Glycated albumin as an indicator of glycemic control in pre-dialysis diabetic chronic kidney disease patients

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ABSTRACT

Glycated albumin as an indicator of glycemic control in pre-dialysis diabetic chronic kidney disease patients

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Background Good glycemic control in diabetic patients is important to prevent progression of diabetic nephropathy and reduce cardiovascular events. Recently, several studies suggested that hemoglobin A1c (HbA1c), a widely used glycemic control marker, has serious limitations by falsely underestimating glycemic state in diabetic patients on hemodialysis. In contrast, glycated albumin (GA), which is not influenced by diseases of shortened RBC life span, and use of iron supplements and erythropoietin (EPO) therapy, is thought to more accurately reflect glycemic state in ESRD patients. Study aim was to validate this finding in pre-dialysis diabetic chronic kidney disease (CKD) patients.

Methods Clinically stable pre-dialysis type 2 diabetic patients were enrolled between March 2009 and August 2012. A total of 497 patients were enrolled and stratified into 5 groups according to 2012 KDIGO CKD guideline that subdivided stage 3 into 3a and 3b stages. Parameters of glycemic control were investigated along with other biochemical and clinical informations.

Results The numbers of patients according to CKD stages 1 to 4-5 were

consisted of 168, 151, 76, 47, and 55 subjects, respectively. The mean serum glucose concentrations did not differ significantly among 5 groups. The HbA1c and GA showed positive correlations at all CKD stages, however, increased steepness in slope of regression line between HbA1c and GA with decline in renal function was shown (control group vs. other CKD stages: $p < 0.05$). The GA/HbA1c and serum glucose/HbA1c in CKD stage 3b and 4-5 were significantly higher than in controls, and the GA/HbA1c increased ($r = 0.22$, $p < 0.001$) with progression of renal failure. In contrast, the GA and glucose/GA remained constant throughout the all CKD stages. In multivariate analysis, weekly erythropoietin dose ($p = 0.02$) was associated with HbA1c and, the cut off value in ROC curve of weekly EPO dose altered HbA1c level was 6000 U/week (AUC = 0.91, 95% CI 0.78 - 1.00).

Conclusion Our results indicate that the HbA1c may underestimate glycemic control state even in pre-dialysis diabetic CKD patients, especially those who are on EPO treatment and the GA might be an useful indicator of glycemic control in pre-dialysis diabetic CKD patients.

Key words : diabetic nephropathy, glycated hemoglobin, glycated albumin

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I. INTRODUCTION

Diabetes mellitus (DM) is the leading cause of end-stage renal disease (ESRD) in Korea.[1] The proportion of incident ESRD patients with DM has increased from less than 30 % in early 1990s to almost 50 % in 2011. Good glycemic control in diabetic patients is important to prevent progression of diabetic nephropathy and reduce cardiovascular events. Strict glycemic control has been associated with improved quality of life and survival.[2, 3] The 2012 updated Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for diabetes and chronic kidney disease (CKD) recommend a target hemoglobin A1c (HbA1c) level of 7.0 % in diabetic CKD patients to prevent or delay progression of the microvascular complications.[4] The HbA1c is currently the most widely used glycemic control marker. It is formed by combination of hemoglobin with the circulating serum glucose via irreversible non-enzymatic reaction,[5] and reflects glycemic state over the prior 120 days.[6, 7] However, the HbA1c measurement is influenced by diseases of shortened RBC life span,[8] and use of iron supplements and EPO therapy. Patients with these risk factors frequently show reduced HbA1c levels and clinicians may falsely underestimate their glycemic state.[9] Glycated albumin (GA), the product of condensation of albumin and glucose, reflects glycemic state over a short period of preceding 2–3 weeks and is not influenced

by RBC survival time.[10] Recently, several clinical trials provided evidence that GA provides more accurate index of the glycemic control in advanced CKD patients. Furthermore, the GA predicted the risk of death and hospitalization in hemodialysis patients.[11] However, the significance of GA as a marker of glycemic control in pre-dialysis diabetic CKD patients has not been thoroughly investigated yet.[12, 13]

Our study attempts to validate whether the GA is more suitable than the HbA1c as an indicator of glycemic control in pre-dialysis diabetic CKD patients.

