Dissociation of Glycated Albumin and HbA_{1c} Is Associated With a Decline of Glomerular Filtration Rate as Evaluated by Inulin Clearance

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Hemoglobin A_{1c} (HbA_{1c}), microalbuminuria, and estimated glomerular filtration rate (eGFR) are widely used for assessment of diabetic kidney disease (DKD). However, we have shown that eGFR is inaccurate in DKD (1). Further, HbA_{1c} has several limitations as a glycemic marker (2). Guidelines for hemodialysis patients in Japan recommend evaluation of glycemic control using glycated albumin (GA) rather than HbA_{1c}, which is affected by conditions such as anemia and renal failure (3). Renal anemia is a common complication in chronic kidney disease (CKD), including in predialysis patients with CKD. Thus, we evaluated the correlations between GFR measured accurately by inulin clearance (C_{in}) and the dissociation of GA and HbA_{1c} in nondialysis patients with CKD.

The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (#3506) as an opt-out study. The study was performed between January 2009 and March 2020 at Osaka City University Hospital.

The subjects were 133 patients (60.6 ± 12.5 years, 66 males) with glycemic disorder. Diagnosis of type 2 diabetes (87 subjects) was based on a history of diabetes or criteria in the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" (4). Prediabetes (46 subjects) was evaluated by a 2-h 75-g oral glucose tolerance test. The subjects were restricted to those with CKD stages 1–4. GFR was evaluated by the gold standard C_{in}, determined by the constant input clearance technique with inulin. C_{in} was calculated by the $U_{in}V/P_{in}$ method, where U_{in} is the urinary inulin concentration, V is the urinary volume, and P_{in} is the mean plasma inulin concentration from measurements at the beginning and end of the clearance period. GA was measured by an enzymatic method using a Lucica GA-L kit (Asahi Kasei Pharma Co., Tokyo, Japan).

In single regression analyses (Fig. 1), there were significant positive correlations between GA and HbA_{1c} in each stage of CKD evaluated by eGFR (CKD 1, $r = 0.890$, $P < 0.0001$, slope 2.470; CKD 2, $r = 0.825$, $P < 0.0001$, slope 2.460; CKD 3 or 4, $r = 0.718$, $P = 0.0004$, slope 2.208) and by C_{in} (CKD 1, $r = 0.891$, $P < 0.0001$, slope 2.058; CKD 2, $r = 0.866$, $P < 0.0001$, slope 2.447; CKD 3 or 4, $r = 0.830$, $P < 0.0001$, slope 3.138). In advanced CKD stages evaluated by C_{in} ($P = 0.0024$) but not by eGFR ($P = 0.6495$), the regression slopes for GA and HbA_{1c} were significantly steeper, as evaluated by analyses of covariance. The GA/HbA_{1c} ratio was significantly negatively correlated with eGFR ($r = -0.189$, $P = 0.0302$) and C_{in} ($r = 0.408$, $P < 0.0001$).

In multiple regression analysis using a model including C_{in} or eGFR as an independent variable, C_{in} ($\beta = -0.233$, $P = 0.0097$), but not eGFR ($\beta = -0.007$, $P = 0.9415$), was significantly associated with the GA/HbA_{1c} ratio after adjustments for other clinical parameters. Association of the GA/HbA_{1c} and eGFR/C_{in} ratios was also evaluated, as eGFR may be inaccurate in patients with DKD. eGFR/C_{in} ($\beta = -0.227$, $P = 0.0023$) was significantly associated with GA/HbA_{1c} after adjustments for other clinical parameters.

In this study, the GA/HbA_{1c} ratio was higher in advanced CKD stages evaluated by C_{in} but not by eGFR, which is used in daily practice. Further, eGFR/C_{in} ratios were significantly associated with GA/HbA_{1c} ratios. The prevalence of anemia increases even in the early stage of kidney failure, particularly in diabetes (5).

