

HbA1c Levels as a Primary Predictor of Diabetic Neuropathy in Patients with Diabetes Mellitus

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ABSTRACT

One of the most common and debilitating long-term complications of diabetes mellitus is diabetic neuropathy, whose prevalence varies widely across countries. This condition significantly increases the risk of lower-extremity amputation and diabetic foot ulceration, underscoring the importance of early identification of its predictors. This review aimed to examine recent evidence regarding the association between HbA1c levels and the occurrence of diabetic neuropathy among individuals with diabetes mellitus. A literature search was conducted for articles published between 2015 and 2025 across PubMed, ScienceDirect, and Google Scholar, yielding 12 eligible studies. Of these, eight studies reported a significant association between HbA1c and diabetic neuropathy. Elevated HbA1c levels and wide HbA1c variability were consistently linked to an increased risk and greater severity of neuropathic complications. Longitudinal analyses demonstrated that HbA1c serves as a strong predictor of neuropathy when monitored over time rather than assessed as a single measurement. Moreover, the combination of HbA1c with age and duration of diabetes produced a sensitivity of 78.6% and a specificity of 52.3% ($p < 0.0001$), indicating enhanced predictive accuracy when these variables are evaluated together. These findings highlight the need for clinicians to assess not only absolute HbA1c values but also HbA1c variability over time to prevent progressive nerve damage. Age and duration of diabetes should likewise be considered essential predictors in evaluating neuropathy risk. In conclusion, this literature review demonstrates that HbA1c is a principal predictor of diabetic neuropathy, reinforcing its critical role in comprehensive glycemic monitoring strategies.

Keywords: HbA1c variability; diabetic neuropathy; diabetes mellitus

INTRODUCTION

Diabetes mellitus is a serious chronic metabolic disease characterized by persistently elevated blood glucose levels resulting from impaired insulin production, insulin resistance, or a combination of both mechanisms [1]. The global burden of diabetes mellitus continues to rise at an alarming pace. In 2021, an estimated 537 million individuals were living with diabetes mellitus, and this number is projected to increase to 643 million by 2030 and further escalate to 783 million by 2050. Indonesia, together with other Asian countries such as Japan, India, and China, is consistently listed among the ten countries with the highest prevalence of diabetes mellitus worldwide [2]. This epidemiological trend highlights the urgent need for strengthened prevention strategies, early detection, and optimal long-term management to reduce the risk of complications associated with diabetes mellitus.

Diabetic neuropathy is one of the most common and debilitating long-term complications of diabetes mellitus, particularly when glycemic control is inadequate. Evidence from a multiethnic cohort study reported that 26.71% of individuals with diabetes mellitus developed diabetic neuropathy, although prevalence estimates vary widely across countries, ranging from 0.58% to 79.55% [3]. Diabetic neuropathy develops when chronic hyperglycemia progressively damages sensory nerve fibers in the skin. This damage leads to a reduction in sensory nerve density, which is associated with diminished tactile sensation and delayed wound healing [4]. The characteristic "stocking and glove" pattern of diabetic neuropathy reflects the length-dependent nature of nerve injury, in which the longest nerve fibers are affected first; for example, distal sensory fibers in the feet are damaged earlier than proximal fibers [4]. Over time, this progressive nerve injury can result in severe complications such as lower-extremity ulceration and amputation [6–8], contributing substantially to the global economic burden of diabetes-related morbidity [9].

Diabetic neuropathy encompasses a spectrum of clinical syndromes that differ based on the pattern of nerve involvement. The most prevalent form, distal symmetric polyneuropathy, affects approximately 50% of individuals with diabetes mellitus and is characterized by sensory loss, neuropathic pain, and motor impairment in the extremities. Autonomic neuropathy, which occurs in 20–40% of patients, involves dysfunction of the autonomic nervous system and may impair cardiovascular, gastrointestinal, and urogenital functions. Mononeuropathy, with a prevalence of less than 1%, typically presents as isolated cranial or peripheral nerve involvement, such as oculomotor or facial nerve palsy. Another rare form, radiculoplexopathy, occurring in fewer than 1% of cases, primarily affects the lumbar or cervical plexus and may lead to profound weakness and functional impairment [10].

