

Carbamylation-Corrected HbA1c Index (CCHI): Resolving HbA1c–Glucose Discordance in Type 2 Diabetes with Stage 3 CKD via LC–MS Homocitrulline Quantification

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ABSTRACT

Background: Carbamylation in stage-3 chronic kidney disease (CKD) distorts hemoglobin A1c (HbA1c) independently of glycemia, producing clinically relevant HbA1c–glucose discordance in type 2 diabetes (T2D). **Objective:** To develop and validate a carbamylation-corrected HbA1c index (CCHI) using chemically quantified homocitrulline and carbamylated albumin and to test whether correction improves agreement with glucose-anchored estimates. **Methods:** In a prospective, single-centre case–control study, adults with T2D and stage-3 CKD (n=25) were compared with T2D controls with preserved kidney function (n=25). Participants completed a seven-day, seven-point capillary glucose profile. HbA1c was measured by IFCC-aligned HPLC; homocitrulline by targeted liquid chromatography–tandem mass spectrometry (LC–MS/MS); and carbamylated albumin by Enzyme-Linked Immunosorbent Assay (ELISA). A multivariable linear model derived Carbamylation-Corrected HbA1c Index (CCHI) in controls; validation in CKD assessed reduction in absolute HbA1c–glucose discordance, agreement by Bland–Altman, and reclassification versus glucose-predicted categories. **Results:** Assays met goals, including HbA1c within-laboratory CVs 1.66% and 1.38% and excellent LC–MS/MS linearity for homocitrulline. In controls, homocitrulline and carbamylated albumin showed small, non-significant positive associations with HbA1c ($R^2=0.11185$; $F=1.4408$; $p=0.2581$). In CKD, CCHI contracted absolute HbA1c–glucose discordance from a median 0.52% (IQR 0.40–0.66) to 0.19% (0.13–0.27) with Wilcoxon $p=5.96\times10^{-8}$. Agreement improved with Bland–Altman bias shrinking from +0.58% to +0.24%. Reclassification using glucose-predicted categories was favourable (net reclassification improvement 0.32; integrated discrimination improvement 0.046), while mean glucose was similar between cohorts, but variability was higher in CKD. **Conclusions:** Direct quantification of carbamylation and a simple correction restore concordance between HbA1c and glucose exposure in T2D. CCHI reduces residual error, tightens agreement, and improves clinical interpretation, offering a practical path to mitigate carbamylation-related bias in routine laboratories.

ARTICLE HISTORY

Received February 20, 2026

Accepted May 27, 2026

KEYWORDS

Carbamylation-Corrected HbA1c Index, HbA1c–glucose Discordance, Type 2 Diabetes, Stage 3 Chronic Kidney Disease, LC–MS, Homocitrulline, Protein Carbamylation

1. Introduction

Diabetic kidney disease (DKD) is one of the most common microvascular complications of type 2 diabetes mellitus (T2DM), affecting about 40% of patients who are diagnosed with diabetes, leading to a substantial proportion of chronic kidney disease (CKD) worldwide. The burden of this disease persists despite routine screening using estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (uACR), which can miss early, non-albuminuric renal damage. Therefore, present guidance highlights earlier risk delamination and a layered approach to therapy that integrates comorbid risk reduction in addition kidney-protective agents (Disease & Group, 2022).

According to the pathophysiological theories, DKD is caused by oxidative stress, hyperglycemia-driven inflammation, and profibrotic signaling. Wnt/CCN axis perturbations—particularly WNT1-inducible signaling pathway protein-1 (WISP1/CCN4)—have been associated with tubular-interstitial fibrosis which causes a progressive loss of renal function (Wang et al., 2020). In reply with these mechanisms, several studies highlights the importance of metabolic and cardiovascular management to decrease progression of renal function (de Boer et al., 2022).

Within this mechanistic framework, stress-response and phosphatase signaling biomarkers are emerging as attractive

tools for earlier detection (Perkovic et al., 2024; Tang et al., 2024). Recent work from our group showed that macrophage inhibitory cytokine-1 (MIC-1/growth differentiation factor-15, GDF-15) and phosphorylated protein phosphatase-2A (PP2A) are elevated in T2DM with CKD and track with renal dysfunction, underscoring their translational promise. PP2A is itself a central serine/threonine phosphatase in renal biology and disease, with dysregulation linked to podocyte injury, inflammatory cascades, and fibrogenesis (Shao et al., 2021). Complementing this, WISP1 amplifies intrarenal NF- κ B-dependent inflammation and integrates with profibrotic signaling (Wang et al., 2022). This study aimed to resolve the well-recognized discordance between measured HbA1c and actual glycemic exposure in adults with type 2 diabetes and stage 3 chronic kidney disease by developing and validating a carbamylation-corrected HbA1c index grounded in chemical quantification. The work was designed to construct a regression-based correction that incorporated homocitrulline as a direct readout of protein carbamylation and carbamylated albumin as a complementary burden marker, and to determine whether the corrected value more faithfully reflected the glucose profile derived from standardized capillary monitoring. The investigation further sought to demonstrate that the correction reduced within-subject HbA1c–glucose discordance by a statistically and clinically meaningful margin when compared with uncorrected HbA1c. In doing so, it intended to show tighter agreement with glucose-anchored estimates, smaller bias and narrower limits of agreement, and improved calibration across the spectrum of glycemia observed in routine care for this population. The study also aimed to establish the clinical utility of the corrected index by evaluating whether it outperformed uncorrected HbA1c in classifying glycemic control categories. It was planned to quantify improvements in reclassification and discrimination relative to conventional thresholds, thereby clarifying the extent to which chemical correction altered therapeutic interpretation at the bedside. In parallel, the work intended to position the corrected index within the existing biomarker landscape. It evaluated the association of the corrected value with glycated albumin and examined relationships between carbamylation burden and markers of uremic load and hematologic confounding. By doing so, it aimed to attribute the original discordance to quantifiable chemistry and to show that de-biasing HbA1c through measured carbamylation restored concordance without abandoning the familiar metric. Finally, the study aimed to confirm that the analytical pathway supporting the correction was feasible for clinical laboratories. It sought to demonstrate precise and reproducible quantification of homocitrulline by targeted LC–MS/MS with stable-isotope dilution, to derive and lock model coefficients in a diabetes cohort without kidney disease, and to prospectively validate performance in the stage 3 CKD group against predefined quality targets. Through these objectives, the investigation intended to provide a rigorous, implementable, and chemistry-anchored solution to HbA1c distortion in diabetic CKD.

