

# Continuous Glucose Monitoring Metrics in the Assessment of Glycemia in Moderate-to-Advanced CKD in Diabetes



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**Introduction:** Glycated hemoglobin A1c (HbA1c) has reduced reliability in advanced chronic kidney disease (CKD) owing to factors influencing red cell turnover. Recent guidelines support the use of continuous glucose monitoring (CGM) in glycemic assessment in these patients. We evaluated relationships between HbA1c and CGM metrics of average glycemia and glucose variability (GV) in moderate-to-advanced CKD.

**Methods:** There were a total of 90 patients with diabetes in CKD stages G3b ( $n = 33$ ), G4 ( $n = 43$ ), and G5 (nondialysis) ( $n = 14$ ) (age [mean  $\pm$  SD]  $65.4 \pm 9.0$  years, estimated glomerular filtration rate [eGFR]  $26.1 \pm 9.6$  ml/min per  $1.73 \text{ m}^2$ , and HbA1c  $7.4 \pm 0.8\%$ ). CGM metrics were estimated from blinded CGM (Medtronic Ipro2 with Enlite sensor) and compared with HbA1c in the same week.

**Results:** Correlations between glucose management indicator (GMI) and HbA1c attenuated with advancing CKD (G3b [ $r = 0.68$ ,  $P < 0.0001$ ], G4 [ $r = 0.52$ ,  $P < 0.001$ ], G5 [ $r = 0.22$ ,  $P = 0.44$ ],  $P = 0.01$  for CKD stage). In G3b and G4, HbA1c correlated significantly with time-in-range (TIR) (3.9–10.0 mmol/l) ( $r = -0.55$  and  $r = -0.54$ , respectively) and % time  $> 13.9$  mmol/l ( $r = 0.53$  and  $r = 0.44$ , respectively), but not in G5. HbA1c showed no correlation with % time  $< 3.0$  mmol/l ( $r = -0.045$ ,  $P = 0.67$ ) or % coefficient of variation (CV) ( $r = -0.05$ ,  $P = 0.64$ ) in any CKD stage. Only eGFR was a significant determinant of bias for the difference between GMI and HbA1c (difference  $-0.28\%$ , 95% CI  $[-0.52$  to  $-0.03]$  per 15 ml/min per  $1.73 \text{ m}^2$  decrement,  $P = 0.03$ ).

**Conclusion:** CGM-derived indices might serve as an adjunct to HbA1c monitoring to guide glycemic management, especially in those with eGFR  $< 30$  ml/min per  $1.73 \text{ m}^2$ . Time in hypoglycemia and glycemic variability are relevant glycemic targets for optimization not reflected by HbA1c.

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KEYWORDS: chronic kidney disease; continuous glucose monitoring; HbA1c; type 1 diabetes; type 2 diabetes

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Optimal glycemic management delays progression of microvascular complications in patients with type 1 and type 2 diabetes with CKD.<sup>1–3</sup> Patients with CKD are more vulnerable to hypoglycemia owing to high use of insulin, long disease duration, reduced insulin clearance, and impaired renal gluconeogenesis, which in turn is associated with increased mortality.<sup>4,5</sup> The latest Kidney Disease: Improving Global Outcomes clinical practice guideline on diabetes management in

CKD recommended measurement of HbA1c twice yearly in those with stable control.<sup>6</sup> However, HbA1c has poor reliability in advanced stages of CKD owing to altered red cell survival, use of iron and erythropoiesis-stimulating agents (ESAs), and blood transfusions.<sup>7,8</sup> This has been described in patients on hemodialysis where average glucose values were underestimated by HbA1c.<sup>9</sup> Alternative glycemic markers such as fructosamine and glycated albumin were no more reliable than HbA1c in advanced CKD and are subject to other biases, such as hypoalbuminemia.<sup>10–12</sup> There may be potential for harm in basing treatment decisions solely on an underestimated or overestimated HbA1c, especially in patients who do not perform home blood glucose monitoring regularly. Because HbA1c does not

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capture the extent of hypoglycemia, clinicians are less inclined to intensify treatment in patients with seemingly on-target HbA1c without additional glycemic indices, which in fact could be an underestimate. Conversely, hypoglycemia could still occur in patients with above-target HbA1c.

Direct measurement of capillary blood glucose or interstitial glucose with CGM can avoid some of the issues of unreliability of HbA1c in CKD. CGM measures minute-to-minute interstitial glucose profiles and provides information on both absolute values and variability in daily blood glucose. The latest Kidney Disease: Improving Global Outcomes 2020 guidelines also support the use of continuous GMI<sup>13</sup> derived from mean CGM glucose, as an index for glycemia assessment in whom HbA1c may not be reliable, particularly in CKD G4 to G5.<sup>6</sup> CGM can also provide data on percentage of TIR (3.9–10 mmol/l), time in hyperglycemic, and hypoglycemic ranges. The latter is particularly important in guiding treatment decisions by capturing hypoglycemic episodes that may be asymptomatic and potentially harmful.<sup>14</sup> A TIR of 70% is the recommended target in patients with type 1 or type 2 diabetes, which corresponds to an average HbA1c of 7% in non-CKD populations.<sup>13</sup> However, there are little data evaluating the correlation of these CGM targets with HbA1c and hyperglycemia/hypoglycemia specifically in CKD populations.

There are a few published studies using the latest CGM metrics (GMI and TIR) in glycemia assessment in moderate-to-advanced CKD, especially in those with eGFR <30 ml/min per 1.73 m<sup>2</sup>.<sup>11,15,16</sup> Most studies have focused on the relationships between HbA1c and measures of average glycemia, and none have evaluated relationships with TIRs or indices of glycemic variability. In this study, we investigated the correlation and agreement of GMI and laboratory HbA1c in patients with CKD G3b, 4, and 5 (nondialysis). In addition, we evaluated the relationships between HbA1c and TIR, time in hyperglycemia, and time in hypoglycemia with advancing CKD stages.<sup>13</sup> We also evaluated the distribution of CGM-reported TIRs according to different HbA1c strata and determinants of bias between GMI and HbA1c, including demographic variables, renal function, blood hemoglobin (Hb), and albumin.

