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Usefulness of glycated albumin as a predictor of mortality in chronic hemodialysis patients with diabetes: a multi-center, prospective cohort study

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Abstract

Background: The association of glycated albumin (GA) with mortality is unclear in chronic hemodialysis patients with diabetes. We investigated the usefulness of GA by comparing it with hemoglobin A1c (HbA1c) in this patient population.

Research design and methods: This was a multi-center, prospective cohort study of 841 Japanese chronic hemodialysis patients with diabetes. There were 235 women and 606 men included, with a mean age of 64 years. The primary and secondary endpoints were the incidence of all-cause and cause-specific mortality, respectively. The hazard ratios of GA and HbA1c for the endpoints were estimated using the values at baseline and during the study period.

Results: During the mean follow-up period of 3.1 years, there were 184 deceased cases, in which 30 and 154 resulted from atherosclerotic cardiovascular disease (ASCVD) and non-ASCVD, respectively. The hazard ratio for a 1% increase in GA was 1.033 (95% confidence interval 1.006–1.060, $p = 0.017$) for all-cause mortality with a statistical significance when GA was treated as a time dependent variable, but not when the baseline levels or the mean levels during the follow-up period were used in the analysis ($p = 0.815$ and 0.517 , respectively). GA was a significant predictor for ASCVD-related mortality in the above 3 models, but was not for non-ASCVD mortality. Higher levels of HbA1c were only associated with ASCVD-related mortality when HbA1c was treated as a time-dependent variable.

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Conclusions: GA may be useful compared to HbA1c for predicting all-cause and ASCVD-related mortality in Japanese patients with diabetes undergoing chronic hemodialysis.

Background

The importance of glycemic control for preventing the development and progression of microvascular complications in patients with diabetes has been well established through substantial randomized controlled trials [1]; nonetheless, the role in these patients undergoing chronic dialysis remains unclear, due to a lack of the randomized controlled trials in this patient population. Previous cohort studies have reported that higher levels of hemoglobin A1c (HbA1c), the gold standard indicators of glycemic control, predicted all-cause and cardiovascular mortality in patients with diabetes undergoing chronic hemodialysis [2–4]. However, in patients with advanced stage of diabetic kidney disease (DKD), HbA1c values are underestimated due to unpredictable changes in the survival time of erythrocyte, leading to the unreliability of the HbA1c values [5, 6].

Glycated albumin (GA), reflecting average glucose levels during the preceding 2 to 3 weeks, has been shown to be preferable to HbA1c for the assessment of glycemic control in chronic hemodialysis patients with diabetes because GA levels are not affected by the life span of erythrocytes [5–7]. To date, few large cohort studies have reported an association between GA and mortality in such patient population [8, 9]; moreover, these studies were retrospectively designed and did not evaluate GA values during the study period, although these levels can vary over time. Here, we prospectively investigated the usefulness of GA, assessed based on both baseline and follow-up values, with respect to mortality by comparing it with HbA1c in Japanese chronic hemodialysis patients with diabetes.

Materials and methods

Study design and participants

This multi-center, prospective cohort study (UMIN clinical trial registry number: UMIN000009036) was designed in adherence to the Declaration of Helsinki, and was approved by the Ethics Committee of Tokyo Women's Medical University School of Medicine. All patients provided written informed consent. A total of 972 adult patients with diabetes receiving chronic hemodialysis at 39 Japanese medical institutions were recruited between April 2013 and August 2015 for the present study. At baseline, patients with a dialysis vintage less than 6 months or unknown ($n = 40$) were excluded. This was because previous large cohort studies of chronic hemodialysis patients have shown that the effects of glycemic control on mortality with short dialysis vintage, especially of less than 6 months, were noticeably different from those with the

longer vintage [4, 10]. Patients who had malignant disease ($n = 22$), acute severe infection ($n = 16$), or who had missing baseline profile values ($n = 6$) were excluded. Patients with liver cirrhosis ($n = 7$) or dysthyroidism ($n = 40$) were also excluded because these conditions may impact GA [11, 12]. Overall, data obtained from 841 participants were analyzed in the present study (Supplementary Figure 1).