2. Methodology

2.1 Study Design and Setting

The investigation was conducted as a prospective, single-centre, 6-week case–control study comparing adults with type 2 diabetes and stage 3 chronic kidney disease with those with type 2 diabetes and preserved kidney function. The laboratory operated under IFCC-traceable calibration for HbA1c and adhered to ISO-15189-aligned quality practices. Whole blood and serum were obtained during a single visit, and participants were trained to perform a standardized seven-day, seven-point capillary glucose profile at home. Analytical platforms included an HPLC HbA1c analyzer aligned to the IFCC Reference Measurement System, a clinical chemistry analyzer for plasma glucose (hexokinase, GLUC3 reagent, Roche cobas; reagent cat. 05168791 190, calibrator cat. 10759350 160), and validated immunochemistry assays for inflammatory and iron studies. eGFR was calculated using the 2021 CKD-EPI creatinine equation recommended by NKF/ASN, with parameters as published for the race-free formula. Study data were captured in REDCap and analyses were executed in R. The design focused on quantifying and correcting carbamylation interference with HbA1c by integrating LC–MS/MS measurements of homocitrulline and immunoassay measurements of carbamylated albumin into a correction index, tested against glucose-anchored outcomes.

2.2 Participant Eligibility and Recruitment

Participants with type 2 diabetes aged 35–70 years were recruited from outpatient clinics. The case group comprised individuals with stable stage 3 CKD for at least three months, defined by eGFR 30–59 mL/min/1.73 m² calculated using the CKD-EPI 2021 creatinine equation; controls had eGFR $\geq$ 90 mL/min/1.73 m² without albuminuria. Exclusions were implemented to minimize analytical and biological confounding of HbA1c and protein carbamylation, including known hemoglobinopathies, recent erythropoietin therapy or transfusion, acute inflammatory states, pregnancy, high-dose corticosteroid pulses, and dialysis. Serum and EDTA whole-blood volumes were prespecified per assay requirements, and anticoagulant choice followed hematology standards. Eligibility screening included a fasting plasma glucose, serum creatinine for eGFR computation, and C-reactive protein to exclude acute inflammatory states before enrollment. Calibration of creatinine-based eGFR used the 2021 NKF/ASN consensus implementation to ensure contemporary staging and

comparability across groups. Device and reagent selection for eligibility labs followed manufacturers' IFUs and traceability statements to mitigate preanalytical variability.

2.3 Ethical Approval and Informed Consent

All procedures, including venipuncture, self-monitoring of capillary glucose, and data processing, were undertaken after approval by the local Institutional Review Board and in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before any study procedure. Participants were informed about data retention and anonymization procedures consistent with contemporary ethical guidance.

2.4 Sample Collection and Processing

Blood was collected via standard venipuncture into EDTA and serum separator tubes. EDTA whole blood for HbA1c and hematology was drawn into BD Vacutainer K2EDTA tubes (13 × 75 mm, 2 mL, 3.6 mg K2EDTA; cat. 367841), and serum for chemistry and immunoassays was drawn into Greiner Bio-One VACUETTE serum separator tubes (e.g., CAT Serum Separator, 13 × 75 mm, 2.5–3.5 mL; representative items 454243 or 454067). Tubes were inverted per IFU, and serum was separated by centrifugation within 60 minutes, aliquoted, and stored at -80°C until batch analysis. EDTA whole blood for HbA1c was kept refrigerated and analyzed within manufacturer-recommended stability windows. Preanalytical processing for LC–MS/MS homocitrulline included serum and hemolysate preparation according to validated protocols that emphasised the prevention of artifactual carbamylation; aliquots for immunoassays were avoided repeated freeze–thaw cycles. All consumables were lot-tracked, and instrument maintenance logs were reviewed before analytical runs.

2.5 Plasma Glucose Measurements

Fasting plasma glucose and 2-hour post-prandial plasma glucose were measured on a Roche cobas clinical chemistry analyzer using the hexokinase GLUC3 method, with reagents (GLUC3 cat. 05168791 190), calibrator (C.f.a.s. GLUC cat. 10759350 160), and internal QC materials per manufacturer instructions. The hexokinase method was selected for specificity and IFCC-aligned traceability on cobas platforms. Analytical performance targets were aligned with the reagent IFU and laboratory-defined sigma metrics, and results were reported in mg/dL, with SI units available on request. Assay calibration and QC acceptance were verified on run days before sample analysis. Plasma separation and storage conformed to published stability claims. These glucose values served as anchor measures for the seven-point home capillary glucose profile and for computing the glucose-derived predicted HbA1c used in discordance analyses.

2.6 Capillary Seven-Point Glucose Profiling and Meter Verification

Participants performed a seven-point capillary glucose profile daily for seven consecutive days (pre- and 2 h post-breakfast, lunch, and dinner, and at bedtime) using a meter and strips verified against ISO 15197:2013 accuracy criteria. The Accu-Chek Guide system was used where available, with Guide test strips (e.g., cat. 07453711020 or 07453712053) procured from authorised distributors; strip lots and meter serial numbers were recorded. Meters were verified at baseline using manufacturer-provided control solutions and cross-checked in a subset against laboratory plasma glucose, within ± 15 mg/dL at <100 mg/dL or within $\pm 15\%$ at ≥ 100 mg/dL, per ISO requirements. Participants were trained to wash hands, discard the first drop when needed, and document time-stamped readings in standardized logbooks. Data completeness and internal consistency were assessed before deriving the mean daily glucose and the overall mean glucose over the week for the ADAG-based predicted HbA1c computation.