## METHODS

This was a prospective, single-center study at the Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong Special Administrative Region. Data were collected as part of baseline measurements among patients participating in a randomized clinical trial of CGM use in CKD stages G3b to 5

(NCT0406155) between July 2019 and December 2020. The study was approved by the Joint New Territories East Cluster—The Chinese University of Hong Kong Clinical Research Ethics Committee. All participants provided written informed consent.

## Study Participants

Patients were included if they were aged  $\geq 18$  and  $\leq 75$  years, diagnosed with having type 1 or type 2 diabetes for at least 6 months with CKD stages G3b, 4, or 5 as defined by eGFR <45 ml/min per m<sup>2</sup> by the CKD Epidemiology Collaboration equation at screening.<sup>17</sup> Type 1 diabetes was defined as history of unprovoked ketosis, diabetic ketoacidosis, or continuous insulin requirement within 12 months of diagnosis. All patients reported 1 or more episodes of severe or nonsevere hypoglycemia in the past 12 months. Patients on dialysis were excluded from the study. Additional exclusion criteria included current pregnancy or plan of pregnancy, extensive skin/changes that precluded wearing of the CGM system on normal skin, known allergy to medical-grade adhesives, current or recent alcohol or drug abuse, history of admissions owing to diabetic ketoacidosis or hyperosmolar hyperglycemic state in the 6 months before screening, HbA1c >8.5% at screening, participation in another investigational protocol, or any acute or chronic illness that in the opinion of the investigator might interfere with the performance of the study. None of the patients were treated with ESA. Patients with known hemoglobinopathies were not included.

## Continuous Glucose Monitoring

All participants wore an iPro2 professional blinded CGM with Enlite sensor (Medtronic Diabetes, Northridge, CA) for a 7-day period on the abdominal region in accordance with the manufacturer's instructions. The CGM system measured interstitial glucose levels every 5 minutes with a detection range between 2.22 and 22.2 mmol/l. Calibrations were performed in accordance with the manufacturer's instructions using home capillary blood glucose readings from CONTOUR PLUS glucometer (Ascensia Diabetes Care, Basel, Switzerland). A subset of 24 patients in stage G3b and 35 patients in stages G4 and 5 had repeated blinded CGM and HbA1c after 4 months. CGM data were downloaded using CareLink Pro software (Medtronic Diabetes, Northridge, CA). All CGM raw data were inspected by qualified study personnel. Invalid data, where there was evidence of CGM malfunction or sensor loss, were excluded from further analyses. Only patients with >70% valid sensor data were included in the final analysis. No changes were made to the glucose-lowering drugs during the week of blinded CGM recording.

## CGM Metrics

CGM metrics were determined in accordance with the latest international consensus on standards of CGM reporting.<sup>13,18</sup> Mean CGM glucose was calculated as average of all sensor glucose readings within the recording period. The GMI was calculated as  $3.31 + 0.02393 \times \text{mean CGM glucose (mg/dl)}$ .<sup>19</sup> We determined time in different glucose ranges according to the following definitions: TIR (3.9–10 mmol/l), time in hypoglycemia (<3.9 and <3.0 mmol/l), and time in hyperglycemia (>10 and >13.9 mmol/l).<sup>13</sup> GV was estimated using the SD of CGM glucose and the % CV (defined as  $\text{SD}/\text{mean glucose} \times 100\%$ ).

## Laboratory Markers

All blood and urine samples were collected within 1 week of the CGM recording. HbA1c determination was based on the turbidimetric inhibition immunoassay for hemolyzed whole blood analyzed by cobas c513 analyzer (Roche Diagnostics, Basel, Switzerland) standardized against the approved International Federation of Clinical Chemistry and Laboratory Medicine reference method. The CV was 2.0% and 1.3% at HbA1c of 5.0% and 10.2%, respectively. The anti-HbA1c antibodies used had minimal interference from Hb variants with no cross-reactions with HbA0, HbA1a, HbA1b, acetylated Hb, carbamylated Hb, glycosylated albumin, and labile HbA1c. Carbamylated Hb is commonly formed under uremic conditions.<sup>20</sup> The plasma glucose assay was based on the principle of enzymatic reference method with hexokinase by cobas C8000 Analyzer (Roche Diagnostics, Basel, Switzerland) with CV of 1.4% at 5.7 mmol/l and 1.3% at 15.7 mmol/l. The plasma creatinine kinetic colorimetric assay was based on the Jaffe method analyzed by cobas C8000 Analyzer (Roche Diagnostics, Basel, Switzerland) with CV of 3.7% at 73.1  $\mu\text{mol/l}$ . Plasma albumin was assayed using a bromocresol purple assay with CV of 2.6%. Urine albumin was measured using an immunoturbidimetric assay and urine creatinine by a kinetic colorimetric assay. Blood Hb was determined using the Beckman Coulter DXH800 hematology analyzer (Beckman Coulter Inc., Brea, CA).

