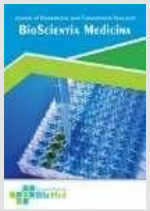
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Uncoupling Phenomenon: Dissociation Between Albuminuria and Glomerular Filtration Rate in an Advanced Diabetic Kidney Disease Phenotype

Naufal Fathi Ashari[1], Harnavi Harun[2*], Russilawati[3], Dinda Aprilia[4], SM Rezvi[5]

[1]Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[3]Department of Pulmonology and Respiratory Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[4]Division of Medical Endocrine Metabolic, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[5]Department of Microbiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFO

Keywords:
Albuminuria
Diabetic kidney disease
Glomerular filtration rate
Renal pathophysiology
Uncoupling phenomenon

***Corresponding author:**
Harnavi Harun

E-mail address:
harnavi@med.unand.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i2.1521

A B S T R A C T

Background: The classical paradigm of diabetic kidney disease (DKD) assumes a synchronous, linear trajectory where increasing albuminuria predicts the decline of glomerular filtration rate (GFR). However, emerging epidemiology suggests these markers may dissociate in advanced disease stages, particularly under modern renoprotective pharmacotherapy. We aimed to investigate this uncoupling phenomenon by evaluating the correlation between urine albumin creatinine ratio (UACR) and estimated GFR (eGFR) in a specific cohort of advanced DKD patients in Indonesia. **Methods:** We conducted a cross-sectional analytic study from January to November 2025 at Dr. M. Djamil General Hospital Padang, a tertiary referral center. The study population comprised 30 patients with established DKD, predominantly in CKD Stages 3b and 4. The primary outcome was the Spearman rank correlation (r) between UACR and eGFR, reported with 95% Confidence Intervals (CI). An exploratory sub-analysis compared trends in patients receiving SGLT2 inhibitors (n=12) versus standard care (n=18). **Results:** The cohort was elderly (mean age 61.93 years) with critical renal reserve depletion (median eGFR 32.50 mL/min/1.73 m²). Median UACR was 403.90 mg/g, yet exhibited massive heterogeneity (IQR: 170.82–1779.27). Spearman analysis revealed a complete lack of linear correlation between albuminuria and filtration function (r = 0.041; 95% CI: -0.322 to 0.395; p = 0.830). While SGLT2 inhibitor users (n=12) demonstrated numerically lower median UACR than non-users (n=18), the dissociation from eGFR persisted in both subgroups. **Conclusion:** We demonstrate a distinct dissociation between albuminuria severity and filtration function in advanced DKD. This uncoupling suggests that in late-stage nephropathy, structural glomerulosclerosis and tubulointerstitial fibrosis progress independently of permeability changes. Consequently, albuminuria cannot serve as a sole surrogate for disease progression in this phenotype, supporting a dual-biomarker strategy where UACR and eGFR are monitored as independent risk factors.

1. Introduction

Diabetic kidney disease (DKD) stands as the defining nephrological challenge of the 21st century. It remains the preeminent driver of end-stage kidney disease (ESKD) globally, contributing to substantial morbidity, cardiovascular mortality, and a healthcare economic burden that threatens to overwhelm public health systems.[1] The trajectory of this epidemic is particularly alarming in the developing world. In the context of Southeast Asia, and specifically Indonesia,

the prevalence of DKD is accelerating at a rate that outpaces global averages.[2] This surge is driven by a demographic perfect storm: a rapidly aging population combined with the rising incidence of Type 2 diabetes mellitus (T2DM), often occurring at younger ages and lower body mass indices compared to Western populations.[3]

The clinical reality in Indonesia presents unique challenges. Unlike the structured screening programs often available in high-income nations, the Indonesian healthcare landscape—while rapidly improving under universal coverage schemes—still faces the issue of late presentation.[4] Indonesian tertiary centers, such as Dr. M. Djamil General Hospital Padang, frequently manage patients presenting with late-stage phenotypes. These are individuals who have largely bypassed the window of early detection and intervention, presenting for the first time with established renal insufficiency (CKD Stage 3b or 4).[5] In this specific demographic, the window for prevention has closed, and the clinical mandate shifts to salvage: arresting the progression before the catastrophic transition to renal replacement therapy. Understanding the biomarker kinetics in this advanced, often neglected population is not merely academic; it is crucial for tailoring management strategies that are economically and clinically viable for the region.

For nearly forty years, the clinical understanding and management of DKD were governed by a singular, elegant heuristic known as the classical paradigm.[6] First conceptualized by Mogensen and colleagues in the pivotal literature of the 1980s, this natural history model described a sequential, synchronous, and linear evolution of diabetic nephropathy. The narrative of the classical paradigm was compelling in its simplicity. It posited that renal damage followed a fixed chronological order: (1) Hemodynamic stress: The disease began with glomerular hyperfiltration, driven by hyperglycemia-induced vasodilation of the afferent arteriole; (2) The window of opportunity: This pressure eventually compromised the glomerular filtration barrier, leading to the onset of microalbuminuria (30–300 mg/g)—the canary in the coal mine for renal risk; (3) Overt disease: Without intervention, microalbuminuria invariably progressed to overt macroalbuminuria (greater than 300 mg/g); (4) Functional collapse: Finally, the presence of heavy proteinuria would drive a relentless, linear decline in glomerular filtration rate (GFR) toward end-stage failure. Under this dogma, albuminuria was elevated to a status of supreme importance. It was viewed not merely as a marker of glomerular damage but as the direct surrogate for disease progression.[7] The underlying pathophysiological theory was the protein toxicity hypothesis. This theory posited that the leakage of albumin across the damaged podocyte slit diaphragm was not just a symptom, but a toxic effector. The filtered protein load was thought to overwhelm the reabsorption capacity of the proximal tubules, triggering pro-inflammatory and pro-fibrotic cytokines (such as TGF-beta) that actively destroyed the renal interstitium. Consequently, for decades, the clinical algorithm was binary and linear: as albuminuria rises, GFR falls. Conversely, if a therapy could lower albuminuria, it was assumed that GFR was being saved. This albumin-centric view became the cornerstone of all major clinical trials and guidelines, shaping the definition of renoprotection for a generation.