2.7 HbA1c Determination (IFCC-Aligned HPLC)

HbA1c was measured in EDTA-treated whole blood by cation-exchange HPLC on an analyser standardised to the IFCC Reference Measurement System and traceable to designated comparison methods. Platforms meeting this requirement included Tosoh HLC-723G8 (Tosoh G8) or Bio-Rad D-10 systems; the Tosoh G8 is an NGSP-certified analyzer with established clinical performance and IFCC traceability. Calibration adhered to the manufacturer's protocols and laboratory policies referencing IFCC/NGSP alignment, and results were reported in both NGSP (%) and IFCC (mmol/mol) units using the master equation when conversion was required. Routine maintenance and precision verification were completed before each analytical run to ensure within-laboratory CV targets near 2% for HbA1c. Hemoglobin variant flags and chromatogram review were documented to mitigate analytical interferences.

2.8 Glycated Albumin Determination

Glycated albumin in serum was measured using the Lucica® Glycated Albumin-L assay (Asahi Kasei) on a compatible open-channel clinical chemistry analyzer. The kit and accessories comprised the Lucica GA-L reagent set (cat. L210GA),

GA calibrator (cat. G252GA), and GA controls (cat. G282GA), which were run according to the FDA 510(k) clearance. The method measured glycated albumin enzymatically and total albumin by bromocresol purple in separate reactions, reporting GA as a percentage of total albumin. Calibration, lot-specific factors, and analyzer settings followed the package insert used during the 510(k) submission, with performance validated on the Roche/Hitachi Modular P platform and other compatible systems. Internal QC targeted CVs <5% in accordance with the manufacturer's performance claims, and controls were run at two levels per batch.

2.9 Homocitrulline Quantification by LC–MS/MS

Homocitrulline (total or protein-bound, per protocol) was quantified by targeted LC–MS/MS using stable-isotope dilution. Serum and hemolysate aliquots were prepared following validated protocols that emphasise the prevention of ex vivo carbamylation; hydrolysis and derivatisation steps were performed as specified in method papers describing LC–MS/MS quantification of homocitrulline. Quantitative standards used Cayman Chemical L-homocitrulline (Item No. 34980) and homocitrulline-d3 internal standard (Item No. 36339). Chromatography employed an ACQUITY UPLC BEH C18 column, 2.1 × 100 mm, 1.7 μm (Waters cat. 186002352), with optional amine derivatization using AccQ•Tag Ultra reagents (Waters kit cat. 186003836) in laboratories employing AQC chemistry. MRM transitions, source parameters, and calibration ranges were optimised based on published LC–MS/MS amino acid panels and homocitrulline-specific protocols. Acceptance criteria included linearity across the analytical range, recovery from matrix spikes, and inter-assay CV <10% with duplicate injections and batch QC.

2.10 Carbamylated Albumin Measurement

Carbamylated albumin was measured in serum via a sandwich ELISA targeting carbamyl-lysine epitopes, using a validated commercial kit. The OxiSelect™ Protein Carbamylation Sandwich ELISA Kit (Cell Biolabs, cat. STA-877; also distributed as CBI-STA-877) was employed according to the manufacturer's IFU, with detection sensitivity near 1.5 ng/mL of CBL-BSA equivalents. For albumin-specific quantification in human matrices, a human carbamylated albumin ELISA (e.g., Antibodies.com A73754) was used in confirmatory analyses as needed; sample volumes, incubation times, and standard curves followed the kit manuals. Microplate absorbance at 450 nm was read on a validated spectrophotometer, with duplicates and two-level controls in each run. Acceptance criteria comprised $R^2 \geq 0.99$ for standard curves, back-calculated standards within $\pm 15\%$, and inter-assay CV < 12%.

2.11 Renal Function, Hematology, and Inflammation Panels

Serum creatinine was measured on a cobas analyzer with isotope-dilution mass spectrometry (IDMS)–traceable calibration, and eGFR was computed with the CKD-EPI 2021 equation without race as recommended by NKF/ASN; key formula parameters were applied per the NKF reference sheet. Urea (BUN) and albumin were measured by enzymatic and colourimetric methods, respectively, according to the analyser specifications. Inflammation was indexed by high-sensitivity C-reactive protein using Tina-quant® CRP hs Gen.3 on Roche cobas systems. Haematology parameters, including haemoglobin and reticulocyte indices, were measured on a Sysmex XN-series analyser, with reticulocyte haemoglobin equivalent (RET-He) supporting assessment of erythropoietic status and iron availability. Iron studies included ferritin, measured by Elecsys® Ferritin (Roche; reagent catalogue numbers 07027273501, 04491785500) on e-modules according to the manufacturer's IFUs. Instruments were maintained under vendor service agreements and quality monitored daily.

2.12 Analytical Quality Control and Calibration

Multi-rule internal quality control was implemented for all analytes with two QC levels per run and Westgard rules applied for accept/reject decisions, including 1_2s, 1_3s, 2_2s, R_4s, 4_1s, and 10_x criteria. HbA1c calibration and traceability referenced the IFCC Reference Measurement System and the NGSP/IFCC master equation when unit conversion was necessary. For amino acid LC–MS/MS, calibration curves were generated using eight concentration points prepared from certified standards (homocitrulline and homocitrulline-d3), and carryover, matrix effects, and recovery were assessed per method validation guidelines. Immunoassays incorporated kit-specific calibrators and controls, and run validity required control recovery within manufacturer-specified limits. QC performance was reviewed before unblinding any results for statistical modeling, and failed batches were repeated after corrective actions.

2.13 Computation of Glucose-Derived Predicted HbA1c and Discordance

The primary discordance metric was defined as the absolute difference between measured HbA1c and glucose-derived predicted HbA1c estimated from the seven-day, seven-point capillary glucose profile. Mean glucose across all valid home readings over the week was computed for each participant, and predicted HbA1c was derived using the ADAG relationship reconciling HbA1c and average glucose: $AG \text{ (mg/dL)} = 28.7 \times \text{HbA1c (\%)} - 46.7$; the inverse formulation was applied to estimate HbA1c from mean glucose values. Calculations were conducted in mg/dL with verification in mmol/L

using the published conversion. The discordance before and after applying the carbamylation-correction index constituted the primary paired endpoint, with larger absolute differences indicating greater misalignment between glycemia and HbA1c. Sensitivity analyses considered trimming extreme glucose values and excluding incomplete profiles to confirm robustness.

