

# The variability of glycated hemoglobin is associated with renal function decline in patients with type 2 diabetes

Chia-Lin Lee, Cheng-Hsu Chen, Ming-Ju Wu and Shang-Feng Tsai 

## Abstract

**Background:** The effect of glucose control, especially variability of glycated hemoglobin (HbA1c), on estimated glomerular filtration rate (eGFR) decline in type 2 diabetes is still debatable.

**Methods:** We used tertiles of coefficient of variation (CV) to determine the variability of HbA1c (HbA1c\_CV). Mixed model repeated measures (MMRM) were used to evaluate the annual eGFR decline rate.

**Results:** In 1383 type 2 diabetic patients, we found the greater the HbA1c\_CV, the greater the eGFR decline ( $p=0.01$ ,  $-0.99$  in low,  $-1.73$  in mid, and  $-2.53$  ml/min/1.73 m<sup>2</sup>/year in high HbA1c\_CV). Regardless of eGFR ( $\geq 60$  or  $< 60$  ml/min/1.73 m<sup>2</sup>), the same result holds ( $p=0.019$  and  $p=0.007$ , respectively). In subgroup analysis of baseline HbA1c (%) (HbA1c  $< 7$ ,  $7 \leq$  HbA1c  $< 9$ , and HbA1c  $\geq 9$ ), tertiles of HbA1c\_CV showed similar effects on annual decline of eGFR ( $p=0.193$ ,  $0.300$ ,  $0.182$ , respectively), although a trend for a steeper decline in renal function in the highest HbA1c\_CV tertile was observed for all HbA1c strata, and even for HbA1c  $< 7\%$ . A similar behavior was observed in patients with macroalbuminuria or normoalbuminuria ( $p=0.219$ , and  $0.109$ , respectively), with a significant trend in those with microalbuminuria ( $p=0.019$ ). Even in patients with HbA1c  $< 7$ , high HbA1c\_CV also predicts rapid eGFR decline. Before macroalbuminuria, minimizing HbA1c\_CV also has renal benefit.

**Conclusions:** HbA1c variability is an independent risk factor for deterioration of renal function. Even with well-controlled HbA1c levels ( $< 7\%$ ), patients with high HbA1c\_CV still experienced faster eGFR decline. Early minimization of glycemic variability (before macroalbuminuria) can curb deterioration of renal function. Monitoring and lowering of HbA1c\_CV is highly recommended for diabetic care.

**Keywords:** diabetic kidney disease, glomerular filtration rate, glycated hemoglobin, glycemic variability

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## Introduction

Type 2 diabetes mellitus (DM) is the leading cause of end-stage renal disease (ESRD) with high prevalence.<sup>1</sup> Nearly half of diabetic patients develop chronic kidney disease (CKD) eventually.<sup>2</sup> Patients with DM-related CKD receiving early renal replacement therapy have outcomes worse than in ESRD related to other causes. Aggressive treatment for DM, while it reduces

consequences such as acute myocardial infarction, stroke, amputation, and death from hyperglycemic crisis, does not change DM-related ESRD.<sup>3</sup> The reasons for the poor control of diabetic kidney disease (DKD) are related to the involvement of complicated pathophysiological mechanisms that affect nearly all kidney tissues, such as glomeruli, tubules, interstitia, and blood vessels.<sup>4,5</sup>