However, the landscape of clinical nephrology is currently undergoing a fundamental shift, moving away from the simplified linear models of the past. Contemporary longitudinal data and modern epidemiology have revealed that the trajectory of DKD is far more heterogeneous than Mogensen could have predicted in the 1980s. A growing body of evidence indicates that the classical trajectory is not universal. A significant proportion of patients with T2DM—up to 40% in some cohorts—experience a progressive decline in GFR without ever developing significant albuminuria. This phenotype, termed Normoalbuminuric DKD, fundamentally challenged the idea that proteinuria is a prerequisite for renal failure. But while Normoalbuminuric DKD is well-

described, a more complex and less understood phenomenon occurs in the advanced stages of the disease (CKD Stages 3b and 4): the Uncoupling Phenomenon. In this advanced state, the tight physiological correlation between glomerular permeability (represented by UACR) and filtration function (represented by eGFR) appears to disintegrate.[8] Clinicians increasingly encounter patients with discordant biomarkers: (i) Phenotype A: Patients with massive, nephrotic-range proteinuria (UACR > 2000 mg/g) who remarkably maintain stable GFR over long periods; (ii) Phenotype B: Patients with dry failure—rapid filtration decline and aggressive tubulointerstitial fibrosis—occurring in the presence of minimal or stable albuminuria.

This divergence suggests that in late-stage disease, the two markers track different pathological processes. Albuminuria is primarily a marker of glomerular health—specifically, the integrity of the endothelium and the podocyte slit diaphragm. In contrast, GFR decline in the elderly, Type 2 diabetic patient is increasingly attributed to tubulointerstitial and vascular health. Pathophysiological mechanisms such as macrovascular atherosclerosis, chronic ischemic nephropathy, and senile nephrosclerosis can drive the loss of filtration capacity via tubular atrophy and interstitial fibrosis, completely independently of the glomerular filtration barrier's permeability. This uncoupling represents a crisis of prognostication. If albuminuria and GFR dissociate in advanced disease, then the standard practice of using UACR to predict the slope of GFR decline may be statistically invalid for Stage 4 patients. The assumption that structure follows function breaks down, necessitating a more nuanced understanding of renal kinetics.[9]

Complicating this biological relationship is the widespread adoption of potent, modern pharmacological agents. In the era of Mogensen, patients were often untreated or treated with agents that had little impact on renal hemodynamics. Today, the standard of care includes maximal blockade of the renin-angiotensin-aldosterone system (RAAS) via ACE inhibitors or ARBs, and more recently, the widespread initiation of sodium-glucose cotransporter-2 (SGLT2) inhibitors. These agents are powerful hemodynamic modulators. RAAS inhibitors dilate the efferent arteriole, while SGLT2 inhibitors constrict the afferent arteriole via tubuloglomerular feedback. Both mechanisms achieve the same goal: a reduction in intraglomerular hydrostatic pressure. By reducing the physical pressure inside the capillary, these drugs mechanically reduce the amount of albumin being pushed into the urine.

This introduces a phenomenon we term therapeutic masking. In a heavily treated patient, the UACR may be artificially suppressed by hemodynamic unloading. A patient may present with a cosmetically improved UACR (dropping from 500 to 100 mg/g) solely due to pressure reduction, while the underlying non-hemodynamic pathways of fibrosis—driven by metabolic memory, oxidative stress, and inflammation—continue to silently erode the GFR. This therapeutic masking creates a statistical noise that further decouples the biomarkers. In a tertiary care cohort where medication adherence is high, the correlation between UACR and GFR is likely to be far weaker than in the natural history cohorts of the past. The presence of these drugs creates a pharmacological discordance that must be accounted for when interpreting renal risk.

Despite the critical implications of this phenotypic heterogeneity, there is a significant gap in the literature regarding the Southeast Asian experience. The vast majority of correlation studies underpinning our guidelines are derived from Western populations or focus on early-stage disease (Stage 1 and 2), where hyperfiltration ensures that markers track synchronously. There is a paucity of data interrogating this relationship when renal reserve is critically depleted—specifically in the pre-dialysis window of Stage 3b and 4. This distinction is vital because the pathophysiology of a Stage 1 kidney (hyperfiltering, large surface area) is fundamentally different from a Stage 4 kidney (sclerotic, reduced surface area, tubulointerstitial dominance). Applying the logic of early-stage disease to late-stage survivors

may be a clinical error.[10]

This study aims to address this gap by focusing specifically on the correlation between UACR and eGFR in a real-world cohort of advanced DKD patients in a tertiary care setting in West Sumatra, Indonesia. Unlike previous studies that aggregate all stages of CKD, our focus on Stages 3 and 4 allows us to interrogate the biomarker relationship at the specific point where the glomerular filtration surface area is severely compromised. We hypothesize that in this advanced phenotype, the classical linear relationship between proteinuria and filtration failure breaks down. Validating this uncoupling in an Indonesian cohort is essential for justifying the shift toward a Dual-Biomarker Strategy—where albuminuria and GFR are monitored as independent, rather than redundant, risk factors

2. Methods

This research was designed as an observational, cross-sectional, analytic study, prioritizing a real-world assessment of biomarker kinetics. The investigation was conducted within the specialized ecosystem of the Internal Medicine and Nephrology outpatient clinics at Dr. M. Djamil General Hospital Padang. As a tertiary referral center in West Sumatra, Indonesia, this institution serves as a central catchment area for complex, multi-morbid pathology, making it the ideal setting to recruit patients with the specific advanced disease phenotype required for this analysis. The study period spanned ten months, from January 2025 to November 2025, capturing a representative longitudinal slice of the clinic's population. The research protocol was developed in strict adherence to the ethical principles outlined in the Declaration of Helsinki, ensuring the protection of human subjects. Ethical clearance was formally granted by the Health Research Ethics Committee of Dr. M. Djamil General Hospital Padang (Reference No: DP.04.03/D.XVI.XI/260/2024). Prior to any data collection or biological sampling, all participants were provided with a detailed explanation of the study aims and provided written informed consent.

