Dynamic and Dual Effects of Glycated Hemoglobin on Estimated Glomerular Filtration Rate in Type 2 Diabetic Outpatients

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Key Words

Chronic kidney disease · Diabetes mellitus · Estimated glomerular filtration rate · Glycemic control · Glycated hemoglobin · HbA_{1c}

Abstract

Background: Diabetic nephropathy is the leading cause of incident end-stage renal disease in Taiwan. Previous studies on the consistent benefits of glycemic control in diabetic nephropathy focused primarily on delaying microalbuminuria. However, this effect on glomerular filtration rate (GFR) remains controversial. This study aims to establish a model that explains the controversial effects of glycated hemoglobin (HbA_{1c}) on GFR. **Methods:** This retrospective cohort study followed subjects with type 2 diabetes mellitus, who were enrolled between June 2006 and December 2006, for 4 years. The effects of HbA_{1c} on estimated GFR (eGFR) were examined both cross-sectionally and longitudinally. The dual effects of HbA_{1c} on eGFR, and how renal function interferes with these effects, were investigated. **Results:** Of the 1,992 subjects enrolled, 1,699 completed the follow-up. HbA_{1c} was positively correlated with eGFR in the cross-sectional study (β coefficient = 1.44, 95% CI: 0.71–2.17, $p = 0.0001$). In the longitudinal study, higher baseline HbA_{1c} re-

sulted in a greater decline in eGFR. The annual eGFR decline rates were -1.89 , -1.29 , and -0.68 ml/min/1.73 m²/year for baseline HbA_{1c} >9 , 7 to ≤ 9 , and $\leq 7\%$, respectively. The eGFR value was simultaneously affected by concurrent (β coefficient = 0.78, 95% CI: 0.48–1.08, $p < 0.0001$) and preceding HbA_{1c} (-0.52 , -0.82 to -0.23 , $p < 0.0001$). The positive effects of concurrent HbA_{1c} on eGFR reached statistical significance at all stages of chronic kidney disease (CKD); however, the negative effects of preceding HbA_{1c} only applied to CKD stages 3 and 4. **Conclusions:** We developed a new model that demonstrates how preceding and concurrent HbA_{1c} simultaneously affect eGFR in opposing ways. The dynamic effects varied among different CKD stages. The deterioration in eGFR at CKD stages 3 and 4 may be postponed by intensive glycemic control. Further prospective studies may be necessary to clarify the specific CKD stage(s) that will benefit from intensive glycemic control.

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Introduction

Diabetic nephropathy is the leading cause of incident end-stage renal disease (ESRD) in Taiwan [1]. The incidence of chronic kidney disease (CKD) increases with in-

creasing levels of glycated hemoglobin (HbA_{1c}) [2]. The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control decreased the risk of microvascular complications [3]. The Diabetes Control and Complications Trial (DCCT) further proved that intensive glycemic control reduced the incidence of microalbuminuria in patients with type 1 diabetes mellitus (DM) [4]. Likewise, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study, intensive glucose control resulted in a reduction in renal events [5]. Although the benefits of glycemic control, such as renal protection, have been widely and consistently reported, previous investigations have primarily focused on delaying the development of microalbuminuria. Intensive diabetic therapy was only recently shown to be associated with a slower reduction in glomerular filtration rate (GFR) than conventional therapy in type 1 DM patients via the long-term follow-up of the Epidemiology of Diabetes Interventions and Complications (EDIC) study [6]. However, the effects of intensive glycemic control on the preservation of GFR in type 2 DM patients remain unclear.

A previous cross-sectional study in early type 1 DM patients demonstrated that HbA_{1c} positively correlated with GFR [7]. This positive correlation existed not only in early type 1 DM, but also in type 2 DM patients [8]. Conversely, results from a longitudinal observational study demonstrated that higher baseline HbA_{1c} resulted in a more rapid GFR decline [9]. These seemingly opposing correlations suggest that the actual relationship between HbA_{1c} and GFR cannot be explained by a simple linear model. Additionally, the positive correlation between concurrent HbA_{1c} and GFR also raised the question of how glycemic status alters renal function. Thus far, no literature has provided an ideal model to account for the inconsistent relationship between HbA_{1c} and GFR. To clarify these issues, this study aims to establish a model that explains the controversial effects of HbA_{1c} on GFR via cross-sectional and longitudinal analyses.

