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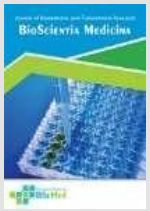

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Beyond Glycemia: Independent Hemodynamic and Metabolic Drivers of Incident Diabetic Kidney Disease in a 5-Year Prospective Indonesian Primary Care Cohort

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A B S T R A C T

Background: The relative contributions of hyperglycemia, hypertension, and metabolic adiposity to the progression of diabetic kidney disease (DKD) are debated, particularly in Southeast Asian populations and in the context of modern polypharmacy. We aimed to prospectively quantify the independent impact of glycemic burden, hemodynamic stress, and central adiposity on the 5-year incidence of DKD in an Indonesian primary care cohort. **Methods:** We conducted a 5-year, multi-center, prospective cohort study at 25 primary care clinics in Indonesia. We randomly sampled and enrolled 1,250 T2DM patients without pre-existing DKD (eGFR > 60 mL/min/1.73m² and normoalbuminuria). The primary composite outcome was incident DKD, defined as persistent albuminuria (ACR ≥ 30 mg/g on 2 of 3 occasions) or a sustained eGFR decline of ≥ 30%. Baseline predictors included HbA1c, Systolic Blood Pressure (SBP), and Waist-to-Height Ratio (WHtR). Multivariable Cox proportional-hazards models were used to estimate Hazard Ratios (HRs), adjusting for demographics, baseline eGFR, and baseline use of RAAS inhibitors (RAASi) and SGLT2 inhibitors. **Results:** Of 1,250 participants, 980 (78.4%) completed the 5-year follow-up. Over a median 4.9 years, 215 participants (21.9%) developed the composite DKD outcome. In the fully-adjusted multivariable Cox model, all three pathways were strong, independent predictors of incident DKD. The standardized HR for SBP (per 1-SD increase) was 1.68 (95% CI: 1.40–2.01; p<0.001), for HbA1c (per 1-SD increase) was 1.45 (95% CI: 1.22–1.73; p<0.001), and for WHtR (per 1-SD increase) was 1.39 (95% CI: 1.18–1.65; p<0.001). **Conclusion:** In this prospective primary care cohort, hemodynamic stress (SBP), glycemic burden (HbA1c), and metabolic adiposity (WHtR) were all independent, potent drivers of incident DKD, even after controlling for the use of protective cardio-renal medications. These findings confirm that a multi-pillar strategy, aggressively targeting blood pressure, glucose, and weight/metabolic health simultaneously, is essential for DKD prevention.

1. Introduction

Type 2 diabetes mellitus (T2DM) represents a defining global health crisis of the 21st century.[1] The International Diabetes Federation (IDF) projects that the number of adults living with diabetes will surge from 537 million in 2021 to 783 million by 2045, with the most precipitous increases occurring in low- and middle-income countries (LMICs). Indonesia, the world's fourth most populous nation, is at the epicenter of this pandemic, ranking among the top ten countries for diabetes prevalence. This epidemic of dysglycemia carries with it a devastating wave of micro- and macrovascular complications, which drive premature mortality and place an unsustainable economic and logistical burden on healthcare systems.[2]

Among these complications, diabetic kidney disease (DKD) is arguably the most feared and resource-intensive.[3] DKD has unequivocally become the leading global cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), accounting for nearly 50% of all ESRD cases in developed nations. It is estimated that DKD develops in approximately 40% of all individuals with T2DM, marking the beginning of a relentless progression for many toward renal failure, necessitating life-sustaining renal replacement therapies.[4] This trajectory imposes a profound socioeconomic burden, particularly for healthcare systems in LMICs like Indonesia, which are ill-equipped to manage the exponential rise in demand for complex, long-term renal care.

For decades, the paradigm of DKD pathogenesis has been overwhelmingly glucose-centric. This model, cemented by the findings of the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), posited a linear pathway of renal injury initiated and propagated by chronic hyperglycemia. This traditional understanding is rooted in robust biochemical evidence, describing how sustained, elevated glucose levels activate several key intracellular injurious pathways.[5]