Measurements

Laboratory data were collected before each dialysis session in 808 patients. For the remaining 33 patients, random spot blood samples were taken when they visited Tokyo Women's Medical University School of Medicine for the purpose of glycemic control. The samples were analyzed at a central laboratory. GA, HbA1c, and glucose levels, most of them were sampled postprandially, were determined by an enzymatic method using the following: Lucica GA-L, Asahi Kasei Pharma Co., Ltd., Tokyo, Japan; MetaboLead HbA1c, Kyowa Medex Co., Ltd., Tokyo, Japan; and IatroLQ GLU, Unitika Co., Ltd., Osaka, Japan; respectively. GA, HbA1c, and glucose levels were measured at baseline and every 6 months thereafter during the follow-up period. Other laboratory data were measured at baseline. Information on dialysis vintage, type of diabetes, medication, atherosclerotic cardiovascular disease (ASCVD), smoking status, body mass index (BMI), and blood pressure at baseline were obtained from medical records at each institution.

Endpoints and follow-up

The primary and secondary endpoints were the incidence of all-cause and cause-specific mortality, respectively, the latter of which was classified into ASCVD-related and non-ASCVD-related mortality. Ischemic heart diseases including acute myocardial infarction, cerebral hemorrhage, and cerebral infarction were defined as causes of ASCVD-related death. Patients were censored when they underwent kidney transplantation, transferred to a different medical institution, lost to follow-up, or at the administrative censoring date (December 31, 2017).

Statistical analysis

All analyses were completed using the SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as the arithmetic mean \pm standard deviation (SD), or median (interquartile range, IQR), as appropriate. Categorical data were expressed as number (%). A linear correlation between 2 variables was assessed using the Pearson correlation coefficient. A

cumulative incidence of the endpoints was estimated using the Kaplan-Meier method. The multivariate Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CIs). Possible nonlinear associations were examined using the multivariable-adjusted restricted cubic spline model [13], with the 3 knots placed at the 10th, 50th, and 90th percentile levels. A comparison regarding the predictability of GA and HbA1c levels for time to the endpoints was assessed using the Uno's overall C-statistics [14]. Three sets of models were used to calculate the hazard ratios (and 95% CI) of GA and HbA1c levels for the endpoints: model 1, in which the hazard ratios were estimated using baseline GA or HbA1c values; model 2, which used mean values of GA or HbA1c during the follow-up period; and model 3, in which GA or HbA1c values during the follow-up period were treated as time-dependent variables. All hazard ratios were adjusted by the following variables: age, sex, dialysis vintage, type of diabetes, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, history of ASCVD, BMI, systolic blood pressure, hemoglobin, serum albumin, corrected calcium, phosphate, and non-high-density lipoprotein cholesterol. Original clinical factors used for the calculation of the overall C-statistics consisted of the above 13 variables. Variation inflation factors (VIF) were calculated to check the multicollinearity of the 13 variables; the values greater than 10 indicate severe multicollinearity [15], and all VIFs among the 13 variables were less than 2. The measurements of GA and HbA1c in 118 patients were partly missed after the study began. The imputation of the missing data was not conducted and only available data during the periods were used in the analyses. A two-tailed p value less than 0.05 was considered significant.

We conducted several sensitivity analyses as follows. First, we tested whether there are differences in the effects of GA levels on the endpoints depending on the serum levels of albumin. Second, we used the Fine and Gray subdistribution hazards model, considering the presence of competing risks [16, 17]. In the present study, non-ASCVD-related death was treated as a competing risk in the analysis examining time to ASCVD-related death, and vice versa. Third, we made a model added diabetes therapy as covariates. Finally, we analyzed a model added levels of logarithmically transformed high-sensitivity C-reactive protein, closely associated with mortality in dialysis patients [18].

Results

Baseline characteristics

Of the 841 patients studied, there were 235 women and 606 men, with a mean (\pm SD) age of 64 ± 12 years. Median (IQR) dialysis vintage was 4.5 years (2.4–7.9 years).

Mean values of GA and HbA1c at baseline were $21.4 \pm 5.0\%$ and $6.4 \pm 1.1\%$, respectively. There was a positive and significant association between GA and HbA1c ($r = 0.705$, $p < 0.001$). Glucose levels also had a significant positive association with GA ($r = 0.419$, $p < 0.001$) and HbA1c levels ($r = 0.390$, $p < 0.001$), respectively. Other clinical characteristics and laboratory data are presented in Table 1.