II. MATERIALS AND METHODS

1. Patients

Clinically stable pre-dialysis type 2 diabetic patients treated at Gangnam Severance Hospital, South Korea were enrolled between March 2009 and August 2012. This study was composed of 329 pre-dialysis CKD patients with type 2 diabetes, and 168 patients with type 2 diabetes and normal renal function. The diagnosis of diabetes was based on medical records or criteria in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[14] All medications, including oral hypoglycemic agents, insulin or erythropoietin (EPO), had not been altered within 3 months prior to measurement of the HbA1c and GA. Patients were stratified into 5 groups according to 2012 Kidney Disease Improving Global Outcome (KDIGO) CKD guideline. Estimated GFR (eGFR, ml/min per 1.73 m^2) was calculated using the 4-variable Modification of Diet and Renal Disease (MDRD) study equation.[15] CKD stage 3 was further subdivided into 3a and 3b as recent data demonstrated substantial differences in those who have eGFR values between 45 and 60 versus 30 and 45 ml/min per 1.73 m^2.[16] Demographic and medical information including age, gender, height, weight, body mass index (BMI), weekly EPO dose and other medications were collected at baseline from electronic medical records. Parameters of glycemic control, HbA1c and GA, as well as fasting serum glucose, hemoglobin, blood urea nitrogen,

creatinine, total protein, albumin and urine protein were assessed. The mean value of the 3 monthly measurements of fasting serum glucose prior to determination of HbA1c and GA were used in this study.[17] Exclusion criteria were age under 18 or older than 90 years old, hemoglobinopathy, anemia not associated with CKD, chronic liver disease, endocrinopathy including thyroid disease, adrenal disease, pregnancy, recent infection, pre-existing malignancy and kidney transplantation.[13] The patients who have taken medications that could influence serum glucose concentration within three months prior to the study were also excluded. This study was approved by Institutional Review Board for Human Research at Yonsei University College of Medicine (#IRB 3-2014-0150).

2. Assay of HbA1c and GA

Parameters of glycemic control, HbA1c and GA, were measured along with other biochemical and clinical parameters. The HbA1c level was analyzed using the Automated Glyco-hemoglobin Analyzer, HLC-723G8 (Tosoh corp., Tokyo, Japan), a high performance liquid chromatography system designed to measure HbA1c. The GA level was measured by an enzymatic method that converts GA to glycated amino acids using the Lucica GA-L kit (Asahi Kasei Pharma Corp., Tokyo, Japan). The GA was calculated as the percentage of GA relative to total albumin.

3. Statistical Analyses

All values are expressed as means ± standard deviations (SD) or number and percentages. Statistical analysis was performed using SPSS for Windows Ver. 17.0 (SPSS, Inc., Chicago, IL, USA). The comparisons of HbA1c, GA and other continuous variables between the patients at different CKD stages and controls were analyzed by independent t-test. Pearson's correlation coefficients were calculated for evaluation of correlation between glycemic parameters by simple regression analysis. In addition, independent factors associated with the HbA1c

and GA were determined by multiple linear regression analysis. Furthermore, the cut-off values of weekly EPO dose were evaluated by constructing receiver operating characteristic (ROC) curve. The *p*-values less than 0.05 were considered to be statistically significant.

III. RESULTS

Blood samples were collected from 497 diabetic patients, 329 were pre-dialysis diabetic CKD patients and 168 were diabetic patients without nephropathy.

Table 1. Demographic and laboratory characteristics of study population

Variable	Diabetes, No nephropathy n=168	Diabetes, CKD stage 2 n=151	Diabetes, CKD stage 3a n=76	Diabetes, CKD stage 3b n=47	Diabetes, CKD stage 4-5 n=55
Age (years)	60.5±9.9	62.1±9.6	67.7±8.8*	68.9±8.5*	73.9±10.6*
Male, n (%)	104 (61.9)	107 (70.9)	49 (64.5)	34 (72.3)	31 (56.4)
BMI (kg/m^2)	24.8±3.0	25.2±3.1	24.9±3.5	25.9±3.1†	23.7±3.2†
eGFR (ml/min per 1.73 m^2)	99.3±11.0	77.3±7.7*	53.5±4.4*	37.8±4.7*	22.9±6.3*
Hemoglobin (g/dL)	13.8±2.6	13.8±1.6	12.9±2.3*	12.0±1.7*	10.9±1.3*
BUN (mg/dL)	14.4±4.3	16.0±4.3*	22.1±11.7*	29.0±8.2*	45.4±22.4*
Cr (mg/dL)	0.7±0.1	1.0±0.2*	1.4±0.7*	1.8±0.3*	2.9±1.3*
Serum Glucose, fasting (mg/dL)	137.8±38.9	135.4±28.6	135.9±36.9	136.2±40.6	144.5±47.4
Total protein (g/dL)	6.7±0.7	6.9±0.5†	7.0±0.5*	7.0±0.5*	6.6±0.7
Albumin (g/dL)	4.4±0.4	4.4±0.4	4.4±0.4	4.3±0.3†	4.0±0.5*
Urine protein (mg/day)	70.3±499.4	120.3±508.6	482.4±940.7*	1020.4±2070.6*	2128.7±3026.1*
Medications					
OHAs/Insulin, n (%)	133 (79.2)	142 (94.0)*	58 (76.3)	37 (78.7)	42 (76.4)
ARBs/ACEIs, n (%)	121 (72.0)	120 (79.5)	66 (86.8)†	40 (85.1)	50(90.9)†
BB, n (%)	49 (29.2)	46 (30.5)	30 (39.5)	21 (44.7)†	34 (61.8)*
CCB, n (%)	73 (43.5)	74 (49.0)	39 (51.3)	15 (31.9)	34 (61.8)†
Diuretics, n (%)	9 (5.4)	17 (11.3)	20 (76)*	19 (40.4)*	28 (50.9)*
EPO, n (%)	0	0	2 (2.6)*	8 (17.0)*	22 (40)*

