Original Article

Angiotensin-converting enzyme gene insertion/deletion (I/D) polymorphism and diabetic peripheral neuropathy: A multi-center cross-sectional study

Jimmy FA. Barus[1,2*], Poppy K. Sasmita[1,3], Anzhela Himawan[4], Herlina Uinarni[3], Isadora G. Sahusilawane[5], Veronika M. Sidharta[6], Harvey Sudharta[1], Marson Putra[1] and Aurelia Vania[1,2]

[1]Atma Jaya Neuroscience and Cognitive Center, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia; [2]Department of Neurology, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia; [3]Department of Anatomy, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia; [4]School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia; [5]Department of Dentistry, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia; [6]Department of Histology, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia

*Corresponding author: jimmy.barus@atmajaya.ac.id

Abstract

Diabetic peripheral neuropathy (DPN) is the most common microvascular complication of type 2 diabetes mellitus (T2DM), leading to sensory, motor, and autonomic dysfunction. Its prevalence varies globally, with Indonesian cases projected to rise significantly. The aim of this study was to determine the relationship between the insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme (*ACE*) gene and the prevalence of DPN in T2DM patients. The secondary objective was to investigate the association of DPN severity with several other major risk factors. This cross-sectional observational study recruited 152 patients with T2DM from primary health centers in North Jakarta between August 2024 and March 2025. Participants underwent clinical, biochemical, electrophysiological, and genetic assessments. Diabetic peripheral neuropathy was diagnosed using diabetic neuropathy symptom (DNS) and diabetic neuropathy examination (DNE) scores and/or nerve conduction study (NCS). Genotyping employed PCR amplification of *ACE* I/D polymorphisms. Statistical analyses included chi-square, Fisher's exact test, Independent-samples t-test, Pearson correlation, and odds ratios, with significance set at $p<0.05$. Among 152 patients with T2DM, 95 (62.5%) had DPN, with affected patients significantly older than non-DPN cases. *ACE* I/D polymorphism frequencies showed no significant differences and were consistent with Hardy–Weinberg equilibrium. No significant association was observed between *ACE* gene I/D polymorphism and DPN among T2DM patients in the Indonesian population under any of the tested genetic models, including dominant, recessive, homozygous, heterozygous, and allelic models. Higher DNE scores were associated with higher HbA1c, blood glucose, and HDL values. This study underscores the importance of ethnicity in shaping neuropathy risk.

Keywords: Angiotensin-converting enzyme, gene polymorphism, INDEL mutation, diabetic neuropathy, ethnicity

Introduction

Diabetic peripheral neuropathy (DPN) is the most common microvascular complication of type 2 diabetes mellitus (T2DM) in general. Hyperglycemia in T2DM induces neuropathy affecting not

Copyright: © 2026 by the authors. This is an open access article distributed under the terms and conditions of the CC BY-NC 4.0.

Received: July 20, 2026 - Revised: September 17, 2026 - Accepted: October 16, 2026 - Published online: October 20, 2026

only sensory nerves but also autonomic and motor nerves. Diabetic peripheral neuropathy is the most common form of diabetic neuropathy, affecting the outer part of the limbs. It is directly linked to a variety of abnormal sensory functions (numbness and pain), leading to ulceration and amputation in severe cases [1]. The prevalence of DPN was estimated to be around 20–78.8%, depending on the country, diabetes duration, blood glucose control, and assessment methods. According to a study conducted in Indonesia, the prevalence of DPN was 8.5% in 2018 and is expected to increase to 16.1% (40.7 million cases) by 2045 [2]. The relative risks of patients with T2DM for microvascular complications are at least 10–20% higher compared to those without T2DM. A multi-center prospective cohort study in Indonesia reported that 28% of T2DM patients suffered from microvascular complications, including neuropathy (17.6%), followed by nephropathy (7.7%), and retinopathy (2.7%) [3]. The exact cause of DPN in T2DM is unknown, but oxidative stress, advanced glycation end products, and polyol buildup all contribute to the development of this disorder [4].

The angiotensin-converting enzyme (ACE) is an enzyme in the renin-angiotensin system that converts angiotensin (Ang) I to Ang II. In T2DM, hyperglycemia increases the levels of Ang II in the tissue, causing endothelial damage, inflammation, and oxidative stress that can lead to the formation of thrombus, vasoconstriction, and vascular remodeling. Ang II has been shown to increase oxidative stress in the kidney and promote NADPH oxidase (Nox), leading to the production of reactive oxygen species (ROS) in the vascular tissue and neuropathy [5]. In addition, glucose absorption by the nerve tissue due to excess blood glucose also potentially harms nerve tissue or affects the neural vasculature, causing neural ischemia. The excessive glucose metabolism in nerve tissue may lead to the accumulation of other sugars, resulting in hyperosmolarity. This, in turn, may cause degeneration of the myelin sheath, nerve tissue edema, and impaired nerve conduction [6].