The "glucose toxicity" hypothesis describes four primary mechanisms of cellular damage: (1) The Polyol Pathway: In hyperglycemic states, excess glucose is shunted to the polyol pathway, where aldose reductase converts it to sorbitol. This reaction consumes the critical cofactor NADPH. The depletion of NADPH starves the enzyme glutathione reductase, crippling the cell's primary antioxidant defense (glutathione recycling) and rendering glomerular cells, particularly podocytes, highly susceptible to oxidative stress; (2) Advanced Glycation End-Products (AGEs): Non-enzymatically, glucose reacts with proteins and lipids to form advanced glycation end-products (AGEs). These AGEs cross-link irreversibly with proteins in the glomerular basement membrane (GBM), causing pathological stiffening and thickening. Furthermore, AGEs bind to their receptor (RAGE) on mesangial cells and podocytes, triggering a cascade of pro-inflammatory and pro-fibrotic signaling via NF-κB, leading to the overproduction of cytokines like Transforming Growth Factor-beta 1 (TGF-β1); (2) Protein Kinase C (PKC) Activation: Hyperglycemia increases the de novo synthesis of diacylglycerol (DAG), a potent activator of Protein Kinase C (PKC) isoforms, particularly PKC-β. Activated PKC induces profound endothelial dysfunction, increases vascular permeability (contributing directly to albumin leakage), and upregulates the expression of pro-fibrotic molecules, including TGF-β1 and plasminogen activator inhibitor-1 (PAI-1), driving mesangial matrix expansion; (3) The Hexosamine Pathway: Excess glucose shunted through the hexosamine pathway leads to the production of UDP-N-acetylglucosamine. This molecule mediates a post-translational modification called O-GlcNAcylation on numerous intracellular proteins, including transcription factors. This aberrant signaling alters gene expression, further promoting the transcription of pro-fibrotic (TGF-β1, PAI-1) and inflammatory (NF-κB) mediators. These four pathways converge on a final common outcome of glomerular endothelial dysfunction, podocytopathy (foot process effacement and detachment), mesangial cell expansion, and progressive GBM thickening. This structural damage culminates in the breakdown of the glomerular filtration barrier, leading to albuminuria, the clinical hallmark of early DKD.[6]

Despite the robustness of the glucose-centric model, it has become increasingly clear that it is incomplete. Large-scale clinical trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease (ADVANCE) trials, demonstrated that intensive glycemic control, while beneficial, had only a modest effect on major renal outcomes and failed to eliminate the significant residual risk of DKD progression.[7] This observation, coupled with the rising prevalence of "non-albuminuric" DKD (eGFR decline without albuminuria), highlighted that other drivers must be at play. This has led to the ascendance of a multi-pillar model, where hemodynamic stress (hypertension) is recognized as a powerful,

independent, and synergistic driver of renal pathology. Hypertension co-exists in over 70-80% of patients with T2DM, and its damaging effects are both mechanical and biological.

The hemodynamic hypothesis posits that the primary injury is not metabolic, but mechanical. In a healthy kidney, the afferent (inflow) arteriole masterfully autoregulates its tone to buffer the delicate glomerular capillary tuft from changes in systemic blood pressure. In T2DM, this autoregulation fails. This failure is compounded by a profound over-activation of the Renin-Angiotensin-Aldosterone System (RAAS), not only systemically but also within the renal parenchyma itself. The primary effector, Angiotensin II, exerts a preferential constrictive effect on the efferent (outflow) arteriole.[8]

This combination—a dilated afferent arteriole that fails to buffer and a constricted efferent arteriole—is a hemodynamic catastrophe. It allows the full, pulsatile force of systemic hypertension to be transmitted directly into the glomerulus, creating a state of severe intraglomerular hypertension. This relentless hemodynamic shear stress physically stretches the podocytes, causing their foot processes to efface and detach (podocyturia), widens endothelial fenestrations, and directly promotes the leakage of albumin. This mechanical stress is not passive; it is a potent biological signal, directly activating mechanotransducers on the podocyte and mesangial cell that trigger the same pro-fibrotic pathways (such as TGF-β1) as hyperglycemia, driving glomerulosclerosis independent of ambient glucose levels. Concurrently, this high filtration pressure, or glomerular hyperfiltration (GHF), which is often an early adaptive response to obesity-driven hyperinsulinemia, becomes the primary maladaptive force driving progressive renal damage.

Concurrently, the global obesity pandemic has unmasked visceral adipose tissue (VAT) as the "third pillar" of DKD pathogenesis. Far from being an inert storage depot, VAT in the obese, insulin-resistant state is a highly active and dysfunctional endocrine organ, precipitating a state of chronic, low-grade systemic inflammation. This metabolic pathway of renal injury is multi-faceted: (1) Adipokine Dysregulation: VAT becomes hypertrophic and inflamed, infiltrated by M1-polarized (pro-inflammatory) macrophages. This dysfunctional tissue shifts its adipokine secretion profile, reducing the secretion of protective, anti-inflammatory, and insulin-sensitizing adiponectin, while massively overproducing pro-inflammatory and pro-fibrotic adipokines such as leptin, TNF-α, IL-6, and MCP-1. Leptin, for example, directly stimulates pro-fibrotic signaling (TGF-β1) in glomerular cells, while low adiponectin levels are one of the strongest predictors of progression to albuminuria. This systemic inflammatory state promotes glomerular endothelial dysfunction and insulin resistance; (2) Renal Lipotoxicity: In a state of systemic energy surplus and insulin resistance, ectopic lipids accumulate within renal parenchymal cells, particularly podocytes and proximal tubular cells. This "renal steatosis" or lipotoxicity is directly toxic (18). This intracellular lipid overload induces: (i) severe mitochondrial dysfunction, impairing fatty acid oxidation and generating massive quantities of reactive oxygen species (ROS); (ii) profound endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR), which can trigger apoptosis; and (iii) activation of pro-inflammatory pathways (including the NLRP3 inflammasome). This lipotoxic podocyte injury and apoptosis is a direct, glucose- and pressure-independent mechanism of albuminuria; (3) Adipose-Derived RAAS: Visceral fat is now recognized as a major extra-renal source of RAAS components, including angiotensinogen. This adipose-derived RAAS activation directly contributes to systemic hypertension and volume expansion, creating a vicious cycle that links the metabolic and hemodynamic pillars.[9]

