narra R

Narrative Review

Advanced computational approaches for detecting subclinical diabetic peripheral neuropathy: Current prospects and future directions

Ghulbuddin Robbani[1], Andi A. Mappajanci[2] and Roy N. Ramadhan[1]*

[1]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [2]Medical Study Program, Faculty of Medicine, Universitas Muslim Indonesia, Makassar, Indonesia

*Corresponding author: roynofri28@gmail.com

Abstract

Diabetic peripheral neuropathy (DPN) is one of the most common and debilitating complications of diabetes mellitus. Early, subclinical stages of DPN are often asymptomatic and remain undetected until significant nerve damage occurs, limiting treatment options. Artificial intelligence (AI) has emerged as a promising tool to enhance early detection by identifying subtle patterns in electrophysiological, imaging, or sensor-based data that may not be recognized by conventional diagnostic methods. However, the current landscape of AI applications in subclinical DPN remains unclear. The aim of this study was to map and synthesize the existing literature on the use of AI-based methods for the early detection of subclinical DPN. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was conducted up to August 25, 2025. Eligible studies included those applying AI or machine learning techniques to identify or predict subclinical DPN in patients with type 1 or type 2 diabetes. Non-English articles, studies without AI implementation, and reviews were excluded. Data were charted on study characteristics, AI methodology, dataset type, and reported outcomes. Preliminary evidence suggests that AI has been applied across multiple modalities, including nerve conduction studies, corneal confocal microscopy, wearable sensor data, and electrophysiological signals. Techniques ranged from traditional machine learning models such as support vector machines and random forests to deep learning architectures including convolutional neural networks. While several studies reported high sensitivity and accuracy for early detection, most were limited by small sample sizes, lack of external validation, and heterogeneous definitions of "subclinical" DPN. In conclusion, AI-based approaches demonstrate substantial potential for the early identification of subclinical DPN, which could enable earlier interventions and improve patient outcomes. Nonetheless, the field is still in its early stages, and robust multicenter datasets, standardized definitions, and explainable AI models are required to facilitate clinical adoption. Future research should focus on validation in diverse populations and integration into routine diabetic care pathways.

Keywords: Artificial intelligence, early detection, diabetic peripheral neuropathy, non-communicable diseases, machine learning

Introduction

Diabetes mellitus is one of the most pressing public health challenges of the 21st century, with an estimated global prevalence exceeding 500 million adults in 2021 and projections indicating that this number could rise to 783 million by 2045 [1]. In addition to hyperglycemia and metabolic

Received: August 30, 2025 - Accepted: November 25, 2025 - Published online: November 30, 2025

disturbances, diabetes is associated with a range of chronic microvascular and macrovascular complications that significantly impair quality of life and increase healthcare costs [2]. Among these complications, diabetic peripheral neuropathy (DPN) is particularly concerning, as it affects up to half of patients with longstanding diabetes and is a major contributor to disability, morbidity, and premature mortality. DPN can present with neuropathic pain, sensory deficits, gait disturbances, and a heightened risk of foot ulceration leading to lower-limb amputation. The socioeconomic impact of DPN is profound, placing strain not only on healthcare systems but also on patients' functional independence and mental health [3].

The development of DPN is a progressive process that begins with subtle alterations in nerve function, often referred to as subclinical DPN, long before overt symptoms emerge. During this stage, patients may have no complaints, yet pathological changes such as axonal degeneration, demyelination, and microvascular compromise are already underway [4]. Once clinical neuropathy is established, therapeutic options are largely palliative, as neuronal damage is often irreversible. Consequently, early identification of subclinical DPN is crucial for timely interventions that may halt or slow progression, such as optimization of glycemic control, lifestyle modification, and emerging neuroprotective strategies. Unfortunately, conventional diagnostic modalities are limited in this regard. Bedside clinical examination and sensory testing are subjective and often lack reproducibility, while standard nerve conduction studies, though objective, are relatively insensitive to the earliest neuropathic changes and may miss subtle functional impairment. These limitations underscore the urgent need for novel, sensitive, and accessible diagnostic tools capable of detecting subclinical neuropathy before irreversible damage occurs [5].