## Statistical Analysis

Data were evaluated for normality and summarized as mean and SD or median and interquartile range. Differences in baseline characteristics were investigated using 1-way analysis of variance, Kruskal-Wallis test, or  $\chi^2$  test for proportions as appropriate. We performed scatter plots and derived Pearson and Spearman correlation coefficients ( $r$ ) to investigate the relationships between paired GMI and HbA1c overall and stratified by CKD stage. Pearson's  $r$  is reported in the text unless

otherwise stated. Correlations were also evaluated between HbA1c and mean CGM glucose, % TIR 3.9 to 10.0 mmol/l, % time >10 mmol/l, >13.9 mmol/l, <3.9 mmol/l, and <3 mmol/l. Correlation coefficients were transformed using the Fisher's  $r$  to  $z$  transformation and compared between CKD stages using the test of heterogeneity.<sup>21</sup> We performed Bland-Altman analysis to evaluate the difference between GMI and HbA1c versus mean GMI. We described the TIRs, SD, and % CV stratified by HbA1c range and determinants of bias between GMI and HbA1c by performing linear regression. The difference between GMI and HbA1c was the dependent variable whereas age, body mass index, diabetes duration, eGFR, Hb, and plasma albumin were included as predictor variables. In a subset of patients with repeated CGM-HbA1c measurements at 4 months, we evaluated the correlation between these changes. Analyses were performed using R version 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

Of 94 enrolled participants, 4 withdrew consent. There were 90 patients (1 with type 1 diabetes, 89 with type 2 diabetes) with valid CGM recordings included in this analysis (age:  $65 \pm 9$  years; 57 [63%] men; duration of diabetes:  $21.8 \pm 8.0$  years; mean Hb:  $11.8 \pm 1.9$  g/dl; [Table 1](#)). The mean eGFR of the study cohort was  $26.1 \pm 9.6$  ml/min per  $1.73 \text{ m}^2$  with 33 patients in CKD G3b, 43 in G4, and 14 in G5. The mean HbA1c was  $7.4 \pm 0.8\%$  which was similar across CKD stages. Overall, 99% of the patients were on insulin and 66% were treated with dipeptidyl-peptidase 4 inhibitors. Patients with G3b were more likely to be on metformin and sodium-glucose cotransporter 2 inhibitors ([Supplementary Table S1](#)). There were significant differences in Hb, urine ACR, and albumin levels between CKD stages ([Table 1](#)). There were 4 patients on oral iron therapy (G3b,  $n = 2$ ; G4,  $n = 1$ ; G5,  $n = 1$ ). Mean GMI was  $7.0 \pm 0.8\%$ , and TIR was  $66.8 \pm 18.9\%$  in the overall cohort with no differences between CKD stages.

### Correlation and Agreement Between CGM Measures of Average Glycemia and HbA1c

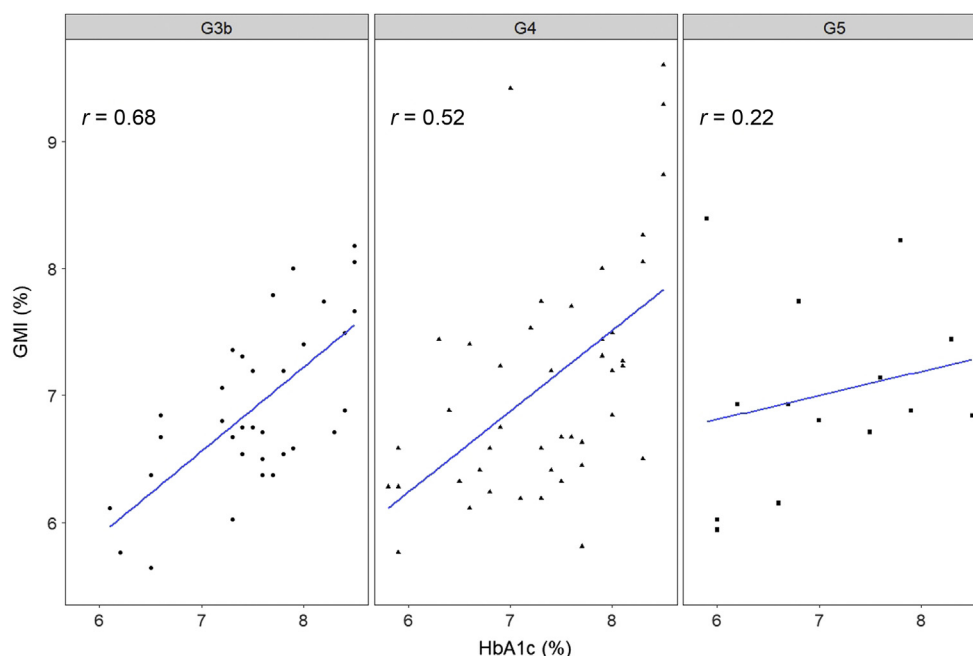
There was a significant correlation between HbA1c and GMI in CKD overall in stages G3b to 5 ( $r = 0.49$ ,  $P = 1.2 \times 10^{-6}$ ). The correlation between GMI and HbA1c decreased with advancing CKD stages and became nonsignificant in G5 (G3b [ $r = 0.68$ ,  $P = 1.2 \times 10^{-5}$ ], G4 [ $r = 0.52$ ,  $P = 0.0003$ ], G5 [ $r = 0.22$ ,  $P = 0.44$ ];  $P_{\text{difference}} = 0.01$  by CKD stage; [Figure 1](#) and [Table 2](#)). Bland-Altman analysis (GMI minus HbA1c) showed a

