

# Modifiable Risk Factors for Diabetic Nephropathy in Type 2 Diabetes Patients: A Case-Control Study from South Kalimantan, Indonesia

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## ABSTRACT

**Background:** Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) globally, affecting up to 40% of patients with type 2 diabetes mellitus (T2DM). Despite the rising burden of T2DM in Indonesia, the fifth largest diabetic population worldwide, population-specific evidence on DN risk factors from geographically distinct Indonesian regions remains scarce, limiting the development of locally relevant prevention strategies.

**Objective:** To identify modifiable and non-modifiable clinical risk factors for DN among T2DM patients at a tertiary referral center in South Kalimantan, Indonesia.

**Methods:** A case-control study was conducted using data from the Borneo Wetland Study on Diabetes (Best-Diab) registry (2019–2024), a longitudinal diabetes database from Ulin Hospital, South Kalimantan, Indonesia. Clinical data from 503 diabetic patients were analyzed using multivariable logistic regression to identify independent risk factors of DN.

**Results:** DN was identified in 203 of 503 participants (40.4%). Multivariable analysis identified elevated HbA1c >7% (adjusted OR = 1.976; 95% CI 1.079–3.619;  $p = 0.027$ ), elevated LDL cholesterol  $\geq 100$  mg/dL (adjusted OR = 1.769; 95% CI 1.008–3.104;  $p = 0.047$ ), and obesity (BMI  $\geq 23.5$  kg/m<sup>2</sup>; adjusted OR = 3.305; 95% CI 2.207–4.949;  $p < 0.001$ ) as significant risk factors for DN.

**Conclusion:** HbA1c, LDL cholesterol, and obesity are key modifiable risk factors for DN in T2DM patients in South Kalimantan, with obesity conferring the highest risk. Targeted interventions addressing glycemic control, lipid management, and weight reduction are essential to reduce the burden of DN, particularly in resource-limited settings.

**Keywords:** *diabetic nephropathy; type 2 diabetes mellitus; modifiable risk factors; obesity; HbA1c; LDL cholesterol; logistic regression; South Kalimantan; Indonesia*

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## 1. INTRODUCTION

Diabetic nephropathy (DN) is the leading microvascular complication of type 2 diabetes mellitus (T2DM) and the primary cause of end-stage renal disease (ESRD) worldwide, accounting for approximately 40% of all ESRD cases [1,2]. Globally, the prevalence of DN among T2DM patients is estimated between 20–40%, with projections suggesting further increases as the diabetes pandemic continues to expand [3,4]. Beyond its clinical severity, DN imposes an enormous socioeconomic burden, as renal replacement therapy remains inaccessible or

unaffordable for the majority of patients in low- and middle-income countries (LMICs), where diabetes prevalence is growing most rapidly [5].

Indonesia currently ranks fifth globally in absolute number of adults with diabetes, with an estimated 19.5 million cases as of 2021 [3]. The country faces a compounding challenge: a high and rising prevalence of T2DM alongside fragmented healthcare infrastructure, particularly in geographically remote provinces such as South Kalimantan. While national registries provide aggregate data, regional

heterogeneity in risk factor profiles, dietary patterns, healthcare access, and clinical management practices means that findings from Java-centric or global datasets cannot be straightforwardly applied to populations in Kalimantan [6,7]. South Kalimantan, home to over four million people and served by a limited number of specialist endocrinology centers, represents a population in which DN burden and its determinants remain incompletely characterized.

Established risk factors for DN include poor glycemic control, dyslipidemia, hypertension, obesity, and prolonged diabetes duration [8,9,10]. However, the relative magnitude and interaction of these risk factors may vary substantially across ethnic groups, dietary contexts, and healthcare settings. For instance, studies from Malaysia, Thailand, and the Philippines have reported DN prevalences and risk factor constellations that differ meaningfully from Western cohorts, highlighting the importance of regionally specific evidence to guide clinical practice and public health policy [6,11,12]. To date, no published study has characterized DN risk factors specifically among T2DM patients in South Kalimantan using a registry-based approach.