In recent years, artificial intelligence (AI) has emerged as a disruptive innovation in medicine, offering unprecedented opportunities to enhance diagnostic accuracy and efficiency by uncovering clinically meaningful patterns within high-dimensional data. Through machine learning and deep learning algorithms, AI-driven models have matched or exceeded specialist performance in multiple clinical domains, including automated detection of diabetic retinopathy from fundus images, arrhythmia prediction from electrocardiograms, dermatological lesion classification, and oncologic decision support [6]. Further, AI has demonstrated robust utility across diabetes-related complications, enabling accurate retinal screening in resource-limited settings [7], effective identification of cardiac autonomic neuropathy using advanced ECG-based learning strategies [8], and reliable prediction of diabetic foot and ulcer risk through integrative predictive models [9]. In the context of neuropathy, AI offers a distinct advantage by integrating heterogeneous inputs from nerve conduction studies, corneal confocal microscopy, skin biopsies, quantitative sensory testing, and wearable-derived physiological signals [10].

Although the application of AI in diabetes-related complications has gained momentum, research focusing specifically on subclinical DPN remains fragmented. Most available studies are limited to small cohorts, employ heterogeneous methodologies, and are often restricted to proof-of-concept or pilot analyses. To date, there has been no comprehensive scoping review that systematically synthesizes and maps the evidence on AI approaches for the early detection of subclinical DPN. Such a review is essential not only to summarize what is currently known but also to highlight methodological strengths, identify recurring limitations, and define areas for future research. Addressing this gap is particularly important in light of the growing global diabetes burden and the unmet need for early detection tools. Therefore, the aim of this study was to comprehensively chart the existing literature on the application of AI techniques for early detection of subclinical DPN, thereby providing a foundation for further research, clinical translation, and ultimately improved patient outcomes.

Methods

This review was conducted to synthesize and discuss the existing literature on the use of AI for the early detection of subclinical DPN. Subclinical DPN was defined as early peripheral nerve dysfunction in individuals with diabetes mellitus without overt neuropathic symptoms, identified using objective measures. These included abnormalities detected through nerve conduction studies, quantitative sensory testing, imaging-based nerve assessments, wearable sensor outputs,

or validated biochemical or clinical markers, as defined by the original studies. No single diagnostic criterion was imposed.

A literature search was performed in PubMed, Scopus, Web of Science, and Epistemonikos to identify relevant studies published between July 28 and August 25, 2025. The search strategy combined controlled vocabulary and free-text keywords related to diabetes, neuropathy, and AI. The main search terms included: “artificial intelligence” OR “machine learning” OR “deep learning” AND “diabetic neuropathy” OR “peripheral neuropathy” OR “subclinical diabetic neuropathy” AND “early detection” OR “screening” OR “prediction.” The search syntax was adapted for each database.

Articles were included if they were published in English and examined AI- or machine learning–based approaches relevant to early or subclinical DPN in individuals with type 1 or type 2 diabetes mellitus. Eligible studies used clinical, electrophysiological, imaging, wearable, or biochemical data for model development or validation. Reviews, editorials, case reports, and non-English publications were excluded from formal evidence synthesis but were used as complementary sources to contextualize findings. The review was not restricted by AI model type, algorithm architecture, data modality, healthcare setting, geographic region, or study design, provided that the study evaluated AI-based approaches with potential relevance to early neuropathy detection. Internal and external validation strategies were considered during interpretation but were not applied as exclusion criteria.

Importantly, because relatively few studies explicitly enrolled cohorts labeled as having subclinical DPN, this review deliberately extrapolated findings from studies conducted in clinically diagnosed DPN populations when their input features, analytical targets, or biological signals were plausibly relevant to earlier disease stages. Such extrapolation was based on the rationale that many AI models leverage markers, such as small-fiber structural changes, microvascular dysfunction, metabolic burden, or functional gait alterations, that are known to precede overt neuropathic symptoms. Studies were therefore interpreted with explicit distinction between validated diagnostic performance and potential applicability to subclinical DPN, and no model was assumed to be directly transferable without further validation.