The integrity of a correlation study rests entirely on the homogeneity of its population. The study population comprised patients with a confirmed diagnosis of diabetic kidney disease (DKD). However, to move beyond generic observations and capture the specific uncoupling phenomenon hypothesized to occur in late-stage disease, we eschewed broad recruitment in favor of strict phenotypic criteria. We aimed to isolate a cohort where the renal reserve was critically depleted, yet the patient remained independent of renal replacement therapy.

Eligibility was restricted to patients who met the following three criteria: (1) Confirmed Etiology: Patients were required to have a confirmed diagnosis of Type 2 Diabetes Mellitus with chronic kidney disease attributed specifically to diabetic etiology. This attribution was based on the standard clinical composite of long-standing diabetes, presence of retinopathy, and absence of signs suggesting alternative etiologies; (2) The Advanced/Established Window: We specifically targeted the Advanced or Established phenotype, defined predominantly as CKD Stages 3 and 4 (eGFR 15–59 mL/min/1.73 m2). This eGFR window represents the critical transition period. It is the phase where the kidney has lost significant functional mass (more than 50%), and where the trajectory toward failure often accelerates. It is precisely in this window that we hypothesized the dissociation between structure (glomerulosclerosis) and function (filtration) would be most evident; (3) Measurable Albuminuria: To perform a valid correlation analysis, patients were required to have persistent albuminuria (UACR greater than 30 mg/g).

To ensure that the observed relationship (or lack thereof) was driven by diabetic pathology and not by external confounders, we rigorously excluded: (1) Non-diabetic kidney disease (NDKD): The kinetics of proteinuria in non-diabetic diseases differ fundamentally from DKD. Therefore, we excluded any patient with biopsy-proven glomerulonephritis, obstructive nephropathy (hydronephrosis), or drug-induced nephrotoxicity; (2) The Hyperfiltration and Dialysis Artifacts (Stage 1 and 5): We excluded Stage

1 CKD because glomerular hyperfiltration can artificially inflate GFR, masking the true extent of tissue loss. Conversely, we excluded Stage 5 (End-Stage Kidney Disease) because dialysis therapy artificially lowers serum creatinine (rendering eGFR equations invalid) and oliguria makes UACR interpretation erratic and unreliable; (3) Transient Albuminuria Triggers: Albuminuria is a dynamic marker that can flare reactively. We excluded patients with acute infections (systemic or urinary), active malignancies, uncompensated heart failure (where venous congestion causes proteinuria), or those who reported strenuous exercise within 24 hours of sampling. This ensured that the measured UACR reflected chronic glomerular permeability, not acute hemodynamic stress. While the protocol was designed to target established disease (Stage 3 and 4), one patient with Stage 2 CKD (eGFR 60-89 mL/min/1.73 m2) was retained in the final dataset. This exception was made because the patient presented with overt macroalbuminuria and significant diabetic comorbidity, consistent with the biological phenotype of established disease, despite a preserved GFR calculation.

The determination of sample size was driven by the specific statistical requirement of the primary hypothesis: to detect a correlation coefficient. The study was not designed to estimate prevalence, but to test the strength of the linear relationship between UACR and eGFR; (1) Hypothesis: We tested the null hypothesis that there is no correlation (rho = 0) against the alternative hypothesis that the classical Mogensen paradigm holds true (rho is not equal to 0); (2) Target Effect Size: We powered the study to detect a strong correlation (r = 0.50); (3) Parameters: With a statistical power (1-beta) of 80% and a two-tailed significance level (alpha) of 0.05, the calculation indicated a minimum required sample size of 29 subjects. To account for potential data loss, we recruited 30 subjects. We acknowledge that powering for a strong correlation (r = 0.50) technically limits the ability to detect weak or moderate associations. However, this decision was grounded in clinical pragmatism. In the context of biomarker monitoring, if the correlation between UACR and eGFR is weak (r less than 0.3), the predictive utility of using one marker to surmise the other is negligible. If UACR only explains 9% of the variance in GFR (r-squared = 0.09), it is clinically useless as a surrogate. Therefore, this sample size is sufficient to answer the clinically relevant question: Is there a strong predictive relationship that justifies the current single-marker monitoring strategy?

To minimize pre-analytical variation, data collection adhered to a strict standardization protocol. Anthropometric measurements and hemodynamics were captured after a mandatory 5-minute rest period to ensure baseline stability. Blood pressure was measured using a validated oscillometric device to avoid auscultatory bias. The timing of urine collection was a critical methodological control. We utilized the first morning void for all UACR measurements. Albumin excretion follows a circadian rhythm and is heavily influenced by posture (orthostatic proteinuria) and physical activity. By restricting collection to the first morning void, we minimized these hemodynamic confounders, obtaining a sample that best reflects the basal permeability of the glomerular filtration barrier. Albumin concentration was quantified using immunoturbidimetry, the gold standard for specific protein detection, while creatinine was measured enzymatically. Serum creatinine was measured using the Jaffe method, calibrated to Isotope Dilution Mass Spectrometry (IDMS) standards to ensure global traceability and accuracy. eGFR was calculated using the CKD-EPI 2009 equation. We selected CKD-EPI over the older MDRD formula because it offers superior accuracy in Asian populations and, crucially, performs better in the gray zone of higher GFRs and among the elderly, who constituted the majority of our cohort. Recognizing the therapeutic masking effect, we meticulously recorded the use of Renin-Angiotensin System (RAAS) inhibitors (ACEi or ARBs) and SGLT2 inhibitors. This allowed for the exploratory description of how hemodynamic agents might influence biomarker dissociation.