The Borneo Wetland Study on Diabetes (Best-Diab) is a prospective longitudinal clinical registry established at Ulin Hospital, the largest tertiary referral center in South Kalimantan, designed to systematically capture clinical, laboratory, and outcome data among diabetic patients in this underserved region [13]. Leveraging the Best-Diab dataset, this study aimed to identify independent modifiable and non-modifiable risk factors for DN among T2DM patients in South Kalimantan using a case-control design. The findings are intended to provide evidence-based guidance for clinicians and policymakers in the region and to contribute to the growing body of DN literature from Southeast Asia.

## 2. METHODS

### 2.1. Study Design and Setting

This case-control study was conducted using data from the Best-Diab registry, a longitudinal clinical diabetes database established at the Endocrinology, Metabolism, and Diabetes Clinic of Ulin Hospital, South Kalimantan Province, Indonesia. Ulin Hospital is the largest tertiary referral center in South Kalimantan,

serving patients from across the province including predominantly rural and peri-urban communities. Data were collected from 2019 to 2024.

### 2.2. Participants

The study population comprised T2DM patients aged  $\geq 18$  years who attended the clinic during the study period and had at least one complete clinical and laboratory assessment recorded in the Best-Diab registry. Patients with type 1 DM, secondary diabetes, incomplete records, or a known primary non-diabetic cause of renal disease (e.g., lupus nephritis, IgA nephropathy, or obstructive uropathy) were excluded.

Cases were defined as T2DM patients with confirmed DN, based on the presence of persistent albuminuria (urine albumin-to-creatinine ratio  $\geq 30$  mg/g on at least two separate measurements at least three months apart) and/or reduced estimated glomerular filtration rate (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>) calculated using the CKD-EPI equation, in the absence of other identifiable primary renal etiologies. Controls were T2DM patients from the same registry without evidence of DN (normal urine albumin-to-creatinine ratio and eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>). A total of 503 patients met the eligibility criteria and were included in the analysis (203 cases, 300 controls).

### 2.3. Variables and Measurements

Clinical and laboratory data were extracted from the Best-Diab registry. The following variables were assessed as potential risk factors: sex, age group (dichotomized as  $< 45$  vs.  $\geq 45$  years based on the established higher risk threshold for diabetes complications in Asian adults), HbA1c level (categorized as  $\leq 7\%$  vs.  $> 7\%$  per ADA glycemic target recommendations), duration of DM ( $< 5$  vs.  $\geq 5$  years), fasting blood glucose (FBG, mg/dL), LDL cholesterol (dichotomized at  $\geq 100$  mg/dL per ADA/ESC lipid targets for diabetic patients at high cardiovascular risk), triglyceride (TG) level ( $\geq 150$  mg/dL per ATP III criteria), BMI (dichotomized at  $\geq 23.5$  kg/m<sup>2</sup> using the WHO Asia-Pacific obesity threshold for Asian adults), history of hypertension (physician-diagnosed or on antihypertensive medication), and the triglyceride-glucose (TyG) index, calculated as  $\ln[\text{fasting TG (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$ , a validated surrogate marker of

insulin resistance [14].

#### 2.4. Statistical Analysis

Categorical variables were reported as frequencies and percentages. Bivariate associations between each candidate risk factor and DN status were assessed using Pearson's chi-square test or Fisher's exact test where appropriate. Variables with a p-value <0.25 in bivariate analysis were entered into multivariable logistic regression as a liberal inclusion threshold to minimize the risk of omitting clinically relevant confounders [15]. Multivariable logistic regression was performed using a backward stepwise elimination approach, with variable removal based on the likelihood ratio test. The fit of the final model was assessed using the Hosmer-Lemeshow goodness-of-fit test. Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Multicollinearity among independent variables was assessed using variance inflation factors (VIF); VIF >10 was considered indicative of problematic multicollinearity. A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

#### 2.5. Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the

Ethics Committee of Ulin Hospital, South Kalimantan. Patient data were anonymized prior to analysis, and informed consent was waived given the retrospective registry-based design.