Note : Data expressed as mean ± standard deviation or percentage.
Abbrevations : CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Cr, creatinine OHAs, oral hypoglycemic agents; BB, beta-blocker; CCB, calcium-chennel blocker; EPO, erythropoietin.
$^\dagger P < 0.05$ compared with control.
$^* P < 0.001$ compared with control.

Demographic and laboratory characteristics of study population are summarized in Table 1. All patients were stratified into 5 groups,[16] and the continuous variables in CKD groups including stage 2, 3a, 3b and 4-5 were compared with the results in diabetic controls without nephropathy. The number of patients in controls and CKD stage 2, 3a, 3b and 4-5 were consisted of 168, 151, 76, 47 and 55 subjects, respectively. Diabetic controls had an eGFR of 99.3 ± 11.0 ml/min per 1.73 m^2 and the eGFR in CKD stage 2, 3a, 3b and 4-5 were 77.3 ± 7.7, 53.5 ±

4.4, 37.8 ± 4.7 and 22.9 ± 6.3 ml/min per 1.73 m^2, respectively. Worsening of anemia was observed in advanced CKD stages, the hemoglobin level in CKD stage 3a (12.9 ± 2.3 g/dL), 3b (12.0 ± 1.7 g/dL) and 4-5 (10.9 ± 1.3 g/dL) was significantly lower than the controls (13.8 ± 2.6 g/dL). The number of patients receiving EPO supplementation increased as their renal function worsened. Less than 3 % of patients in stage 3a were receiving EPO. In contrast, up to 40 % of patients in stage 4-5 were receiving EPO supplementation and mean weakly dose of EPO in stage 3a, 3b, and 4-5 were 72.37 ± 445.0, 579.8 ± 1474.5 and 1259.1 ± 1976.1 U/week, respectively. A similar results were observed for the serum albumin with significantly lower levels in CKD stage 3b (4.3 ± 0.3 g/dL) and 4-5 (4.0 ± 0.5 g/dL) than the controls (4.4 ± 0.4 g/dL). In addition, urine protein in CKD stage 3a (482.4 ± 940.7 mg/day), 3b (1020.4 ± 2070.6 mg/day) and 4-5 (2128.7 ± 3026.1 mg/day) was significantly higher than the controls (70.3 ± 499.4 mg/day). Interestingly, 15 patients (3%) showed nephrotic range proteinuria and they were found in CKD stage 1 (n = 1), 2 (n = 1), 3a (n = 1), 3b (n = 3) and 4-5 (n = 9), respectively.

Table 2. The parameters of glycemic control for 5 groups

Variable	Diabetes, No nephropathy n=168	Diabetes, CKD stage 2 n=151	Diabetes, CKD stage 3a n=76	Diabetes, CKD stage 3b n=47	Diabetes, CKD stage 4-5 n=55
Glucose, fasting (mg/dL)	137.8±38.9	135.4±28.6	135.9±36.9	136.2±40.6	144.5±47.4
HbA_{1c} (%)	7.4±1.6	7.5±1.2	7.3±1.3	7.5±1.5	6.9±1.1†
GA%	19.0±6.2	19.2±5.6	19.7±6.4	20.8±7.3	20.8±6.3
GA/HbA_{1c}	2.5±0.4	2.5±0.4	2.6±0.5	2.7±0.6†	3.0±0.6*
Serum glucose/HbA_{1c}	18.2±2.8	18.2±2.6	18.7±3.5	17.9±3.6	20.8±4.9*
Serum glucose/GA	7.2±1.0	7.2±1.2	7.3±1.7	7.0±1.4	7.0±0.7

Note : Data expressed as mean ± standard deviation or percentage.
Abbrevations : CKD, chronic kidney disease; GA, clycated albumin; HbA1c, hemoglobin A1c.
$^{\dagger}P < 0.05$ compared with control.
$^{*}P < 0.001$ compared with control.