Genes encoding renin-angiotensin-aldosterone system (RAAS) components have been studied because they are associated with susceptibility to T2DM and the risk of developing DPN. The most common *ACE* gene variant is an insertion/deletion (I/D) polymorphism in intron 16. The I/D polymorphism of the *ACE* gene accounted for about half of the total phenotypic variance in plasma *ACE*. I/D polymorphisms are classified into three genotypes: D/D homozygotes, I/I homozygotes, and I/D heterozygotes. The DD genotype was related to higher circulatory ACE levels when compared to the other two [7]. A limited number of studies have linked I/D polymorphisms to the development and progression of DPN in T2DM. The aim of this study was to determine the relationship between the *ACE* gene I/D polymorphisms and the prevalence of DPN in Indonesian populations. The secondary objective was to investigate the association between DPN severity, assessed using the diabetic neuropathy examination (DNE), and several other major risk factors for DPN.

Methods

Study design and approaches

The multicenter cross-sectional observational study was carried out by Atma Jaya Catholic University of Indonesia in association with Atma Jaya Hospital. All participants were recruited from Atma Jaya Catholic University Clinic and three community health centers (Puskesmas Kecamatan Penjaringan, Puskesmas Kelurahan Penjaringan, and Puskesmas Kelurahan Pluit). All healthcare facilities were in North Jakarta, Indonesia. Data were collected from August 2024 to March 2025. These participants were outpatients enrolled in the PROLANIS (Chronic Diseases Management) program who received routine medical checks for chronic conditions, including hypertension, hypercholesterolemia, hyperuricemia, hyperglycemia, and may have been taking drugs [8]. After receiving a brief description of the procedure and purpose of the current investigation, participants provided informed consent. To protect privacy, all participants' identities were kept anonymous.

Study subjects and selection criteria

A total of 152 patients with T2DM participated in the present study. All participants were invited to undergo clinical, laboratory (blood tests including genetic tests), and electrophysiological examinations at the outpatient clinic in Atma Jaya Hospital. A combination of convenience and

snowball sampling methods was employed to recruit the patients. Eligible participants were initially recruited through participating primary healthcare centers. Existing participants subsequently referred other eligible patients enrolled in the same PROLANIS program, constituting a snowball recruitment strategy. Adults of any gender were eligible for inclusion. All participants were divided into two groups: Group 1 consisted of 95 patients with T2DM and DPN, whereas Group 2 consisted of 57 patients with T2DM without DPN. Data were collected from each participant through clinical history and comprehensive clinical examinations.

All participants who met the following criteria were included: (1) patients with T2DM, irrespective of DPN status, (2) adults aged >18 years, (3) who complied with physical examination and nerve conduction study (NCS), and (4) willing to undergo blood and genetic testing. Type 2 diabetes mellitus (T2DM) was diagnosed using the American Diabetes Association's criteria [9], whereas DPN was diagnosed when patients fulfilled the clinical criteria based on the diabetic neuropathy symptom (DNS) and diabetic neuropathy examination (DNE) scores and/or demonstrated compatible electrophysiological abnormalities on nerve conduction studies. Based on the clinical scoring assessment, DPN was considered present when the DNS score was ≥1 and the DNE score was >3. For NCS, findings were considered consistent with DPN when either (1) abnormalities were detected in at least two separate nerves or (2) abnormalities were identified in at least two nerves, including the sural nerve [10].

Participants meeting any of the following criteria were excluded: (1) patients with comorbidities directly associated with or causing secondary DPN, such as active infections, distal vasculopathy, and autoimmune diseases; (2) patients with arrhythmia, acute myocardial infarction, and pacemaker placement; (3) patients who have undergone hemodialysis, chemotherapy, or foot amputation; (4) patients who have had a stroke in the previous month with significant motor deficit; (5) patients with psychiatric illnesses; and (6) those who refused to provide informed consent.

Clinical assessment and genotyping

Assessments included demographic data collection, neurological evaluation using the DNS and DNE scores, NCS, and laboratory investigations including fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol, triglycerides (TAG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Peripheral venous blood samples were subsequently collected for genomic DNA extraction and genotyping.