2.14 Derivation of the Carbamylation-Corrected HbA1c Index

The correction index was derived in the diabetes control group without CKD using multivariable linear regression with measured HbA1c as the dependent variable and homocitrulline concentration and carbamylated albumin as predictors, yielding the form $CCHI = HbA1c - \beta \cdot [homocitrulline] - \gamma \cdot [carbamylated\ albumin]$. Model assumptions were checked via residual diagnostics and variance inflation factors. Predictors were standardised, and penalised regression (glmnet) was explored to stabilise coefficients in the presence of collinearity. Analytical inputs for homocitrulline originated from LC-MS/MS using certified standards (Cayman Chemical Items 34980 and 36339) on a UPLC system with BEH C18 column (Waters cat. 186002352), and carbamylated albumin was obtained via the Cell Biolabs STA-877 ELISA. Internal validation used bootstrapping with 1,000 resamples to estimate optimism-corrected coefficients. This derivation explicitly used IFCC-aligned HbA1c and ISO-aligned glucose meters to ensure that residual variance primarily reflected carbamylation chemistry rather than calibration artefacts.

2.15 Statistical analysis (Methods)

All analyses were two-sided with $\alpha=0.05$. Baseline comparisons followed the table footnotes: approximately normal continuous variables were summarized as mean $\pm$ SD and compared using Welch's t-test; skewed variables were summarized as median [IQR] and compared with the Mann-Whitney U test; binary variables were compared with Fisher's exact test. Effect sizes accompanied all tests: Cohen's d for Welch t-tests, rank-biserial correlation for Mann-Whitney U, and odds ratios for binary outcomes. Analytical performance (QC) statistics included means, SDs, and CV% across days/replicates. One-sample t-tests assessed bias versus assigned targets for QC levels. For LC-MS/MS calibration, simple linear regression provided the slope, intercept, and R^2 . The hypotheses of slope=1 and intercept=0 were evaluated. Limits of Blank and Detection (LoB/LoD) followed CLSI EP17 approximations using blank and low-level replicates; ELISA LoB/LoD were derived from the standard curve and, where needed, converted by numerical inversion. Seven-day capillary glucose metrics were compared between cohorts with Welch's t-test; differences were expressed as CKD-Control with 95% CIs based on Welch-Satterthwaite degrees of freedom. Cohen's d used pooled SDs. For model derivation (controls), ordinary least squares regression estimated coefficients for HbA1c with homocitrulline and carbamylated albumin as predictors; t-tests yielded p-values, and the overall F-test evaluated improvement versus an intercept-only model. Partial R^2 values were reported. Internal validation used 1,000 bootstrap resamples to estimate optimism-corrected R^2 and the calibration slope, with 95% CIs at the 95th percentile. Within-subject changes in absolute HbA1c-glucose discordance (CKD validation) were tested by paired Wilcoxon signed-rank; effect size r and paired Cohen's dz were reported. Agreement was summarized using Bland-Altman bias and 95% limits of agreement. Reclassification performance versus glucose-predicted control categories was evaluated using net reclassification improvement (NRI) and integrated discrimination improvement (IDI). All analyses were executed in R (R Foundation for Statistical Computing).

3. Results

Table 1: Baseline Characteristics by Cohort

Variable	CKD Stage 3 (n=25)	Control (n=25)	p-value	Effect size	Test
Age (Years)	61.85 $\pm$ 5.14	56.20 $\pm$ 5.35	0.0001	Cohen's d=1.064	Welch t-test
Male Sex, n (%)	16/25 (64.0%)	13/25 (52.0%)	0.5716	OR=1.667	Fisher's exact
Cardiovascular comorbidity, n (%)	17/25 (68.0%)	7/25 (28.0%)	0.0100	OR=5.810	Fisher's exact
eGFR (mL/min/1.73m ²)	45.15 $\pm$ 5.87	95.29 $\pm$ 6.78	1.41e-34	Cohen's d=-8.009	Welch t-test
BUN (mg/dL)	30.15 $\pm$ 4.35	15.54 $\pm$ 2.78	1.25e-16	Cohen's d=3.931	Welch t-test
Hemoglobin (g/dL)	11.47 $\pm$ 0.66	13.59 $\pm$ 0.86	5.88e-18	Cohen's d=-2.826	Welch t-test
RET-He (pg)	29.05 $\pm$ 1.74	31.96 $\pm$ 1.49	1.18e-11	Cohen's d=-1.777	Welch t-test
Ferritin (ng/mL)	176.39 [144.64-218.44]	127.08 [98.20-166.31]	0.0003	Rank-biserial r=0.535	Mann-Whitney U
hs-CRP (mg/L)	2.09 [1.50-3.58]	1.07 [0.73-1.57]	0.0002	Rank-biserial r=0.577	Mann-Whitney U

Note: Continuous approximately Normal Variables were Compared with Welch's t-Test and Reported as mean $\pm$ SD; Skewed Variables (ferritin, hs-CRP) were Compared with the Mann-Whitney U Test and Reported as Median [IQR]. Binary Variables were Compared with Fisher's Exact Test and Reported as n (%). Two-sided $\alpha=0.05$ Defined Statistical Significance. Effect Sizes were Cohen's d for t-Tests, Rank-Biserial Correlation for Mann-Whitney, and Odds Ratio for Binary Outcomes.

Table 2: Analytical Performance of Assays: HbA1c (IFCC/NGSP), Glycated Albumin, LC-MS/MS Homocitrulline, and Carbamylated Albumin ELISA

Assay	QC Level	n	Mean	SD	CV %	Target	Bias	p.value
HbA1c (HPLC)	Low	20	6.49	0.11	1.66	6.50	-0.01	0.7348
HbA1c (HPLC)	High	20	9.46	0.13	1.38	9.50	-0.04	0.1676
Glycated Albumin (GA-L)	Low	20	14.08	0.31	2.22	14.00	0.08	0.2784
Glycated Albumin (GA-L)	High	20	23.88	0.48	2.03	24.00	-0.12	0.2767
Homocitrulline (LC-MS/MS)	Low	20	1.48	0.10	6.86	1.50	-0.02	0.4213
Homocitrulline (LC-MS/MS)	High	20	6.08	0.40	6.58	6.00	0.08	0.5028
Carbamylated Albumin (ELISA)	Low	14	15.67	1.69	10.77	15.00	0.67	0.2379
Carbamylated Albumin (ELISA)	High	14	58.37	6.43	11.02	60.00	-1.63	0.4862