While this three-pillar (glycemic, hemodynamic, metabolic) cardio-renal-metabolic model is now widely accepted, a critical knowledge gap persists. Most epidemiological data supporting this model originate from cross-sectional studies or from prospective

cohorts in Western populations. Cross-sectional designs are notoriously unable to determine causality and are fatally plagued by "confounding by indication"—whereby the very medications used to treat the risk factors (such as SGLT2 inhibitors, RAAS inhibitors) obscure the true underlying relationship between the risk factor (like HbA1c or SBP) and the outcome (albuminuria). This gap is particularly acute in Indonesia, a nation grappling with a severe T2DM epidemic managed through its national primary care (Puskesmas) chronic disease program, Prolanis. There is a scarcity of longitudinal data from this specific population that prospectively evaluates the independent contributions of all three pathogenic pillars while simultaneously controlling for the confounding effects of modern, guideline-directed medical therapies.[10] Therefore, the aim of this study was to prospectively evaluate the independent and combined contributions of glycemic control (HbA1c), hemodynamic factors (SBP), and metabolic adiposity (Waist-to-Height Ratio) on the 5-year incidence of DKD progression in a large, multi-center Indonesian primary care cohort. The novelty of this study lies in its prospective, longitudinal design, its use of a robust, composite definition of DKD progression (incident persistent albuminuria or eGFR decline), and its sophisticated multivariable analysis that, for the first time in this population, simultaneously quantifies all three pathogenic pillars while statistically controlling for the confounding effects of RAAS inhibitors and SGLT2 inhibitors.

2. Methods

We conducted a 5-year, prospective, multi-center, observational cohort study. The study was conducted from January 2019 to January 2025. The study cohort was recruited from 25 primary healthcare facilities (Puskesmas) participating in the national Chronic Disease Management Program (Prolanis) across five districts in West Kalimantan, Indonesia. The Prolanis program provides structured, government-sponsored care for patients with T2DM and hypertension. All participating clinics utilized a standardized electronic medical record, and all laboratory analyses were performed by a single, central, accredited laboratory to ensure consistency.

The study population consisted of all adult patients with a physician-diagnosis of T2DM who were actively enrolled in the Prolanis program at the 25 participating clinics as of January 2019. Inclusion criteria were (1) Physician-diagnosed T2DM for at least 1 year; (2) Age 18 years or older; (3) Active enrollment in the Prolanis program; (4) Willingness and ability to provide informed consent and attend annual follow-up. Exclusion criteria (at baseline) were (1) Pre-existing DKD, defined as an eGFR < 60 mL/min/1.73m² or a urinary ACR ≥ 30 mg/g on a single screening test; (2) Diagnosis of Type 1 Diabetes Mellitus; (3) Known non-diabetic kidney disease (such as polycystic kidney disease or biopsy-proven glomerulonephritis); (4) Previous renal transplant or current dialysis (ESRD); (5) Severe co-morbidities (such as active cancer or severe heart failure NYHA Class IV) with a life expectancy < 2 years. From a total eligible population of 3,840 T2DM patients without pre-existing DKD, we used a computer-generated random sampling algorithm, stratified by clinic, to invite 1,500 individuals to participate. Of these, 1,250 (83.3%) provided written informed consent and constituted the final baseline cohort (enrolled between January 2019 and December 2019).