Association of GA and HbA1c with mortality

During the mean (\pm SD) follow-up period of 3.1 ± 1.3 years, there were 184 deceased cases, in which 30 and 154 resulted from ASCVD and non-ASCVD, respectively (Fig. 1). The details of death from ASCVD were ischemic heart diseases in 12 patients and stroke in the other 18 patients. These from non-ASCVD were heart failure in 44 patients, infection in 23 patients, cancer in 16 patients, other causes in 30 patients, and unknown causes in the other 41 patients. Five patients underwent kidney transplantation, 143 were transferred to another institution, and 17 were lost to follow-up. As shown in Table 2, the hazard ratio for a 1% increase in GA was 1.033 (95% CI 1.006–1.060, $p = 0.017$) for all-cause mortality, with a statistical significance in the analysis treating GA as a time dependent variables (model 3). GA was a significant predictor for ASCVD-related mortality in all 3 models, but was not for non-ASCVD-related mortality. Higher levels of HbA1c were only associated with ASCVD-related mortality in model 3; meanwhile, the lower levels had a significant association with non-ASCVD-related mortality in the analysis using baseline HbA1c levels (model 1).

Next, we verified whether there is nonlinearity in the associations of GA and HbA1c with the time to reach the endpoints. The nonlinear association was rejected in all analyses using baseline GA and HbA1c values (Fig. 2). In the analyses using the mean values during the follow-up period, the results were not changed (Supplementary Figure 2).

Finally, we compared the predictability of GA and HbA1c for each endpoint (Table 3). When adding GA or HbA1c values to the 13 original clinical factors, there was no significant improvement in the overall C-statistics in any analysis. The C-statistics of original factors plus GA were not significantly different from those adding HbA1c in any analysis (Table 3).

Sensitivity analyses

There was no interaction between albumin and GA levels with respect to the endpoints in any analysis (Supplementary Tables 1). When patients were classified into 2 groups by the median of serum albumin levels (3.6 g/dL), similar results to the above were obtained (Supplementary Tables 1). In the Fine and Gray subdistribution

Table 1 Baseline demographic and laboratory data

	Overall (n = 841)
Age	64 ± 11 years
Men	606 (72.1%)
Dialysis vintage	4.5 years (2.4–7.9)
Type 1 diabetes	75 (8.9%)
Diabetes therapy	
Insulin	344 (40.9%)
Other medication	369 (43.9%)
ACE inhibitors or ARBs	552 (65.6%)
Other antihypertensive drugs	600 (71.3%)
Statins	272 (32.3%)
History of ASCVD	333 (39.6%)
Current smoker	168 (20.0%)
Body mass index	23.5 ± 4.0 kg/m ²
SBP	154 ± 23 mmHg
DBP	78 ± 13 mmHg
Laboratory data	
GA	21.4 ± 5.0%
HbA1c	6.4 ± 1.1%
Glucose	145 ± 55 mg/dL
Hemoglobin	10.8 ± 1.1 g/dL
Albumin	3.6 ± 0.3 g/dL
Urea nitrogen	59.3 ± 15.2 mg/dL
Creatinine	10.5 ± 2.6 mg/dL
Potassium	4.9 ± 0.7 mEq/L
Corrected calcium	9.5 ± 0.7 mg/dL
Phosphate	5.6 ± 1.4 mg/dL
HDL cholesterol	45 ± 15 mg/dL
Non-HDL cholesterol	109 ± 32 mg/dL

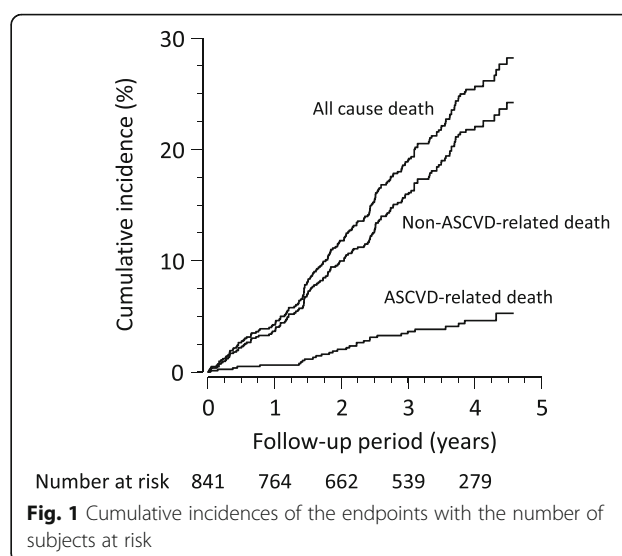
Data are expressed as mean (standard deviation), median (interquartile range), or number (percentage)