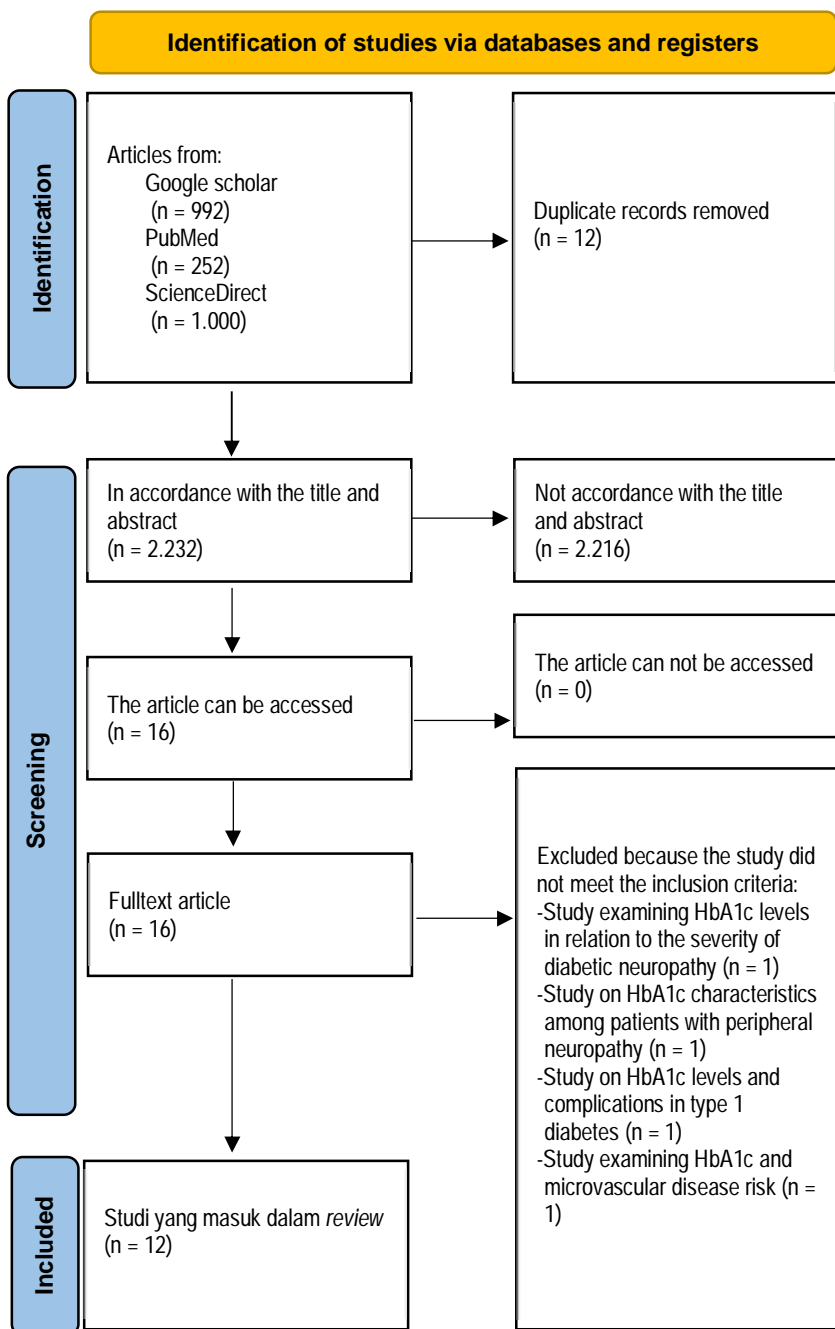
Hemoglobin A1c (HbA1c) is a glycosylated form of hemoglobin that reflects average blood glucose levels over the preceding two to three months and is widely used to assess long-term glycemic control. According to the American Diabetes Association (ADA), HbA1c levels in individuals with diabetes mellitus should ideally be maintained at $\leq 7\%$ to reduce the risk of complications. Elevations above this threshold are associated with an increased likelihood of developing diabetic neuropathy and other microvascular complications [11]. A study by Lai et al., 2019 demonstrated that HbA1c is a significant risk factor for the development of diabetic neuropathy among patients with diabetes mellitus [12]. Individuals with higher HbA1c levels exhibit reduced amplitudes of compound muscle action potentials, diminished sensory nerve action potentials, slowed motor nerve conduction velocities, and delayed sensory conduction velocities in the sural nerve. These electrophysiological abnormalities are accompanied by increased composite scores of lower-extremity dysfunction, indicating more severe neuropathic impairment [12].