Participants attended a comprehensive baseline visit (V0) and were subsequently followed annually for 5 years (V1-V5). Baseline (V0) measurements were (1) Sociodemographics and History: Data on age, sex, self-identified ethnicity, educational attainment, smoking status (never, former, current), and physician-diagnosed duration of diabetes were collected via a standardized questionnaire; (2) Anthropometrics: Height was measured to the nearest 0.1 cm (stadiometer). Weight was measured to the nearest 0.1 kg (calibrated digital scale), and BMI was calculated. Waist circumference (WC) was measured to the nearest 0.1 cm at the midpoint between the iliac crest and the lowest rib. Waist-to-Height Ratio (WHtR) was calculated as WC (cm) / Height (cm); (3)

Hemodynamic Profile: After 5 minutes of seated rest, blood pressure was measured three times, 1 minute apart, using a calibrated automated oscillometric device (Omron HEM-7121). The mean of the second and third readings was used for analysis; (4) Laboratory Analysis: All participants provided fasting (≥ 8 hours) blood and a first-morning spot urine sample, which were transported to a central laboratory; (i) Glycemic Control: HbA1c was measured by High-Performance Liquid Chromatography (HPLC); (ii) Lipid Profile: Total cholesterol, HDL-C, and triglycerides were measured by enzymatic colorimetry. LDL-C was calculated using the Friedewald equation; (iii) Renal Function: Serum creatinine was measured using an IDMS-traceable enzymatic method. Estimated Glomerular Filtration Rate (eGFR) was calculated using the CKD-EPI 2021 equation (without race). Urinary albumin and creatinine were measured to determine the ACR; (5) Medication Data: A comprehensive medication inventory was performed by clinical pharmacists at baseline via patient interview and electronic record review. This included specific recording of all anti-hyperglycemic (SGLT2 inhibitors, GLP-1 receptor agonists, metformin, sulfonylureas, insulin), anti-hypertensive (ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, diuretics), and lipid-lowering therapies (statins, fibrates). At each annual visit (V1-V5), all baseline measurements were repeated, including anthropometrics, seated BP, laboratory analyses (HbA1c, lipids, serum creatinine, spot urine ACR), and a full medication inventory update.

The primary composite outcome was incident DKD progression, defined as the first occurrence of either: (1) Incident persistent albuminuria: A spot urine ACR ≥ 30 mg/g at an annual follow-up visit, which was subsequently confirmed by at least one of two additional ACR measurements obtained within the following 3-6 months (at least 2 of 3 measurements ≥ 30 mg/g). or (2) Significant eGFR Decline: A sustained decline in eGFR of ≥ 30% from the baseline (V0) measurement, confirmed by a subsequent eGFR measurement 3-6 months later. Participants were censored at the date of their first outcome event, date of death, last known follow-up, or the end of the 5-year study period (January 2025), whichever came first.

All statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant. First, descriptive statistics were used to characterize the baseline cohort. Normally distributed continuous variables were presented as mean ± standard deviation (SD), while non-normally distributed variables (identified by Shapiro-Wilk test) were presented as median and interquartile range (IQR). Categorical data were presented as frequencies and percentages (n, %). We compared baseline characteristics between participants who completed the 5-year follow-up and those who were lost to follow-up using t-tests, Mann-Whitney U tests, and Chi-square tests. We also compared baseline characteristics between participants who did and did not develop the primary composite outcome. Second, Kaplan-Meier curves were constructed to estimate the 5-year DKD-free survival, and curves were stratified by tertiles of baseline HbA1c, SBP, and WHtR. The log-rank test was used to assess for significant differences between strata. Third, the primary analysis used Multivariable Cox Proportional Hazards Regression to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the risk of the composite DKD outcome. To allow for a standardized comparison of effect sizes, the three primary continuous predictors of interest (baseline HbA1c, SBP, and WHtR) were standardized (converted to *z*-scores, with a mean of 0 and SD of 1).

We constructed three nested, pre-specified regression models to assess the independent contributions of these factors: (1) Model 1: Unadjusted HRs for each standardized predictor; (2) Model 2: Adjusted for core demographic and clinical confounders: Age (continuous), Gender (female vs. male), Duration of diabetes (continuous), Smoking status (current vs. former/never), and baseline eGFR (continuous); (3) Model 3 (Fully-Adjusted Model): Model 2 + adjustment for baseline use of key cardio-

renal medications: RAAS inhibitor use (ACEi or ARB; yes/no), SGLT2 inhibitor use (yes/no), and Statin use (yes/no). The proportional hazards assumption for all models was verified by examining Schoenfeld residuals ($p > 0.05$ indicated no violation). Multicollinearity among predictors was assessed using the variance inflation factor (VIF), with VIF < 3.0 considered acceptable. Sensitivity analyses were planned, including analyzing the two components of the composite outcome (albuminuria, eGFR decline) separately. The study protocol was approved by the Local Health Research Ethics Committee. All participants provided written informed consent prior to any study procedures. The study was conducted in accordance with the Declaration of Helsinki.

3. Results

Of the 1,250 participants enrolled at baseline, 980 (78.4%) completed the 5-year follow-up and were included in the primary analysis. A total of 270 participants (21.6%) were lost to follow-up (due to relocation, death from non-renal causes, or withdrawal of consent). Participants who were lost to follow-up were slightly older, had a longer duration of diabetes, and had a higher baseline SBP (all $p<0.05$), but did not differ significantly in baseline HbA1c, WHtR, or eGFR.