Methods

Study Population

This retrospective cohort study was performed by physicians at a medical center in central Taiwan. Subjects were recruited from the outpatient department between June 2006 and December 2006 based on a documented diagnosis of type 2 DM by an endocrinologist. Their medical records were reviewed, and their clinical parameters were recorded. The baseline variables assessed included age, sex, HbA_{1c}, estimated GFR (eGFR), number of oral anti-diabetic drugs (OAD), systolic blood pressure (SBP), and diastolic

blood pressure (DBP). Any use of insulin, and antihypertensive and antihyperlipidemic medication during enrollment was also recorded. From 2007 to 2010, HbA_{1c} and eGFR were followed up at 12-month intervals. HbA_{1c} was measured with boronate affinity high-performance liquid chromatography (CLC385™, Primus, Kansas City, Mo., USA). Inter- and intra-assay coefficients of variation for HbA_{1c} (range 4.2–19.6%) were <0.9 (0.73) and <2.9% (1.93%), respectively. The eGFR was calculated using the modification of diet in renal disease (MDRD) equation: $\text{MDRD} = 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{years}^{-0.203} \times (0.742, \text{ if female}) \times (1.210, \text{ if African American})$. The MDRD formula was chosen over the Cockcroft and Gault formula due to its superior accuracy in diabetic patients with impaired renal function [8]. Although CKD-EPI (Epidemiology Collaboration) is more accurate than the MDRD equation for subjects with eGFR >60 ml/min/1.73 m², the MDRD formula was applied in the Taiwan National Database to evaluate dialysis initiation and CKD prevalence [10–12]. Subjects whose baseline eGFR was >180 ml/min/1.73 m² were excluded. This study was approved by the Human Research Review Committee of the Taichung Veterans General Hospital.

Study Design

The design of this study was divided into the following sequential parts. First, we examined the positive correlation between HbA_{1c} and eGFR using a cross-sectional analysis. Then, the negative correlation between HbA_{1c} and future GFR values was identified, and the annual eGFR decline was calculated to represent the rate of renal impairment over time. If HbA_{1c} was negatively correlated with future eGFR, then it may be assumed that a higher baseline HbA_{1c} may cause a greater annual eGFR decline in subsequent years. If HbA_{1c} was positively correlated with eGFR in the cross-sectional analysis but negatively correlated with future eGFR, then it may be deduced that the impact of HbA_{1c} on eGFR varies with time. Lastly, we investigated the possibility that the two opposite effects may coexist, and how renal function status may interfere with these effects.

Statistical Analyses

Descriptive statistics for continuous variables are expressed as means and standard deviations. All reported p values were two sided and considered significant when $p < 0.05$. Additionally, 95% confidence intervals are reported. For the correlation between HbA_{1c} values and eGFR in the cross-sectional analysis, the fixed effect model analysis was used, with baseline eGFR as the dependent variable, to determine the individual related variables with univariate linear regression analysis. The variables that significantly contributed to baseline eGFR in univariate analysis were used in multivariate analysis. Due to the collinearity between age and eGFR, age by decades was used instead. For the effects of HbA_{1c} on future eGFR, we used a mixed model repeated measures (MMRM) to evaluate the eGFR decline rate according to different levels of baseline HbA_{1c}. Each eGFR was set as the dependent variable, whereas time was set as the independent variable. Changes in the annual eGFR were defined as the β coefficient of time in MMRM. Baseline HbA_{1c} were categorized according to HbA_{1c} >9%, 7% < HbA_{1c} ≤ 9%, and HbA_{1c} ≤ 7%. Baseline eGFR were categorized according to eGFR ≥ 60 and < 60 ml/min/1.73 m². Other variables that were significantly associated with baseline eGFR in multivariate analysis were also entered into MMRM analysis as covariates. Interaction of time, according to HbA_{1c} category,