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More than 30 years ago, the staging of DKD was first proposed by Mogensen and colleagues.<sup>6</sup> Recently, hyperfiltration has been considered as the most important mechanism in DKD.<sup>7</sup> After hyperfiltration, microalbuminuria occurs, and then proteinuria can be detected, followed by a low estimated glomerular filtration rate (eGFR)  $<60 \text{ ml/min/1.73 m}^2$  (definition of CKD), and, finally, ESRD.<sup>7</sup> Angiotensin converting enzyme inhibitors (ACEi) and angiotensin-receptor blocker (ARB) comprise the standard medical treatment of DKD, with the benefit of GFR according to RENAAL and IDNT.<sup>8,9</sup> Nevertheless, the outcome of DKD remains unsatisfactory. Recently, a number of studies have explained the pleiotropic effects of new diabetic medications, in addition to their ability to control glucose levels.<sup>10–15</sup> These studies show evidence of blocking eGFR decline, and, therefore, major shifts in the algorithm of glucose control have been made in treating type 2 DM.<sup>16,17</sup> All cardiovascular outcome trials (CVOTs) in diabetic populations are designed to have ‘glycemic equipoise’ between treatment and control groups, but modest differences are still detected in glycated hemoglobin (HbA1c).<sup>18</sup> Therefore, renal benefit with reduced decline in GFR may still result in better glycemic control. Despite this, the role of aggressive glycemic control in slowing the progression of DKD remains debatable.<sup>19</sup>

In our previous study,<sup>20</sup> we proposed a new dynamic model linking HbA1c and eGFR, in which HbA1c has dynamic and dual effects on eGFR both cross-sectionally and longitudinally. This new model can explain the discrepancy between glucose control and renal function among many large-scale studies [such as ACCORD (Action to Control Cardiovascular Risk in Diabetes),<sup>21</sup> VADT (Veterans Affairs Diabetes Trial),<sup>22</sup> DCCT (Diabetes Control and Complications),<sup>23</sup> EDIC (Epidemiology of Diabetes Interventions and Complications) study,<sup>24</sup> and UKPDS (UK Prospective Diabetes Study)].<sup>25</sup> But the exact effect of glycemic control on renal function remains elusive.

Typical glycemic control indices for DM are levels of fasting blood sugar (FBS) and HbA1c. These are both short-term markers without longitudinal follow up. Continuous glucose monitoring (CGM) has been created, creating new long-term outcome metrics for clinical management to reduce glycemic variability, such as temporal percentages of

patients in hypoglycemia, or in target range. Recently, a new recommendation for Time In Range (TIR) goals using CGM was posted at the 79th Scientific Sessions of the American Diabetes Association (ADA) in San Francisco. However, the use of CGM to reduce glycemic variability is still not routine in clinical practice. The importance of glycemic variability, in addition to that of FBS and HbA1c, is without doubt now being recognized. A recent study reported that a significantly higher risk of developing albuminuria was associated with variability in HbA1c.<sup>26</sup> However, less is known about the association between eGFR decline and glucose variability.

In this study, we propose a more available marker to represent glycemic variability [i.e. tertile of coefficient of variation of HbA1c (HbA1c\_CV)] to determine the effect of glycemic control on renal function (eGFR decline). Also, we analyzed over 1000 patients in our study to adjust for many confounding variables.

## Patients and methods

### *Study population and data collection*

This cohort study was performed by physicians at a medical center in central Taiwan. Patients were recruited from the outpatient department between June 2006 and December 2006 based on a documented diagnosis of type 2 DM by an endocrinologist. Once enrolled, all patients were followed up for years (at least until December 2011). Their medical records were reviewed, and their clinical data recorded. Baseline variables included age, gender, HbA1c, eGFR, number of oral antidiabetic drugs (OAD), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Any use of insulin, and antihypertensive and antihyperlipidemic medications was also recorded during enrollment. From 2007 to 2010, HbA1c and eGFR were followed up at 12-month intervals. HbA1c was measured with boronate affinity high-performance liquid chromatography (CLC385 TM, Primus, Kansas City, MO, USA). For HbA1c (range 4.2–19.6%), the inter- and intra-assay coefficients of variation were  $<0.9$  (0.73) and  $<2.9\%$  (1.93%), respectively. The equation of modification of diet in renal disease (MDRD) was used to calculate eGFR:  $\text{MDRD} = 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{years}^{-0.203} \times (0.742, \text{ if female}) \times (1.210, \text{ if African American})$ .<sup>27</sup> The MDRD formula was chosen instead of the