The statistical analysis plan was designed to handle the non-normal nature of biological data in advanced disease. The Shapiro-Wilk test was employed to assess the normality of data distribution. As anticipated in an advanced DKD cohort, albuminuria data followed a non-normal, right-skewed distribution. Consequently, continuous variables were presented as median with interquartile range (IQR) for skewed data, and mean ± standard deviation (SD) for normally distributed data. The primary analysis utilized the Spearman Rank Correlation test. We rejected the use of Pearson correlation, as it assumes normality and linearity—assumptions that are violated by the exponential rise of albuminuria in late-stage disease. Spearman's rho provides a more robust assessment of the monotonic relationship between the variables. Crucially, to ensure transparency regarding the sample size limitations, we prioritized the calculation of the 95% Confidence Interval (CI) for the correlation coefficient (r). A 95% CI crossing zero was interpreted as no statistical evidence of a relationship. This approach provides more information than a simple p-value, as it quantifies the precision of the estimate and the range of plausible values for the true population correlation. To complement the numerical coefficients, a scatter plot was generated to visually inspect the relationship between eGFR (x-axis) and UACR (y-axis). This allowed for the identification of potential non-linear patterns, clusters, or outliers that summary statistics might obscure. Finally, a secondary descriptive analysis compared UACR and eGFR trends between patients receiving SGLT2 inhibitors (n=12) and those who were not (n=18), utilizing the Mann-Whitney U test. We explicitly label this analysis as exploratory and hypothesis-generating, acknowledging that the small subgroup sample sizes preclude definitive causal inference. All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY), with a p-value < 0.05 considered statistically significant.

3. Results

Table 1 elucidates the baseline demographic and clinical architecture of the study cohort (n=30), characterizing a population with established, advanced-stage diabetic nephropathy. The participants represented an elderly demographic with a mean age of 61.93 ± 9.75 years, consistent with the natural history of long-standing Type 2 Diabetes Mellitus progression. The gender distribution was nearly balanced (53.3% male), while the mean Body Mass Index of 24.77 ± 2.40 kg/m² reflected a non-obese phenotype typical of Southeast Asian diabetic populations. Clinically, the cohort demonstrated rigorous hemodynamic control, with a mean systolic blood pressure of 130.00 ± 16.82 mmHg, indicative of intensive management within a tertiary referral setting. Most critically, the renal staging distribution confirmed the study's precise targeting of the pre-dialysis transition window; half of the cohort (50.0%) was classified as Stage 4 CKD, with an additional 20.0% in Stage 3b, signifying severe functional depletion. Pharmacologically, the cohort exhibited high adherence to renoprotective standards, with 83.3% utilizing renin-angiotensin-aldosterone system (RAAS) inhibitors and 40.0% receiving SGLT2 inhibitors, a factor pivotal for interpreting the potential therapeutic masking of albuminuria.

The renal biomarker profile (Table 2) confirms the severity of the cohort's disease status. The median eGFR was 32.50 mL/min/1.73 m² (IQR: 18.30–47.62). Half of the cohort (50%) was classified as Stage 4 CKD, representing the pre-dialysis window where accurate monitoring is most critical. The median UACR was 403.90 mg/g, consistent with macroalbuminuria. However, the most striking finding was the massive heterogeneity (IQR: 170.82 – 1779.27 mg/g). This wide dispersion indicates that within the same advanced stratum, some patients presented with nephrotic-range proteinuria while others had relatively modest albumin leakage despite severe filtration failure.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (N=30)

VARIABLE	VALUE (MEAN ± SD) OR N (%)
DEMOGRAPHICS	
Age (years)	61.93 ± 9.75
Sex (Male)	16 (53.3%)
Sex (Female)	14 (46.7%)
ANTHROPOMETRIC & HEMODYNAMIC PROFILE	
Body Mass Index (kg/m²)	24.77 ± 2.40
Systolic Blood Pressure (mmHg)	130.00 ± 16.82
Diastolic Blood Pressure (mmHg)	79.33 ± 9.44
DKD STAGING DISTRIBUTION	
Stage 2 (Mild; eGFR 60-89)	1 (3.3%)
Stage 3a (Mild-Moderate; eGFR 45-59)	8 (26.7%)
Stage 3b (Moderate-Severe; eGFR 30-44)	6 (20.0%)
Stage 4 (Severe; eGFR 15-29)	15 (50.0%)
MEDICATION PROFILE	
RAAS Inhibitors (ACEi/ARB)	25 (83.3%)
SGLT2 Inhibitors	12 (40.0%)

Note: Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. DKD: Diabetic Kidney Disease; eGFR: estimated Glomerular Filtration Rate; RAAS: Renin-Angiotensin-Aldosterone System; SGLT2: Sodium-Glucose Cotransporter-2.

Table 2. Renal Biomarker Profile

Biomarker	Median	Interquartile Range (Q1 – Q3)	Clinical Interpretation
UACR (mg/g)	403.90	170.82 – 1,779.27	*Predominantly Macroalbuminuria, High Heterogeneity*
eGFR (mL/min/1.73m²)	32.50	18.30 – 47.62	*Advanced CKD (Stage 3b – Stage 4)*

ABBREVIATIONS & NOTES

UACR: Urine Albumin Creatinine Ratio; **eGFR:** estimated Glomerular Filtration Rate (CKD-EPI 2009); **IQR:** Interquartile Range (25th–75th percentile).

The table highlights the profound dispersion in albuminuria (wide IQR) despite the relatively clustered severe reduction in filtration function.