Despite these findings, the pathophysiological mechanisms linking HbA1c levels to diabetic neuropathy remain incompletely understood. Some studies, such as that by Billa et al., 2023, have reported a strong association between well-controlled HbA1c levels and a lower incidence of diabetic neuropathy [13]. However, other investigations, including those by Matasak et al., 2018 and Tanhardjo et al., 2016, found no significant relationship between HbA1c and diabetic neuropathy [14, 15]. These conflicting results highlight ongoing controversy regarding the predictive value of HbA1c for diabetic neuropathy and suggest that additional factors, such as glycemic variability, duration of diabetes mellitus, age, and comorbidities may influence neuropathy risk.

Given these inconsistencies, the present literature review aims to examine the association between HbA1c levels and diabetic neuropathy among patients with diabetes mellitus by synthesizing evidence from studies published over the past ten years. This review also seeks to explore potential explanations for the divergent findings reported in previous research, thereby contributing to a more comprehensive understanding of the role of HbA1c in the development of diabetic neuropathy.

METHODS

This study employed a literature review design and was conducted in November 2025. The search strategy involved a systematic exploration of three major scientific databases, namely PubMed, Google Scholar, and ScienceDirect, to ensure comprehensive coverage of relevant empirical evidence. Searches performed through PubMed and ScienceDirect utilized the keywords *HbA1c*, *diabetic neuropathy*, and *peripheral neuropathy*, reflecting standardized terminology commonly used in international publications. Meanwhile, searches conducted through Google Scholar



incorporated the keywords *HbA1c*, *neuropati perifer*, and *neuropati diabetik* to capture both English- and Indonesian-language studies and to broaden the scope of potentially eligible literature.

The inclusion criteria for this review consisted of full-text journal articles published between 2015 and 2025 that examined the association between HbA1c levels and the occurrence of diabetic neuropathy among individuals with diabetes mellitus. Only quantitative research designs were considered eligible, and articles written in either Indonesian or English were included to ensure linguistic accessibility and methodological rigor. Exclusion criteria comprised grey literature, conference abstracts, letters to the editor, review articles, and any journal articles that were not accessible in full text. These criteria were established to ensure that only primary research with complete methodological and analytical information was incorporated into the synthesis.

Article selection was conducted independently by SAPA and UAH. In instances where discrepancies or disagreements arose during the screening process, the final decision was reached through discussion with AF to maintain objectivity and consistency. The selection workflow was facilitated using Rayyan AI, which supported the systematic identification and removal of duplicate records, screening of titles and abstracts, assessment of access availability, and evaluation of full-text eligibility based on predefined criteria. The overall selection process was organized and documented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure transparency, reproducibility, and adherence to international reporting standards.

Data extraction was performed collaboratively by SAPA, UAH, and AF for all studies that met the eligibility criteria. Extracted components included the authors and year of publication, study location, article title, research design, study population, and key findings. These elements were selected to enable a structured comparison across studies and to facilitate a comprehensive synthesis of the relationship between HbA1c levels and diabetic neuropathy in individuals with diabetes mellitus.

Figure 1. PRISMA flow diagram for article selection

RESULTS

The studies included in this review demonstrate substantial methodological diversity in terms of setting, sample size, diagnostic instruments, and analytical approaches, yet collectively provide a coherent overview of the relationship between HbA1c levels and diabetic neuropathy. Research was conducted across a wide range of clinical environments, including primary health centers, tertiary hospitals, pediatric endocrinology units, and specialized outpatient clinics, reflecting the broad clinical relevance of this complication. Sample sizes varied considerably, from small cross-sectional investigations involving fewer than 40 participants to large prospective cohort studies enrolling more than 1,700 individuals. Measurement tools also differed across studies, encompassing monofilament testing, nerve conduction studies, thermal and vibration threshold assessments, symptom-based scoring systems, and electrophysiological ratios such as the Sural Radial Amplitude Ratio. Despite these variations, a consistent pattern emerged in which many studies reported a significant association between elevated HbA1c levels or HbA1c variability and the presence or severity of diabetic neuropathy. However, several studies found no such association, underscoring the heterogeneity of findings and suggesting that additional factors, such as duration of diabetes, age, glycemic variability, and methodological differences may influence the observed outcomes. Overall, the body of evidence presented in Table 1 highlights both the complexity of diabetic neuropathy pathogenesis and the need for more standardized approaches to evaluating the role of HbA1c in neuropathy development.