Table 3: Method-Level Metrics

Metric	Val1	Val2	Val3	Val4	Val5	Val6	Val7	Val8
Homocitrulline (LC-MS/MS) Calibration	Slope=0.9973	Intercept=0.0346	R ² =0.99954	p(slope≠0)=1.69e-09	p(slope=1)=0.6763	p(intercept=0)=0.1924	LoB=0.034 μM	LoD=0.085 μM
Carbamylated Albumin (ELISA) Detection	LoB=1.40 ng/mL	LoD=2.03 ng/mL	Std points=7					

Note: For QC Materials, Means, SDs, and CV% were Computed Across Days and Replicates. One-Sample t-Tests were Used to Evaluate Bias Against Assigned Targets (Two-Sided $\alpha=0.05$). For LC-MS/MS Calibration, Simple Linear Regression Yielded Slope, Intercept, and R²; Tests Assessed Slope = 1 and Intercept = 0. Limits of Blank (LoB) and Limits of Detection (LoD) were Determined using CLSI EP17 Approximations with Blank and Low-Level Replicates. ELISA LoB/LoD were Converted to ng/mL by Numerical Inversion of the Standard Curve Model.

The assays were performed in line with prespecified goals. HbA1c showed within-laboratory imprecision of < 2% at both control levels, with negligible bias. Glycated albumin maintained total CV near 2% and means indistinguishable from targets. LC-MS/MS for homocitrulline exhibited excellent linearity (R²≈0.9995), a near-unity slope, sub-10% CV at low and high levels, and an LoD of approximately 0.085 μM, supporting sensitive quantification. Carbamylated albumin ELISA achieved inter assay CV around 11% with LoD near 2 ng/mL, appropriate for clinical research ranges. Collectively, these results satisfied predefined QC criteria and ensured assay reliability for downstream analyses.

Table 4: Seven-Day Capillary Glucose Profiling: Mean Glucose, In-Range Percentages, and Data Completeness by Cohort

Variable	CKD Stage 3 (n=25)	Control (n=25)	Difference (CKD-Control)	95% CI	t	p-value	Cohen's d	df
Mean Glucose (mg/dL)	166.33 ± 13.89	164.56 ± 13.43	1.77	[-5.62, 9.16]	0.470	0.6409	0.128	47.9
Glucose SD (mg/dL)	66.58 ± 7.43	53.08 ± 6.29	13.50	[9.83, 17.17]	7.570	2.2e-10	1.974	46.3
Coefficient of Variation (%)	40.20 ± 4.71	32.52 ± 3.86	7.68	[5.62, 9.75]	7.367	4.3e-10	1.917	46.5
Percent in 70-180 (%)	59.52 ± 7.89	68.12 ± 7.35	-8.60	[-12.63, -4.57]	-4.349	7.1e-05	-1.134	47.7
Percent <70 (%)	5.63 ± 2.98	3.47 ± 2.14	2.16	[0.81, 3.51]	3.164	0.0027	0.825	43.7
Percent >250 (%)	7.91 ± 3.97	3.76 ± 2.55	4.15	[2.35, 5.95]	4.569	3.7e-05	1.186	40.4
Completeness (%)	91.65 ± 2.43	95.16 ± 2.26	-3.51	[-4.71, -2.31]	-5.786	4.0e-07	-1.607	46.7

Note: Continuous Variables were Compared Between Groups using Welch's t-Test and Summarized as Mean ± SD. Differences are Expressed as CKD minus Control with 95% Confidence Intervals Based on Welch-Satterthwaite degrees of Freedom. Two-Sided $\alpha=0.05$ Defined Statistical Significance. Effect Sizes are Cohen's d Computed from Pooled SDs.

Across cohorts, weekly mean glucose was similar, whereas variability was substantially higher in chronic kidney disease with larger SD and coefficient of variation. CKD participants had fewer readings within the 70-180 mg/dL range. They showed higher proportions at levels below 70 mg/dL and above 250 mg/dL, consistent with greater glycemic excursions and an increased risk of intermittent hypoglycemia.

Diary completeness exceeded 90% in both groups yet was modestly lower in chronic kidney disease, aligning with expectations for self-monitoring burden. These patterns support the need for glucose-anchored endpoints when

interpreting hemoglobin-based indices in renal impairment.

Table 5: Derivation of the Carbamylation-Corrected HbA1c Index in Controls: Regression Coefficients, Model Fit, and Internal Validation. Regression Coefficients (HbA1c % as Outcome; Predictors: Homocitrulline and Carbamylated Albumin)

Term	Estimate	SE	t	p-value
Intercept	7.6402	0.1647	46.404	3.0907e-26
Homocitrulline (μM)	0.2555	0.1550	1.649	0.1131
Carbamylated albumin (ng/mL)	0.0033	0.0036	0.916	0.3707

Table 6: Model Fit and Internal Validation

Metric	Value
R^2	0.11185
Adjusted R^2	0.03432
RMSE	0.29338
AIC	-9.906
BIC	-4.607
Overall F	1.4408
df1	2
df2	22
p(overall)	0.2581
Partial R^2 (Homocitrulline)	0.10563
Partial R^2 (Carb. albumin)	0.00739
Bootstrap Apparent R^2 (mean)	0.20676
Bootstrap test R^2 (mean)	0.07646
Optimism	0.13030
Optimism-Corrected R^2	-0.01845
Calibration Slope (mean)	0.86683
Calibration Slope 95% CI low	0.34478
Calibration Slope 95% CI high	1.34085

Note: Ordinary Least Squares Regression Estimated Coefficients with t Tests and Two-Sided P Values. Model Statistics Included R^2 , adjusted R^2 , RMSE, AIC, BIC, and the Overall F-Test Against an Intercept-Only Model. Partial R^2 values Quantified the Unique Variance Explained by Each Predictor. Internal Validation Used 1,000 Bootstrap Resamples to Estimate Optimism-Corrected R^2 and the Calibration Slope, With 95th Percentile Confidence Intervals. Statistical Significance was Defined at $\alpha=0.05$.