ACE angiotensin-converting enzyme, ARBs angiotensin receptor blockers, ASCVD atherosclerotic cardiovascular disease, SBP systolic blood pressure, DBP diastolic blood pressure, GA glycated albumin, HbA1c hemoglobin A1c, HDL high-density lipoprotein

hazards models, similar findings to the above were obtained (Supplementary Tables 2). In models added diabetes therapy or levels of logarithmically transformed high-sensitivity C-reactive protein, similar results were obtained (Supplementary Tables 3 and 4).

Discussion

In this prospective cohort study, we have shown the usefulness of GA, assessed based on both baseline and follow-up values, for predicting all-cause and ASCVD-related mortality in chronic hemodialysis patients with diabetes. The robustness of this finding was strengthened by conducting sensitivity analyses. Meanwhile, higher levels of HbA1c were only associated with



ASCVD-related mortality when treated as a time-dependent variable, suggesting that GA is a preferable predictor for mortality compared to HbA1c in chronic hemodialysis patients with diabetes.

In the present study, GA levels at baseline were not associated with all-cause mortality, unlike those assessed as time-dependent variables, which was inconsistent with previous reports [8, 9, 19, 20]. It is considered that the Cox regression model with time-dependent variables estimates the short-time effects of exposures, while that with baseline variables estimates the long-time effects [21, 22]. Therefore, the present findings may suggest that short-term glycemic control has effects on mortality in chronic hemodialysis patients with diabetes, consistent with the present results showing no association of mean GA values during the follow-up period with all-cause mortality. A large retrospective cohort study in a similar patient population from Japan showed a significant association between increased GA levels at baseline and all-cause mortality over a short follow-up duration of 1 year [9], although the difference from the present findings may simply be explained by the sample size. Another retrospective study with the longer follow-up periods of 4 years using the German Diabetes and Dialysis Study cohort showed that higher levels of GA at baseline were a significant predictor for all-cause mortality [8]. However, the incidence of cardiovascular mortality in chronic hemodialysis patients in Western countries is obviously higher than that in Japan [23–25]. In the present study, higher levels of GA were associated with ASCVD-related mortality in all models; therefore, the difference in the incidence of cardiovascular disease as the cause of death might explain the inconsistency between the German Diabetes and Dialysis Study and present study.

Table 2 Hazard ratio of 1% increase in GA and HbA1c levels for each endpoint

Cause of death	GA			HbA1c	
		Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
All-causes	Model 1	1.00 (0.97–1.03)	0.815	0.87 (0.74–1.02)	0.088
	Model 2	1.01 (0.98–1.05)	0.517	0.92 (0.77–1.11)	0.392
	Model 3	1.03 (1.01–1.06)	0.017	1.01 (0.87–1.17)	0.888
ASCVD	Model 1	1.08 (1.01–1.15)	0.016	1.12 (0.80–1.58)	0.518
	Model 2	1.09 (1.02–1.17)	0.013	1.14 (0.78–1.66)	0.501
	Model 3	1.10 (1.05–1.16)	< 0.001	1.35 (1.02–1.77)	0.033
Non-ASCVD	Model 1	0.99 (0.95–1.02)	0.477	0.82 (0.68–0.99)	0.034
	Model 2	0.99 (0.96–1.03)	0.686	0.88 (0.71–1.08)	0.206
	Model 3	1.01 (0.98–1.05)	0.409	0.93 (0.78–1.10)	0.374

Model 1, in which the hazard ratios were estimated using baseline GA or HbA1c values; model 2, which used mean values of GA or HbA1c during the follow-up period; and model 3, in which GA or HbA1c values during the follow-up period were treated as time-dependent variables
 ASCVD atherosclerotic cardiovascular disease, GA glycated albumin, HbA1c hemoglobin A1c

Unlike previous studies [4, 9], the present study did not find a nonlinear association of GA and HbA1c with the study endpoints. This inconsistency may be due to a difference in the sample size. Indeed, the above study from Japan showed a linear mortality trend for GA; however, a sub-analysis using a larger cohort found that very low levels of GA (< 12.5%) were significantly associated with increased mortality

[9]. In the present study, the higher levels of HbA1c in the analysis treating HbA1c as a time dependent variables were associated with ASCVD-related mortality; meanwhile, the lower levels at baseline were a predictor for non-ASCVD-related mortality, consistent with previous large cohort studies showing a U-shaped association between HbA1c values and all-cause mortality [4, 9].