Cockcroft and Gault formula due to its superior accuracy in diabetic patients with impaired renal function.<sup>28</sup> Although CKD-EPI (Epidemiology Collaboration) is more accurate than the MDRD equation for patients with  $eGFR > 60 \text{ ml/min/1.73 m}^2$ , the MDRD formula was applied in the Taiwan National Database to evaluate dialysis initiation and CKD prevalence.<sup>29–31</sup> CKD was defined as  $eGFR < 60 \text{ ml/min/1.73 m}^2$ . Patients whose baseline  $eGFR$  was  $> 120 \text{ ml/min/1.73 m}^2$  were excluded. There were no incretin-based medications or sodium-glucose cotransporter 2 inhibitors (SGLT2i) for our patients during the period of this study. Our study was approved by the Human Research Review Committee of the Taichung Veterans General Hospital (CE16235A).

### Statistical analyses

Descriptive statistics for continuous variables were expressed as means and standard deviation (SD). All reported  $p$ -values were two-sided, and considered significant with  $p < 0.05$ . Additionally, 95% confidence intervals (CI) were reported. We used coefficient of variation (CV) of HbA1c (HbA1c\_CV) to represent its variability. Furthermore, tertiles of HbA1c/HbA1c\_CV were used for subsequent subgroup analyses. Mixed model repeated measures (MMRM) were used to evaluate the annual rate of  $eGFR$  decline. Each  $eGFR$  value was set as the dependent variable, with time set as the independent variable. Changes in the annual rate of  $eGFR$  were defined as the  $\beta$  coefficient of time in MMRM. Interactions with time, according to gender, and to HbA1c\_CV category, were determined. Subgroup analyses were done according to baseline HbA1c category (%) (HbA1c  $< 7\%$ ,  $7\% \leq \text{HbA1c} < 9\%$ , and HbA1c  $\geq 9\%$ ), baseline  $eGFR$  status (CKD or not) ( $eGFR \geq 60$  and  $eGFR < 60 \text{ ml/min/1.73 m}^2$ ), and baseline urinary albumin excretion (UAE) (UAE  $< 30$ ,  $30 \leq \text{UAE} < 300$ , and UAE  $\geq 300 \text{ mg/g}$ ). For the MMRM, the age-adjusted and multivariable-adjusted models [adjusted for gender, the number of OADs, insulin usage, antihypertensive medication, hyperlipidemia medication, age, baseline HbA1c (%), and SBP] were reported separately. The  $eGFR$  trajectories were generated from the adjusted MMRM. Statistical analyses were performed using the Statistical Package for the Social Science (version 15.0; SPSS Inc, Chicago, IL, USA).

### Results

We recruited a total of 1383 patients were recruited for this study (Table 1). Most of them (72.6%) received antihypertensive medication. The glucose control outcome was only fair ( $8.0 \pm 1.8\%$ ), and BP was under control ( $132 \pm 16 \text{ mmHg}$  of SBP, and  $76 \pm 9.7 \text{ mmHg}$  of DBP). The baseline renal function was relatively good, at an  $eGFR$  of  $63.0 \pm 23.8 \text{ ml/min/1.73 m}^2$ .

We evaluated factors associated with the average of annual  $eGFR$  adjusted for age and any other variables (age, gender, numbers of OADs, insulin usage, hypertensive medications, hyperlipidemic medications, and SBP). Age and gender were adjusted because they were both confounding factors for  $eGFR$ . Medications for hypertension (ACEi or ARB) were also adjusted because of their long-term renal benefits according to RENAAL and IDNT.<sup>8,9</sup> We also adjusted the usage of statin because of its potential effect on renal function.<sup>32</sup> In the multivariable-adjusted regression model, we evaluated factors associated with changes of renal function change as the result of controlled glucose level (i.e. variability of HbA1c) (Table 2).