Table 1. Baseline characteristics of the study subjects

Variable	Total n = 1,992
Gender, male	1,067 (53.6)
Mean age, years	66.1 (12.7)
Mean SBP, mm Hg	132 (16.0)
Mean DBP, mm Hg	76 (9.6)
Mean HbA _{1C} , %	8.1 (1.82)
Mean eGFR, ml/min/1.73 m ²	62.1 (24.35)
Number of OAD used	1.4 (0.8)
0 OAD	253 (12.7)
1 OAD	810 (40.7)
2 OAD	766 (38.5)
3 OAD	156 (7.8)
4 OAD	7 (0.4)
Insulin usage	374 (18.8)
Hypertensive treatment	1,486 (74.6)
Hyperlipidemia medication	663 (33.3)

Values are presented as n (%) or means (SD).

eGFR category, and gender, were tested. If the interaction reached statistical significance, stratified analyses were performed. The crude and adjusted MMRM models were reported separately. By the MMRM method, a HbA_{1C} trend was also analyzed for each subject. Each HbA_{1C} was set as the dependent variable, whereas time was set as the independent variable. The HbA_{1C} trend was defined by the β coefficient of time. If the impact of HbA_{1C} on eGFR varied with time, we assumed that each eGFR value was simultaneously influenced by concurrent and preceding HbA_{1C}. Concurrent HbA_{1C} was defined as the HbA_{1C} value recorded at the same time as the eGFR value was examined. Preceding HbA_{1C} was defined as the HbA_{1C} recorded 1 year before the eGFR was examined. Preceding eGFR was defined as the eGFR value recorded 1 year before the examined eGFR. Consequently, we constructed another model via MMRM analysis, with eGFR recorded between 2007 and 2010 as the dependent variable. Concurrent and preceding HbA_{1C} were assigned as independent variables. Preceding eGFR, time, and gender were adjusted as covariates. Analyses were also performed separately according to baseline CKD stages. CKD stages 1, 2, 3, 4, and 5 were defined as baseline eGFR ≥ 90 , 60–89.99, 30–59.99, 15–29.99, and <15 ml/min/1.73 m², respectively. Statistical analyses were performed using the Statistical Package for Social Sciences (version 15.0; SPSS Inc., Chicago, Ill., USA).

Results

Of the total 1,992 subjects that were enrolled, 1,699 completed the follow-up. Table 1 summarizes the baseline characteristics of the subjects that were included in the study. Their mean age was 66.1 years, and the mean baseline HbA_{1C} was 8.1%. Over the 4-year follow-up period, the mean HbA_{1C} levels were 8.1, 7.9, 7.7, and 7.7%

(p for trend <0.0001). The mean number of OADs was 1.4. At baseline, 18.8% of the subjects were on insulin. The mean eGFR at baseline was 62.1 ml/min/1.73 m², which then decreased to 59.5, 57.6, 57.9, and 56.9 ml/min/1.73 m² in the following 4 years (p for trend <0.0001).

The results of fixed effect model analyses, with eGFR as a dependent variable, are shown in table 2. In univariate analysis, gender, age (by decade), HbA_{1C}, number of OAD, insulin usage, use of antihypertensive medication, SBP, and DBP were associated with baseline eGFR. There was no correlation between hyperlipidemic medication and baseline eGFR. However, due to the possible confounding effects of hyperlipidemic treatment, this variable was also used in multivariate analysis [13, 14]. In multivariate analysis, the effects of SBP and DBP on baseline eGFR were no longer significant due to collinearity with antihypertensive medications. Meanwhile, age (by decade), number of OAD, and use of antihypertensive medication still correlated with baseline eGFR in multivariate analysis. As expected, baseline HbA_{1C} positively correlated with baseline eGFR, both in univariate and multivariate models. Furthermore, this correlation was still present with the HbA_{1C} and eGFR values for the following years. The adjusted β coefficient of HbA_{1C} for eGFR was 1.59 ($p < 0.001$), 1.60 ($p < 0.001$), 1.72 ($p < 0.001$), and 1.70 ($p < 0.001$) for years 1, 2, 3, and 4, respectively.