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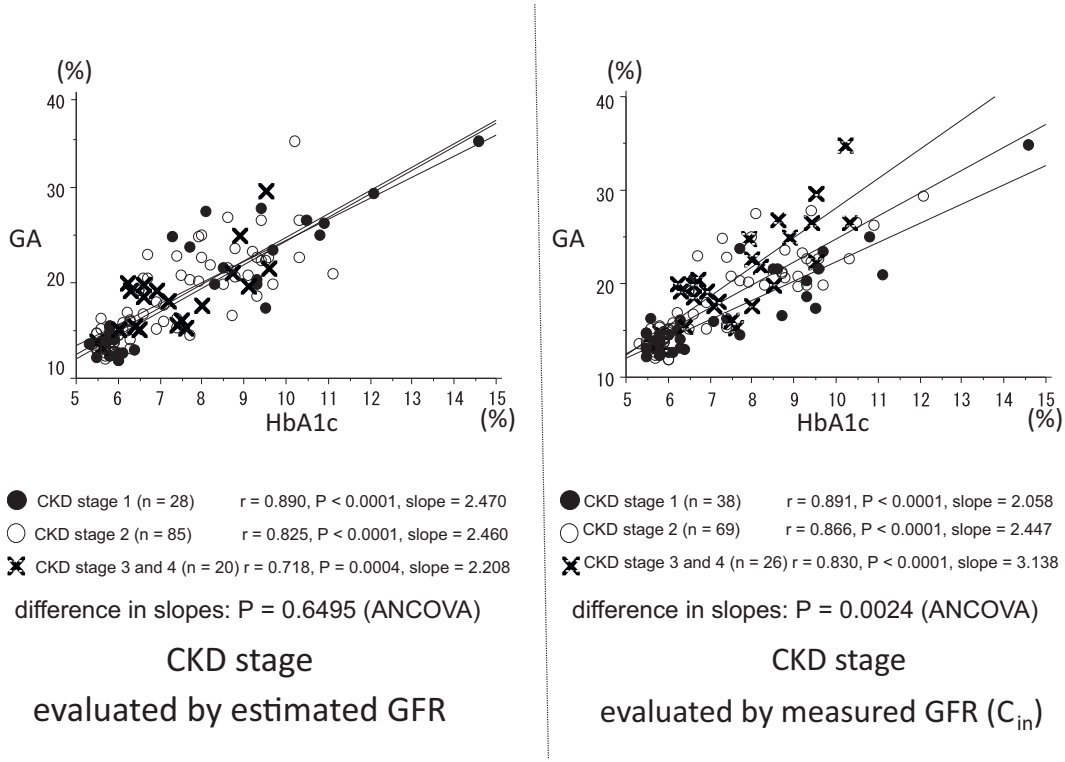

Figure 1–Relationship between glycated albumin (GA) and hemoglobin A1c (HbA_{1c}) in CKD stages evaluated by estimated GFR (left) and measured GFR (inulin clearance: C_{in}) (right).

Fujita et al. (5) found that low erythropoietin levels, which are common even in patients without CKD, predict a rapid decline of kidney function in patients with type 2 diabetes with anemia. Thus, the diathesis of renal anemia in diabetes may exist even before actualization of renal dysfunction. Evaluation of kidney function by eGFR calculation in patients with diabetes is less accurate than in subjects without diabetes (1). Thus, kidney injury and/or erythropoietin deficiency might already be present in patients with seemingly normal kidney function evaluated by a relatively incorrect eGFR, and dissociation of GA and HbA_{1c} induced by reduction of GFR may not be detected by evaluation with eGFR. We consider that HbA_{1c} is inaccurate and that GA may be a better marker of glycemic control in predialysis subjects as well as in dialysis patients.

This study has some limitations. First, it was performed in a relatively small number of patients. Second, we did not measure erythropoietin and iron metabolism markers as causes of lower hemoglobin because no cases warranted treatment for this condition. Finally, we only included Japanese subjects.

In conclusion, GA and HbA_{1c} are dissociated by GFR reduction in patients with glycemic disorder, and eGFR and HbA_{1c} may not provide an accurate measure of the risk of DKD. Thus, care is needed in evaluating glycemic control using HbA_{1c} in patients with kidney dysfunction.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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