Overall, patients experienced  $1.70 \text{ ml/min/1.73 m}^2$  of annual decline of  $eGFR$ , regardless of gender ( $p = 0.889$ ). Patients who had a higher HbA1c\_CV, they had a more rapid decline of renal function ( $0.99 \text{ ml/min/1.73 m}^2$  for low HbA1c\_CV,  $1.73 \text{ ml/min/1.73 m}^2$  for middle HbA1c\_CV, and  $2.53 \text{ ml/min/1.73 m}^2$  for high HbA1c\_CV,  $p = 0.01$ ). In the subgroup analysis (baseline  $eGFR \geq 60$  or  $eGFR < 60 \text{ ml/min/1.73 m}^2$ ), patients with higher HbA1c/HbA1c\_CV had a more rapid deterioration of renal function, a phenomenon found in both subgroups ( $p = 0.019$  and  $p = 0.007$ , respectively). Comparing groups of different baseline levels of ( $\geq 60$  or  $eGFR < 60 \text{ ml/min/1.73 m}^2$ ), HbA1c\_CV played a more important role when  $eGFR$  was  $\geq 60 \text{ ml/min/1.73 m}^2$  ( $-1.50$  versus  $-0.21$ ,  $-2.02$  versus  $-1.29$ ,  $-2.95$  versus  $-1.94$ ). At low baseline  $eGFR$  ( $< 60 \text{ ml/min/1.73 m}^2$ ), patients with aggressive glucose control and low variability of HbA1c showed no significant renal function decline (annual  $eGFR$  decline =  $-0.21 \text{ ml/min/1.73 m}^2$ , 95% CI =  $-1.04$ – $0.61$ ). Similarly, poor baseline glucose control (HbA1c  $< 7\%$ ,  $7\% \leq \text{HbA1c} < 9\%$ , and HbA1c  $\geq 9\%$ ) had greater functional decline (high HbA1c\_CV:  $-0.51$  versus  $-1.36$  versus  $-1.61$ ; middle HbA1c\_CV:  $-0.89$  versus  $-1.71$  versus  $-1.80$ ; high HbA1c\_CV:  $-2.07$

**Table 1.** Baseline characteristics of the study patients.

Variable	All patients (n = 1383)
Gender (male %)	719 (52.0%)
Age (years)	65.6 ± 12.6
Duration of diabetes (years)	10 ± 3.5 (4.2–13.0)
SBP (mmHg)	132 ± 16.0
DBP (mmHg)	76 ± 9.7
HbA1c (%)	8.0 ± 1.8 (n = 1194)
HbA1c < 7%	6.39 ± 0.46
7% ≤ HbA1c < 9%,	7.91 ± 0.56
HbA1c ≥ 9%	10.59 ± 1.43
HbA1c_CV	10.24 ± 5.32
HbA1c_CV in low tertile	5.15 ± 1.57%
HbA1c_CV in middle tertile	9.23 ± 1.2%
HbA1c_CV in high tertile	16.33 ± 4.31%
eGFR (ml/min/1.73 m <sup>2</sup> )	63.0 ± 23.8
eGFR decline (ml/min/1.732 m <sup>2</sup> ) per year	-1.79 [-2.20, -1.38]
Number of OADs	1.4 ± 0.8
0	186 (13.4%)
1	534 (38.6%)
2	534 (38.6%)
3	123 (8.9%)
4	6 (0.4%)
Insulin usage	287 (20.8%)
HTN medication	1004 (72.6%)
ACEi or ARB (%)	796 (57.6%)
Hyperlipidemia medication	513 (37.1%)

Data are presented as n (%) or mean ± SD.  
 ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HTN, hypertension; OAD, oral anti-diabetic drug; SBP, systolic blood pressure; SD, standard deviation.

versus -2.46 versus -3.32). For those patients with the best glucose control (baseline HbA1c < 7 and low/middle HbA1c\_CV), we found no deterioration in their renal function.