Study selection was based on relevance to the review objective, with titles, abstracts, and full texts assessed to identify studies that contributed meaningfully to understanding AI-based approaches for early DPN detection. The included literature was synthesized narratively, with emphasis on data sources, analytical methods, diagnostic targets, and potential clinical applicability. Two reviewers independently performed a two-stage screening process. In the first stage, titles and abstracts were screened for relevance. In the second stage, the full text of potentially eligible studies was reviewed against the inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer. The study selection process and criteria are presented in **Table 1**.

Pathophysiology of subclinical DPN

DPN is the most prevalent form of diabetic neuropathy and classically follows a length-dependent pattern, initially involving the distal toes and feet before progressing proximally along the lower limbs [11]. Importantly, DPN does not emerge abruptly as a symptomatic disorder; rather, it evolves through a prolonged subclinical phase characterized by early neural dysfunction in the absence of overt sensory or motor complaints. During this stage, injury preferentially affects small unmyelinated C fibers and thinly myelinated Aδ fibers, which are particularly vulnerable to metabolic and microvascular stress due to their high energy demand and limited regenerative capacity. As a result, substantial neural injury may accumulate before clinical recognition, rendering this phase frequently underdiagnosed in routine practice.

Accumulating electrophysiological and quantitative sensory testing data indicate that subclinical DPN is common. Nearly half of asymptomatic individuals with type 2 diabetes demonstrate abnormalities in nerve conduction or small-fiber function, despite lacking classical neuropathic symptoms [12]. These findings underscore that normal neurological examination or symptom-based screening does not reliably exclude early nerve injury. Instead, functional impairments such as reduced conduction velocity, altered thermal perception, or decreased

intraepidermal nerve fiber density may already be present, reflecting early axonal and Schwann cell dysfunction rather than irreversible structural loss.

Several clinical and biochemical factors have been consistently associated with this early stage of nerve damage, including longer diabetes duration, reduced fasting C-peptide levels, and the presence of albuminuria [12-14]. Collectively, these markers capture converging pathophysiological pathways central to DPN development, namely chronic metabolic stress, microvascular dysfunction, low-grade inflammation, and impaired neurotrophic support [15-17]. Prolonged diabetes duration reflects cumulative exposure to hyperglycemia-driven mechanisms such as mitochondrial oxidative stress, activation of the polyol and hexosamine pathways, and accumulation of advanced glycation end-products, all of which disrupt axonal transport and ion channel function prior to overt axonal degeneration [16,18].

Reduced C-peptide levels may further accelerate subclinical neuropathy by removing its protective actions on peripheral nerves. Experimental and clinical evidence suggests that C-peptide supports endoneurial blood flow, preserves Na^+/K^+-ATPase activity, stabilizes neuronal membranes, and attenuates inflammatory signaling. Deficiency in this peptide therefore predisposes nerves to ischemic vulnerability and metabolic injury even in the absence of marked hyperglycemia [19,20]. In parallel, albuminuria serves as a systemic marker of endothelial dysfunction and microvascular injury, reinforcing the concept that early DPN is part of a broader microangiopathic process linking renal, retinal, and neural tissues. Without timely management, these subclinical abnormalities gradually extend from small sensory fibers to larger sensory and motor fibers [18,21]. Therefore, early identification is critical as it provides a window for intervention before permanent axonal loss occurs, highlighting the need for reliable screening methods of subclinical DPN.