Table 2 summarizes the parameters of glycemic control in study patients. The last three monthly fasting serum glucose concentrations did not differ significantly among 5 groups. Also, the GA and serum glucose/GA ratio were constant throughout all of 5 groups. In contrast, the HbA1c level in CKD stage 4-5 (6.9 ±

1.1 %) was significantly lower than the controls (7.4 ± 1.6 %), and the GA/HbA1c and serum glucose/HbA1c ratio in CKD stage 4-5 were 3.0 ± 0.6 and 20.8 ± 4.9, respectively, all of which were significantly higher than the corresponding results of 2.5 ± 0.4 and 18.2 ± 2.8 in diabetic controls.

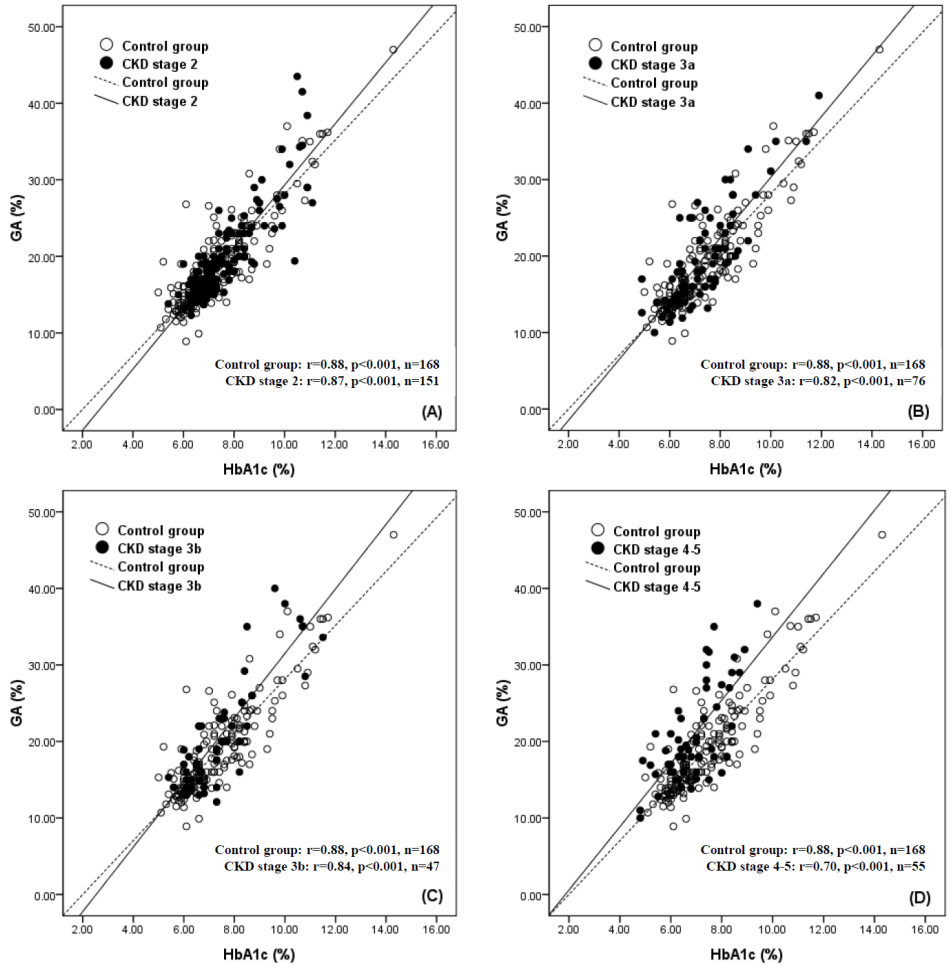

Figure 1. The correlations between the HbA1c and GA in pre-dialysis diabetic CKD patients compared with the controls.