In the subgroup analysis of baseline UAE (UAE < 30, 30 ≤ UAE < 300, and UAE ≥ 300 mg/g) (Table 3), patients with poor baseline UAE (mg/g) had a more rapid decline in eGFR (UAE < 30: -0.33

**Table 2.** Age-adjusted and multivariable-adjusted annual mean changes in eGFR.

Group	Subgroup	Number of patients	Age-adjusted annual decline of eGFR	95% CI	Multivariable-adjusted annual decline of eGFR	95% CI	<i>p</i> value
Total		1383	-1.70***	(-2.10, -1.30)	-1.79***	(-2.20, -1.38)	
Male		719	-1.57***	(-2.11, -1.02)	-1.77***	(-2.34, -1.21)	<i>p</i> =0.889
Female		664	-1.84***	(-2.42, -1.27)	-1.79***	(-2.38, -1.20)	
Tertile of HbA1c_CV		1194					
	Low	397	-1.17***	(-1.85, -0.49)	-0.99*	(-1.67, -0.31)	<b><i>p</i>=0.01</b>
	Middle	399	-1.75***	(-2.41, -1.09)	-1.73***	(-2.38, -1.08)	
	High	398	-2.66***	(-3.43, -1.90)	-2.53***	(-3.28, -1.78)	
<b>Baseline eGFR</b>							
Baseline eGFR ≥ 60	Tertile of HbA1c_CV	1193					
	Low	241	-1.70***	(-2.30, -1.09)	-1.50***	(-2.12, -0.89)	<b><i>p</i>=0.019</b>
	Middle	241	-1.98***	(-2.60, -1.37)	-2.02***	(-2.64, -1.39)	
	High	241	-3.04***	(-3.82, -2.27)	-2.95***	(-3.75, -2.16)	
Baseline eGFR < 60	Tertile of HbA1c_CV						
	Low	156	-0.35	(-1.16, -0.46)	<b>-0.21</b>	(-1.04, 0.61)	<b><i>p</i>=0.007</b>
	Middle	157	-1.29***	(-2.01, -0.58)	-1.29***	(-1.98, -0.59)	
	High	157	-1.92***	(-2.65, -1.19)	-1.94***	(-2.66, -1.21)	
<b>Baseline HbA1c</b>							
Baseline HbA1c < 7	Tertile of HbA1c_CV	1195					
	Low	112	-0.63	(-1.93, 0.65)	<b>-0.51</b>	(-1.76, 0.74)	<i>p</i> =0.193
	Middle	113	-0.77	(-2.13, 0.58)	<b>-0.89</b>	(-2.19, 0.40)	
	High	112	-1.87*	(-3.18, -0.56)	-2.07*	(-3.47, -0.67)	
7 < Baseline HbA1c < 9	Tertile of HbA1c_CV						
	Low	189	-1.66***	(-2.56, -0.76)	-1.36*	(-2.29, -0.43)	<i>p</i> =0.300
	Middle	189	-1.56***	(-2.47, -0.65)	-1.71***	(-2.68, -0.75)	
	High	189	-2.72***	(-3.73, -1.70)	-2.46***	(-3.43, -1.49)	
Baseline HbA1c ≥ 9	Tertile of HbA1c_CV						

*(Continued)*

Table 2. (Continued)

Group	Subgroup	Number of patients	Age-adjusted annual decline of eGFR	95% CI	Multivariable-adjusted annual decline of eGFR	95% CI	p value
	Low	96	-1.87*	[-3.14, -0.60]	-1.61*	[-2.82, -0.41]	p=0.182
	Middle	97	-1.98*	[-3.26, -0.70]	-1.80*	[-3.14, -0.46]	
	High	97	-3.27***	[-4.80, -1.75]	-3.32***	[-4.97, -1.66]	

Adjusted for gender, the number of OADs, insulin usage, HTN medication, hyperlipidemia medication, age, baseline HbA1c (%), systolic blood pressure (mmHg).

CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HTN, hypertension; OAD, oral anti-diabetic drug.