Table 1. Data extraction summary of studies examining the association between HbA1c and diabetic neuropathy

Authors	Location	Title	Sample	Instrument	Design	Findings
Hanifah et al., 2021 [16]	Pediatric Endocrinology Outpatient Clinic, Dr. Soetomo General Hospital, Surabaya	Association Between HbA1c Levels and the Sural Radial Amplitude Ratio (SRAR) in Patients With Type 1 Diabetes Mellitus and Peripheral Diabetic Neuropathy	38	Sural Radial Amplitude Ratio (SRAR)	Cross-sectional	A negative correlation was identified between HbA1c levels and the sural-to-radial nerve amplitude ratio ($p = 0.021$; odds ratio 6.933; 95% CI 1.173–40.981). Low SRAR values were observed in 83.87% of patients with elevated HbA1c and 16.13% with normal HbA1c, whereas normal SRAR values were found in 42.85% of patients with elevated HbA1c and 57.14% with normal HbA1c.
Matasak et al., 2018 [14]	Kimia Farma Husada Sario Outpatient Clinic, Manado	Association Between HbA1c Levels and Neuropathy in Patients With Type 2 Diabetes Mellitus at Kimia Farma Husada Sario Clinic	31	Michigan Neuropathy Screening Instrument	Cross-sectional	No significant association was found between HbA1c levels and neuropathy among patients with type 2 diabetes mellitus ($p = 0.707$). A total of 96.8% of participants did not exhibit neuropathy, while 3.2% presented with neuropathy.
Tanhardjo et al., 2016 [15]	Bethesda Hospital, Yogyakarta	Comparison of Mean HbA1c Levels in Patients With Diabetes Mellitus With and Without Sensorimotor Neuropathy	64	Diabetic Neuropathy Symptoms, Diabetic Neuropathy Examination, Monofilament Test	Cross-sectional	Mean HbA1c levels were not significantly associated with neuropathy ($p = 0.368$). Half of the participants (50%) exhibited neuropathy, while the remaining 50% did not.
Billa et al., 2023 [13]	Dr. Bratanata Hospital, Jambi	Association Between Glycemic Control and Duration of Diabetes With the Occurrence of Diabetic Peripheral Neuropathy at Dr. Bratanata Hospital, Jambi	72	Neuropathy Symptom Score	Cross-sectional	A significant association was found between HbA1c levels and diabetic neuropathy ($p = 0.000$). Among participants, 25% had no neuropathy, 12.5% had mild neuropathy, 19.1% had moderate neuropathy, and 43.1% had severe neuropathy.
Rachman & Dwipayana, 2020 [17]	Sanglah General Hospital	Prevalence and Association Between Glycemic Control and Diabetic Peripheral Neuropathy in Patients With Type 2 Diabetes Mellitus at Sanglah General Hospital	96	Monofilament Test	Cross-sectional	A significant association was observed between HbA1c levels and peripheral neuropathy ($p = 0.000$). A total of 40 participants exhibited neuropathy, while 56 did not.
Fikri et al., 2024 [18]	Gatak Primary Health Center, Sukoharjo	Association Between HbA1c Levels and Age With the Occurrence of Diabetic Neuropathy in Patients With Diabetes Mellitus	65	Monofilament Test	Cross-sectional	A significant association was found between HbA1c levels and diabetic neuropathy ($p = 0.000$). Patients with uncontrolled HbA1c had a 45.3-fold increased risk of developing diabetic neuropathy.
Su et al., 2018 [19]	The Second Affiliated Hospital of Nantong University	HbA1c Variability and Diabetic Peripheral Neuropathy in Patients With Type 2 Diabetes	563	Nerve Conduction Evaluation	Cross-sectional	Significant associations were observed between initial HbA1c ($p = 0.001$), mean HbA1c ($p < 0.001$), and the coefficient of variation of HbA1c ($p < 0.001$) with peripheral neuropathy.
Lou et al., 2024 [20]	The First People's Hospital of Linping District, Hangzhou	Predictive Value of Combined HbA1c and Neutrophil-to-Lymphocyte Ratio for Diabetic Peripheral Neuropathy in Type 2 Diabetes	100	Five Diagnostic Tests (ankle reflex, vibration, pressure, pinprick, temperature)	Case-control	Univariate logistic analysis demonstrated a significant association between HbA1c and peripheral neuropathy ($p < 0.01$; OR 1.92; 95% CI 1.35–2.88). The coefficient of variation of HbA1c and mean HbA1c showed a sensitivity of 66.67% and a specificity of 65.73%.
Virk et al., 2016 [21]	Tertiary Pediatric Hospital	Association Between HbA1c Variability and Risk of Microvascular Complications in Adolescents With Type 1 Diabetes	1706	Thermal and Vibration Threshold Testing	Cohort	No significant association was found between mean HbA1c and peripheral neuropathy ($p = 0.122$; OR 1.19; 95% CI 0.95–1.49).
Lai et al., 2024 [22]	Tertiary Medical Center and Primary Referral Hospital	Prognostic Value of Longitudinal HbA1c Variability in Predicting Diabetic Sensorimotor Polyneuropathy in Patients With Type 2 Diabetes	176	Nerve Conduction Studies (NCS)	Cohort	Univariate analysis showed a significant association between mean real variability of HbA1c and diabetic sensorimotor polyneuropathy ($p = 0.023$; OR 6.06; 95% CI 1.28–28.8), consistent with multivariate results ($p = 0.031$; OR 7.56; 95% CI 1.2–