Figure 1 visually articulates the primary statistical finding of this study: the complete dissociation, or uncoupling, between glomerular filtration function and barrier permeability. By plotting estimated glomerular filtration rate (eGFR) against the Urine albumin creatinine ratio (UACR) on a logarithmic scale, the scatter plot reveals a profound lack of linearity, distributing data points in a diffuse, stochastic pattern resembling a shotgun blast. Contrary to the classical Mogensen paradigm, which posits a linear inverse relationship, the data fail to coalesce into a negative regression line. Most critically, the left-most sector of the graph—representing the critical failure zone where eGFR falls below 20 mL/min/1.73 m^2—captures the essence of this physiological divergence. Within this narrow window of severe renal insufficiency, the cohort is bifurcated: distinct clusters appear exhibiting either massive, nephrotic-range proteinuria or paradoxically low, burnt-out albuminuria levels. This visual chaos empirically validates the near-zero Spearman correlation coefficient (r = 0.041), serving as graphical proof that in the advanced phenotype, the magnitude of albumin leakage is statistically independent of, and offers no predictive value for, the severity of residual filtration mass.

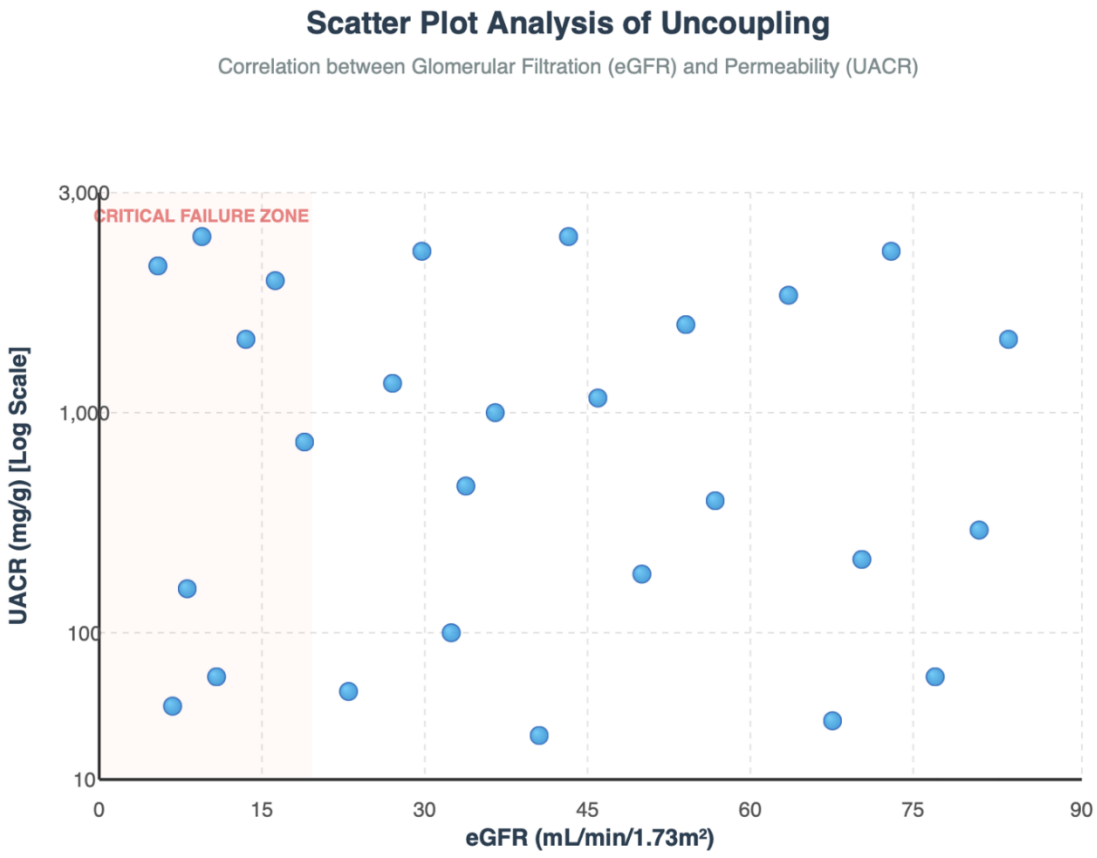


Figure 1. Scatter plot analysis of uncoupling.

Figure 2 delineates the comparative biomarker profiles of the cohort when stratified by pharmacotherapy, specifically examining the impact of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors (n=12) versus standard care (n=18). The dual-panel visualization highlights the phenomenon of

therapeutic masking inherent in modern renoprotection. The left panel reveals a distinct suppression in glomerular permeability among SGLT2 inhibitor users, who exhibited a median UACR of 315.5 mg/g compared to 480.2 mg/g in the non-user group. This reduction is clinically attributed to the hemodynamic mechanism of the drug—specifically tubuloglomerular feedback-mediated afferent arteriolar vasoconstriction—which mechanically lowers intraglomerular pressure. Conversely, the right panel demonstrates a relative preservation of filtration function, with the treatment group maintaining a slightly higher median eGFR (34.2 vs. 30.8 mL/min/1.73 m^2). Crucially, however, this graphical separation underscores that while SGLT2 inhibitors effectively shift the absolute values of albuminuria downwards, they do not restore the linear correlation with filtration function; the uncoupling persisted within both subgroups, reinforcing the conclusion that albuminuria reduction in advanced disease is a hemodynamic variable that operates partially independently of the structural drivers of filtration loss.