The baseline characteristics of the 980 participants in the final analytical cohort are presented in Table 1. The mean age was 54.1 years, 58.2% were female, and the median diabetes duration was 6.0 years. The cohort was characterized by a significant cardio-renal-metabolic risk burden at baseline, despite being free of established DKD. The median HbA1c was 7.8% (IQR: 6.9%–9.0%), mean SBP was 131.5 ± 12.4 mmHg, and median WHtR was 0.57 (IQR: 0.52–0.61). At baseline, 48.0% of participants were on a RAAS inhibitor (ACEi/ARB), 15.3% were on an SGLT2 inhibitor, and 62.1% were on a statin. Over a median follow-up of 4.9 years (IQR 4.7–5.0), a total of 215 participants (21.9%) developed the primary composite DKD outcome. Of these, 168 (78.1%) developed incident persistent albuminuria, 22 (10.2%) developed a sustained eGFR decline ≥ 30%, and 25 (11.6%) met both criteria simultaneously.

Table 1 provides a detailed comparison of baseline characteristics between participants who remained free of DKD (n=765) and those who developed incident DKD (n=215). Participants who developed DKD were, at baseline, slightly older, had a longer duration of diabetes, and had significantly higher levels of HbA1c (Median 8.8% vs 7.5%), SBP (Mean 142.1 vs 128.4 mmHg), and WHtR (Median 0.61 vs 0.56) (all $p<0.001$). As expected, baseline use of RAAS inhibitors (59.1% vs 45.0%) and SGLT2 inhibitors (24.2% vs 12.8%) was significantly higher in the group that progressed, demonstrating clear evidence of confounding by indication, which necessitates statistical adjustment.

Kaplan-Meier analysis demonstrated a clear, graded relationship between the baseline levels of all three predictors and 5-year DKD-free survival. As shown in Figure 1, participants in the highest baseline tertile of SBP (>138 mmHg) had a 5-year DKD-free survival of only 68.2%, compared to 89.5% for those in the lowest tertile (<125 mmHg) (log-rank $p < 0.001$). Similar significant, dose-dependent relationships were observed for tertiles of HbA1c ($p<0.001$) and WHtR ($p<0.001$).

The primary results from the nested multivariable Cox regression models are presented in Table 2. The predictors (HbA1c, SBP, WHtR) were standardized (z-scored) so that their Hazard Ratios are comparable, representing the increased risk per 1-SD increase in the baseline variable. In the unadjusted analysis (Model 1), all three predictors were strongly associated with incident DKD, with SBP showing the largest effect size (HR 1.89 per 1-SD). In Model 2, after adjusting for age, gender, diabetes duration, smoking, and baseline eGFR, all three predictors remained highly significant ($p<0.001$). In the Fully-Adjusted Model (Model 3), which additionally controlled for the baseline use of RAAS inhibitors, SGLT2 inhibitors, and statins, all three factors remained strong, independent predictors of incident DKD. Systolic Blood Pressure (SBP) was the most potent predictor, with a 68% increase in risk per 1-SD increase (HR = 1.68; 95% CI: 1.40–2.01;

p<0.001). Glycated Hemoglobin (HbA1c) was the second strongest predictor, with a 45% increase in risk per 1-SD increase (HR = 1.45; 95% CI: 1.22–1.73; p<0.001). Waist-to-Height Ratio (WHtR) was also a significant independent predictor, with a 39% increase in risk per 1-SD increase (HR = 1.39; 95% CI: 1.18–1.65; p<0.001). As expected, baseline use of RAAS inhibitors (HR 0.75; 95% CI: 0.58–0.97; p=0.030) and SGLT2 inhibitors (HR 0.70; 95% CI: 0.51–0.96; p=0.028) were independently associated with a reduced risk of DKD progression, confirming their protective effects and the critical importance of adjusting for their use.

Table 1. Baseline characteristics of the analytical cohort (N=980).