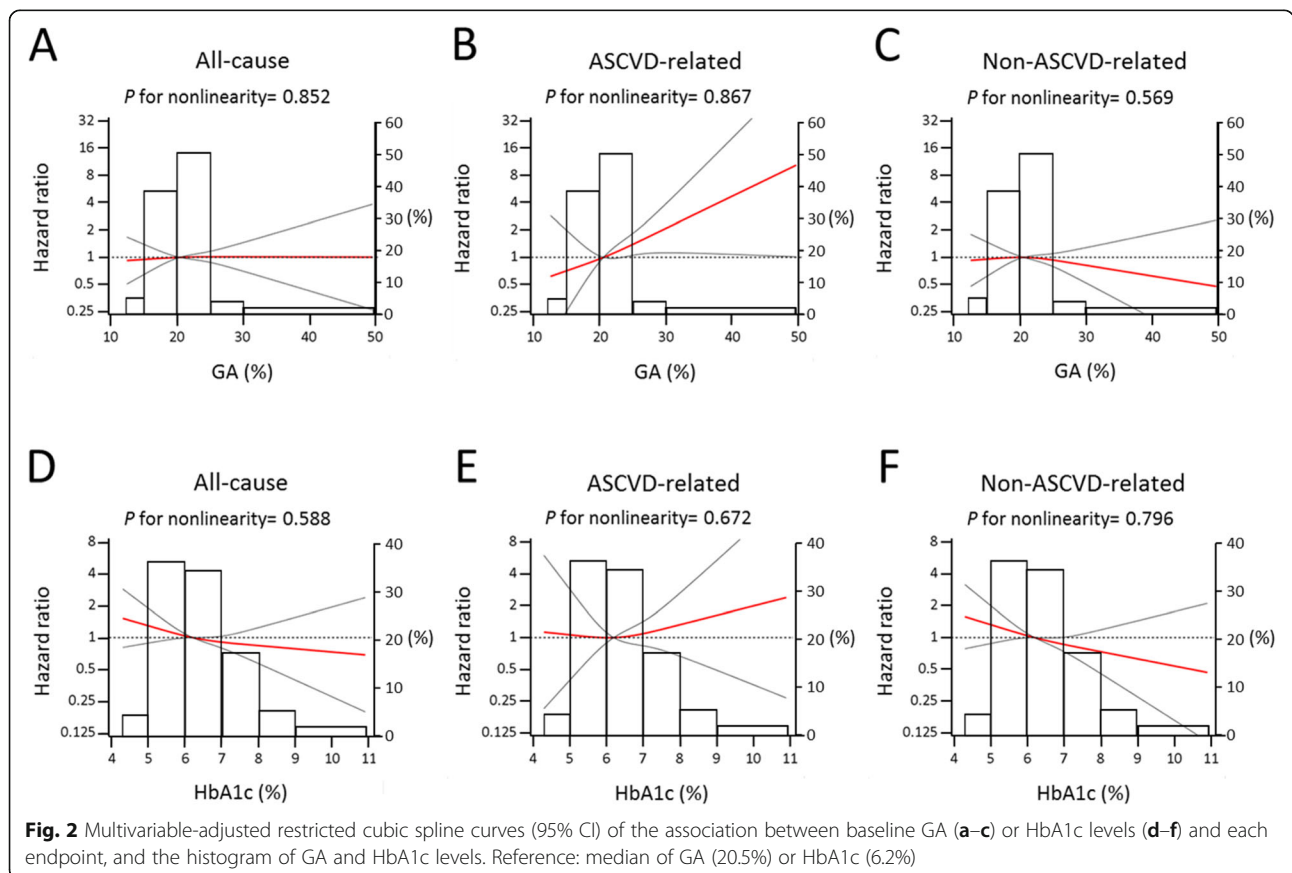


Table 3 Comparison of Uno's C-statistics for each endpoint

Model 1	Original factors	Original factors + GA	Original factors + HbA1c
All-causes	0.718 (0.024)	0.718 (0.020)	0.720 (0.019)
ρ value*		0.963	0.655
ρ value**			0.638
ASCVD	0.806 (0.049)	0.824 (0.055)	0.810 (0.053)
ρ value*		0.239	0.714
ρ value**			0.141
Non-ASCVD	0.728 (0.026)	0.730 (0.025)	0.735 (0.022)
ρ value*		0.622	0.264
ρ value**			0.279
Model 2	Original factors	Original factors + GA	Original factors + HbA1c
All-causes	0.718 (0.019)	0.718 (0.018)	0.718 (0.023)
ρ value*		0.871	0.993
ρ value**			0.921
ASCVD	0.806 (0.061)	0.817 (0.049)	0.809 (0.073)
ρ value*		0.464	0.794
ρ value**			0.430
Non-ASCVD	0.728 (0.027)	0.729 (0.023)	0.731 (0.026)
ρ value*		0.729	0.480
ρ value**			0.595

Model 1, in which the hazard ratios were estimated using baseline GA or HbA1c values; and model 2, which used mean values of GA or HbA1c during the follow-up period

ASCVD atherosclerotic cardiovascular disease, GA glycated albumin, HbA1c hemoglobin A1c

*vs Uno's C-statistics of original factors; **vs Uno's C-statistics of original factors plus GA

The addition of GA or HbA1c values to existing risk factors for mortality did not significantly improve predictability in the present study. Interestingly, a large cohort study of Canadian patients with diabetes reported that the increased risk of end-stage kidney disease associated with poor glycemic control was attenuated with lower kidney function [26], in spite of glycemic control being established as a major prognostic and interventional factor for early stage of DKD [1]. In light of these previous findings, together with the present study, glycemic control in patient with advanced stage of DKD has the modest or little impact on kidney function or mortality.

The present study had several limitations. First, study participants were from an ethnically homogenous population in Japan. Therefore, the generalizability of the present findings may be limited. Second, we were unable to clarify the causal relationship between GA or HbA1c and the endpoints because of the study design. Third, we did not evaluate time-dependent changes in blood

pressure, BMI, medication, or laboratory data other than indicators of glycemic control. Further, we did not obtain information regarding the use of erythropoiesis-stimulating agents. Fourth, we were also unable to conduct the analyses using the spline model and overall C-statistics considering time-dependent effects of GA and HbA1c values. Fifth, we did not conduct methods encouraging to account for bias due to missing data such as multiple imputation and inverse probability weighting. Finally, a considerable number of patients were transferred to a different medical institution or lost to follow-up, possibly biasing the present findings.