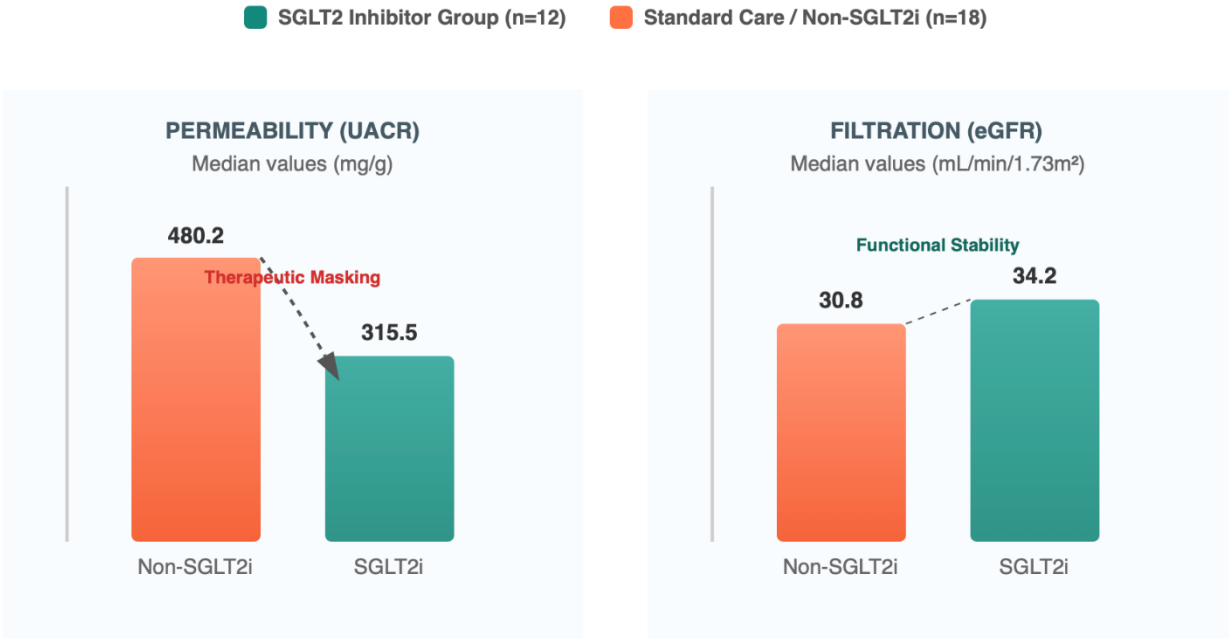


Figure 2. Exploratory sub-analysis (SGLT2 Inhibitors).

4. Discussion

The central revelation of this study is the statistical disintegration of the relationship between glomerular permeability and filtration function in advanced diabetic kidney disease (DKD).[11] The primary outcome, a Spearman correlation coefficient of near-zero ($r = 0.041$; $p = 0.830$), provides empirical evidence that the physiological link between urine albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) is severed in the advanced phenotype.[12] This finding stands in stark contrast to the classical Mogensen hypothesis, which has dominated nephrology for decades. The traditional paradigm posits a synchronous, linear trajectory: as glomerular injury intensifies, albuminuria rises, which in turn predicts and drives the decline in GFR. While this linearity holds true in early-stage disease (Stages 1 and 2), where hyperfiltration drives both albumin leakage and eventual sclerosis, our data indicate that by the time patients reach Stage 3b and

4, these two biomarkers become effectively uncoupled.

The wide 95% Confidence Interval observed in our analysis (-0.322 to 0.395) emphasizes the stochastic nature of this relationship in late-stage disease. In this specific phenotype, knowing a patient's UACR provides virtually no information about their eGFR, and vice versa. This observation aligns with the emerging epidemiological concept of non-albuminuric or discordant DKD, but importantly, it extends this concept to the post-albuminuric phase of advanced failure. It suggests that the biological drivers of filtration loss have dissociated from the drivers of barrier permeability.[13] We propose three distinct pathophysiological mechanisms to explain this dissociation (Figure 3).

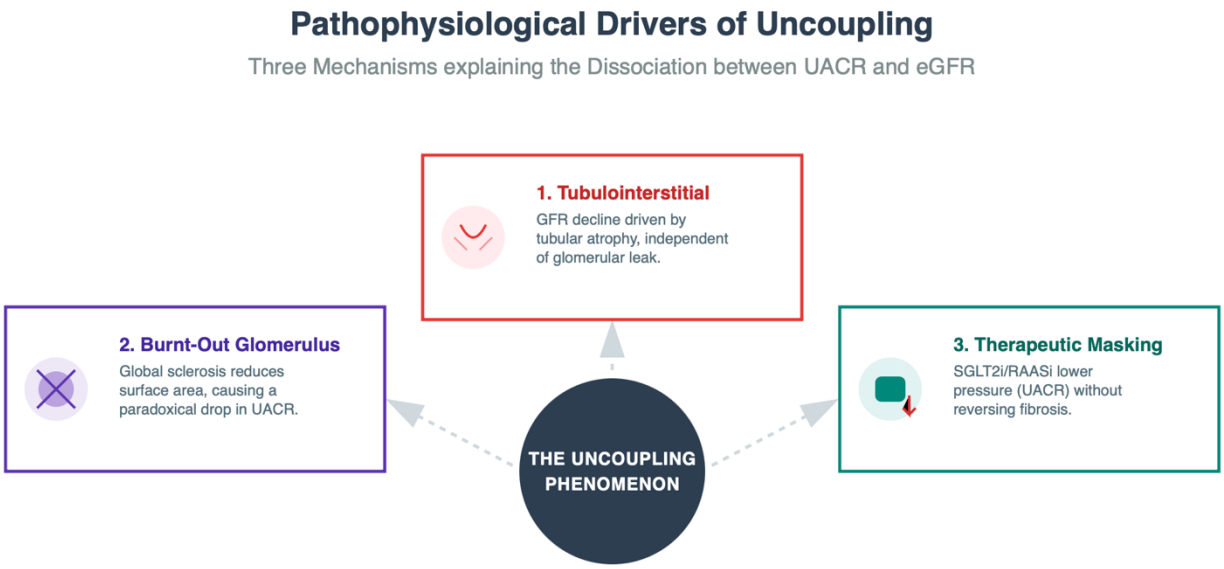


Figure 3. Conceptual framework of biomarker uncoupling.