Genomic DNA from the peripheral blood was extracted according to the guidelines from the Genomic DNA Mini Kit (Blood/Cultured Cell) (Geneaid Biotech Ltd., New Taipei City, Taiwan). The extracted DNA was analyzed qualitatively and quantitatively using a NanoDrop (Thermo Fisher Scientific, Waltham, United States). The specific primers used for amplifying this insertion/deletion (I/D) polymorphism were 5′-CTG GAG ACC ACT CCC ATC CTT TCT-3′ (forward) and 5′-GAT GTG GCC ATC ACA TTC GTC AGA T-3’ (reverse). The polymerase chain reaction (PCR) of the targeted I/D polymorphism was amplified using thermocycler in a total volume of 50 µL containing 25 µL PowerPol 2x PCR Mix with Dye (ABclonal), 0.5 µL forward primer (20 µM), 0.5 µL reverse primer (20 µM), 2 µL DNA template, and 22 µL nuclease-free water (NFW). The thermal conditions comprised one cycle of 3 min at 94°C, followed by 35 cycles of 10 sec at 94°C, 30 sec at 60°C, and 30 sec at 72°C, with a final extension of 5 min at 72°C. The PCR products were verified using gel electrophoresis with 1% (w/v) agarose gel in 1X Tris-Borate-EDTA (TBE) buffer. The DNA was stained with FluoroVue™ Nucleic Acid Gel Stain (SMOBIO), and electrophoresis was performed at 100 V for 75 min. The 100 bp DNA ladder (ExcelBand, SMOBIO, Hsinchu, Taiwan) was used to refer to the size of the PCR product. The gel was documented with GelDoc (Bio-Rad, California, United States). Genotypes were determined based on PCR product size following agarose gel electrophoresis. Samples showing a single 490-bp fragment were classified as homozygous insertion (I/I), those with a single 190-bp fragment as homozygous deletion (D/D), and those with both 490-bp and 190-bp fragments as heterozygous (I/D).

Statistical analysis

Categorical variables were reported as frequency and percentage, and continuous variables as mean ± standard deviation (SD). Hardy–Weinberg equilibrium was assessed using Pearson's chi-

square goodness-of-fit test. Categorical variables along with various genetic inheritance models were compared between the case (with DPN) and control (without DPN) groups using the chi-squared test or Fisher's exact test. Continuous variables were compared using the independent-samples t-test after assessment of data distribution. In the correlation analysis, we utilized Pearson's correlation coefficient (PCC) to determine a linear relationship between the *ACE* gene I/D polymorphisms and various other factors [11]. The risk estimate was calculated using the odds ratio (OR) with 95% confidence interval (95%CI). A level of $p<0.05$ was considered statistically significant. All statistical analyses were carried out using SPSS Statistics version 27.

Results

The baseline demographic and clinical features of all participants are presented in **Table 1**. A total of 152 patients with T2DM were included in the study, comprising 95 patients with DPN (Group 1) and 57 patients without DPN (Group 2). Most of the participants were female (75%), with a mean age of 57 years. DPN was present in 62.5% of participants. Patients with DPN were significantly older (58.43±7.83 years) than those without DPN (55.42±8.66 years, $p=0.019$). The DNE score ($p<0.001$) and HDL levels ($p=0.001$) were significantly higher in the DPN-positive group.

Genotyping results

PCR was performed to identify the I/D polymorphism of the *ACE* gene. The genotype distribution of the *ACE* I/D polymorphism is summarized in **Table 1**. No significant difference in genotype frequencies was observed between groups. The D allele was slightly more frequent in the DPN-negative group (23.7%) than in the DPN-positive group (21.6%). However, the difference was not statistically significant ($p=0.865$). Representative agarose gel electrophoresis images demonstrating the three *ACE* genotypes are presented in **Figure 1**. The I/I genotype produced a single 490-bp fragment, the D/D genotype produced a single 190-bp fragment, whereas the I/D genotype showed both the 490-bp and 190-bp fragments.

Table 1. Demographic and clinical features of all participants

Characteristics	Overall (n=152)	DPN-positive (n=95)	DPN-negative (n=57)	*p*-value
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	57.30±8.25	58.43±7.83	55.42±8.66	0.019
Sex, n (%)				0.629
Female	114 (75.0)	70 (73.7)	44 (77.2)	
Male	38 (25.0)	25 (26.3)	13 (22.8)	
Genotype, n (%)				0.865
D/D	8 (5.3)	5 (5.3)	3 (5.3)	
I/D	52 (34.2)	31 (32.6)	21 (36.8)	
I/I	92 (60.5)	59 (62.1)	33 (57.9)	
DNE score	3.43±2.48	4.73±2.17	1.26±1.08	<0.001
HbA1c (%)	6.68±1.15	6.79±1.26	6.48±0.92	0.110
FBG (mg/dL)	144.39±33.43	147.95±36.34	138.46±27.18	0.090
Cholesterol (mg/dL)	183.28±14.33	183.65±10.73	182.67±18.97	0.720
TAG (mg/dL)	139.60±32.90	140.88±26.87	137.46±41.23	0.577
HDL (mg/dL)	41.39±4.47	42.27±3.93	39.91±4.93	0.001
LDL (mg/dL)	114.18±14.83	113.48±11.78	115.35±18.91	0.504