**Table 1.** Clinical and biochemical characteristics of participants with CKD and CGM metrics

Variables	Overall	G3b	G4	G5	P
<i>n</i>	90	33	43	14	
Age (yr)	65.4 (9.0)	65.2 (7.5)	64.8 (10.8)	67.8 (5.7)	0.56
Sex	57M/33F	21M/12F	27M/16F	9M/5F	0.98
BMI (kg/m <sup>2</sup> )	28.7 (5.1)	29.0 (5.8)	28.6 (4.7)	28.3 (4.9)	0.90
Weight (kg)	76.5 (15.2)	79.3 (16.6)	75.5 (14.4)	73 (14.0)	0.37
Diabetes duration (y)	21.8 (8.0)	24.2 (7.2)	21.0 (8.2)	18.5 (7.8)	0.05
eGFR, ml/min per 1.73 m <sup>2</sup>	26.1 (9.6)	36.3 (4.1)	22.9 (4.6)	11.7 (2.5)	<0.0001
Plasma creatinine (μmol/l)	230 (89.6)	156 (23.3)	232 (45.3)	398 (51.8)	<0.0001
SBP (mm Hg)	139 (19.2)	136 (18.1)	139 (20.3)	142 (19.0)	0.67
DBP (mm Hg)	72.5 (11.4)	73.9 (12.2)	72.4 (10.5)	69.4 (12.2)	0.47
uACR (mg/mmol)	100 (28-305)	26 (5-105)	163 (41-271)	353 (125-423)	0.001
<3 mg/mmol, <i>n</i> (%)	9 (10)	7(21)	2 (5)	0	0.03
3–30 mg/mmol, <i>n</i> (%)	14 (16)	10 (31)	4 (9)	0	0.006
>30 mg/mmol, <i>n</i> (%)	67 (74)	16 (48)	37 (86)	14 (100)	<0.0001
Blood hemoglobin (g/dl)	11.8 (1.9)	12.5 (1.6)	11.9 (1.7)	10.1 (1.7)	0.0006
Anemia, <i>n</i> (%)	62 (68.9)	17 (51.5)	32 (74.4)	13 (92.9)	0.0028
Plasma albumin (g/dl)	34.8 (3.7)	36.5 (3.7)	34.0 (3.7)	33.4 (2.9)	0.004
HbA1c, <i>n</i> (%)	7.4 (0.8)	7.5 (0.7)	7.3 (0.8)	7.1 (0.9)	0.24
HbA1c (mmol/mol)	57.0 (8.2)	58.6 (7.3)	56.7 (8.4)	53.6 (9.6)	0.24
FPG (mmol/l)	7.0 (2.4)	7.5 (2.4)	6.7 (2.4)	7.0 (2.0)	0.36
Mean CGM glucose	8.6 (1.9)	8.4 (1.5)	8.8 (2.2)	8.6 (1.7)	0.62
GMI, <i>n</i> (%)	7.0 (0.8)	6.9 (0.6)	7.1 (0.9)	7.0 (0.7)	0.62
% TIR (3.9–10 mmol/l)	66.8 (18.9)	70.3 (15.0)	64.5 (22.2)	65.7 (15.8)	0.40
% Time >10 mmol/l	29.1 (20.5)	26.2 (16.1)	31.1 (23.9)	30.0 (18.9)	0.59
% Time <3.9 mmol/l	4.07 (5.13)	3.45 (4.72)	4.47 (5.46)	4.29 (5.27)	0.69
% CV	33 (7)	33.4 (7)	32.7 (8)	33.7 (6)	0.88

ANOVA, analysis of variance; BMI, body mass index; CKD, chronic kidney disease; CGM, continuous glucose monitoring; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate by CKD-Epidemiology Collaboration; F, female; FPG, fasting plasma glucose; GMI, glucose management index; HbA1c, glycated hemoglobin A1c; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; M, male; SBP, systolic blood pressure; TIR, time in range (3.9–10.0 mmol/l); uACR, urine albumin-to-creatinine ratio.

Data are mean (SD) or *n* (%) except for uACR expressed in median [IQR]. *P* values difference between CKD stage are analyzed by one-way ANOVA for parametric and Kruskal-Wallis test for nonparametric data,  $\chi^2$  for difference in proportions. Anemia defined as per KDIGO: male <13.0 g/dl, female <12.0 g/dl.



**Figure 1.** Correlation between continuous GMI and HbA1c by CKD stage. Pearson correlation coefficients are shown in patients with CKD G3b (*n* = 33), G4 (*n* = 43), and G5 (*n* = 14). Line of best fit are shown and expressed by the following equations: for G3b,  $HbA1c = 0.265 + 0.71 \times GMI$  ( $R^2 = 0.46$ ,  $RSME = 0.48$ ); G4,  $HbA1c = 4.28 + 0.43 \times GMI$  ( $R^2 = 0.28$ ,  $RSME = 0.80$ ). Regression equation for G5 not shown owing to lack of correlation. CKD, chronic kidney disease; GMI, glucose management index; HbA1c, glycated hemoglobin A1c; RSME, root squared mean error.