The crude and adjusted annual mean changes in eGFR are presented in table 3. In regard to the significant interactions, only time by HbA_{1C} and time by eGFR reached statistical significance. However, the difference in the annual mean changes in eGFR between genders did not reach statistical significance ($p = 0.791$). Stratified analysis was then performed according to the HbA_{1C} and eGFR categories. The annual mean change in eGFR did differ between the HbA_{1C} and eGFR categories. The adjusted annual decline in eGFR was -1.90 (ml/min/1.73 m²/year), -1.46 , and -0.85 , for baseline HbA_{1C} $>9\%$, $7\% < \text{HbA}_{1C} \leq 9\%$, and $\text{HbA}_{1C} \leq 7\%$, respectively. The adjusted annual changes in eGFR were -2.56 and -0.78 ml/min/1.73 m²/year for baseline eGFR ≥ 60 and <60 ml/min/1.73 m², respectively. Higher baseline HbA_{1C} and eGFR were both associated with more rapid annual eGFR decline. We also used a new category combining both baseline HbA_{1C} and eGFR status. In subjects with baseline eGFR ≥ 60 ml/min/1.73 m², higher baseline HbA_{1C} was still associated with a greater decline in annual eGFR ($p = 0.046$). In those with baseline eGFR <60 ml/min/1.73 m², higher baseline HbA_{1C} still demonstrated a tendency towards a faster eGFR decline, although this did not reach statistical significance ($p = 0.219$). Furthermore, for the HbA_{1C} trend,

Table 2. Fixed effect model analyses with eGFR as the dependent variable

Variable	Univariable		Multivariable adjustment ^a	
	β coefficient	95% CI	β coefficient	95% CI
HbA _{1C}	1.75	1.04, 2.46	1.44	0.71, 2.17
Male	-3.04	-5.36, -0.72	-0.48	-2.94, 1.98
Age by decade	-7.24	-8.07, -6.40	-6.39	-7.43, -5.36
Number of OAD	4.27	2.89, 5.65	2.48	0.73, 4.23
Insulin usage	-9.80	-12.68, -6.92	-9.43	-13.18, -5.68
Hypertensive treatment	-15.15	-17.72, -12.59	-8.71	-11.67, -5.75
Hyperlipidemia medication	-1.19	-3.61, 1.23	-2.36	-4.90, 0.17
SBP, mm Hg	-0.11	-0.18, -0.03	-0.04	-0.14, 0.04
DBP, mm Hg	0.25	0.12, 0.37	0.11	-0.03, 0.26

^a Covariates are shown with a significant contribution to the multivariable model.

Table 3. Crude and adjusted annual mean changes in eGFR

Group/ subgroup	Patients n	Crude annual decline in eGFR	95% CI	Adjusted annual decline in eGFR	95% CI	p value for interaction
<i>Total</i>	1,699	-1.24	-1.68, -0.84	-1.39	-1.74, -1.04	0.791
Male	923	-1.17	-1.70, -0.64	-1.34	-1.82, -0.85	
Female	776	-1.34	-1.94, -0.74	-1.46	-1.98, -0.95	
<i>Baseline HbA_{1C}</i>						0.023
>9%	316	-1.89	-2.92, -0.85	-1.90	-2.79, -1.01	
7-9%	592	-1.29	-1.90, -0.67	-1.46	-2.01, -0.91	
<7%	409	-0.68	-1.46, 0.10	-0.85	-1.55, -0.16	<0.0001
<i>Baseline eGFR >60 ml/min/1.73 m²</i>	924	-2.54	-2.93, -2.15	-2.56	-2.92, -2.19	
HbA _{1C}						0.046
>9%	188	-3.39	-4.47, -2.31	-3.24	-4.23, -2.25	
7-9%	341	-2.34	-2.92, -1.76	-2.35	-2.88, -1.82	
<7%	217	-1.92	-2.59, -1.24	-1.94	-2.58, -1.30	0.219
<i>Baseline eGFR <60 ml/min/1.73 m²</i>	775	-0.68	-1.09, -0.28	-0.78	-1.17, -0.39	
HbA _{1C}						
>9%	128	-1.10	-2.09, -0.12	-1.26	-2.21, -0.31	0.219
7-9%	251	-0.95	-1.60, -0.31	-1.07	-1.69, -0.44	
<7%	192	-0.16	-1.04, 0.71	-0.31	-1.13, 0.51	