Authors	Location	Title	Sample	Instrument	Design	Findings
		Mellitus: A Prospective Cohort Observational Study				47.57). When combined with age and duration of diabetes, mean real variability of HbA1c demonstrated a sensitivity of 78.6% and a specificity of 52.3% (<0.0001).
Lai et al., 2025 [23]	Tertiary Hospital, Taiwan	Impact of HbA1c Variability and Time-in-Range Fluctuations on Large and Small Nerve Fiber Dysfunction in Well-Controlled Type 2 Diabetes: A Prospective Cohort Observational Study	82	Toronto Clinical Neuropathy Score (TCNS), Quantitative Thermal Testing (QTT), Sudoscan, Nerve Conduction Studies (NCS)	Cohort	Neuropathy assessed using the Toronto Clinical Neuropathy Score (TCNS) increased significantly in patients with high HbA1c ARV ($p = 0.001$). TCNS scores decreased to 2.2 ± 1.8 in patients with HbA1c ARC below the median and to 5.3 ± 3.9 in those with HbA1c ARC at or above the median.
Solomos et al., 2025 [24]	Doctors of the World Central Polyclinic	Prevalence of Peripheral Neuropathy, Diabetic Foot, and Glycemic Control Among Refugees and Migrants Residing in Greece	67	Neuropathy Disability Score (NDS), Neuropathy Symptoms Score (NSS), Monofilament Test	Cross-sectional	No significant association was found between HbA1c levels and diabetic neuropathy ($p = 0.921$; OR 0.99; 95% CI 0.77–1.26).

DISCUSSION

Across the twelve studies analyzed in this review, eight reported a statistically significant association between HbA1c levels and the occurrence or severity of diabetic neuropathy, indicating a consistent pattern across diverse populations and methodological approaches. Lai et al. (2024) demonstrated that mean real variability in HbA1c was significantly associated with neuropathy in univariate analysis, a finding that remained robust in multivariate modeling, suggesting that fluctuations in glycemic control may play a critical role in neuropathic progression [22]. This observation is consistent with the results of Lou et al. (2024), who also identified a significant association between HbA1c levels and diabetic neuropathy, reinforcing the notion that chronic hyperglycemia and its variability contribute meaningfully to nerve dysfunction [20].

Rachman and Dwipayana (2020) emphasized that diabetic neuropathy is a multifactorial complication influenced by several metabolic disturbances, including glycemic indices [17]. Persistent hyperglycemia disrupts both sensory and motor nerve pathways, leading to progressive neuronal injury. Hanifah et al. (2021) and Su et al. (2018) further elaborated that pancreatic β -cell impairment triggers excessive mitochondrial electron transport, resulting in heightened production of reactive oxygen species. This oxidative burden initiates a cascade of metabolic disturbances involving sorbitol accumulation, formation of advanced glycation end products, overactivation of protein kinase C isoforms, and increased flux through the hexosamine pathway [16,19]. Lai et al. (2024) added that elevated HbA1c not only induces oxidative stress but also promotes chronic low-grade inflammation, which exacerbates peripheral nerve damage. Collectively, these findings provide strong pathophysiological support for the relationship between HbA1c and peripheral neuropathy [22].

An important insight emerging from this review concerns the role of HbA1c variability. Several studies suggest that fluctuating glycemic levels may exert more deleterious effects on peripheral nerves than stable hyperglycemia. This phenomenon aligns with the concept of cellular metabolic memory, wherein cells retain the harmful imprint of previous hyperglycemic exposure. This mechanism operates through persistent epigenetic modifications, sustained oxidative stress, and continuous formation of advanced glycation end products. Epigenetic alterations modify gene expression without altering DNA structure, while excessive activation of the p53 protein, triggered by glycemic variability may accelerate neuronal apoptosis [19,22]. These findings underscore the importance of not only achieving glycemic targets but also maintaining stable glycemic patterns over time.