Stratified by 5-Year Incident DKD Status

CHARACTERISTIC	NO DKD PROGRESSION (N=765)	INCIDENT DKD PROGRESSION (N=215)	P-VALUE
Demographics			
Age (years), mean (SD)	53.4 (10.1)	56.8 (11.2)	<0.001
Female Sex, n (%)	452 (59.1%)	119 (55.3%)	0.284
Diabetes Duration (years), median (IQR)	5.0 (3.0–8.0)	8.0 (5.0–12.0)	<0.001
Current Smoker, n (%)	181 (23.7%)	60 (27.9%)	0.201
Glycemic Pillar			
HbA1c (%), median (IQR)	7.5 (6.7–8.5)	8.8 (7.8–10.1)	<0.001
FBG (mg/dL), median (IQR)	141 (120–168)	165 (140–198)	<0.001
Hemodynamic Pillar			
SBP (mmHg), mean (SD)	128.4 (10.5)	142.1 (13.8)	<0.001
DBP (mmHg), mean (SD)	78.2 (6.1)	84.0 (7.2)	<0.001
Metabolic Pillar			
BMI (kg/m²), mean (SD)	26.8 (4.1)	28.5 (4.8)	<0.001
WHtR, median (IQR)	0.56 (0.51–0.60)	0.61 (0.57–0.66)	<0.001
Triglycerides (mg/dL), median (IQR)	150 (112–205)	195 (145–278)	<0.001
HDL-C (mg/dL), mean (SD)	48.5 (10.2)	44.1 (9.8)	<0.001
Renal Function (Baseline)			
eGFR (mL/min/1.73m²), mean (SD)	94.5 (18.2)	90.1 (19.5)	0.004
ACR (mg/g), median (IQR)	8.5 (5.1–14.2)	15.6 (9.8–22.4)	<0.001
Baseline Medication Use			
RAAS Inhibitor (ACEi/ARB), n (%)	344 (45.0%)	127 (59.1%)	<0.001
SGLT2 Inhibitor, n (%)	98 (12.8%)	52 (24.2%)	<0.001
Statin, n (%)	468 (61.2%)	140 (65.1%)	0.301
Metformin, n (%)	696 (91.0%)	190 (88.4%)	0.245
Insulin, n (%)	199 (26.0%)	78 (36.3%)	0.004

*p-values from t-test (for mean), Mann-Whitney U test (for median), or Chi-square test (for n, %). WHtR = Waist-to-Height Ratio. **Red p-values** indicate significance at p<0.001. **Amber p-values** indicate significance at p<0.05.*

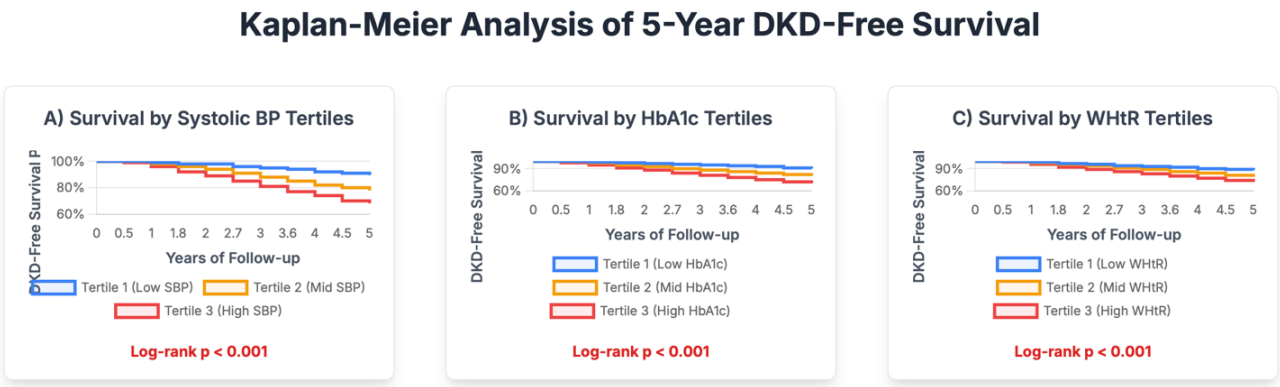

Figure 1. Kaplan-Meier analysis of 5-year DKD free-survival.

Table 2. Multivariable cox proportional hazard models.

VARIABLE (PER 1-SD INCREASE)	MODEL 1 (UNADJUSTED) HR (95% CI)	MODEL 2 (ADJUSTED) HR (95% CI)	MODEL 3 (FULLY-ADJUSTED) HR (95% CI)
Primary Predictors			
HbA1c (per 1-SD)	**1.62 (1.40–1.88)** *p < 0.001*	**1.50 (1.28–1.76)** *p < 0.001*	**1.45 (1.22–1.73)** *p < 0.001*
SBP (per 1-SD)	**1.89 (1.63–2.19)** *p < 0.001*	**1.75 (1.48–2.07)** *p < 0.001*	**1.68 (1.40–2.01)** *p < 0.001*
WHtR (per 1-SD)	**1.55 (1.33–1.81)** *p < 0.001*	**1.43 (1.21–1.69)** *p < 0.001*	**1.39 (1.18–1.65)** *p < 0.001*
Adjustment Covariates			
Age (per 1 year)	---	**1.02 (1.00–1.04)**	**1.02 (1.00–1.04)**
Sex (Female vs Male)	---	0.95 (0.72–1.26)	0.94 (0.71–1.25)
Duration (per 1 year)	---	**1.06 (1.03–1.09)**	**1.05 (1.02–1.08)**
Baseline eGFR	---	**0.98 (0.97–0.99)**	**0.98 (0.97–0.99)**
Medication Covariates (Baseline Use)			
RAASi Use (Yes/No)	---	---	**0.75 (0.58–0.97)**
SGLT2i Use (Yes/No)	---	---	**0.70 (0.51–0.96)**
Statin Use (Yes/No)	---	---	0.91 (0.70–1.18)