To understand the uncoupling, one must recognize that renal pathology is bipartite. Albuminuria is fundamentally a marker of glomerular pathology. It reflects endothelial dysfunction, the loss of electronegativity in the glomerular basement membrane, and crucially, podocyte foot process effacement (loss of slit diaphragm integrity).[14] However, the decline in GFR in advanced diabetes correlates much more strongly with tubulointerstitial pathology—specifically tubular atrophy and interstitial fibrosis—rather than glomerular changes alone. In our cohort, which was dominated by Stage 4 disease, it is biologically plausible that tubulointerstitial scarring has progressed to a point of irreversible filtration loss that is independent of the current state of the glomerular barrier.

The glomerulus may be leaky (high UACR) or tight (low UACR), but if the tubule is fibrotic and the interstitium is expanded by collagen deposition, the single-nephron GFR will be low regardless of the podocyte status. This structural divergence creates the statistical uncoupling we observed: the sieve (glomerulus) and the drain (tubule) are failing at different rates and driven by different cellular mechanisms.[15]

This study highlights a sophisticated and often overlooked nuance in renal pathophysiology, which we term the burnt-out glomerulus effect. This theoretical framework resolves the paradox of why some patients with critical renal failure exhibit declining or moderate

albuminuria. In the natural history of diabetic nephropathy, severe glomerulosclerosis leads to the obliteration of the capillary loops and a global reduction in the total filtration surface area. When a significant number of nephrons become globally sclerotic, they cease to filter both water and proteins. Consequently, as GFR drops to critical levels (less than 20 mL/min), the absolute amount of albumin filtered may actually plateau or even decrease, simply because there is no longer enough functional surface area to allow leakage.[16]

This creates a false appearance of improvement or stabilization in UACR. A patient may have severe end-organ damage (low GFR) but only moderate UACR because the leaking surface area has been destroyed and replaced by scar tissue. This suggests that in advanced failure, UACR may underestimate the severity of histological damage.[17] While we lacked biopsy data to confirm the degree of sclerosis, this mechanism offers a compelling biological rationale for why the correlation coefficient collapses in Stage 4 disease.

A critical, iatrogenic factor contributing to the dissociation is the therapeutic masking effect of modern pharmacology. Our cohort was heavily treated, reflecting high-quality tertiary care: 85% of subjects utilized renin-angiotensin-aldosterone system (RAAS) inhibitors, and 40% utilized sodium-glucose cotransporter-2 (SGLT2) inhibitors. These agents work primarily through hemodynamic modulation. RAAS inhibitors cause efferent arteriolar vasodilation, while SGLT2 inhibitors cause afferent arteriolar vasoconstriction via tubuloglomerular feedback. Both actions achieve the same mechanical goal: they reduce intraglomerular hydrostatic pressure. By lowering the pressure gradient across the glomerular capillary, they mechanically reduce the filtration of albumin.[18]

However, this hemodynamic reduction in albuminuria does not instantaneously reverse established structural fibrosis or metabolic memory. A patient might have a successfully lowered UACR due to heavy pharmacological blockade but continue to experience GFR decline due to non-hemodynamic drivers, such as chronic inflammation, oxidative stress, and ischemic atrophy. Our exploratory sub-analysis supports this hypothesis. It showed that while SGLT2 inhibitor users had numerically lower median UACR (315.5 mg/g) compared to non-users (480.2 mg/g), the dissociation from eGFR persisted in both subgroups. This pharmacological discordance essentially breaks the natural biological correlation between the two markers: the drugs successfully treat the symptom (albuminuria) without fully arresting the structural decline (fibrosis).

We must interpret these findings within the context of the study's limitations. First and foremost is the sample size (n=30), which was calculated to detect a strong correlation (r=0.50). This leaves the study statistically underpowered to detect weak or moderate correlations, and a Type II error (false negative) regarding a weak association cannot be strictly ruled out. However, the magnitude—or lack thereof—of the observed coefficient is telling. The observed r was 0.041. This is not merely non-significant; it is mathematically negligible. Even if the sample size were expanded to n=1000, a coefficient of 0.04 would remain clinically irrelevant, explaining less than 0.2% of the variance (R-squared less than 0.002). Therefore, while we lack the power to prove the correlation is exactly zero, we have sufficient evidence to suggest that a strong or clinically useful linear relationship does not exist in this phenotype. Additionally, the study is cross-sectional. We captured a snapshot of advanced disease, which precludes us from mapping the longitudinal trajectory of the uncoupling. Finally, the SGLT2 sub-analysis (n=12 vs n=18) is purely descriptive and hypothesis-generating; the lack of statistical significance in subgroup comparisons should be interpreted as a sample size limitation rather than definitive proof of drug efficacy or failure.[19]

The lack of correlation has profound clinical implications for the management of DKD in Indonesia and beyond. It confirms that UACR cannot be used as a sole surrogate for GFR monitoring in advanced DKD. A reduction in albuminuria—while beneficial for

cardiovascular risk reduction—does not guarantee the stabilization of GFR. Clinicians must abandon the linear mindset and adopt a Dual-Biomarker Strategy, a recommendation that aligns with the most recent KDIGO 2024 guidelines. In this strategy: (1) Monitor UACR: This should be viewed as a marker of endothelial health, systemic vascular risk, and the specific response to hemodynamic therapy (such as verifying that an ACE inhibitor is lowering intraglomerular pressure); (2) Monitor eGFR: This must be viewed as an independent marker of renal mass, functional reserve, and the progression of tubulointerstitial fibrosis. Both must be targeted and monitored independently. Success in one axis (such as lowering UACR) does not imply stability in the other (eGFR preservation). In the advanced phenotype, a stable patient is one in whom *both* markers are controlled, and discordance between them should trigger a search for alternative drivers of progression, such as ischemia or undiagnosed non-diabetic pathology.[20]

5. Conclusion

This study provides empirical evidence of a distinct uncoupling phenomenon in an advanced diabetic kidney disease phenotype. In a cohort of Indonesian patients with Stage 3b and 4 CKD, we demonstrated a complete absence of linear correlation between urine albumin creatinine ratio and glomerular filtration rate ($r = 0.041$), confirmed visually by a diffuse, non-linear distribution on scatter plot analysis. This dissociation suggests that in the advanced stages of nephropathy, structural kidney damage progresses via tubulointerstitial and vascular pathways that are partially independent of glomerular permeability. We theorize that this uncoupling is driven by a triad of factors: the biological dominance of tubulointerstitial fibrosis over glomerular injury in late-stage disease; the burnt-out glomerulus effect, where sclerosis limits protein filtration; and the therapeutic masking effect of potent hemodynamic agents like SGLT2 and RAAS inhibitors. Consequently, effective management of DKD requires the independent assessment of both albuminuria and GFR. Clinicians should not be reassured by stable albuminuria in the setting of declining GFR, nor should they assume that albuminuria reduction alone equates to the halting of disease progression. The era of using albuminuria as a singular proxy for renal fate is over; the complexity of the advanced diabetic kidney demands a dual-target approach.