The study by Fikri et al. (2024) further supports the significance of glycemic control, reporting that patients with uncontrolled HbA1c levels had a 45.3-fold increased risk of developing diabetic neuropathy. However, age emerged as an even stronger predictor, with individuals aged 44–59 years and those older than 59 years exhibiting a 53.3-fold higher risk of neuropathy [18]. This aligns with the findings of Lai et al. (2024), who observed that although HbA1c was significantly associated with neuropathy, age demonstrated an even stronger effect. These results suggest that uncontrolled HbA1c in older individuals may produce disproportionately severe consequences due to age-related increases in oxidative stress and diminished neuronal repair capacity [22]. Aging is known to impair mitochondrial function, reduce antioxidant defenses, and weaken regenerative mechanisms, all of which contribute to heightened vulnerability to neuropathic injury [18].

Despite the predominance of significant findings, several studies including those by Matasak et al. (2018), Tanhardjo et al. (2016), Solomos et al. (2025), and Virk et al. (2016) reported no significant association between HbA1c levels and diabetic neuropathy [14,15,21,24]. Tanhardjo et al. (2016) noted that although HbA1c was not significantly associated with neuropathy, the duration of diabetes mellitus was a critical determinant, with longer disease duration significantly increasing neuropathy risk [15]. Solomos et al. (2025) similarly reported that each additional year of diabetes increased neuropathy risk by approximately 7% [24]. Prolonged diabetes duration contributes to intracellular sorbitol accumulation, osmotic stress, and progressive axonal degeneration, which may overshadow the influence of HbA1c alone [13–15].

While some studies highlighted the greater importance of diabetes duration and age compared with HbA1c levels [15,24], the findings of Lai et al. (2024) offer a more integrative perspective. Their analysis demonstrated that combining HbA1c, age, and diabetes duration yielded higher sensitivity and specificity than using age and duration alone. This combined model also outperformed the use of HbA1c or duration independently, suggesting that neuropathy risk is best understood through a multidimensional assessment rather than reliance on a single biomarker [22]. Lou et al. (2024) further supported this conclusion, as their study showed that HbA1c alone had lower predictive accuracy compared with the three-parameter model proposed by Lai et al. (2024) [20,22].

The nonsignificant findings reported by Matasak et al. (2018) and Tanhardjo et al. (2016) may be attributed to methodological limitations, including small sample sizes and reliance on subjective questionnaire-based assessments [14,15]. In contrast, studies such as Su et al. (2018) and Lai et al. (2024) employed nerve conduction studies, which provide more objective and sensitive measures of neuropathic impairment [19,22]. Matasak et al. (2018) also noted that HbA1c levels may be influenced by confounding factors such as anemia, alcohol consumption, and age, while lower HbA1c levels may occur in individuals with liver disease, recent blood transfusions, or gastrointestinal bleeding [14]. Virk et al. (2016)

similarly suggested that residual confounding may have contributed to their nonsignificant findings, highlighting the complexity of interpreting glycemic indices in clinical research [21].

Although HbA1c is not the sole determinant of peripheral neuropathy, maintaining optimal and stable HbA1c levels remains a critical strategy for slowing the progression of diabetes-related complications. The collective evidence suggests that both absolute HbA1c levels and their variability play important roles in neuropathic risk, and that integrating HbA1c with age and diabetes duration may provide a more accurate assessment of neuropathy risk than any single parameter alone [13,20].

CONCLUSION

Elevated HbA1c levels and wide HbA1c variability increase both the risk and severity of diabetic neuropathy, and HbA1c has been shown to be a strong predictor when assessed longitudinally. Inconsistent findings across several studies are likely attributable to differences in sample size and the sensitivity of diagnostic instruments used. Clinicians are therefore encouraged not only to evaluate single-point HbA1c values but also to monitor HbA1c variability over time to prevent progressive nerve damage. Age and duration of diabetes should likewise be considered, as both contribute meaningfully to neuropathy risk. Overall, HbA1c remains a principal predictor in the development of diabetic neuropathy.

Ethical consideration, competing interest and source of funding

-This study no need ethical clearance because only comparing results of some studies that had been published open before (information of public domain). Every result of the involved studies had been mentioned in the citation and references, include the name of the authors, title of the journal and year of publication.

-There is no conflict of interest related to this publication.

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