Model Definitions:

Model 1: *Unadjusted.*
Model 2: *Adjusted for Age, Sex, Diabetes Duration, Smoking Status, and Baseline eGFR.*
Model 3: *Fully-Adjusted. Includes all covariates from Model 2 plus Baseline RAASi use, SGLT2i use, and Statin use.*

HR = Hazard Ratio. CI = Confidence Interval. All models passed VIF (<2.0) and Schoenfeld residuals (p>0.1) tests.

Red text *indicates a statistically significant risk factor (HR > 1, 95% CI does not cross 1).*
Green text *indicates a statistically significant protective factor (HR < 1, 95% CI does not cross 1).*

4. Discussion

This 5-year prospective cohort study, one of the first of its kind in an Indonesian primary care population, provides robust, longitudinal evidence that the pathogenesis of incident DKD is irrefutably multifactorial.[11] Our primary finding is that after rigorously controlling for demographic, clinical, and, most critically, confounding medication variables, three distinct pathways remain as potent and independent drivers of renal progression: hemodynamic stress (SBP), glycemic burden (HbA1c), and metabolic adiposity (WHtR). Of these, baseline systolic blood pressure emerged as the most powerful independent predictor (HR 1.68 per 1-SD increase). This finding elevates the hemodynamic pathway from a "co-morbidity" to a primary etiological force in DKD. The robust significance of HbA1c (HR 1.45) realigns our understanding with foundational evidence, confirming that glycemic control is a non-negotiable pillar of renal preservation. Finally, the independent contribution of WHtR (HR 1.39) unmasks the critical role of central adiposity, acting likely through inflammatory and lipotoxic mechanisms, as a co-equal partner in this pathogenic triad. These findings decisively refute simpler, cross-sectional analyses that may have suggested a "silencing" of one pathway (such as glycemia). Our data, which prospectively track incidence and correct for the confounding by indication that plagues prior research, confirm that all three pathways are simultaneously active and must be simultaneously targeted.

A crucial finding of our study is the strong, independent, and graded association between baseline HbA1c and the 5-year risk of incident DKD (HR 1.45). This confirms that, despite the ascendance of other risk factors, chronic hyperglycemic burden remains a fundamental, non-negotiable driver of microvascular injury. Our results reaffirm the "glycemic legacy" findings of the UKPDS and DCCT/EDIC follow-ups, which established that early and sustained glycemic control confers long-term renal protection.[12]

The prior "silencing" of HbA1c in some cross-sectional analyses is, as hypothesized, likely a statistical artifact of confounding by indication. In such studies, patients with the highest HbA1c are preferentially prescribed SGLT2 inhibitors—drugs that potently lower albuminuria.[13] This creates a spurious inverse association that masks the true, positive biological relationship. Our prospective study, by adjusting for baseline SGLT2i use, unmasks this true relationship, confirming that for every 1-SD increase in HbA1c, the 5-year risk of DKD increases by 45%.

The pathophysiological basis for this is clear and involves the cumulative, slow-acting "glucose toxicity" pathways introduced earlier: the relentless formation of AGEs leading to GBM stiffening, the activation of PKC isoforms driving endothelial dysfunction, and the polyol and hexosamine pathways generating oxidative stress and aberrant pro-fibrotic gene signaling.[14] Our findings serve as a critical reminder that while new therapeutic pillars have emerged, the foundational pillar of glycemic control cannot be neglected.

The most potent predictor identified in our fully-adjusted model was SBP (HR 1.68). This finding highlights that the hemodynamic hypothesis of DKD is not merely a "hypothesis" but a primary, dominant driver of renal progression.[15] In our cohort, a 1-SD increase in SBP (approx. 12 mmHg) conferred a 68% increase in 5-year DKD risk, an effect size that surpassed both glycemic and metabolic factors. This supports a model where the glomerulus is viewed as a delicate filter under direct mechanical assault. As discussed, T2DM creates a "perfect storm" of failed afferent autoregulation and RAAS-driven efferent constriction. This allows systemic pressure to be transmitted directly to the glomerular tuft, generating severe intraglomerular hypertension. Our data suggest that this relentless, pulsatile shear stress is the most immediate and damaging insult to the filtration barrier's integrity. This mechanical force physically damages podocytes, degrades the protective endothelial glycocalyx, and directly activates mechanotransducers that stimulate TGF-β1 production. It is plausible that while hyperglycemia provides the "tinder" of slow-moving metabolic injury

and inflammation, it is the "bellows" of hemodynamic force from SBP that fans the flames and accelerates the structural breakdown of the filtration barrier.[16] This underscores that aggressive blood pressure control, specifically with RAAS blockade, is arguably the most critical intervention for preserving renal function.