Adjusted for the number of OAD, insulin usage, hypertensive and hyperlipidemia medication, age (by decade), eGFR and annual eGFR decline (eGFR/year).

we defined HbA_{1C} increasers and decreasers for the β coefficient of time >0 and <0, respectively. HbA_{1C} increasers were with more rapid annual eGFR decline than HbA_{1C} decreasers, although no statistically significant difference was reached (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000351803). Apart from baseline HbA_{1C} and eGFR category, urinary albumin excretion rate (UAER) also plays an important role in GFR outcome [15]. Supplement 1 also showed

the rate of eGFR decline stratified by baseline UAER status. Higher baseline HbA_{1C} still demonstrated a tendency toward a faster annual eGFR decline, especially in patients with macroalbuminuria (UAER >300 mg/g creatinine; p for interaction = 0.025). Although the p value for interaction did not reach significance among normo- (UAER <30 mg/g creatinine) and microalbuminuria (30 ≤ UAER ≤ 300 mg/g creatinine), it may be due to the limited sample size.

HbA_{1C} was found to be positively correlated with eGFR (table 2), but it also induced a further decline in eGFR (table 3). This finding suggests that the impact of HbA_{1C} on eGFR varies at different time points. Table 4 summarizes the dynamic effect of HbA_{1C} on eGFR at different time points, as determined via MMRM. Current HbA_{1C} was found to be positively correlated with eGFR, whereas preceding HbA_{1C} was found to be negatively correlated with eGFR. The dual effects of concurrent and preceding HbA_{1C} on eGFR, according to CKD stages, are presented in figure 1. Concurrent HbA_{1C} was positively correlated with eGFR at all CKD stages. In contrast, preceding HbA_{1C} was negatively correlated with eGFR in the next year, although differences were only statistically significant at CKD stages 3 and 4. Except CKD stages, different time of preceding HbA_{1C} was further analyzed using a dynamic model. The adjusted β coefficient of preceding HbA_{1C} was -0.52 ($p < 0.001$), -0.51 ($p = 0.002$), -0.54 ($p = 0.005$), and -0.34 ($p = 0.209$) for the preceding 1, 2, 3, and 4 years (data not shown).

Discussion

The present study revealed that HbA_{1C} was positively correlated with eGFR via a cross-sectional analysis. A higher baseline HbA_{1C} and higher eGFR resulted in a greater decline in eGFR. Furthermore, preceding HbA_{1C} had a negative effect on eGFR, whereas concurrent HbA_{1C} had a positive effect on eGFR. The dynamic and dual effects of preceding and concurrent HbA_{1C} on eGFR also varied among different CKD stages.

Cross-Sectional Relationship between HbA_{1C} and eGFR

Using the fixed effect model, HbA_{1C} was positively correlated with eGFR. Previous studies showed that hyperglycemia increased GFR in subjects with impaired fasting glucose [16]. Similar studies also showed that GFR was significantly correlated with HbA_{1C}, both in early type 1 and 2 DM subjects [7, 8]. Thus, these reports were in accordance with our findings.

Longitudinal Relationship between HbA_{1C} and eGFR

We demonstrated that a higher baseline HbA_{1C} results in a greater decline in eGFR. This trend was more obvious in those with eGFR ≥ 60 ml/min/1.73 m² or UAER > 300 mg/g creatinine. In a longitudinal study on type 1 diabetics with nephropathy, there was a positive correlation between HbA_{1C} and the decline in GFR [17].

Fig. 1. The dynamic effect of concurrent and preceding HbA_{1C} on current eGFR, according to CKD stage. Current eGFR was estimated using the β coefficients of concurrent and preceding HbA_{1C} after adjusting for gender, time, and preceding eGFR. The effects of concurrent and preceding HbA_{1C} on eGFR were opposite. The dependent variable used in the modeling was the annual eGFR value. Separate modeling with MMRM analysis was performed at each CKD stage. Error bars denote the standard error of the β coefficients. * p of β coefficient < 0.05 .