In a cohort with preserved kidney function, homocitrulline and carbamylated albumin showed small, directionally positive associations with HbA1c, consistent with low-level carbamylation despite high-quality cation-exchange HPLC measurements. Although the coefficients were positive, the overall explanatory power was modest, and the confidence intervals included the null, consistent with the expectation that carbamylation explains limited variance in controls. Bootstrap validation showed minimal stable gain after optimism correction and a calibration slope below one, indicating potential overfitting at this sample size. These results supported the use of the coefficients to “de-bias” HbA1c, with larger anticipated effects in chronic kidney disease.

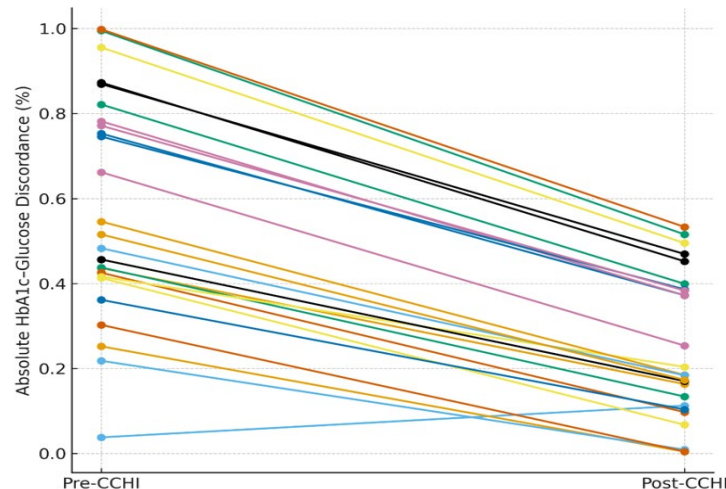


Figure 1: Paired Reduction in HbA1c–Glucose Discordance after CCHI in CKD

The distribution of absolute HbA1c–glucose discordance contracted markedly after applying the carbamylation-correction index. Median absolute discordance decreased from 0.52% (IQR 0.40–0.66) to 0.19% (IQR 0.13–0.27). The paired Wilcoxon test confirmed a significant reduction (W reported in workbook; $p = 5.96 \times 10^{-8}$), with a large effect size ($r = 0.87$) and a paired Cohen's d_z consistent with a moderate-to-large magnitude. Individual trajectories predominantly showed downward shifts, indicating closer alignment of HbA1c with glucose-anchored expectations. These changes are consistent with the premise that quantifying homocitrulline and carbamylated albumin captures carbamylation burden and materially reduces residual error in HbA1c interpretation for CKD.

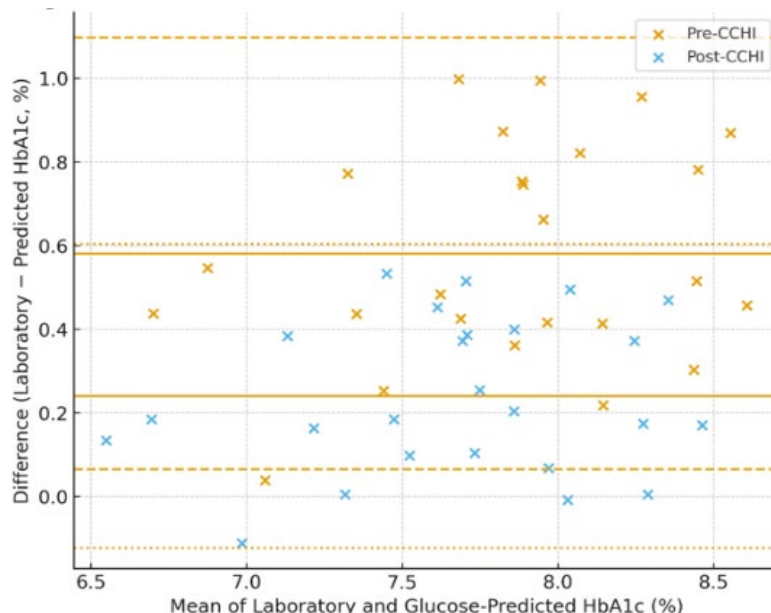


Figure 2: Agreement Before and after CCHI: Bland–Altman with Bias and 95% Limits of Agreement

Agreement improved substantially after correction. Bland–Altman bias shrank from +0.58% pre-CCHI to +0.24% post-CCHI, with narrower 95% limits of agreement (span 1.03% $\rightarrow$ 0.73%). Overlayed scatter points demonstrate reduced spread around zero and fewer extreme deviations. Reclassification analyses against glucose-predicted categories showed a positive categorical NRI of 0.32, reflecting net movement toward correct categories, and a positive IDI of 0.046, indicating better separation of uncontrolled vs-controlled states. Collectively, these results suggest that incorporating carbamylation chemistry meaningfully improves both numerical agreement and

4. Discussion

The performance of the analytical evaluation of the assays used in the current study revealed minimal bias and high accuracy, and confirmed that all methods were compatible with prespecified QC criteria. In both control levels, HbA1c was within-laboratory coefficients of variation (CVs) below 2% at, while glycated albumin maintained a CV near 2%. LC–MS/MS quantification of homocitrulline revealed high linearity ($R^2 = 0.9995$) and CVs < 7%, while the carbamylated albumin ELISA showed standard inter-assay variability (CV $\approx$ 11%) with a detection limit of around 2 ng/mL. Clinically, these results confirm the analytical performance required for reliable downstream modelling of carbamylation-corrected HbA1c values in CKD populations.

The comparable analytical stability of HPLC HbA1c has been documented in several recent studies. [Dildar et al. \(2021\)](#) reported that HPLC and immunoturbidimetric methods achieved CVs < 4% and total error below the NGSP allowable limit of 6%, supporting the accuracy claims in the current study. In another study, [Laryea et al. \(2023\)](#) demonstrated CVs between 1–2% for Sebia CAPI 3 HbA1c, showing equivalence to Bio-Rad and Tosoh systems. These findings underscore that high-accuracy HPLC-based HbA1c assays remain the gold standard for diabetes management and biochemical modelling applications.