D: deletion; DNE: diabetic neuropathy examination; DPN: diabetic peripheral neuropathy; FBG: fasting blood glucose; HbA1c: hemoglobin A1c/glycated hemoglobin; HDL: high-density lipoprotein; I: insertion; LDL: low-density lipoprotein; TAG: triacylglycerol

The Hardy–Weinberg equilibrium analysis of the *ACE* I/D polymorphism is summarized in **Table 2**. The *p*-value of 0.854 indicates no significant deviation from Hardy–Weinberg equilibrium, with the observed genotype frequencies consistent with those expected under equilibrium. The association between the *ACE* I/D polymorphism and DPN was assessed using dominant, recessive, homozygous, heterozygous, and allelic inheritance models (**Table 3**). None of these models demonstrated a significant association with DPN, with ORs ranging from 0.83 to 1.00 and all 95% confidence intervals crossing the null value. Likewise, both Pearson's χ^2 test and Fisher's exact test yielded non-significant *p*-values (all $p>0.05$), indicating that the *ACE* I/D polymorphism was not associated with DPN susceptibility in the study population irrespective of the assumed mode of inheritance.

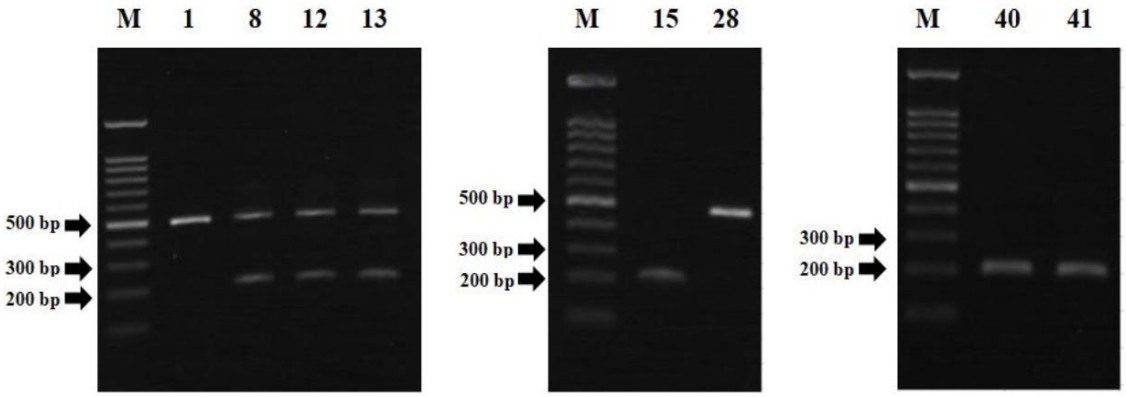


Figure 1. Representative agarose gel electrophoresis of *ACE* insertion/deletion (I/D) genotypes. Representative PCR products showing the three *ACE* I/D genotypes. Samples 1 and 28 represent the homozygous insertion genotype (I/I), characterized by a single 490-bp fragment. Samples 8, 12, and 13 represent the heterozygous genotype (I/D), characterized by both 490-bp and 190-bp fragments. Samples 15, 40, and 41 represent the homozygous deletion genotype (D/D), characterized by a single 190-bp fragment. M indicates the 100-bp DNA ladder (100–1500 bp). Numbers above each lane indicate the sample identification numbers.

Table 2. Chi-squared test for Hardy–Weinberg equilibrium of the *ACE* I/D gene

Genotype *ACE* I/D polymorphism	Observed count	Expected count	H-W frequency (%)
I/I	92	91.61	60.27
I/D	52	52.79	34.73
D/D	8	7.61	5.00

ACE: angiotensin-converting enzyme; D/D: deletion/deletion; H-W: Hardy–Weinberg equilibrium; I/D: insertion/deletion; I/I: insertion/insertion
Allele frequency p: 0.7763; Allele frequency q: 0.2237; chi-squared value: 0.034; *p*-value: 0.854

The consistency of these findings across all inheritance models suggests that no significant association was detected between the *ACE* I/D polymorphism and DPN risk in this cohort. These findings are consistent with the comparable genotype frequencies between DPN-positive and DPN-negative participants presented in **Table 1**, suggesting that this polymorphism alone does not explain differences in DPN status.