\* $p < 0.05$  \*\*\* $p < 0.001$ . compared with baseline renal function.

versus -0.75 versus -2.43;  $30 \leq \text{UAE} < 300$ : -1.33 versus -2.36 versus -3.56;  $\text{UAE} \geq 300$ : -1.34 versus -2.36 versus -4.20). In good baseline renal condition ( $\text{UAE} < 30 \text{ mg/g}$  and  $30 \leq \text{UAE} < 300 \text{ mg/g}$ ), aggressive glucose control (low HbA1c\_CV) did not lead to a decline in renal function (95% CI=-1.11~0.43; 95% CI=-1.93 to 0.42). Once macroalbuminuria is reached ( $\text{UAE} > 300 \text{ mg/g}$ ), aggressive glucose control (low HbA1c\_CV) still produced eGFR decline (95% CI=-4.27 to -0.59).

### Discussion

After 2008, the United States Food and Drug Administration (US FDA) regulated all new anti-diabetic agents used in CVOTs to ensure consideration of ensure their safety in case of CV disease. Those prespecified CVOTs usually set albuminuria or eGFR as their secondary outcome. Studies on SGLT2i seemed to support renal benefits, including albuminuria and eGFR. On the other hand, a number of recent studies (including EMPAREG,<sup>10</sup> DECLARE-TIMI 58,<sup>11</sup> CANVAS,<sup>12</sup> and CREDENCE<sup>13</sup>) support the pleiotropic effects of new diabetic medications, in addition to their ability to control glucose levels. These studies reported a blockade of eGFR decline, and, therefore, the ADA, the American Association of Clinical Endocrinologists, and the American College of Endocrinology have all made major shifts in their algorithms of glucose control for type 2 DM patients.<sup>16,17</sup> Those studies attempted to achieve 'glycemic equipoise' between treatment and control groups, only to find that SGLT2i gave a better glucose control (less HbA1c) than controls.<sup>18</sup> Therefore, the authors concluded that the renal benefits are due to better glucose control. On the other hand, the effect of eGFR on glycemic control

is still debatable, as reviewed by Rossing.<sup>33</sup> For example, in that review,<sup>33</sup> overt proteinuria of DKD has long been considered a 'point of no return' regarding glycemic control. Renal benefits differ across patients of different background status. A number of limitations should also be pointed out in those studies, for example, the monitoring of renal function based on serum creatinine levels, long-term glucose control using FBS, and small sample sizes. Therefore, the exact association between indicator for long-term glucose control (HbA1c or glycemic variability) and renal function monitor (eGFR rather than serum creatinine) remained elusive. HbA1c presents some weaknesses in long-term glucose evaluation: the requirement of months to determine the marker effect, and glycemic control may be underestimated in the case of anemia or uremia. For this reason, we further set a new marker (HbA1c\_CV) to represent glycemic glucose control. In addition, there are many potential confounding factors for the evaluation of eGFR, such as age, gender, value of SBP, ACEi/ARB, and the use of statins. The effects on eGFR of glycemic control needed to be re-evaluated after adjusting for the above confounding factors, just as we have done in this study.

Recently, a new recommendation for TIR goals using a CGM was posted at the 79th Scientific Sessions of the ADA in San Francisco. CGM has benefits for long-term glycemic evaluation and reduces glycemic variability. When linked with artificial intelligence, CGM provides real-time feedback to diabetic patients on modifiable patterns of glycemic excursions.<sup>34</sup> In February 2019, the Advanced Technologies and Treatments for Diabetes Congress launched consensus recommendations for relevant aspects of CGM data

**Table 3.** Age-adjusted and multivariable-adjusted annual mean changes in eGFR stratified by baseline urinary albumin excretion.