### 3. RESULTS

#### 3.1. Participant Characteristics

Among 503 diabetic patients enrolled from the Best-Diab registry, DN was identified in 203 individuals (40.4%). Table 1 presents the demographic and clinical characteristics of participants stratified by DN status. The majority of participants were female (61.0%, n=307) and aged ≥45 years (84.9%, n=427). Most participants had HbA1c >7% (88.5%), a diabetes duration of ≥5 years (63.4%), and a history of hypertension (65.8%). Elevated LDL (≥100 mg/dL) was present in 86.7% of participants, while 58.4% had a BMI ≥23.5 kg/m<sup>2</sup>.

Statistically significant differences between DN and non-DN groups were observed for age group (p <0.001), duration of DM (p = 0.012), TG level (p = 0.006), and BMI (p <0.001). Gender, HbA1c category, LDL category, history of hypertension, TyG index, and fasting blood glucose did not show significant bivariate differences, though several were subsequently included in multivariable analysis based on the p <0.25 inclusion criterion.

**Table 1. Demographic and clinical characteristics of study participants.**

Variables	Total		DN		Non-DN		P-Value
	n	%	n	%	n	%	
<b>Gender</b>							
Female	307	61	134	43.6	173	56.4	0.060
Male	196	39	69	35.2	127	64.8	
<b>Age group (years old)</b>							
≥45	427	84.9	188	44	239	56	<0.001
<45	76	15.1	15	19.7	61	80.3	
<b>HbA1c level (%)</b>							
>7	445	88.5	175	39.3	270	60.7	0.191
≤7	58	11.5	28	48.3	30	51.7	
<b>Duration of DM</b>							
≥5 years	319	63.4	142	44.5	177	55.5	0.012
<5 years	184	36.6	61	33.2	123	66.8	
<b>LDL level (mg/dL)</b>							
≥100	436	86.7	171	39.2	265	60.8	0.185
<100	67	13.3	32	47.8	35	52.2	
<b>TG level (mg/dL)</b>							
≥150	260	51.7	120	46.2	140	53.8	0.006
<150	243	48.3	83	34.2	160	65.8	
<b>BMI level (kg/m<sup>2</sup>)</b>							

Variables	Total		DN		Non-DN		P-Value
	n	%	n	%	n	%	
≥23.5	294	58.4	92	31.3	202	68.7	<0.001
<23.5	209	41.6	111	53.1	98	46.9	
<b>History of hypertension</b>							
Yes	331	65.8	140	42.3	191	57.7	0.219
No	172	34.2	63	36.6	109	63.4	
<b>Triglyceride glucose (TyG) index</b>							
≥9.05	362	72	148	40.9	214	59.1	0.700
<9.05	141	28	55	39	86	61	
<b>Fasting blood glucose level (mg/dL)</b>							
≥130	358	71.2	138	38.5	220	61.5	0.193
<130	145	28.8	65	44.8	80	55.2	

DN: diabetic nephropathy; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein; TG: triglyceride; BMI: body mass index; TyG: triglyceride-glucose index.

### 3.2. Multivariable Logistic Regression Analysis

Stepwise backward logistic regression identified six independent predictors of DN in the final model (Step 4). These are presented in Table 2. HbA1c >7% was associated with significantly increased odds of DN (adjusted OR = 1.976; 95% CI 1.079–3.619; p = 0.027), underscoring the importance of glycemic control. Elevated LDL cholesterol (≥100 mg/dL) was also independently associated with DN (adjusted OR = 1.769; 95% CI 1.008–3.104; p = 0.047).

Obesity (BMI ≥23.5 kg/m<sup>2</sup>) emerged as the strongest risk factor for DN (adjusted OR = 3.305; 95% CI 2.207–4.949; p <0.001), indicating that obese individuals had more than three times the odds of developing DN compared to their non-obese counterparts. Conversely, older age (≥45 years) was associated with a reduced odds of DN (adjusted OR = 0.304; 95% CI 0.163–0.566; p <0.001), as was longer duration of DM (≥5 years; adjusted OR = 0.530; 95% CI 0.350–0.802; p = 0.003) and elevated TG levels (adjusted OR = 0.431; 95% CI 0.289–0.644; p <0.001).