Conventional diagnostic approaches and their limitations

Several diagnostic modalities are currently available for the detection of subclinical DPN, where their summaries are presented in **Table 2**. Conventional clinical examinations, such as monofilament testing and vibration perception, are widely used but have limited sensitivity for early or asymptomatic disease [22,23]. Nerve conduction studies remain the reference standard for diagnosing large-fiber neuropathy, with high specificity. However, they have limited sensitivity for early small-fiber involvement and require specialized equipment and trained personnel [22,23]. The assessment is objective and is based on parameters such as nerve conduction velocity, distal latency, and signal amplitude [22]. However, their sensitivity in detecting subclinical DPN is limited, as early pathophysiological changes typically affect small fibers before large fibers become involved [5]. Skin biopsy with intraepidermal nerve fiber density assessment is considered the gold standard for small-fiber neuropathy and enables detection at subclinical stages [24,25]. Nonetheless, the invasive nature of skin biopsy contributes to its restricted routine use. Corneal confocal microscopy has emerged as a non-invasive imaging technique capable of detecting early small-fiber loss, though its implementation is constrained by equipment availability and technical expertise [26]. Collectively, these non–AI-assisted modalities form the current diagnostic landscape for subclinical DPN, but each presents trade-offs between accuracy, accessibility, and scalability, underscoring persistent gaps in early detection [27]. Furthermore, those assessments are heavily dependent on patient responses and examiner technique which can introduces potential bias and further limits reliability [28].

The subclinical stage of DPN represents a critical window during which neural injury may still be reversible or its progression substantially attenuated. Evidence from the Diabetes Control and Complications Trial (DCCT) showed that early neuropathic changes are modifiable through metabolic intervention [29]. However, the ability to act within this window is constrained by the limitations of existing diagnostic modalities. Conventional clinical examinations lack sensitivity for early disease, while standard nerve conduction studies primarily capture large-fiber dysfunction and may fail to detect early or predominantly small-fiber involvement [27]. Even electrophysiological refinements designed to detect subtle distal conduction slowing are not routinely applied and require specialized expertise for interpretation.

Table 1. Search process and study selection criteria

Items	Specification
Date of search	July 28, 2025 until August 25, 2025
Databases and other sources searched	PubMed, Scopus, Web of Science, and Epistemonikos
Search terms used	"artificial intelligence" OR "machine learning" OR "deep learning" AND "diabetic neuropathy" OR "peripheral neuropathy" OR "subclinical diabetic neuropathy" AND "early detection" OR "screening" OR "prediction"
Inclusion and exclusion criteria	Articles were included if they were published in English and focused on AI- or machine learning (ML)-based approaches for detecting subclinical DPN among patients with diabetes mellitus (Type 1 or Type 2). Eligible studies encompassed the use of clinical, electrophysiological, imaging, wearable, or biochemical datasets for model development or validation. Reviews, editorials, case reports, and non-English publications were excluded.
Selection process	Two reviewers screened the search results independently through titles and abstracts to select the eligible ones

Table 2. Non-artificial intelligence diagnostic modalities for detection of subclinical diabetic peripheral neuropathy

Diagnostic modality	Primary nerve fiber assessed	Typical diagnostic performance*	Skill/specialist requirement	Strengths	Limitations
Clinical examination (monofilament, tuning fork)	Large fiber	Low sensitivity for subclinical disease	Primary care–level	Simple, low cost, widely available	Insensitive to early neuropathy; subjective; poor signal granularity for AI
Nerve conduction study	Large fiber	Sensitivity 40–81%; specificity 90–95%	Neurologist / trained technician	Reference standard for large-fiber neuropathy	Insensitive to early small-fiber damage; time-consuming; limited scalability
Point-of-care nerve conduction study (NCS) (such as sural nerve devices)	Large fiber	Sensitivity 80–96%; specificity 80–97%	Minimal training	Rapid, standardized outputs; scalable	Still misses pure small-fiber neuropathy; population-specific cutoffs
Intraepidermal nerve fiber density (skin biopsy)	Small fiber	Sensitivity 78–88%; specificity 64–90%	Specialist, pathology lab	Gold standard for small-fiber neuropathy	Invasive; sampling variability; poor acceptability; limited repeatability
Quantitative sensory testing (QST)	Small±large fiber	Highly variable (AUC: 0.65–0.80)	Trained operator + cooperative patient	Non-invasive; detects functional impairment	Psychophysical bias; attention-dependent; noisy labels for AI
Contact heat evoked potentials (CHEPs)	Small fiber (Aδ, C)	Sensitivity 80%; specificity 70%	Neurophysiology expertise	Objective cortical response; earlier than NCS	Limited availability; complex acquisition; small datasets
Corneal confocal microscopy	Small fiber	AUC 0.70–0.85 (parameter-dependent)	Ophthalmic imaging + software	Non-invasive; detects early nerve loss; repeatable	Equipment cost; normative variability; image quality dependence
Sudomotor function testing (QSART)	Small fiber (auto)	Sensitivity 60%; specificity 100%	Specialized lab	Objective autonomic assessment	Time-consuming; variable performance; limited adoption
Electrochemical skin conductance	Small fiber (auto)	Moderate accuracy (AUC 0.70–0.80)	Minimal training	Rapid; point-of-care friendly	Influenced by hydration, skin condition; indirect nerve measure