A key finding of our study, novel for this population, is the independent and significant contribution of central adiposity, measured by WHtR (HR 1.39).[17] We specifically chose WHtR over BMI as it is a more accurate and sensitive proxy for visceral adipose tissue (VAT), the dysfunctional endocrine organ at the heart of the metabolic syndrome. The fact that WHtR remained a strong predictor even after adjusting for SBP and HbA1c (which it is known to influence) demonstrates that obesity-driven pathology is not merely a contributor to hypertension and hyperglycemia; it is a distinct and independent pathway of renal injury.

This "metabolic" pillar is likely driven by two primary mechanisms: (1) Adipokine-Driven Inflammation: The high WHtR in our progressive group reflects a high burden of inflamed VAT, which secretes a pro-inflammatory cocktail (TNF-α, IL-6, leptin) and reduces anti-inflammatory adiponectin. Our WHtR variable is likely a proxy for this systemic, low-grade inflammatory state that promotes glomerular endothelial dysfunction and fibrosis; (2) Renal Lipotoxicity: A high WHtR indicates saturated adipose stores and a high likelihood of ectopic lipid deposition within the kidney. This renal steatosis is directly toxic to podocytes and proximal tubular cells, triggering severe mitochondrial dysfunction (ROS production) and ER stress (apoptosis).[18]

Our finding that WHtR is an independent driver strongly suggests that DKD is not just a disease of "glucose and pressure" but also one of "inflammation and lipotoxicity." This has profound clinical implications: a patient with "controlled" HbA1c (6.8%) and "controlled" SBP (125 mmHg) is still at high and unaddressed risk if their WHtR is > 0.6. This highlights the urgent need for interventions that specifically target metabolic health and weight, such as GLP-1 receptor agonists or SGLT2 inhibitors, which (as our data confirm) are protective.

Our data do not suggest these are three separate diseases. There are three deeply intertwined pathways that converge on the glomerulus. Hyperinsulinemia (from metabolic syndrome) drives GHF (hemodynamics); obesity-driven adipose-RAAS (metabolic) causes hypertension (hemodynamic); inflammation (metabolic) worsens endothelial dysfunction (all pathways).[17] The clinical implication is clear and potent: a "siloed" therapeutic approach is doomed to fail. A physician cannot treat one pillar and ignore the others. The "residual risk" that persists after glucose control is, in fact, the unmitigated risk from the hemodynamic and metabolic pillars. Our findings provide a strong mandate for the modern, multi-factorial cardio-renal-metabolic (CRM) approach. This strategy requires the simultaneous and aggressive management of all three pillars, using combination therapies that target each pathway. The independent protective effects of RAASi (hemodynamic) and SGLT2i (glycemic, hemodynamic, metabolic) seen in our model provide direct, real-world validation for this guideline-directed approach.[19]

This study has several major strengths. Its prospective, longitudinal design allows for a more robust assessment of temporal associations than a cross-sectional study.[18] The use of a large, randomly-sampled primary care cohort enhances the generalizability of our findings to real-world clinical practice in Indonesia. The robust, composite outcome definition—requiring confirmation of persistent albuminuria or sustained eGFR decline—is a significant methodological improvement over single-ACR studies and reduces outcome misclassification. Finally, the collection of baseline medication data allowed us to statistically control for confounding by indication, a fatal flaw in much of the preceding literature.[20]

Nevertheless, some limitations must be acknowledged. First, as an observational study, we cannot definitively prove causation, only a strong

temporal association. Second, we adjusted for baseline medication use, but did not model time-varying medication changes, which could introduce residual confounding. Third, we experienced a 21.6% loss to follow-up; while our retention was high, the fact that these participants were slightly sicker at baseline could introduce some attrition bias. Finally, we did not collect data on other important lifestyle confounders, such as diet, physical activity, or genetic factors.

5. Conclusion

In this 5-year prospective study of Indonesian primary care patients with T2DM, we found that incident DKD progression is independently and potently driven by a triad of factors: hemodynamic stress (SBP), glycemic burden (HbA1c), and metabolic central adiposity (WHtR). Systolic blood pressure emerged as the strongest single predictor. These findings, derived from a robust model that corrects for the confounding effects of modern cardio-renal medications, confirm that DKD is a complex cardio-renal-metabolic disease. We cannot conclude that one pathway is "more important" than another; rather, all three are critical, and the failure to address any one of them leaves the patient exposed to significant residual risk. These results provide a powerful, data-driven mandate for abandoning siloed, glucose-centric management in favor of an aggressive, simultaneous, and multi-pillar strategy that targets blood pressure, glucose, and metabolic health with equal urgency.

6. References

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