Conclusions

This multi-center, prospective cohort study provides evidence that GA may be useful compared to HbA1c for predicting all-cause and ASCVD-related mortality in Japanese chronic hemodialysis patients with diabetes. The importance of glycemic managements in this patient population should be confirmed in future randomized controlled trials targeting GA as indicators of glycemic control.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s41100-020-00264-1>.

Additional file 1. The association of GA with the endpoints. These tables show hazard ratios of 1 % increase in GA for each endpoint in sensitivity analyses. (docx 19.5KB)

Additional file 2. A flow diagram of the study population and multivariable-adjusted restricted cubic spline curves (95% CI) of the association between mean GA or HbA1c levels and each endpoint. (pptx 186.8KB)

Abbreviations

ASCVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; CI: Confidence interval; DKD: Diabetic kidney disease; GA: Glycated albumin; HbA1c: Hemoglobin A1c; IQR: Interquartile range; SD: Standard deviation; VIF: Variation inflation factor

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Authors' contributions

KH designed the protocol, contributed to data collection and preparation, analyzed all data, contributed to the interpretation of the results, and wrote the manuscript. MA, AF, HH, YH, YI, MI, TK, HK, KK, HK, MK, TK, KK, SK, IM, JM, SM, KM, JN, SN, YN, SN, TN, YN, NO, SO, SO, HO, SS, TS, TS, YS, MS, TS, HS, MT, HT, TT, YT, MT, HT, YT, ST, ST, MU, IY, and HY contributed to the data collection and preparation and reviewed the manuscript. YU contributed to the interpretation of the results and reviewed the manuscript. TB conceived the study, designed the protocol, contributed to the data collection, contributed to the interpretation of the results, and edited the manuscript. TB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the

accuracy of the data analysis. All the authors have read and approved the final submission of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the presents study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee of Tokyo Women's Medical University School of Medicine and with the tenets of the Declaration of Helsinki of 1964 and its later versions. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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