Group	Subgroup	Number of patients (n = 1069)	Age-adjusted annual decline of eGFR	95% CI	Multivariable-adjusted annual decline of eGFR	95% CI	p value
<b>Baseline UAE &lt; 30 mg/g</b>							
	Low	170	-0.72	(-1.63, 0.19)	<b>-0.33</b>	(-1.11, 0.43)	p = 0.109
	Middle	171	-1.18*	(-2.11, -0.25)	-1.33*	(-2.14, -0.52)	
	High	171	-1.35*	(-2.40, -0.29)	-1.34*	(-2.20, -0.48)	
<b>30 &lt; Baseline UAE &lt; 300 mg/g</b>							
	Low	126	-0.76	(-2.04, 0.52)	<b>-0.75</b>	(-1.93, 0.42)	<b>p = 0.019</b>
	Middle	127	-2.04***	(-3.14, -0.94)	-2.36***	(-3.46, -1.26)	
	High	126	-2.86***	(-4.24, -1.49)	-2.76***	(-3.96, -1.55)	
<b>Baseline UAE &gt; 300 mg/g</b>							
	Low	59	-2.46*	(-4.60, -0.31)	-2.43*	(-4.27, -0.59)	p = 0.219
	Middle	60	-3.97***	(-5.26, -2.68)	-3.56***	(-5.35, -1.76)	
	High	59	-4.51***	(-6.99, -2.03)	-4.20***	(-6.48, -1.93)	
Adjusted for gender, the number of OADs, insulin usage, HTN medication, hyperlipidemia medication, age, baseline HbA1c (%), systolic blood pressure (mmHg). CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HTN, hypertension; OAD, oral anti-diabetic drug; UAE, urinary albumin excretion. *p < 0.05 *** p < 0.001. compared with baseline renal function.							

utilization on various diabetes populations.<sup>35</sup> The importance of long-term glycemic variability is therefore recognized. Despite of this, the routine use such invasive monitoring remains limited in clinical practice. Until now, no glycemic variability marker has been established as the gold standard. Self-monitored blood glucose (SMBG)-based evaluation was reported as easy to use without special software to reduce glucose variability.<sup>36</sup> But not every patient would self-perform the SMBG. Therefore, an easily obtainable marker for glycemic variability was in demand. Here, we used HbA1c<sub>CV</sub> as this marker because all diabetic patients receive HbA1c checkups regularly.

In this study, we found that the higher the variability of glycemic control (i.e. higher HbA1c<sub>CV</sub>), the faster the decline in eGFR, regardless of other patient characteristics like age, gender, ACEi/ARB or not, statin use or not, and BP control. Whether baseline CKD or not (eGFR  $\geq$  or  $<$  60 ml/min/1.73 m<sup>2</sup>), higher HbA1c<sub>CV</sub> was consistently associated with faster renal function deterioration. Even

with baseline eGFR  $<$  60 ml/min/1.73 m<sup>2</sup>, patients with aggressive glucose control with low variability of HbA1c still had stable renal function with no decline (annual eGFR decline = -0.21 ml/min/1.73 m<sup>2</sup>, 95% CI = -1.04~0.61). In other words, physicians would be better not to stop aggressive glucose control (minimize glycemic variability) even with existing CKD status. Patients with better baseline eGFR ( $\geq$  versus  $<$  60 ml/min/1.73 m<sup>2</sup>) had faster eGFR decline (against their corresponding glycemic variability controls). These results suggested that physicians should aim to minimize glycemic variability as early as possible to stop renal function deterioration, especially in patient groups with high eGFR ( $\geq$  60 ml/min/1.73 m<sup>2</sup>).

Similarly, poor baseline glucose control had faster renal function decline. When not achieving the standard HbA1c goal (%) (A1c  $\geq$  7), renal function always declined, even with minimal glycemic variability. This result is consistent with previous studies, supporting the view that better control of HbA1c is associated with smaller eGFR declines.

On the contrary, if patients had best glucose control, their renal function would not deteriorate. Therefore, for those achieving the standard HbA1c goal, their eGFR might still decline if they still had high glucose variability. They should keep achieving and maintaining not only their HbA1c goal but also low HbA1c\_CV.