*Data are proximate from different studies
Reference: [27]

Current electrophysiological approaches tend to evaluate sensorimotor and autonomic dysfunction separately, despite DPN being a condition involving multiple neural domains, leading to incomplete characterization of early disease [30]. AI emerges as a promising approach to address these diagnostic gaps by leveraging data already generated from conventional diagnostic modalities. Using electrophysiological signals, imaging outputs, and functional test results obtained from nerve conduction studies, corneal confocal microscopy, quantitative sensory testing, and autonomic assessments, machine-learning algorithms can identify complex, multivariate patterns that are not readily apparent through conventional threshold-based interpretation [26,31].

AI approaches for early detection of subclinical DPN

Detection of subclinical DPN through AI models, in general, integrates early risk factors, subtle neurophysiological abnormalities, and emerging functional changes that precede overt clinical symptoms [32,33]. The following sections explain how classical machine learning models leverage structured clinical and electrophysiological data, how deep learning approaches uncover latent structural and waveform-level signatures from imaging and signal-based modalities, and how wearable sensor–driven AI captures early functional impairments in real-world settings. The role of explainable AI in translating these complex models into clinically interpretable tools was further discussed. It is worth noting that most AI-based studies cited in the following sections were designed to identify established or clinically manifest DPN rather than subclinical disease. In this context, qualitative extrapolation was performed on the reported methodological approaches and analytical performance to assess the feasibility of applying these models to the identification of subclinical DPN. The summary of studies reporting AI- or machine learning-based models, with feasible application to detect subclinical DPN is presented in **Table 3**.

Machine learning methods

Classical machine learning approaches, including logistic regression, random forests, support vector machines, gradient boosting, and XGBoost, have been widely applied in the detection of clinical DPN [2]. Features or variables incorporated in these models involved structured demographic, clinical, metabolic, and laboratory data for neuropathy-related prediction tasks [34-37]. Machine learning classification models typically use routinely available variables, including age, sex, diabetes duration, body mass index, HbA1c, lipid profiles, renal markers, and cardiovascular indicators; in some studies, electrophysiological or quantitative sensory testing results are also incorporated [34-37]. Logistic regression is often employed as a baseline due to its transparency and interpretability. Meanwhile, the performance often improved after implementing ensemble-based methods such as random forests and gradient boosting [34,36,37]. The ensemble-based methods are considered superior when handling nonlinear relationships and interactions among heterogeneous risk factors [38, 39]. As reported previously, Random Forest, XGBoost, and LightGBM classifiers could reach over 80% of accuracy when detecting prediabetes [40].