Table 4. Dynamic impact of concurrent and preceding HbA_{1C} on eGFR

Grouping for analysis	Concurrent HbA _{1C}		Preceding HbA _{1C}	
	β	95% CI	β	95% CI
Total	0.78	0.48, 1.08	-0.52	-0.82, -0.23
CKD stage 1	1.69	0.36, 3.02	-0.44	-1.80, 0.90
CKD stage 2	0.70	0.21, 1.18	-0.33	-0.80, 0.14
CKD stage 3	0.55	0.16, 0.93	-0.63	-1.01, -0.25
CKD stage 4	0.93	0.27, 1.58	-0.66	-1.26, -0.05
CKD stage 5	0.68	0.07, 1.29	-0.20	-0.74, 0.33

MMRM analyses, with eGFR as the dependent variable, were performed for the total population and at each CKD stage. The impact of concurrent and preceding HbA_{1C} on eGFR were estimated with the β coefficient (β) after adjusting for preceding eGFR, time, and gender.

Additionally, we reported that subjects with baseline eGFR ≥ 60 ml/min/1.73 m² had greater eGFR decline rates than those with baseline eGFR < 60 ml/min/1.73 m². Comparable prospective studies in type 2 DM patients indicated that there was a significant relationship be-

tween baseline GFR and changes in GFR [18]. A previous meta-analysis of type 1 DM patients similarly suggested that those with higher baseline GFR tend to develop diabetic nephropathy [19]. Considering the effects of both baseline HbA_{1C} and eGFR status on eGFR decline, the best way to determine the accurate influence of these on eGFR was to combine the two effects together. Using this new classification, we demonstrated that the rate of eGFR decline had a dose-dependent relationship with baseline HbA_{1C} and eGFR status. Subjects with the most preserved renal function and worst glycemic control presented with the fastest rate of eGFR decline. Those who had the worst renal function, but best glycemic control, presented with the slowest rate of eGFR decline; however, this was not statistically significant. This may be due to the limited size of our study population.

Dynamic Association between HbA_{1C} and eGFR

To the best of our knowledge, this longitudinal study is the first to examine the dynamic and dual effects of HbA_{1C} on eGFR which reflected true clinical conditions. In our dynamic model, the effects of HbA_{1C} on eGFR rely on the 'tug of war' between concurrent and preceding HbA_{1C}. At each CKD stage, concurrent HbA_{1C} had a significantly positive effect on eGFR. Moreover, this positive effect was the most apparent in CKD stage 1. This is compatible with the glomerular hyperfiltration present in early DM [20]. Conversely, preceding HbA_{1C} had a negative effect on eGFR. Although the negative effects of preceding HbA_{1C} on eGFR were seen at each CKD stage, statistical significance was only apparent at CKD stages 3 and 4. This finding suggests that poor glycemic control precipitated the deterioration in eGFR in those at CKD stages 3 and 4. It also suggests that intensive glycemic control may effectively postpone the deterioration in eGFR at these two CKD stages. In fact, the negative effects of preceding HbA_{1C} actually surpassed the positive effects of concurrent HbA_{1C} at CKD stage 3 (table 4). Therefore, our findings suggest that CKD stage 3 may be the critical stage for delaying eGFR deterioration with intensive glycemic control.

The dynamic and dual effects of concurrent and preceding HbA_{1C} varied among CKD stages. This finding also reflects the pathophysiology of DM nephropathy. The significantly positive effects of concurrent HbA_{1C} on eGFR at all CKD stages imply that hyperfiltration existed at each CKD stage, but primarily at stage 1. It is well known that hyperglycemia increases glomerular hyperfiltration by raising the ultrafiltration coefficient and increasing membrane permeability to small dextrans [21].