**Table 2. Final multivariable logistic regression model for risk factors of diabetic nephropathy (Step 4).**

Variables	B	SE	Wald	df	P-Value	OR	95% CI for OR	
							Lower	Upper
Age group (≥45 years old)	-1.190	0.317	14.089	1	<0.001	0.304	0.163	0.566
HbA1c level (>7%)	0.681	0.309	4.862	1	0.027	1.976	1.079	3.619
Duration of DM (≥5 years)	-0.635	0.211	9.015	1	0.003	0.530	0.350	0.802
LDL level (≥100 mg/dL)	0.570	0.287	3.950	1	0.047	1.769	1.008	3.104
TG level (≥150 mg/dL)	-0.841	0.205	16.912	1	<0.001	0.431	0.289	0.644
BMI level (≥23.5 kg/m <sup>2</sup> )	1.195	0.206	33.663	1	<0.001	3.305	2.207	4.949

OR: odds ratio; CI: confidence interval; SE: standard error; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein; TG: triglyceride; BMI: body mass index.

## 4. DISCUSSION

This case-control study identified obesity, elevated HbA1c, and elevated LDL cholesterol as independent modifiable risk factors for DN among 503 T2DM patients at a tertiary referral center in South Kalimantan, Indonesia. A DN prevalence of 40.4% was observed in this clinical cohort, which is consistent with the upper range of

published global estimates (20–40%) and comparable to figures reported from tertiary diabetes centers in Malaysia (38.5%), Thailand (42.3%), and the Philippines (35–45%) [4,5,11,12]. This relatively high prevalence likely reflects a confluence of referral bias, high background rates of suboptimal metabolic control in the region, and limited access to early nephrology

screening outside major urban centers.

The identification of elevated HbA1c (>7%) as an independent risk factor (aOR = 1.976; 95% CI 1.079–3.619;  $p = 0.027$ ) is consistent with a robust body of evidence from both landmark trials and regional observational studies. Prolonged hyperglycemia drives DN pathogenesis through glomerular hypertension, mesangial matrix expansion, podocyte apoptosis, and activation of the RAAS and TGF- $\beta$  signaling pathways [8,16]. The UKPDS 33 and DCCT trials firmly established that intensive glycemic control reduces the incidence of albuminuria and DN by 25–54% in T2DM and type 1 DM patients, respectively [17,18]. In regional context, a large cohort study from the National Diabetes Registry of Malaysia similarly identified HbA1c as one of the strongest predictors of DN progression (OR 1.8 per 1% increase in HbA1c) [11]. In our cohort, where 88.5% of participants had HbA1c >7%, the pervasive burden of suboptimal glycemic control underscores the urgent need to strengthen structured diabetes education, medication adherence programs, and access to point-of-care HbA1c monitoring in South Kalimantan.

Elevated LDL cholesterol ( $\geq 100$  mg/dL) was independently associated with DN (aOR = 1.769; 95% CI 1.008–3.104;  $p = 0.047$ ). The renal lipotoxicity hypothesis posits that elevated circulating LDL promotes glomerular and tubular injury through lipid peroxidation, mesangial cell proliferation, macrophage infiltration, and downstream activation of pro-fibrotic and pro-inflammatory cascades [19,20]. Clinically, this is supported by evidence from statin intervention trials demonstrating attenuation of eGFR decline and albuminuria progression in diabetic patients [21]. A cross-sectional study among T2DM patients in Thailand reported a similarly significant association between LDL >100 mg/dL and DN (OR 1.62; 95% CI 1.18–2.23), reinforcing the generalizability of our finding within the Southeast Asian context [12]. Given that 86.7% of our cohort had LDL  $\geq 100$  mg/dL, statin therapy remains underutilized in this population and should be prioritized as part of comprehensive DN risk reduction.

Obesity (BMI  $\geq 23.5$  kg/m<sup>2</sup>) was the strongest independent predictor of DN in our model (aOR = 3.305; 95% CI 2.207–4.949;  $p < 0.001$ ), conferring more than threefold odds. This robust association is biologically