Table 3. Association between *ACE* gene insertion/deletion (I/D) polymorphism and DPN under different genetic inheritance models

Genetic model	Comparison	DPN (+), n	DPN (-), n	OR (95%CI)	*p*-value
Dominant	D/D+I/D (n=60)	36	24	0.84 (0.43–1.64)	0.607
	I/I (n=92)	59	33	Reference	
Recessive	D/D (n=8)	5	3	1.00 (0.23–4.35)	1.000
	I/D+I/I (n=144)	90	54	Reference	
Homozygous	D/D (n=8)	5	3	0.93 (0.21–4.15)	1.000
	I/I (n=92)	59	33	Reference	
Heterozygous	I/D (n=52)	31	21	0.83 (0.41–1.66)	0.591
	I/I (n=92)	59	33	Reference	
Allelic	D allele	41	27	0.89 (0.51–1.54)	0.670
	I allele	149	87	Reference	

D/D: deletion/deletion; DPN: diabetic peripheral neuropathy; I/D: insertion/deletion; I/I: insertion/insertion; OR: odds ratio

Diabetic peripheral neuropathy severity and other risk factors

Correlations were examined between the DNE score and HbA1c, FBG, total cholesterol, TAG, HDL cholesterol, and LDL cholesterol levels. Weak but statistically significant positive correlations were observed between the DNE score and HbA1c (r=0.176, p=0.030), FBG (r=0.179, p=0.028), and HDL cholesterol (r=0.251, p=0.002) (**Figure 2**). No significant correlations were observed between the DNE score and total cholesterol, TAG, or LDL cholesterol levels (all p>0.05).