**Table 2.** Correlation between CGM metrics and HbA1c by CKD stage

Variables	Overall	G3b (n = 33)	G4 (n = 43)	G5 (n = 14)	P value <sup>a</sup>
<b>GMI</b>					
Pearson <i>r</i>	<b>0.49<sup>b,c</sup></b>	<b>0.68<sup>b,c</sup></b>	<b>0.52<sup>b,c</sup></b>	0.22	<b>0.01<sup>c</sup></b>
Spearman <i>r</i>	<b>0.52<sup>b,c</sup></b>	<b>0.62<sup>b,c</sup></b>	<b>0.53<sup>b,c</sup></b>	0.21	
<b>Mean CGM glucose</b>					
Pearson <i>r</i>	<b>0.49<sup>b,c</sup></b>	<b>0.68<sup>b,c</sup></b>	<b>0.52<sup>b,c</sup></b>	0.23	<b>0.01<sup>c</sup></b>
Spearman <i>r</i>	<b>0.52<sup>b,c</sup></b>	<b>0.62<sup>b,c</sup></b>	<b>0.53<sup>b,c</sup></b>	0.21	
<b>% TIR 3.9–10.0 mmol</b>					
Pearson <i>r</i>	<b>-0.45<sup>b,c</sup></b>	<b>-0.55<sup>b,c</sup></b>	<b>-0.54<sup>b,c</sup></b>	-0.21	0.31
Spearman <i>r</i>	<b>-0.47<sup>b,c</sup></b>	<b>-0.52<sup>b,c</sup></b>	<b>-0.54<sup>b,c</sup></b>	-0.30	
<b>% time &gt;13.9 mmol/l</b>					
Pearson <i>r</i>	<b>0.35<sup>b,c</sup></b>	<b>0.53<sup>b,c</sup></b>	<b>0.44<sup>b,c</sup></b>	-0.74	<b>&lt;0.001<sup>c</sup></b>
Spearman <i>r</i>	<b>0.39<sup>b,c</sup></b>	<b>0.49<sup>b,c</sup></b>	<b>0.42<sup>b,c</sup></b>	0.19	
<b>% time &gt;10 mmol/l</b>					
Pearson <i>r</i>	<b>0.48<sup>b,c</sup></b>	<b>0.63<sup>b,c</sup></b>	<b>0.54<sup>b,c</sup></b>	0.28	0.17
Spearman <i>r</i>	<b>0.53<sup>b,c</sup></b>	<b>0.62<sup>b,c</sup></b>	<b>0.56<sup>b,c</sup></b>	0.37	
<b>% time &lt;3.9 mmol/l</b>					
Pearson <i>r</i>	<b>-0.29<sup>b,c</sup></b>	<b>-0.40<sup>c,d</sup></b>	-0.17	-0.40	0.45
Spearman <i>r</i>	<b>-0.32<sup>b,c</sup></b>	<b>-0.40<sup>c,d</sup></b>	-0.25	-0.024	
<b>% time &lt;3.0 mmol/l</b>					
Pearson <i>r</i>	-0.045	0.02	0.004	-0.15	0.24
Spearman <i>r</i>	-0.91	-0.11	-0.77	-0.02	
<b>% CV</b>					
Pearson <i>r</i>	-0.051	-0.009	-0.033	-0.21	0.83
Spearman <i>r</i>	-0.11	-0.04	-0.11	-0.29	

CKD, chronic kidney disease; CGM, continuous glucose monitoring; CV, coefficient of variation; GMI, glucose management index; HbA1c, glycated hemoglobin A1c; TIR, time in range.

<sup>a</sup>P value for comparison of Pearson's *r* by CKD stage.

<sup>b</sup>Correlation is significant at 0.01 level (2-tailed).

<sup>c</sup>Significant correlations are shown in bold.

<sup>d</sup>Correlation significant at 0.05 level (2-tailed).

Pearson and Spearman correlation coefficients are shown between HbA1c and respective CGM metrics.

negative bias of  $-0.35\%$  (95% limits of agreement  $-1.91\%$  to  $1.20\%$ ) overall, with wider limits of agreement in G4/G5 versus G3b (Figure 2). Mean CGM glucose was positively correlated with HbA1c in the whole group ( $r = 0.49$ ,  $P = 1.2 \times 10^{-6}$ ), but correlations declined with advancing CKD stages (G3b [ $r = 0.68$ ,  $P = 1.1 \times 10^{-5}$ ], G4 [ $r = 0.52$ ,  $P = 0.000243$ ], G5 [ $r = 0.23$ ,  $P = 0.47$ ];  $P_{\text{difference}} = 0.01$ ; Supplementary Figure S1 and Table 2).

### Relationship Between TIR, Time in Hyperglycemia, and Time in Hypoglycemia With HbA1c

There were significant moderate negative correlations between HbA1c and TIR in G3b and G4, but not in G5 (Table 2). HbA1c and % time in level 2 hyperglycemia  $>13.9$  mmol/l showed significant correlations in G3b ( $r = 0.53$ ) and G4 ( $r = 0.44$ ) but not in G5 ( $r = -0.74$ ) ( $P_{\text{difference}} < 0.001$  for CKD stage). Conversely, time in hypoglycemia  $<3.9$  mmol/l was negatively correlated with HbA1c in G3b only ( $r = -0.40$ ,  $P = 0.02$ ) (Table 2). There was no correlation between HbA1c and % time in level 2 hypoglycemia ( $<3.0$  mmol/l) in any CKD stage ( $r = -0.045$ ,  $P = 0.67$ ).

When stratified by CKD stages, generally, patients in CKD G4 to 5 had a lower TIR and higher percent time in