Figure 1 shows the correlations between the HbA1c and GA in pre-dialysis diabetic CKD patients compared with diabetic controls. There were positive and

significant correlations between the HbA1c and GA in controls and CKD patients, respectively. Furthermore, significant differences in the slopes of regression line among controls (slope = 3.52) and CKD patients (slopes in CKD stage 2, 3a, 3b and 4-5 = 4.00, 3.97, 4.22 and 4.14, respectively) was observed ($p < 0.05$, Figure 1). This is demonstrated by increased steepness in slope of regression line between HbA1c and GA with decline in renal function.

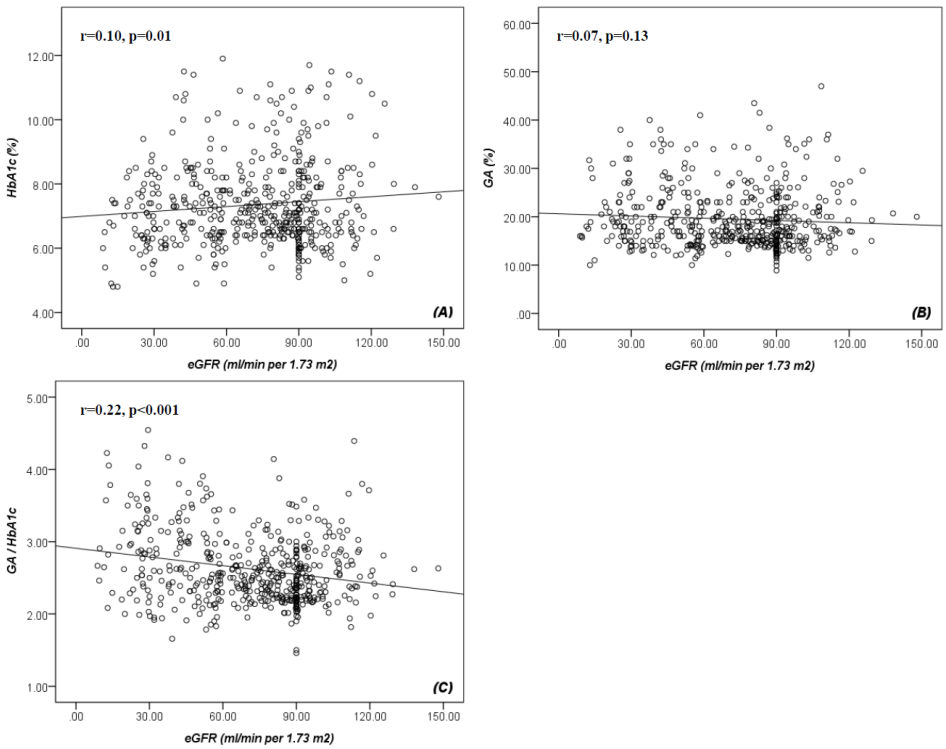

Figure 2. The correlations between eGFR (ml/min per 1.73 m^2) and glycemic control markers.

Moreover, as shown in Figure 2, a positive and significant correlation was observed between the HbA1c and eGFR [$p < 0.05$, Figure 2(A)], and a positive and significant correlation was observed between the GA/HbA1c ratio and eGFR [$p < 0.05$, Figure 2(C)]. In contrast, the GA showed no significant correlation with eGFR [$p = 0.13$, Figure 2(B)].

Table 3. Multivariate analysis of factors associated with HbA1c or GA in CKD stage 3 and 4-5

Variable	HbA_{1c} full model *P*-value	HbA_{1c} reduced model *P*-value	GA full model *P*-value	GA reduced model *P*-value
Age	0.80	NS	0.14	0.03
gender	0.28	NS	0.88	NS
BMI	0.001	<0.001	0.20	NS
Serum glucose	<0.001	<0.001	<0.001	<0.001
Hemoglobin	0.81	NS	0.21	NS
Total protein	0.47	NS	0.58	NS
Albumin	0.61	NS	0.58	NS
Urine protein	0.78	NS	0.16	NS
EPO dose	0.02	0.02	0.79	NS

Multivariate analysis was performed to evaluate which factors independently associated with the HbA1c or GA in CKD stage 3a, 3b and 4-5 (Table 3). In a reduced best-fit model where age, gender, BMI, serum glucose, hemoglobin, total protein, albumin, urine protein (excepted for nephrotic range proteinuria) and EPO dose were included, the HbA1c was significantly associated with BMI ($p < 0.001$), serum glucose ($p < 0.001$) and EPO ($p = 0.02$). And the GA was significantly associated with age ($p = 0.03$) and serum glucose ($p < 0.001$).