plausible: excess adiposity promotes insulin resistance, systemic low-grade inflammation, glomerular hyperfiltration, and activation of adipokine-mediated pathways including leptin upregulation and adiponectin deficiency, all of which collectively accelerate glomerulosclerosis [22,23]. The BMI cutoff of 23.5 kg/m<sup>2</sup> applied here reflects the WHO Asia-Pacific redefined threshold for obesity in Asian populations, which recognizes that Asians experience metabolic dysregulation at lower BMI thresholds than Western populations [24]. A meta-analysis of 11 Asian cohort studies found that each 5 kg/m<sup>2</sup> increase in BMI was associated with a 40% increased risk of DN (RR 1.40; 95% CI 1.28–1.53), consistent with our findings [25]. The magnitude of the obesity effect in our cohort may also reflect the high prevalence of central obesity among Kalimantan adults, a pattern driven by regional dietary patterns high in refined carbohydrates and palm-oil-based fats combined with low levels of habitual physical activity. Weight management interventions, including structured dietary counseling, community-based physical activity programs, and, where appropriate, pharmacological therapy, should be central to DN prevention in this population.

Older age ( $\geq 45$  years) and longer duration of DM ( $\geq 5$  years) demonstrated inverse associations with DN in the final model (aOR = 0.304 and 0.530, respectively), which appears counterintuitive given that both are conventionally recognized as risk factors for DN. This paradox is most plausibly explained by survival bias inherent to the clinic-based sampling strategy: patients who developed DN at younger ages or earlier in their disease course may have progressed to ESRD or experienced premature cardiovascular mortality, rendering them absent from this cross-sectional clinical registry. Additionally, patients with longer-standing diabetes may represent a survivorship cohort who responded well to structured clinical management over time. A similar paradoxical inverse association between diabetes duration and DN was reported in a hospital-based study from Bandung, Indonesia, and attributed to the same survival bias mechanism [6]. These findings should be interpreted with caution and prospective longitudinal designs are needed to clarify the true temporal relationship.

Elevated TG ( $\geq 150$  mg/dL) showed

an unexpected inverse association with DN (aOR = 0.431;  $p < 0.001$ ). While hypertriglyceridemia is generally considered atherogenic and associated with CKD risk in the general population, this inverse finding in our regression model may reflect residual confounding by concurrent lipid-lowering pharmacotherapy (fibrates or combination statin/fibrate therapy), which would simultaneously lower TG and confer renoprotection. It may also reflect dietary or metabolic differences between DN and non-DN patients not fully captured by the registry variables. This finding should be interpreted cautiously and warrants investigation in future studies with comprehensive medication adjustment.

This study contributes novel local evidence on DN risk factors from South Kalimantan, a geographically underrepresented region in the Indonesian and Southeast Asian diabetes literature. The use of a prospective clinical registry (Best-Diab) strengthens the internal consistency of clinical data compared to retrospective chart reviews. Nevertheless, several limitations must be acknowledged. The clinic-based design limits generalizability to the broader South Kalimantan population and introduces referral and survival bias. The retrospective use of registry data precludes assessment of temporal causality. Dichotomization of continuous clinical variables, while necessary for categorical logistic regression in this dataset, may have reduced statistical sensitivity and obscured dose-response relationships. Residual confounding by unmeasured variables including medication adherence, dietary intake, physical activity levels, and socioeconomic status cannot be excluded. Finally, the absence of renal biopsy confirmation for DN diagnosis, while consistent with standard clinical practice, introduces the possibility of misclassification. Future prospective multicenter studies incorporating continuous variable analysis, complete medication records, dietary assessments, and genetic profiling are warranted to comprehensively characterize DN determinants in this region.

## 5. CONCLUSION

This study demonstrates that obesity, elevated HbA1c, and elevated LDL cholesterol are the key independent modifiable risk factors for DN among T2DM patients in South Kalimantan, Indonesia, with obesity conferring the highest risk magnitude. These findings align with

evidence from comparable Southeast Asian settings and reinforce the central importance of comprehensive metabolic risk factor control in preventing DN. Clinicians managing T2DM patients in South Kalimantan and similar resource-limited settings should prioritize structured glycemic optimization, guideline-directed lipid-lowering therapy, and weight management interventions as integral components of DN prevention. Policy efforts should focus on improving access to HbA1c monitoring, lipid testing, and specialist endocrinology care across the province. This study also provides a foundation for future prospective multicenter research on DN determinants in the Kalimantan region.

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## Conflicts Of Interest

The authors declare no conflicts of interest.

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