Additionally, hyperglycemia causes excess deposition of extracellular proteins, mesangial cell expansion by upregulating growth factors, gradual glomerular sclerosis, and, finally, decreased GFR [22]. The decrease in GFR induced by hyperglycemia through multiple factors is consistent with the negative impact of preceding HbA_{1C} on eGFR in our study. Our findings suggest that hyperglycemia may cause glomerular hyperfiltration during earlier rather than later stages of CKD. At CKD stages 3 and 4, poor glycemic control results in increased deposition of extracellular proteins. Thus, in the later stages of CKD, the negative impact of hyperglycemia on GFR becomes more dominant. At CKD stage 5, when glomerular sclerosis is most severe and little renal function remains, the renal-protective effects of intensive glycemic control become less obvious. The classic five stages of nephropathy were previously described by Mogensen et al. [23]. Microalbuminuria plays an important role in this staging system, and adequate glycemic control reduces the development of microalbuminuria [24]. Our study proposed that, at CKD stages 3 and 4, there may be another critical point for delaying the progression of DM nephropathy using strict glycemic control.

In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, intensive glycemic control did not reveal any improvements in serum creatinine [25]. In the VADT (Veterans Affairs Diabetes Trial), there were no benefits of intensive glycemic control on the rate of GFR decline [26]. In the DCCT study, there were no differences in the slopes of creatinine clearance between intensive and conventional glycemic control [27]. However, in the EDIC study, intensive diabetic therapy resulted in a slower eGFR decline than conventional therapy [6]. In the UKPDS study, intensive glycemic control resulted in a significant reduction in the proportion of doubling serum creatinine [24]. With the exception of differences in age, study population, or follow-up duration, the dynamic and dual effects of HbA_{1C} may offer another explanation for the controversial findings among the above-mentioned studies. Since HbA_{1C} at different time points had opposing effects on eGFR, the net effect of HbA_{1C} on eGFR should be the sum of the impact of both preceding and concurrent HbA_{1C}. Therefore, certain studies may fail to observe the direct benefits of good glycemic control on improving GFR. Additionally, the opposing dual effects of HbA_{1C} varied among the different CKD stages. This may cause more heterogeneous results among studies if the study populations are not stratified according to the CKD stages. The dynamic model can apply not only to heterogeneous effects among CKD stages, but also to

the memory effect of HbA_{1c}. The negative effects of preceding HbA_{1c} on eGFR reached statistical significance from preceding years 1–3. In the DCCT trial, HbA_{1c} from preceding years 2–3 were associated with the greatest relative risk of contributing to current retinopathy [28]. Although studying different diabetic complications, our findings revealed a similar time effect of preceding HbA_{1c} in accordance with the DCCT trial. However, we lack sufficient data to show the effect of HbA_{1c} levels before the preceding 4 years on renal function.

Clinical Implications

Based on our study findings, we recommend maintaining HbA_{1c} ≤7% for renal protection in type 2 DM subjects. This may transiently decrease the eGFR due to a correction in hyperfiltration, similar to newly diagnosed DM patients [29]. In the long-term, however, proper glycemic control will provide better renal protection by improving the rate of eGFR decline. In our study, HbA_{1c} increasers presented more rapid annual eGFR decline than HbA_{1c} decreaseers, though no statistically significant difference was reached. This finding also supports maintaining HbA_{1c} ≤7% for eGFR preservation.

The strengths of this study include recruitment from a clinical practice, a regular longitudinal follow-up, a large sample size, and the new concept of dynamic and dual effects of HbA_{1c} on eGFR. However, the following limita-

tions of this study should be mentioned. First, HbA_{1c} variability was not examined in this study, although it was reported as an independent predictor of nephropathy [30]. Second, although we adjusted for baseline covariates that may affect GFR, we did not annually collect all potential covariates, such as variations in blood pressure or changes in medication. This may cause some bias in the estimations. Despite these limitations, different models from cross-sectional, longitudinal, and dynamic analyses revealed a consistent relationship between HbA_{1c} and eGFR. Therefore, we consider our findings robust.

In conclusion, we provided a new model which suggests that preceding and concurrent HbA_{1c} dynamically affect eGFR in opposing ways. The deterioration in eGFR at CKD stages 3 and 4 may be postponed by intensive glycemic control. Further well-designed, prospective studies are needed to further specify the CKD stages that will actually benefit from intensive glycemic control.

Disclosure Statement

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