Barus et al. Narra X 2026; 4 (3): e350 - http://doi.org/10.52225/narrax.v4i3.350

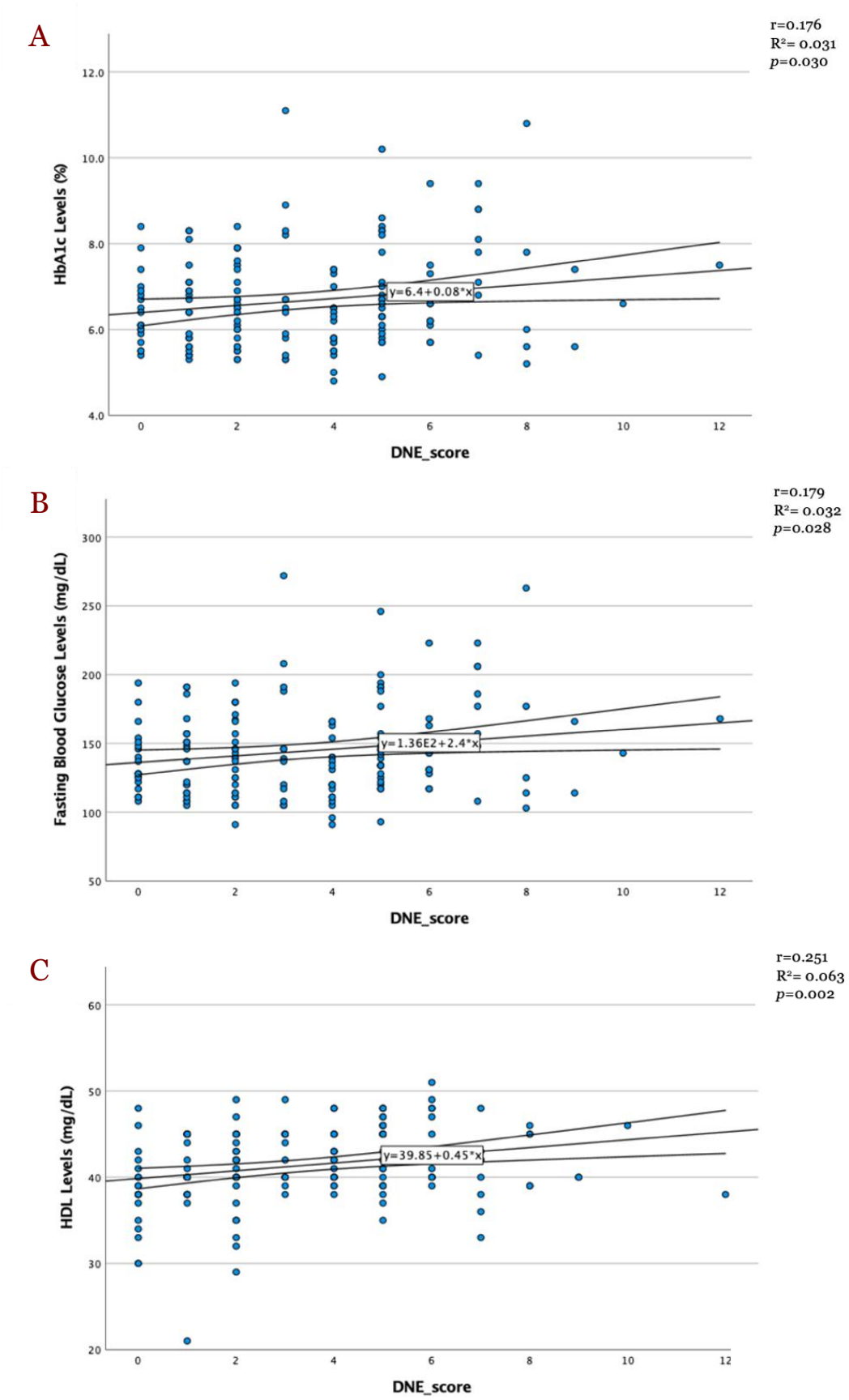


Figure 2. Scatter plots showing the correlations between DNE score and (A) HbA1c (%), (B) FBG (mg/dL), and (C) HDL cholesterol (mg/dL). The solid line indicates the linear regression fit, and the outer lines represent the 95% confidence interval. Pearson's correlation coefficient (*r*), coefficient of determination (R^2), and corresponding *p*-values are displayed in each panel. Weak but statistically significant positive correlations were observed between DNE score and HbA1c, FBG, and HDL cholesterol.

Discussion

The principal finding of the present study is that the *ACE* I/D polymorphism was not associated with diabetic peripheral neuropathy in Indonesian patients with T2DM. This lack of association remained consistent when the polymorphism was analyzed under dominant, recessive, homozygous, heterozygous, and allelic inheritance models, suggesting that the observed findings were robust regardless of the assumed mode of genetic transmission. The D allele was observed to be more frequent in the DPN-negative group.

ACE gene I/D polymorphism is one of the most studied compared to other polymorphisms. It consists of the insertion or deletion (I/D) of a 287-bp fragment in intron 16. The D/D genotype has been reported to play a vital role in the regulation of fibrinolytic systems and inflammation [12]. A previous meta-analysis reported a significant association under the dominant model (OR: 1.25; 95%CI: 1.05–1.48; p=0.01), with Caucasian populations accounting for 97.5% of the pooled participants [13]. In contrast, the present cohort consisted of Indonesian patients. This discrepancy suggests that the association between *ACE* I/D polymorphisms and DPN susceptibility may vary across ethnic backgrounds rather than represent a universal genetic risk factor [13].

One study included in the previous meta-analysis investigated a Japanese population and found no significant difference in *ACE* genotype distribution between patients with and without polyneuropathy. Interestingly, the I allele was significantly higher in those with polyneuropathy [14]. This finding is partly consistent with the present study, in which no substantial differences in genotype frequencies were observed between groups, although the I allele was more frequent in the DPN-positive group. Given the evidence of population differences in genetic polymorphisms, ethnicity may contribute to the variation in findings across studies [15,16]. The observed conformity to Hardy–Weinberg equilibrium suggests that the genotype distribution did not significantly deviate from the expected distribution in the study population [17]. However, conformity to Hardy–Weinberg equilibrium alone does not establish the absence of genotyping errors, selection bias, or population stratification. Therefore, the findings should be interpreted cautiously when considering the representativeness of the study population.

In the present study, higher DNE scores, reflecting greater DPN severity, were associated with higher HbA1c and blood glucose levels. Elevated HbA1c levels are commonly associated with poor glycemic control and, consequently, an increased risk of diabetic complications, including neuropathy. However, within-subject variability exists, and HbA1c levels may be influenced by biological, pre-analytical, and analytical factors [18]. A recent systematic review identified more than 30 studies reporting an association between increased HbA1c variability and DPN in diabetic patients. HbA1c level below 7% was associated with a 60% reduction in the risk of peripheral neuropathy [19]. An increment of 1% in HbA1c was also associated with an increase of 10 to 15% in neuropathy risk [20]. Accumulating evidence also suggests that long-term glycemic variability may predict organ damage, including retinopathy and nephropathy [21].

In the present study, greater DNE scores were also correlated with higher HDL cholesterol levels. Although several studies [22,23] found that individuals with diabetic neuropathy had lower HDL levels than T2DM patients without neuropathy or healthy controls, other studies have found little to no difference [24]. Contrary to previous studies reporting lower HDL concentrations among patients with DPN, higher HDL levels were associated with greater DNE scores in the present cohort. This discrepancy may reflect differences in medication use, particularly statins and fibrates [25], dietary characteristics [26,27], or HDL dysfunction resulting from oxidative modification [28,29]. Therefore, HDL concentration alone may not accurately reflect its biological function in diabetic populations.