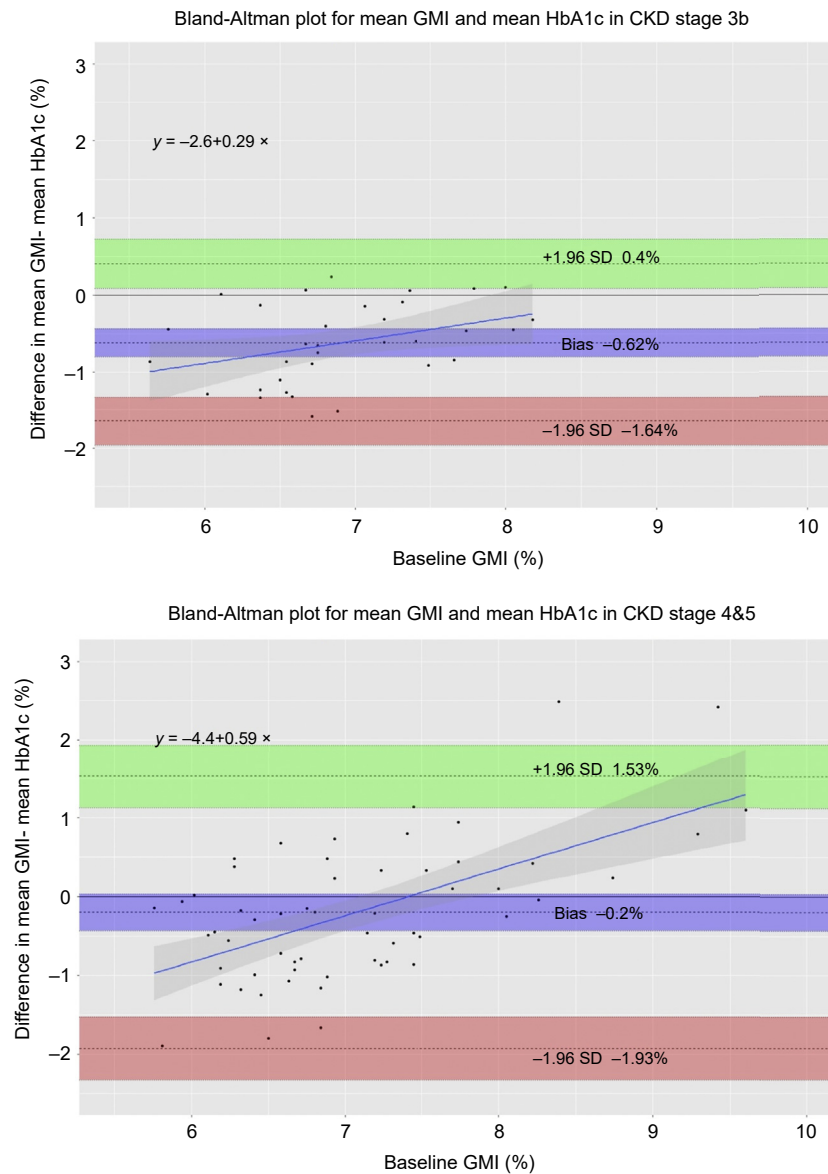
hyperglycemia as compared with those in G3b for the same HbA1c (Table 3). Supplementary Figure S2 shows examples of ambulatory glucose profiles which illustrate the discrepant relationships between HbA1c and CGM metrics.

### Relationship Between HbA1c and Glycemic Variability by CKD Stage

There was no correlation between % CV and HbA1c in the whole group ( $r = -0.05$ ,  $P = 0.64$ ), and this applied across all CKD stages (G3b [ $r = -0.009$ ,  $P = 0.96$ ], G4 [ $r = -0.33$ ,  $P = 0.83$ ], G5 [ $r = -0.21$ ,  $P = 0.46$ ]). % CV was similar across HbA1c strata in different CKD stages (Table 3). % CV was strongly correlated with % time in  $<3.9$  mmol/l ( $r = 0.61$ ,  $P = 1.23 \times 10^{-10}$ ) and % time  $<3.0$  mmol/l ( $r = 0.57$ ,  $P = 6.4 \times 10^{-9}$ ). % CV was not correlated with TIR or time in hyperglycemia.

### Determinants of Bias Between GMI and HbA1c

Age, body mass index, diabetes duration, Hb, and urine ACR were not significant determinants of bias between GMI and HbA1c (Table 4). The only significant predictor in our model was eGFR (difference  $-0.28\%$ , 95% CI  $[-0.52$  to  $-0.03]$  per 15 ml/min per 1.73 m<sup>2</sup> decrement,  $P = 0.03$ ).



**Figure 2.** Bland-Altman plot for difference between mean GMI and HbA1c by CKD stage. Difference between GMI and HbA1c in paired measurements versus GMI. Mean bias and 95% limits of agreement are shown. CKD, chronic kidney disease; GMI, glucose management index; HbA1c, glycated hemoglobin A1c.

### Correlation Between Change in GMI and Change in HbA1c Over Time

A subset of 24 patients with G3b and 35 in G4 to 5 had repeated CGM and HbA1c measurements after 4

months. There was moderate correlation between changes in GMI and change in HbA1c over time in CKD G3b ( $r = 0.44, P = 0.025$ ) and G4 to 5 ( $r = 0.35, P = 0.045$ ), respectively (Supplementary Figure S3).

**Table 3.** CGM metrics stratified by HbA1c bins in patients with moderate versus advanced CKD

HbA1c (%)	CKD stage	n	TIR 3.9–10 mmol/l (%)	Time >10 mmol/l (%)	Mean glucose (mmol/l)	SD (mmol/l)	% CV
6.5–7.4	G3b	12	76.2 [69.2–83.1]	19.6 [12.2–27.0]	7.8 [7.1–8.5]	2.6 [2.3–2.9]	0.33 [0.29–0.37]
	G4–5	20	70.1 [58.1–70.1]	26.4 [16.6–36.1]	8.3 [7.5–9.2]	2.8 [2.5–3.1]	0.34 [0.3–0.37]
7.5–8.5	G3b	16	67.8 [59.9–75.6]	29.3 [21.2–37.3]	8.6 [7.9–9.3]	2.9 [2.5–3.2]	0.34 [0.3–0.38]
	G4–5	23	62.1 [55.2–69.0]	33.4 [26.0–40.8]	8.9 [8.3–9.5]	3.0 [2.7–3.3]	0.34 [0.3–0.37]

CKD, chronic kidney disease; CGM, continuous glucose monitoring; CV, coefficient of variation; HbA1c, glycated hemoglobin A1c; TIR, time in range (3.9–10.0 mmol/l). % Data are mean [95% CI].

**Table 4.** Covariate determinants of bias for difference between GMI and HbA1c

Predictors	% Difference	95% CI	P value
Intercept	-4.78	-7.4 to -2.17	
Age (per 10 yr increment)	-0.00	-0.15 to 0.15	0.995
eGFR (per 15 ml/min per 1.73 m <sup>2</sup> decrement)	-0.28	-0.52 to -0.03	0.03
Hb (per g/dl increment)	-0.04	-0.13 to -0.06	0.42
BMI (per 5 kg/m <sup>2</sup> increment)	0.09	-0.05 to 0.24	0.21
Plasma albumin (per 5 g/dl increment)	0.15	-0.08 to 0.38	0.20
Urine ACR (per 100 mg/mmol/l increment)	0.05	-0.03 to 0.14	0.20

ACR, urine albumin-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; GMI, glucose management index; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c.