UAE is an important monitor of long-term renal function deterioration. Before reaching macroalbuminuria (stage 4 DKD), aggressive suppression of glycemic variability stopped eGFR decline. But once reaching the stage of macroalbuminuria (UAE  $\geq$  300 mg/g), minimizing HbA1c\_CV produced no renal benefits. The so-called 'point of no return' applied also to our present study. Results of eGFR-subgroup analysis are also consistent with the idea that minimizing glycemic variability as early as possible stops eGFR decline. Besides, even in patients with very early DKD (normoalbuminuria, UAE < 30), higher HbA1c\_CV fit the trend of more eGFR decline in our study. This finding is consistent with a recent study showing that the occurrence of a significant drop of eGFR in both type 1 and type 2 DM individuals, even in the presence of normoalbuminuria.<sup>37</sup> All these studies point out the importance of minimizing glucose variability.

A recent study reported that high glucose variability was associated with the development of albuminuria (upper quartile hazard ratio = 1.3; 95% CI = 1.1–1.6), rather than eGFR decline.<sup>26</sup> However, the eGFR decline is significant in patients with higher glucose variability in our study. There are several reasons for this discrepancy. First, the study designs were different. In our study, we focused only on the effect of glucose variability on eGFR decline, whereas, the study of Ceriello and colleagues researched more parameters.<sup>26</sup> More importantly, there were different cohort baseline characteristics. The baseline glucose control was worse in the present study (HbA1c = 8.0%) than in the study of Ceriello and colleagues (HbA1c = 7.1%).<sup>26</sup> The mean duration of diabetes was longer in our study (10 years) than in the Ceriello study (8 years). In addition, the baseline renal function was also worse in our study (eGFR = 63 ml/min/1.732 m<sup>2</sup>) than in the Ceriello study (eGFR = 87 ml/min/1.732 m<sup>2</sup>); patients in the latter cohort had better sugar control, shorter duration of diabetes, and less renal dysfunction. Therefore, we

can analyze the outcome of eGFR (long-term renal outcome) more easily.

We report here an easily obtained marker (HbA1c\_CV) to facilitate the prediction of renal function in clinical practice. Early aggressive glucose control was found to stop eGFR decline, supporting the importance of glycemic variability in the process of eGFR deterioration. High variability of HbA1c may lead to endothelial injuries,<sup>38</sup> even under the situation of low FBS.<sup>39</sup> Glucose excursions likely cause oxidative stress with metabolic memory (legacy effect),<sup>40</sup> which is found to be associated with the AKT signaling pathway in diabetic rats.<sup>41</sup> In another study, glycemic variability is associated with a number of factors that cause endothelial injuries: polyol activity, hexosamine activity, activation of protein kinase C, and generation of advanced glycation end-products.<sup>42</sup> Glucose swings, compared with chronic sustained hyperglycemia, are a more specific trigger of oxidative stress.<sup>40</sup> The legacy metabolic burden could cause DKD even after improvements in glycemic control.<sup>43</sup> A meta-analysis reported that HbA1c variability is independently associated with the progression of renal status in both type 1 and 2 diabetic patients,<sup>44</sup> a finding that is consistent with ours. However, most studies, unlike ours, had not adjusted for potential confounding factors for eGFR decline.

There are some limitations to this study. First, even with more than 1000 patients, still higher case numbers may be needed to adjust for more variables. Second, we found no correlation between HbA1c\_CV and CGM. However, in this study, we proved the correlation of HbA1c\_CV with renal function. Further studies are necessary to compare different markers of glucose variability. Finally, we did not analyze eGFR decline based on ACEi or ARB usage. We plan to analyze this further in our ongoing study.

### Conclusion

In addition to standard glycemic control (HbA1c/HbA1c), HbA1c\_CV is also an important parameter in long-term prediction of eGFR decline. Even under control of HbA1c (<7), patients with high HbA1c\_CV still experienced eGFR decline. Early minimization of glycemic variability (before macroalbuminuria) can stop deterioration of renal function. Regular checking

and minimizing of HbA1c\_CV is highly recommended for daily diabetic care.

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### Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Informed consent

This study was approved by Ethics Committee of Taichung Veterans General Hospital, IRB number: CE16235A. We confirm that all patients gave written informed consent.

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