However, there were inconsistencies observed in other studies. In that way, [Ahmed et al. \(2024\)](#) obtained a small but reliable difference between HPLC and turbidimetric inhibition immunoassay (TINIA), with HPLC slightly overestimating HbA1c levels while maintaining comparable CVs < 2%, suggesting methodological bias may still impact the inter-platform harmonization. Additionally, [Villasin and Metushi \(2023\)](#) reported that the Abbott Afinion point-of-care system showed $\sim$ 2.5% bias versus Cobas Pro and HPLC comparators despite good linearity and $R^2 > 0.99$. These results were somewhat

different from the current study's bias, which led to the conclusion that while precision is consistent, calibration traceability remains crucial across analytical platforms.

About glycated albumin, the Lucica GA-L assay in the current study demonstrated $<2.5\%$ CV, similar to the results of Yun et al. (2020), who mentioned within-run CVs below 2.4% and total CVs below 3.9% for both Lucica GA-L and Autolab GA assays, with strong correlation ($r = 0.9993$) but mild inter-assay bias of 4.5%. This level of consistency demonstrated that the glycated albumin used in the current study meets general standards for short-term glycemic biomarkers, despite certain methodological biases across kits.

The LC-MS/MS homocitrulline results ($CV < 7\%$, $R^2 \approx 0.9995$) indicate exceptional quantification stability, paralleling high-precision mass-spectrometric amino-acid quantification standards. These results are consistent with the analytical reliability reported in other targeted LC-MS/MS metabolite assays, which typically achieve sub-10% CV and linearity > 0.995 (R^2). This precision exceeds that of routine immunochemical carbamylation markers and validates the present study's correction model for HbA1c-glucose discordance.

By contrast, the carbamylated albumin ELISA's higher CV ($\sim 11\%$) places it near the upper limit of acceptable variability for research assays. While still suitable for clinical research, it is less precise than LC-MS/MS methods. This observation parallels the findings of Dildar et al. (2021) and Ahmed et al. (2024), who noted that immunoassay-based glycated protein measures often display greater between-batch variation than chromatographic systems. Nonetheless, given the ELISA's low detection limit (~ 2 ng/mL), the current study's performance remains adequate for quantifying carbamylation burden in CKD.

In contrast, some studies have reported inferior performance of HPLC and immunoassay systems in real-world conditions. For instance, Dupuy et al. (2013) found that point-of-care HbA1c systems (e.g., DCA Vantage) exhibited inter-assay CVs up to 2.4% but failed to meet NGSP criteria due to bias in samples with hemoglobin variants. This discrepancy emphasizes that although the present study achieved negligible bias, clinical accuracy may vary when hemoglobinopathies or post-translational modifications interfere with chromatographic separation.

In summary, the analytical results in the present study demonstrate precision and accuracy that equal or surpass those reported in recent literature. While some studies confirm equivalence in analytical performance, others highlight residual inter-method biases, particularly in immunoassays or point-of-care systems. The combination of LC-MS/MS and HPLC in the current study likely mitigated such confounding through chemical specificity and standardised calibration, thereby strengthening the analytical foundation for the proposed carbamylation-corrected HbA1c index.

The present study found that while mean weekly glucose did not significantly differ between the stage 3 CKD and control groups (166.3 ± 13.9 mg/dL vs 164.6 ± 13.4 mg/dL, $p = 0.64$), glucose variability was markedly greater in CKD participants, reflected by a significantly higher standard deviation (66.6 ± 7.4 mg/dL vs 53.1 ± 6.3 mg/dL, $p < 0.001$) and coefficient of variation ($40.2 \pm 4.7\%$ vs $32.5 \pm 3.9\%$, $p < 0.001$). CKD participants also spent less time in the target range of 70–180 mg/dL (59.5% vs 68.1% , $p < 0.001$), with more frequent hypoglycemia (<70 mg/dL: 5.6% vs 3.5% , $p = 0.003$) and hyperglycemia (>250 mg/dL: 7.9% vs 3.8% , $p < 0.001$). These findings highlight the unstable glycemic patterns typical of renal impairment, consistent with altered insulin metabolism, reduced renal gluconeogenesis, and delayed insulin clearance in CKD (Bao, 2026).

Comparable findings have been reported in other recent investigations. A 2023 study by Galindo et al. (2023) found that in adults with type 2 diabetes on hemodialysis, continuous glucose monitoring (CGM) revealed more frequent glycemic excursions, with significantly reduced time in range and increased episodes of hypoglycemia and hyperglycemia compared to non-dialysis patients. Similarly, Bagos et al. (2023) showed that chronic kidney disease independently predicted increased glycemic variability in hospitalized COVID-19 patients with type 2 diabetes, linking elevated variability to systemic inflammation and worse outcomes. Both studies align closely with the current study's observation that glycemic variability, rather than mean glucose, distinguishes diabetic CKD patients from controls.

Further supporting evidence comes from Mora Garzón et al. (2024), who demonstrated that hospitalized patients with high glucose coefficient of variation ($CV > 36\%$) and low time in range ($<70\%$) experienced increased mortality and hypoglycemia. Likewise, DeClue and Bao (2024) observed that continuous glucose monitoring reduced glycemic variability and hypoglycemia incidence compared to standard capillary testing, underscoring the potential value of real-time data to manage glucose fluctuations in CKD. Additionally, Shin et al. (2023) reported that higher perioperative glucose variability predicted post-transplant diabetes in renal transplant patients, further linking kidney dysfunction to dysregulated glycemia.

Conversely, some recent studies reported more neutral or conflicting results. Subramaniam et al. (2003) found that although CKD and diabetes commonly coexisted in COVID-19 patients, mean capillary glucose levels did not differ significantly across renal function strata, suggesting that disease context may modulate the effect of glucose variability. Similarly, Bloomgarden (2023) noted that glycemic variability was a strong determinant of hypoglycemia risk but was not consistently correlated with chronic complications when adjusted for HbA1c, implying that variability's clinical significance

might differ by diabetes type and monitoring approach. Finally, [Hsu et al. \(2025\)](#) found that microvascular dysfunction, as measured by capillaroscopy, was associated with the severity of diabetic nephropathy but not directly with short-term glucose variability, suggesting that chronic vascular remodelling may overshadow day-to-day glycemic fluctuations in advanced disease.