This study has several limitations. First, important information regarding drug use, including type of drug consumed, frequency of use, and dosage, was not recorded consistently or comprehensively. Consequently, these variables could not be systematically analyzed, limiting the depth of interpretation and potentially affecting the findings. Second, snowball sampling, a non-probability sampling technique, may have introduced selection bias because recruitment depended on participant referrals and may have concentrated participants within closely connected social networks. This could have reduced sample diversity and representativeness, thereby limiting the external validity and generalizability of the findings. Nevertheless,

recruitment across multiple centers was intended to improve the diversity of the study population. Third, although DPN was confirmed electrophysiologically in the present study, conventional clinical examination and nerve conduction studies have recognized limitations in detecting early or subclinical neuropathy. Clinical examination may have limited sensitivity for asymptomatic disease, whereas nerve conduction studies primarily assess large-fiber function and may not detect early or predominantly small-fiber abnormalities [30]. Thus, undetected early small-fiber involvement cannot be completely excluded. Finally, the cross-sectional design precludes establishing causal relationships between *ACE* polymorphism and DPN.

Despite these limitations, the study has several strengths, including multicenter recruitment, electrophysiological confirmation of DPN, and evaluation of multiple genetic inheritance models. These features provide a comprehensive assessment of the relationship between ACE I/D polymorphism and DPN in an Indonesian population. The findings should therefore be interpreted cautiously, and future studies should consider more representative sampling strategies and more comprehensive data collection to strengthen the validity and generalizability of the evidence.

Conclusion

No significant association was observed between *ACE* gene I/D polymorphism and DPN among patients with T2DM in the Indonesian population under any of the tested genetic models, including dominant, recessive, homozygous, heterozygous, and allelic models. Higher DNE scores were associated with higher HbA1c, blood glucose, and HDL values. These results, which diverge from predominantly Caucasian studies, underscore the importance of ethnicity in shaping neuropathy risk. Future longitudinal and multi-ethnic studies are warranted to clarify these complex interactions.

Ethics approval

The study protocol was approved by the Institutional Ethics Committee (Ref. No. 09/07/KEP-FKIKUAJ/2024) dated July 15, 2024.

Acknowledgments

We thank I. Nathania and M. Yashir for providing laboratory and blood test technical support.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This research is funded by the Directorate of Research, Technology, and Community Service, Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia, under the 2024 Fundamental Research Grant, with Universitas Katolik Indonesia Atma Jaya as the recipient institution.

Underlying data

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

Declaration of artificial intelligence use

AI-based language tools, Grammarly and QuillBot, were used solely for language editing, including improving grammar, sentence structure, and readability of the manuscript. These tools were not used for data analysis, interpretation, or generation of scientific content. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

How to cite

Barus JFA, Sasmita PK, Himawan A, *et al.* Angiotensin-converting enzyme gene insertion/deletion (I/D) polymorphism and diabetic peripheral neuropathy: A multi-center cross-sectional study. Narra X 2026; 4 (3): e350 - http://doi.org/10.52225/narrax.v4i3.350.