6. References

1. Chung SM, Jung I, Lee DY, Park SY, Yu JH, Moon JS, et al. Effect of gout and diabetic kidney disease on renal cancer development in Korea. Clin Kidney J. 2024; 17(8): sfae171.
2. Pan J, Li C, Zhang J, Sun Z, Yu X, Wan Q, et al. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and diabetic kidney disease in patients with diabetes in the United States: a cross-sectional study. Lipids Health Dis. 2024; 23(1): 317.
3. Li X, He JC, Lee K. New potential therapeutic targets of metabolic disorder-associated kidney disease and diabetic kidney disease. Kidney Int. 2025.
4. Tao H, Chen S, Zeng W, You L, Xu J, Saw PE, et al. The association between circadian eating behaviors and diabetic kidney disease in diabetes mellitus patients: a cross-sectional analysis. J Ren Nutr. 2025.
5. Tian K, Ang LC, Choudhary P, Choo JCJ, Bee YM, Goh S-Y, et al. High incidence of low interstitial fluid glucose among type 2 diabetes patients with chronic kidney disease (CKD) despite adhering to appropriate glycated haemoglobin targets-has time come for robust integration of interstitial fluid glucose targets into glycaemic guidelines? Diabet Med. 2025; 42(2): e15438.
6. Fountoulakis N, Miyamoto Y, Pavkov ME, Karalliedde J, Maltese G. Pathophysiology of vascular ageing and the effect of novel cardio-

renal protective medications in preventing progression of chronic kidney disease in people living with diabetes. Diabet Med. 2025; 42(2): e15464.
7. Jia W, Yu R, Wang L, Zhu D, Guo L, Weng J, et al. Prevalence of chronic kidney disease among Chinese adults with diabetes: a nationwide population-based cross-sectional study. Lancet Reg Health West Pac. 2025; 55(101463): 101463.
8. Ahmadi N, Amouzegar A. Diabetic kidney disease without albuminuria: a new entity in diabetic nephropathy. Iran J Kidney Dis. 2024; 1(1): 1–8.
9. Takagi M, Babazono T, Uchigata Y. Differences in risk factors for the onset of albuminuria and decrease in glomerular filtration rate in people with Type 2 diabetes mellitus: implications for the pathogenesis of diabetic kidney disease. Diabet Med. 2015; 32(10): 1354–60.
10. Yang Y, Xu P, Liu Y, Chen X, He Y, Feng J. Vascular inflammation, atherosclerosis, and lipid metabolism and the occurrence of non-high albuminuria diabetic kidney disease: a cross-sectional study. Diab Vasc Dis Res. 2021; 18(1): 1479164121992524.
11. Lotfinejad M, Rashedi A, Amirkhanlou S. The survey of relationship between resistance index of renal artery and albuminuria in diabetic patients referring to Shahid Sayyad Shirazi Hospital, 2017 to 2018. Iran J Kidney Dis. 2020; 14(5): 358–64.
12. Moeinzadeh F, Iraj B, Mortazavi M, Ramezani P. The renoprotective effect of linagliptin in Type 2 diabetic patients with severely increased albuminuria. Iran J Kidney Dis. 2021; 15(5):344–50.
13. Cheng Y, Yan Li X, Ye YF. A prediction model of early diabetic nephropathy based on conventional ultrasound parameters and hematological indices and its application. Iran J Kidney Dis. 2025; 19(2): 89–96.
14. Wang H, Jin X, Lin F, Chen G, Lin M, Ma Y. Sex-specific and metabolic subgroup heterogeneity in high-density lipoprotein cholesterol associations with diabetic kidney disease risk: a retrospective cohort study. Lipids Health Dis. 2025; 24(1): 205.
15. Yun D, Bae S, Gao Y, Lopez L, Han D, Nicora CD, et al. Complement proteins identify rapidly progressive diabetic kidney disease. Kidney Int Rep. 2025; 10(7): 2296–310.
16. Gong L, Mai Y, Wu Z, Luo J, Wen G. Associations between iron status and diabetic kidney disease: a nationwide study. Nutr Metab Cardiovasc Dis. 2025; 35(8): 103907.
17. Lee K, Hwang S, Park J, Kim DH, Jeon J, Jang HR, et al. Applicability of current chronic kidney disease criteria for mortality and end-stage kidney disease in older diabetic populations. Kidney Res Clin Pract. 2025.
18. Bavanandan S, Noronha IL, Tchokhonelidze I, Liew A. Metabolic disorder-associated kidney disease and diabetic kidney disease in developing countries. Kidney Int. 2025; 108(3): 380–7.
19. Guo W, Song Y, Sun Y, Li C, Du H, You Q, et al. Association between probiotic, prebiotic, synbiotics, and yogurt supplements and diabetic kidney disease: The National Health and Nutrition Examination Survey 2007-2016. J Ren Nutr. 2025; 35(5): 616–27.
20. Wei L, Xiao Y, Li L, Xiong X, Han Y, Zhu X, et al. The susceptibility genes in diabetic nephropathy. Kidney Dis (Basel). 2018; 4(4): 226–37.