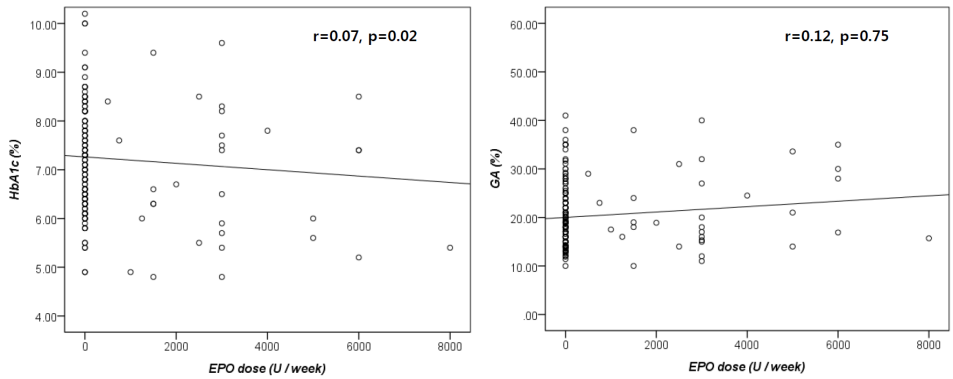

Figure 3. A relationships between the HbA1c or GA level and weekly EPO dose.

Figure 3 shows a relationship between the HbA1c or GA level and weekly EPO dose after adjustment for covariates including age, gender, BMI, serum glucose, hemoglobin, total protein, albumin and urine protein. There was a significant and negative correlation between the HbA1c and weekly EPO dose [$p = 0.02$, Figure 3(A)]. The GA, however, did not significantly correlate with EPO dose [$p = 0.75$,

Figure 3(B)].

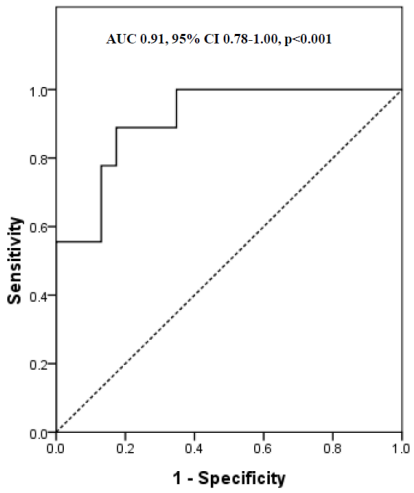

Figure 4. ROC curve for weekly EPO dose altered HbA1c level.

We evaluated the weekly EPO dose altered the HbA1c level in CKD stage 3a, 3b and 4-5 (Figure 4). ROC analysis comparing the HbA1c level in control patients not received the EPO therapy with 32 patients who received EPO supplementation showed an AUC of 0.91 (95% *CI* 0.78 – 1.00, $p < 0.001$, Figure 4), and a cut-off value of weekly EPO dose was 6000 U/week and sensitivity and specificity of this value was 89% and 83%, respectively.

IV. DISCUSSION

In our study, the GA was shown to provide a more accurate marker to assess glycemic control even in pre-dialysis diabetic CKD patients, however, the HbA1c falsely underestimated the glycemic state. The HbA1c is currently the most widely used glycemic control marker, and the diabetic CKD patients were recommended the hemoglobin A1c (HbA1c) level of 7.0 % to prevent or delay progression of the microvascular complications[4]. In previous reports, the HbA1c assay has serious limitations with falsely underestimating glycemic state in ESRD patients on

hemodialysis.[9, 18] However it was unclear whether the limitations of HbA1c extended to pre-dialysis diabetic CKD patients. Although the GA which not influenced by diseases of shortened RBC life span, and use of iron supplements and EPO therapy provides a reliable marker of glycemic control than the HbA1c in ESRD patients, there are not many studies on GA also provides a more appropriate assay to assess glycemic control in pre-dialysis diabetic CKD patients.[12, 13] Our results provide a supportive evidence of relationships between the HbA1c or GA and serum glucose concentration at different CKD stages in pre-dialysis diabetic CKD patients and demonstrate that the HbA1c also underestimates significantly glycemic status in pre-dialysis diabetic CKD patients, especially CKD stage 4-5, whereas the GA was shown to correlate closely with the mean serum glucose concentration.