Estimates are derived from linear regression of difference between GMI and HbA1c on the listed covariate, adjusted for GMI. % Difference is the percent difference in HbA1c per difference in the covariate while adjusting for GMI.

## DISCUSSION

In this study, we found that the correlation between HbA1c and CGM metrics decreased with advancing CKD stages. HbA1c and GMI were positively correlated in CKD G3b, but the correlation was reduced in patients with eGFR <30 ml/min per 1.73 m<sup>2</sup>. HbA1c correlated with TIR and time in hyperglycemia but showed weak correlation with time in hypoglycemia. HbA1c did not correlate with indices of GV. Apart from eGFR, Hb, serum albumin, and urine ACR did not explain the bias between GMI and HbA1c.

This is one of the larger studies to date comparing correlation between HbA1c and latest CGM glucose metrics in patients with advanced CKD (<30 ml/min per 1.73 m<sup>2</sup>) who were not on dialysis. Our findings are in line with Lo *et al.*<sup>22</sup> who reported good correlation of mean CGM glucose with HbA1c ( $r = 0.79$ ) in patients with eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup> but attenuated ( $r = 0.34$ ) in participants with eGFR <30 ml/min per 1.73 m<sup>2</sup>. In another study involving 25 diabetes patients, the authors reported weak correlation ( $r = 0.38$ ) between mean CGM glucose and HbA1c in patients with eGFR <30 ml/min per 1.73 m<sup>2</sup>.<sup>15</sup> Our findings concur with earlier studies evaluating relationships between fasting plasma glucose and HbA1c where correlations were consistently reduced in eGFR <30 ml/min per 1.73 m<sup>2</sup>.<sup>9,10,23</sup> However, in a recent study using the same CGM system, Zelnick *et al.*<sup>11</sup> reported similar correlations between GMI and HbA1c in those with eGFR >30 and <30 ml/min per 1.73 m<sup>2</sup> although the number of patients with eGFR <30 ml/min per 1.73 m<sup>2</sup> was fewer than the current study ( $n = 22$ ). In another study where patients with anemia (Hb <9 g/dl) were excluded, the authors reported good correlation between HbA1c and mean CGM glucose in patients with eGFR >30 and <30 ml/min per 1.73 m<sup>2</sup>.<sup>16</sup>

In our analysis, HbA1c correlated with TIR and time in hyperglycemia (>10.0 and >13.9 mmol/l), albeit correlations were attenuated with advancing CKD

stage. There was a weak inverse correlation between HbA1c and time in hypoglycemia <3.9 mmol/l in G3b. No correlations with level 2 hypoglycemia (<3.0 mmol/l) were observed in any CKD stage. The poor reflection of hypoglycemia by HbA1c had also been reported in non-CKD populations. Using data from 4 randomized controlled trials, Hirsch *et al.*<sup>24</sup> reported that HbA1c was strongly correlated with mean glucose value and TIR but poorly with <3.0 mmol/l ( $r = -0.21$ ). In the T1D Exchange Registry, the extent of hypoglycemia was similar in patients with low and high HbA1c levels.<sup>25</sup> In a large survey of older patients with type 2 diabetes, the relative risk of hypoglycemia was similar across all HbA1c levels.<sup>26</sup> This lack of correlation between hypoglycemia and HbA1c challenges the notion that deintensification of HbA1c targets alone will reduce the risk of hypoglycemia.<sup>6</sup>

In line with other non-CKD populations,<sup>27</sup> we did not find any correlation between indices of GV, reflecting daily fluctuations of glucose and HbA1c. In this light, high GV had been reported to predict hypoglycemia in type 1 diabetes.<sup>27</sup> This was also confirmed in our study where significant correlations were observed between GV (as represented by % CV) and % time <3.9 mmol/l. There are suggestions that high GV may be associated with adverse and microvascular outcomes, independent of the level of glycemia.<sup>28,29</sup> In our cohort, up to a third of patients with CKD G3b to 5 had % CV >36 indicating unstable control. This highlights the vulnerability of this group of patients to high GV and hypoglycemia, which may not be adequately reflected by HbA1c. Thus, GV may be an additional CGM target for optimization in patients with CKD.

In our patients with CKD stage G3b, the correlation between HbA1c and CGM-derived metrics was more modest as compared with  $\sim r = 0.8$  as reported in patients with type 1 and type 2 diabetes without CKD.<sup>24,27</sup> Different CGM glucose-HbA1c relationships have been observed between CGM systems.<sup>30</sup> Besides, as the GMI equation was derived from data in patients with type 1 or type 2 diabetes with normal renal function,<sup>19</sup> the equation may need to be calibrated and validated in CKD populations. Specific HbA1c-serum glucose equations have been derived for dialysis populations which perform better than those derived from non-CKD cohorts.<sup>31,32</sup>

Our study is one of the first to evaluate the relationships between TIRs and HbA1c in moderate-to-advanced CKD. For a particular HbA1c, there was a broad distribution of TIR and exposure to hyperglycemia or hypoglycemia. Patients in CKD G4 to 5 generally had a lower TIR and higher % time in hyperglycemia compared with patients with G3b, for an

equivalent HbA1c. However, given the relatively small number of patients in each HbA1c strata by the CKD subgroup, a larger sample size is needed to confirm these observations. In other studies, researchers also reported that HbA1c may underestimate the level of glycemia as estimated by CGM in advanced CKD stages.<sup>15,22</sup>

In our multivariate analysis, we identified eGFR as the only significant determinant of bias between HbA1c and GMI whereas blood Hb, plasma albumin, and demographic variables were not. Other studies also did not find blood Hb as a confounder of the difference between HbA1c and GMI.<sup>11</sup> In our cohort, the mean Hb was 11.8 g/dl (range: 6.7–16.4g/dl). Anemia was shown to significantly affect plasma glucose–HbA1c relationships only when Hb was <8.1 g/dl.<sup>23</sup> The relatively mild degree of anemia in our cohort may explain this lack of association, in contrast to patients with kidney failure where severe anemia and ESA therapy would be more prevalent.