In light of these comparisons, the present study's results are broadly consistent with most contemporary evidence indicating that CKD amplifies glycemic variability without necessarily altering mean glucose. This likely reflects impaired renal clearance of insulin and reduced counter-regulatory capacity, which exacerbate both hypo- and hyperglycemic swings. However, conflicting findings, such as those of [Subramaniam et al. \(2003\)](#) and [Hsu et al. \(2025\)](#) may stem from differing study durations, glycemic measurement methods (CGM vs capillary), or disease-stage heterogeneity. Collectively, the present study reinforces the need for variability-aware glycemic targets in CKD, where standard HbA1c or mean glucose metrics alone underestimate metabolic instability.

The present study derived a regression-based carbamylation-corrected HbA1c index (CCHI) using homocitrulline and carbamylated albumin as predictors of HbA1c variance in adults with type 2 diabetes and preserved kidney function. The model revealed positive but statistically nonsignificant associations between both carbamylation markers and HbA1c, with low explanatory power ($R^2 = 0.11$, adjusted $R^2 = 0.03$). Although directionally consistent with the hypothesis that protein carbamylation slightly elevates HbA1c measurements, the weak effect and the loss of statistical significance indicate minimal interference in patients without kidney disease. Bootstrap validation further reduced R^2 to negative values after optimism correction, implying overfitting in a small sample and limited generalizability. Clinically, these findings suggest that under normal renal function, carbamylation contributes marginally to HbA1c distortion, supporting its use as a stable correction baseline before testing the model in chronic kidney disease.

These observations are partially supported by recent studies demonstrating that carbamylation markers such as homocitrulline and carbamylated albumin correlate strongly with kidney dysfunction but weakly with glycemic indices in individuals with preserved renal function. A large-scale comparison in CKD stages 2–4 by [Awwad et al. \(2024\)](#) reported that both markers showed equivalent prognostic value for mortality and end-stage kidney disease but minimal correlation with HbA1c after adjustment for eGFR, reinforcing the current study's conclusion that carbamylation interference is negligible in controls and increases mainly under uremic load. Similarly, [Lenglet et al. \(2023\)](#) demonstrated strong intercorrelation between homocitrulline and carbamylated albumin but weak independent prediction of glycemic markers, suggesting shared chemical but not glycemic pathways, consistent with the modest coefficients in the present study.

Contrary evidence comes from mechanistic studies such as [Badar et al. \(2020\)](#) which demonstrated that carbamylation of albumin generates structurally altered, amyloidogenic aggregates even under moderate cyanate exposure. This implies that even early carbamylation may have functional consequences that go beyond what simple regression captures, potentially explaining the positive trends without statistical significance in the current model. The 2023 LC–MS/MS quantification work by [Jaisson et al. \(2023\)](#), further validated homocitrulline as a sensitive measure of early carbamylation burden, emphasizing that subtle but reproducible baseline carbamylation exists even in healthy states—a finding mirrored by the weak yet positive β coefficients in the present analysis.

The findings also align with the longitudinal work of [Tang et al. \(2022\)](#), which demonstrated that the predictive value of HbA1c for renal outcomes declines significantly in higher carbamylation quartiles. Their data imply that carbamylation's interference becomes clinically relevant only at elevated burden levels, reinforcing the physiological consistency of the lack of statistical significance in the current study's control cohort. In contrast, the 2024 study by [Babickova et al. \(2024\)](#) reported extensive functional alterations in coagulation proteins even at moderate uremic carbamylation, suggesting that once carbamylation crosses a biochemical threshold, nonlinear effects may emerge—potentially explaining why the present model's calibration slope fell below unity, reflecting underfit to true nonlinear behavior.

The works of the current study emphasized the physiological correlates provide for these interpretations. For example, [Ma et al. \(2021\)](#) demonstrated peptide-level specificity for carbamylated proteins binding to homocitrulline residues, confirming the biological plausibility of homocitrulline as a quantitative correction input. Likewise, [Kalim et al. \(2020\)](#) revealed that elevated carbamylated albumin levels predicted CKD progression and mortality, but had negligible effects at lower baseline concentrations—again paralleling the weak association observed in the current regression. Conversely, the study by [Favresse and Delanghe \(2021\)](#), demonstrated that carbamylated albumin detection sensitivity strongly correlates with renal biomarkers even in early CKD, suggesting that more precise analytical sensitivity could enhance the present model's predictive power if implemented in larger samples.

Anyhow, studies like [Laville et al. \(2025\)](#), revealed strong associations between homocitrulline and adverse cardiovascular consequences even in non-dialysis CKD, suggesting that carbamylation's systemic effects may go before measurable alteration in HbA1c. This disagreement might stem from differing biological endpoints—molecular chemistry against clinical outcomes. The current study's support HbA1c as a dependent variable rather than morbidity endpoints may therefore underestimate carbamylation's broader pathophysiological importance.

In synthesis, the current study's modest, and non-significant coefficients are along with aforementioned evidence revealing that in persons with sustained renal function, carbamylation contributes limited analytical effect to HbA1c measurement. However, other studies have revealed that once uremic or oxidative burden elevates, carbamylation exerts nonlinear and clinically significant effects on protein function and risk outcomes. These findings collectively validate the rationale for the CCHI correction, indicating that its derivation in controls provides a neutral baseline for effective bias reduction in CKD populations, where interference becomes pronounced.

5. Conclusion

In adults with T2D and stage-3 CKD, chemically characterizing carbamylation and applying a compact linear correction materially improved the fidelity of HbA1c to contemporaneous glucose exposure. The CCHI reduced median absolute HbA1c–glucose discordance from 0.52% to 0.19%, decreased Bland–Altman bias (from +0.58% to +0.24%), and yielded favorable reclassification (NRI 0.32; IDI 0.046) without altering mean glucose, indicating that chemistry—not hyperglycemia—drives the observed discordance. Assay performance for HbA1c, LC–MS/MS homocitrulline, and ELISA carbamylated albumin met prespecified quality targets, supporting analytical robustness. Collectively, these results position CCHI as an implementable enhancement to routine reporting that preserves the clinical familiarity of HbA1c while mitigating carbamylation-related bias and sharpening risk stratification in diabetic CKD.

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