The HbA1c primarily reflects mean serum glucose levels over time and does not reflect glycemic excursions. On the other hand, the GA correlates with maximum blood glucose levels in diabetic patients and reflects glycemic excursions as well as mean serum glucose.[19] Recent the usefulness of the GA/HbA1c ratio (corrected for HbA1c) was shown to reflect the blood glucose variability and glycemic excursions within diabetic treatment. In addition, the GA/HbA1 is consistently increased in ESRD patients, further confirming the notion that HbA1c underestimates and inaccurately reflects long-term glycemia in this population. Therefore many clinical trials have compared the GA/HbA1c ratio between diabetic patients without nephropathy and ESRD patients on hemodialysis to find which glycemic control marker is more appropriate to reflect glycemic control.[10, 17, 20] We also assessed the GA/HbA1c ratio in pre-dialysis diabetic CKD patients. Freedman et al.[20] reported that the GA/HbA1c ratio in diabetic patients without nephropathy was 2.22, and the results in ESRD patients on hemodialysis were 2.93 which were significantly higher than controls ($p < 0.05$). Our data was reported the GA/HbA1c ratio was 2.5 ± 0.4 in diabetic patients without nephropathy, and the results in patients with CKD stage 3b and stage 4-5 were 2.7

± 0.6 and 3.0 ± 0.6, respectively which were significantly higher than in the controls ($p < 0.05$). In addition, the glucose/HbA1c ratio between patients in the controls and CKD stage 4-5 differed significantly, however the glucose/GA ratio was constant among groups. These results indicate that the HbA1c has a severe limitation with underestimation of glycemic control and the GA is to be a better indicator of glycemic control in pre-dialysis diabetic CKD patients, especially CKD stage 4-5. We also identified the reduction of HbA1c in advanced CKD stages by increased steepness in slope of regression line between the HbA1c and GA with decline in renal function (Figure 1).

The HbA1c values are influenced by several factors that alter the survival of red blood cells.[21] Many studies reported that several features including use of iron, EPO treatment,[9, 18] uremia and blood transfusions[8] in ESRD patients on hemodialysis contribute to reduction of 20-50% of normal RBC life-span, and the subsequent increased rate of hemoglobin turnover leads to decreased exposure time to ambient glucose that in turn lowers the extent of non-enzymatic binding of glucose to hemoglobin.[22] In addition, the glycated rate of just-produced young erythrocyte is reported to be lower than that of old cells.[23] As a result, the shortened RBC survival in ESRD patients lowers the HbA1c level, potentially making it unreliable in assessing glycemic control[10]. However the GA is not affected by RBC survival, iron supplement or EPO therapy commonly used in ESRD patients. Also, the GA was not associated with serum albumin concentration since the GA value is determined as ratio of GA concentration to total serum albumin.[24] Consistent with previous study,[10, 20] we also performed the multivariate analysis to investigate factors that influence on HbA1c and GA. The HbA1c was independently associated with serum glucose, weekly dose of EPO and BMI (Table 3), and the HbA1c level was shown to be significantly lower with increasing of EPO, while the GA was not associated with EPO (Figure 3). In addition, the GA was significantly associated with serum glucose and age (Table 3). Kaysen et al.[25] resulted the influence of proteinuria on serum albumin in

patients with nephrotic syndrome that albumin synthesis and fractional catabolic rate of albumin is increased, resulting in rapid albumin turnover and decreased GA values. Okada et al.[26] also reported that nephrotic-range proteinuria (urine protein ≥ 3.5 g/day) decreases the GA values independent of the glycemic state, however, non-nephrotic range proteinuria (urine protein ≤ 3.5 g/day) has no significant influence on the GA values in diabetic CKD patients. In our study, almost patients except for 15 people has urine protein ≤ 3.5 g/day, and we also demonstrated the result that GA was not affected by non-nephrotic range proteinuria. Furthermore some clinical trials reported that BMI negatively influenced GA levels in diabetic patients since the turnover of serum albumin may be increased in obese subjects, which sets serum GA at lower levels relative to plasma glucose concentrations.[27, 28] However, we failed to find a correlation between GA levels and BMI in our study.

Additionally, we evaluated the weekly EPO dose altered the HbA1c level in 32 patients who received EPO therapy. The cut-off value for weekly EPO dose was 6000 U/week, and sensitivity and specificity of this value were 89% and 83%, respectively. Use of EPO in CKD patients under the health insurance system in Korea is allowed upto hemoglobin level of less than 11.0 mg/dL and considered mainly so that the hemoglobin level is maintained between 10 - 11 mg/dL. For this reason, patients who received EPO therapy in this study were just 32 people and 3 months mean hemoglobin variation (delta Hb) in these patients was -0.01 mg/dL. Although the cut-off value for weekly EPO dose in this study was 6000 U/week and was relatively low level, it is very meaningful to measure the EPO dose altered the HbA1c level. Therefore, additional studies including more patients using EPO therapy and larger dose of EPO are needed to obtain the reliable cut-off value.

