)	0.340	0.708	0.048	0.011	NS
Body Mass Index (kg/m ²)	-0.511	2.696	-0.190	-0.042	NS
Duration of Diabetes (years)	-0.209	0.928	-0.225	-0.042	NS
HbA1c (%)	31.494	4.238	7.431	0.857	<0.001
Constant	-42.128	66.299	-0.635		NS

Table 4. Multivariate regression analysis of HbA1c associated with average random blood glucose in patients with diabetic nephropathy undergoing hemodialysis

Clinical Variable	B	SE(B)	T	Partial Rsq	P
Age (years)	0.340	0.708	0.048	0.011	NS
Body Mass Index (kg/m ²)	-0.511	2.696	-0.190	-0.042	NS
Duration of Diabetes (years)	-0.209	0.928	-0.225	-0.042	NS
HbA1c (%)	31.494	4.238	7.431	0.857	<0.001
Constant	-42.128	66.299	-0.635		NS

Relation between glycated albumin and average random blood glucose (aRBG)

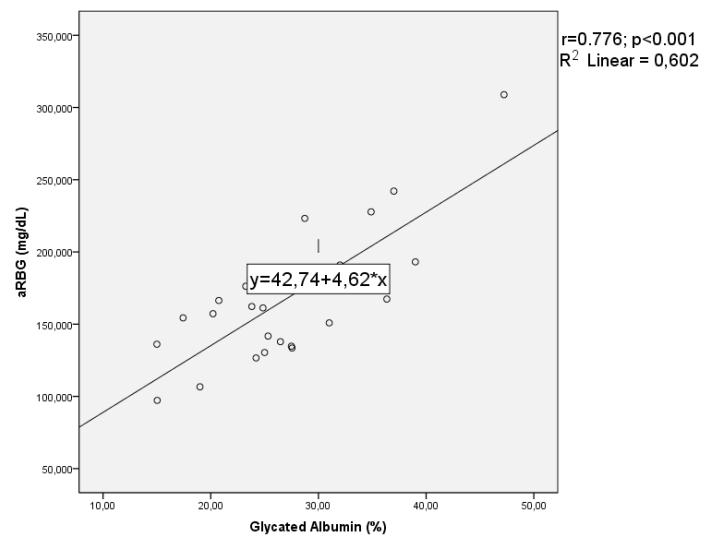


Figure 1. Relation between glycated albumin and average random blood glucose (aRBG). The solid line represents the regression line of all data. Glycated albumin ($r=0.776$; $p<0.001$) did have significant positive correlation with aRBG.

Relation between HbA1c and average random blood glucose (aRBG)

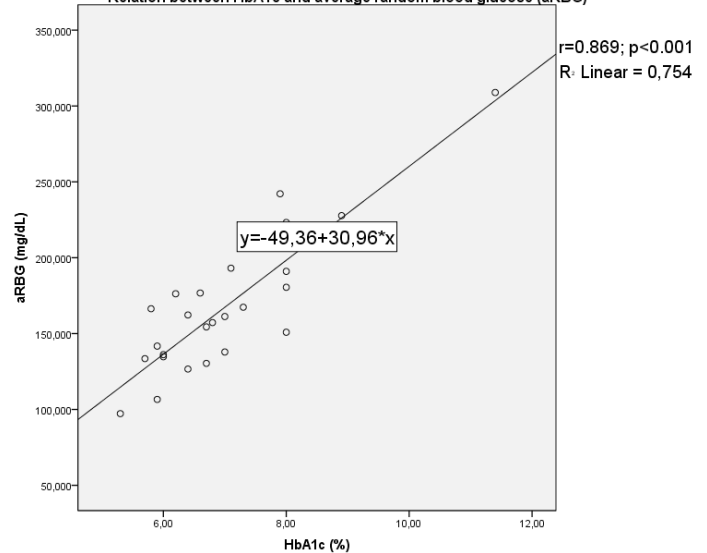


Figure 2. Relation between HbA1c and average random blood glucose (aRBG). The solid line represents the regression line of all data. HbA1c ($r=0.869$; $p<0.001$) did have significant positive correlation with aRBG. In table 4, which included HbA1c in place of GA, HbA1c emerged as an independent and significant factor that was positively correlated with aRBG.

DISCUSSIONS

Glycemic control in the study was depicted by aRBG which was the average plasma glucose concentration measured before HD, 2 times a week for 4 weeks duration (8 times measurement in total). GA was strongly correlated with aRBG ($p<0.05$ $r=0.776$). The similar result was also identified by Sany et al who identified a significant positive correlation be-

tween GA and aRBG ($p < 0.01$, $r = 0.54$) and Inaba et al which also showed the significant correlation ($r = 0.52$, $p < 0.01$)^{10,13}. The correlation between HbA1c and aRBG in the study was significant and very strong ($p < 0.05$, $r = 0.869$), tending to be stronger compared to Sany et al ($r = 0.51$, $p < 0.01$) and Inaba et al ($r = 0.52$, $p < 0.01$)^{10,13}. This study and Inaba et al showed a stronger correlation between HbA1c and aRBG compared to GA and aRBG. During hemodialysis, the uremic condition, blood loss due to therapy, and the increased frequency of blood sampling contributed to shortening the erythrocyte lifespan. Thus, in theory, the shortening of erythrocyte lifespan and erythrocyte transfusion made HbA1c becoming less reliable in the measurement of glycemic control in patients with DN-HD.¹⁶

GA/HbA1c ratio and aRBG in the study showed a weak correlation value and statistically insignificant. The contradictory result was shown by Lee et al which reported that there was a significant association between GA/HbA1c ratio and insulin secretion function¹⁷. Kim et al included *standardized liquid meal test* for the subject, in comparison to the current study which did not perform the test. The correlation coefficient of GA and aRBG in this study was strong and the correlation coefficient of HbA1c and aRBG was very strong. This finding was similar to Ichikawa et al who stated that HbA1c was the gold standard measurement to monitor the glycemic status of patients with DN-HD¹⁴. The dissimilar finding was shown by Freedman et al who reported GA was superior in monitoring glycemic control compared to HbA1c in patients with DN-HD because GA measured glycemic control for 2-3 weeks duration compared HbA1c which measured in 1-3 months duration²¹. The conflicting results might be reflected by the factors affecting serum albumin and hemoglobin, such as blood loss and inflammation. Acute and chronic blood loss, besides decreased red cell survival, did lower HbA1c results in patients with chronic kidney disease²². Chronic inflammation, commonly found in patients with DN-HD, affected glycosylation of both GA and HbA1c in intricate fashion^{23,24}, thus interfering the result.

Further studies should consider blood loss and inflammation as factors affecting correlation among GA, HbA1c, and glycemic control. Examining the clinical details of the outlier patients, where GA and HbA1c do not correlate with each other (or with aRBG), may help clarify the risk factors for false-positive and/or false-negative results. With serum half-life of 12–21 days, GA provided information over a period of 1 month compared to 3–6 months with HbA1c²⁵. Future research is warranted to validate our findings in follow-up studies which compared the three months GA value and HbA1c. In the current study, the glycemic control measurement of self-monitoring blood glucose according to ADA recommendation in 2017, could not be performed due to impracticality. The glycemic control which was determined

by 2 times a week measurement for 4 weeks duration could give a bias because of the high variation about nutritional intake and patients' physical stress. The study also did not perform *standardized liquid meal* in an attempt to minimize the bias which could be produced by blood glucose measurement methods.

CONCLUSIONS

GA was strongly correlated toward glycemic control in patients with DN-HD, but that HbA1c was correlated even better.

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