References

1. Dinh Le T, Phi Thi Nguyen N, Thanh Thi Tran H, *et al.* Diabetic peripheral neuropathy associated with cardiovascular risk factors and glucagon-like peptide-1 concentrations among newly diagnosed patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2022;15:35-44.
2. Wahidin M, Achadi A, Besral B, *et al.* Projection of diabetes morbidity and mortality till 2045 in Indonesia based on risk factors and NCD prevention and control programs. Sci Rep 2024;14:5424.
3. International Diabetes Federation. IDF diabetes atlas. 10th edition. Brussels; 2021.
4. Galiero R, Caturano A, Vetrano E, *et al.* Peripheral neuropathy in diabetes mellitus: Pathogenetic mechanisms and diagnostic options. Int J Mol Sci 2023;24:3554.
5. Lee SR, An EJ, Kim J, Bae YS. Function of NADPH oxidases in diabetic nephropathy and development of NOX inhibitors. Biomol Ther 2020;28(1):25-33.
6. Ramanathan B, Velayutham K. Association between angiotensin-converting enzyme gene insertion/deletion polymorphism with diabetic peripheral neuropathy and its importance as a genetic biomarker. Bangladesh J Endocrinol Metab 2023;3(1):19-25.
7. Sabir JS, Omri AE, Ali Khan I, *et al.* ACE insertion/deletion genetic polymorphism, serum ACE levels and high dietary salt intake influence the risk of obesity development among the Saudi adult population. J Renin Angiotensin Aldosterone Syst 2019;20(3):1470320319870945.
8. BPJS Kesehatan. Panduan praktis PROLANIS. Available from: https://unitkesehatan.ipb.ac.id/wp-content/uploads/2022/07/PANDUAN-PROLANIS.pdf. Accessed: 2 March 2026.
9. American Diabetes Association Professional Practice Committee. Diagnosis and classification of diabetes: Standards of care in diabetes-2024. Diabetes Care 2024;47(Suppl 1):S20-S42.
10. Meijer JWG, Bosma E, Lefrandt JD, *et al.* Clinical diagnosis of diabetic polyneuropathy with the diabetic neuropathy symptom and diabetic neuropathy examination scores. Diabetes Care 2003;26(3):697-701.
11. Rovetta A. Raiders of the lost correlation: A guide on using Pearson and Spearman coefficients to detect hidden correlations in medical sciences. Cureus 2020;12(11):e11794.
12. Thakur S, Sharma V, Kaur D, *et al.* Angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism as a conjoint regulator of coagulation, fibrinolytic, and RAAS pathway in infertility and associated pregnancy complications. J Renin Angiotensin Aldosterone Syst 2022;2022:1695769.
13. Xu W, Qian Y, Zhao L. Angiotensin-converting enzyme I/D polymorphism is a genetic biomarker of diabetic peripheral neuropathy: Evidence from a meta-analysis. Int J Clin Exp Med 2015;8(1):944-948.
14. Ito H, Tsukui S, Kanda T, *et al.* Angiotensin-converting enzyme insertion/deletion polymorphism and polyneuropathy in type 2 diabetes without macroalbuminuria. J Int Med Res 2002;30(5):476-82.
15. Xiao QY, Fang XC, Li XQ, *et al.* Ethnic differences in genetic polymorphism associated with irritable bowel syndrome. World J Gastroenterol 2020;26(17):2049-2063.
16. Zabaleta J, Schneider BG, Ryckman K, *et al.* Ethnic differences in cytokine gene polymorphisms: potential implications for cancer development. Cancer Immunol Immunother 2007;57(1):107-114.
17. Saadat M. Evaluation of Hardy–Weinberg equilibrium in genetic association studies. Int J Immunogenet 2024;51(3):183-186.
18. Gough A, Sitch A, Ferris E, *et al.* Within-subject variation of HbA1c: A systematic review and meta-analysis. PLoS One 2023;18(8):e0289085.
19. Casadei G, Filippini M, Brognara L. Glycated hemoglobin (HbA1c) as a biomarker for diabetic foot peripheral neuropathy. Diseases 2021;9(1):16.
20. Lai YR, Chiu WC, Huang CC, *et al.* HbA1C variability is strongly associated with the severity of peripheral neuropathy in patients with type 2 diabetes. Front Neurosci 2019;13:90.
21. Nozawa K, Ikeda M, Kikuchi S. Association between HbA1c levels and diabetic peripheral neuropathy: A case–control study of patients with type 2 diabetes using claims data. Drugs Real World Outcomes 2022;9(3):403-414.

22. Zhen R, Wang S, Chen S. The relationship between UA/HDL and diabetic peripheral neuropathy: A cross-sectional analysis. Diabetes Metab Syndr Obes 2024;17:969-980.
23. Chang KC, Pai YW, Lin CH, *et al.* The association between hyperlipidemia, lipid-lowering drugs and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus. PLoS One 2023;18(6):e0287373.
24. Huma K, Mehboob K, Rashid A, *et al.* Comparison of lipid profile in patients with diabetic neuropathy and without neuropathy: A cross sectional study. Pak Armed Forces Med J 2021;71(Suppl-1):S202-06.
25. Aslani S, Razi B, Imani D, *et al.* Effect of statins on the blood lipid profile in patients with different cardiovascular diseases: A systematic review with meta-analysis of randomized clinical trials. Curr Med Chem 2023;30(32):3702-3724.
26. Nurhasan M, Ariesta DL, Utami MMH, *et al.* Dietary transitions in Indonesia: the case of urban, rural, and forested areas. Food Sec 2024;16(6):1313-1331.
27. Liang H, Jiang F, Cheng R, *et al.* A high-fat diet and high-fat and high-cholesterol diet may affect glucose and lipid metabolism differentially through gut microbiota in mice. Exp Anim 2021;70(1):73-83.
28. Nazir S, Jankowski V, Bender G, *et al.* Interaction between high-density lipoproteins and inflammation: Function matters more than concentration! Adv Drug Deliv Rev 2020;159:94-119.
29. Brock JWC, Jenkins AJ, Lyons TJ, *et al.* Increased methionine sulfoxide content of apoA-I in type 1 diabetes. J Lipid Res 2008;49(4):847-855.
30. Robbani G, Mappajanci AA, Ramadhan RN. Advanced computational approaches for detecting subclinical diabetic peripheral neuropathy: Current prospects and future directions. Narra Rev 2025;1(3):e14.