In conclusion, our findings are interpreted that the GA rather than HbA1c is a better indicator of glycemic control even in pre-dialysis diabetic CKD patients, especially using weekly EPO dose more than 6000 U/week.

There are some limitations in this study. The mean serum glucose concentration was calculated by the mean values of the 3 monthly measurements of fasting serum glucose. Previous studies reported that fasting hyperglycemia is the predominant factor contributing to the overall diurnal hyperglycemia status in poorly controlled diabetic patients, whereas postprandial glucose elevations play the greater role in subjects with better glycemic control.[29, 30] These discrepancy between fasting serum glucose and postprandial serum glucose is a weakness of this study.

V. CONCLUSION

In conclusion, our results indicate that the HbA1c underestimates the glycemic control state even in pre-dialysis diabetic CKD patients, especially those who are on EPO treatment and the GA might be an useful indicator of glycemic control in pre-dialysis diabetic CKD patients.

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ABSTRACT(IN KOREA)

투석 전 단계의 당뇨병성 만성 신부전 환자에서 혈당 조절의 지표로서 당화 알부민

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배 성 창

ABSTRACT

배경 당뇨환자에서 적절한 혈당 조절은 신질환의 진행을 늦추고 심혈관계 합병증을 줄여준다. 최근, 혈당 조절의 지표로서 일반적으로 사용되고 있는 당화 혈색소가 혈액투석 치료를 받는 당뇨병성 말기 신부전 환자에서 혈당을 정확히 측정하지 못한다는 여러 연구들이 있었다. 반면, 당화 알부민은 말기 신부전 환자에서 흔히 나타나는 적혈구 수명의 단축, 철분제의 및 조혈제의 사용 등에 의해 영향을 받지 않기 때문에 말기 신부전 환자에서 혈당을 보다 정확히 측정한다는 많은 보고들이 있었다. 본 연구에서는 투석 전 단계의 당뇨병성 만성 신부전 환자에서 혈당 조절의 지표로서 당화알부민의 유용성을 연구하고자 하였다.

방법 2009년 3월부터 2012년 8월까지 본원 신장내과와 내분비내과에서 3개월 이상 안정적으로 치료를 받고 있는 투석 전 단계의 제2형 당뇨 환자 497명이 연구에 참여되었다. 연구에 참여된 모든 환자는 2012 KDIGO 에서 제시하는 만성 신부전 분류에 따라 5 그룹으로

나뉘어졌고, 나이, 성별, 체질량 지수, 혈액 검사, 소변 검사 및 약제 복용력 등의 임상 정보와 함께 공복 혈당, 당화 혈색소, 당화 알부민 등의 혈당 지표를 측정 하였다.

결과 각 그룹별로 환자의 수는 1단계 (대조군)부터 4-5단계까지 각각 168, 151, 76, 47, 55 명이었다. 모든 그룹에서 당화 혈색소와 당화 알부민은 유의한 양의 상관 상관관계를 보였지만 당화 혈색소와 당화 알부민 사이의 회귀 곡선의 기울기는 신부전이 진행함에 따라 통계적으로 유의하게 커지는 양상을 보였다. (대조군 vs. 그 외 만성 신부전 그룹: $p < 0.05$). 당화알부민/당화혈색소의 비와 평균 공복 혈당/당화혈색소의 비는 3b단계와 4-5단계에서 대조군에 비해 유의하게 높았고 당화알부민/당화혈색소의 비는 신부전이 진행함에 따라 증가하는 경향을 보였다 ($r = 0.22$, $p < 0.001$). 하지만 평균 공복 혈당/당화알부민의 비는 모든 그룹에서 일정하였다 ($r = 0.07$, $p = 0.06$). 몇 가지 인자들을 보정한 후에 시행한 다변량 분석에서는 조혈제가 당화혈색소와 통계적으로 유의하게 관련이 있었고 ($p = 0.02$), 이 때 당화혈색소 값을 변화시키는 조혈제 용량을 ROC curve 를 통해 구한 결과 cut off 값은 주당 6000 단위로 나타났다 (AUC = 0.91, 95% CI 0.78 - 1.00).

결론 투석 전 단계의 당뇨병성 만성 신부전 환자에서 특히 조혈제를 사용하는 경우, 당화 혈색소는 혈당을 적절히 반영하지 못하며, 당화 알부민이 당화 혈색소보다 유용한 혈당 조절의 지표일 수 있다.

핵심되는 말 : 당뇨병성 만성 신질환, 당화 혈색소, 당화 알부민