Our study has several limitations. Only 7 days of blinded CGM data was recorded which was shorter than the 10- to 14-day recommended period. However, other researchers had reported similar correlation between GMI and HbA1c with 1-week or 2-week CGM recordings.<sup>11</sup> We acknowledge that a longer period of recording would provide more representative assessment of CGM metrics. CGM reflects a shorter period of glycemic control, which could be influenced by acute illness or lifestyle change, whereas HbA1c reflects a longer period of 8 to 12 weeks. These data were collected at baseline from participants of a CGM intervention trial with history of hypoglycemia and a restricted HbA1c range. Together with the nonuse of ESA in these patients, our findings might not generalize to other patients with CKD. Iron and ESA therapy are known to have large effects on red cell turnover and HbA1c levels.<sup>7,8</sup> We did not measure iron status of the patients; however, only 4 patients were on oral iron therapy, which were at stable doses 3 months before enrollment. After excluding these 4 patients, the overall results remained similar. We acknowledge as a limitation that the number of patients in G5 (nondialysis) was relatively small. In our study, we purposely excluded patients on dialysis because CGM sensors might be subject to interference from hemodialysis and peritoneal dialysates.<sup>33</sup> There are now ongoing trials evaluating the utility of CGM in this important patient group, and our finding requires further confirmation in larger cohorts. We only recruited Chinese patients with CKD and recognized that there may be interethnic differences in HbA1c–CGM glucose relationships.

Our study also has implications for practice. Optimal glycemic targets in patients with CKD have

traditionally been defined using HbA1c. In the latest Kidney Disease: Improving Global Outcomes guidelines, a HbA1c target range of 6.5% to 8.0% was recommended in CKD populations,<sup>6,34</sup> which had been associated with reduced progression of CKD and mortality.<sup>3,35–37</sup> Future studies should define and validate the optimal CGM-based glycemic targets across CKD stages. Using data from the Diabetes Complications Clinical Trial, each 10% lower TIR was associated with 40% increase in microalbuminuria outcome.<sup>38</sup> The association between TIR and diabetic retinopathy has also been shown in large-scale surveys.<sup>39</sup> Taken together, our results add to the call for conducting further studies to evaluate the prognostic significance of CGM and their utility in decision-making in patients with CKD. Besides, questions such as optimal frequency and duration of CGM monitoring, types of CGM device (blinded, real-time vs. intermittently scanned CGM), user acceptability, and cost-effectiveness also need to be systematically addressed in this high-risk population.

In conclusion, in patients with moderate-to-advanced CKD, CGM-derived indices might serve as an adjunct to HbA1c monitoring to guide glycemic management, especially in those with eGFR <30 ml/min per 1.73 m<sup>2</sup> where reliability of HbA1c is lower. Importantly, CGM provided more reliable and comprehensive assessment of glucose profiles which would increase the confidence of patients and practitioners to optimize glycemic targets while minimizing risk of hypoglycemia.

## DISCLOSURE

RCWM reports receiving grants from AstraZeneca, Bayer, Pfizer, Novo Nordisk, Sanofi, and Tricida Inc.; honorarium from AstraZeneca, Boehringer Ingelheim, and Medtronic; and personal fees from Worldwide Initiative for Diabetes Education (WorldWIDE Diabetes), outside of the submitted work. All proceeds have been donated to Chinese University of Hong Kong to support diabetes research. APSK reports receiving honorarium from Abbott, Boehringer Ingelheim, and Eli Lilly; grants and honorarium from AstraZeneca, Bayer, and Sanofi, outside of the submitted work. AOYL reports receiving nonfinancial support from AstraZeneca and Boehringer Ingelheim; grants and nonfinancial support from Sanofi Hong Kong Ltd.; and research grant from Amgen, outside of the submitted work. EC reports receiving grants and speaker honoraria from Sanofi; speaker fees from Novartis; and grants from Medtronic Diabetes and Powder Pharmaceuticals, Inc., to institution, outside of the submitted work. All the other authors declared no competing interests.



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## Data Sharing Statement

Derived data supporting the findings of this study are available from the corresponding author on reasonable request.

## AUTHOR CONTRIBUTIONS

EC, JL, and JCNC contributed to conception of the article. EC and JL contributed to data collection, statistical analysis, result interpretation, manuscript drafting, revision of the manuscript critically, and final version approval. JKCN and JSSK contributed to data collection, result interpretation, and manuscript revision. ESHL, RCWM, APSK, AOYL, and CCS contributed to statistical analysis, result interpretation, revision of the manuscript critically, and approval of the final version. EC is the guarantor of this work, has 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.

## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

**Figure S1.** Correlation between HbA1c and mean continuous glucose monitoring (CGM) glucose by chronic kidney disease stages.

**Figure S2.** Examples of ambulatory glucose profiles and continuous glucose monitoring metrics showing discrepant relationships with HbA1c.

**Figure S3.** Correlation between change in HbA1c and change in continuous glucose monitoring index (CGMI) by chronic kidney disease stage.

**Table S1.** Glucose-lowering drug use by chronic kidney disease stage.

**STROBE Statement.**

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