Across studies, age and diabetes duration consistently emerged as the most influential predictors, reflecting cumulative metabolic exposure and time-dependent neurodegenerative processes that are insufficiently represented by short-term biochemical indices alone [34-37]. Glycemic control, commonly measured by HbA1c, contributed to model performance but showed limited discriminative value when considered in isolation [41,42]. This is consistent with clinical observations that neuropathy may develop despite apparently adequate glycemic control in individuals with prolonged diabetes duration [43, 44]. In contrast, renal markers such as urine albumin-to-creatinine ratio and serum creatinine were repeatedly selected as strong predictors [45,46]. This is likely because they reflect shared microvascular and endothelial dysfunction underlying both diabetic nephropathy and peripheral neuropathy [47]. Patterns showed by the aforementioned studies suggests that systemic microvascular compromise may serve as a more sensitive early signal of neuropathic risk than glycemic metrics alone [48,49].

Table 3. AI-based study and applicability for subclinical diabetic peripheral neuropathy

Author, year (ref)	AI method	Input data	Neuropathy stage studied	Applicability for subclinical DPN
Zhang *et al.*, 2023 [35]	Random Forest (best); LR, SVM, GBDT, XGBoost	PORH, LTH, $TcPO_2$ + clinical variables	Clinical DPN	Variables can be measured in subclinical stage
Baskozos *et al.*, 2022 [34]	Random Forest (best); Adaptive Regression Splines; Naïve Bayes	Clinical, metabolic, QoL, psychological, lifestyle variables	Clinical DPN (painful vs painless)	Multidimensional risk profiles in subclinical stage
Jiang *et al.*, 2024 [36]	Random Forest (best); Logistic Regression + SHAP	Clinical, laboratory, and TCM features	Clinical DPN	Early-risk profiling using routine clinical data
Wu *et al.*, 2024 [37]	XGBoost (best); Random Forest; Logistic Regression + SHAP	Demographic, clinical, and routine laboratory data	Clinical DPN	Shared risk factors measurable before overt neuropathy; based on routine labs
Wu *et al.*, 2024 [37]	XGBoost (best); Random Forest; Logistic Regression + SHAP	Demographic, clinical, and routine laboratory data	Clinical DPN	Shared risk factors measurable before overt neuropathy; based on routine labs
Williams *et al.*, 2020 [50]	CNN (U-Net; Liverpool Deep Learning Algorithm)	Corneal confocal microscopy images	Clinical DPN (Toronto criteria)	Small-fibre pathology detectable before clinical symptoms
Qiao *et al.*, 2024 [51]	U2Net (best); U-Net, U-Net++, Deeplabv3+, SegNet	Corneal confocal microscopy images	Clinical DPN (Toronto criteria)	Small-fiber changes occur early; imaging markers measurable before symptoms
Sartore *et al.*, 2025 [10]	XGBoost-based risk prediction algorithm (MetaClinic)	HbA1c, glucose, BP, lipids, creatinine, albuminuria	Asymptomatic T2D; DPN assessed by biothesiometer	Designed for pre-symptomatic risk stratification; supports early screening before clinical neuropathy

AI: artificial intelligence; BMI: body mass index; BP: blood pressure; CNBD: corneal nerve branch density; CNFD: corneal nerve fiber density; CNFL: corneal nerve fiber length; CNN: convolutional neural network; DPN: diabetic peripheral neuropathy; EQ-5D: EuroQol five-dimension questionnaire; GBDT: gradient boosting decision tree; HbA1c: glycated hemoglobin; LR: logistic regression; LTH: local thermal hyperemia; PORH: post-occlusion reactive hyperemia; QoL: quality of life; SHAP: SHapley Additive exPlanations; SVM: support vector machine; T2D: type 2 diabetes; $TcPO_2$: transcutaneous oxygen pressure; TCM: traditional Chinese medicine; UACR: urine albumin-to-creatinine ratio; VPT: vibration perception threshold; XGBoost: extreme gradient boosting.

Several studies which used machine learning–based models also incorporated cardiovascular and vascular-related variables, including blood pressure parameters and carotid stenosis [10,47]. This suggests that macrovascular disease contributes to nerve ischemia and impaired axonal repair and is captured by these models [52,53]. A model developed from systematic review included hypertension, determined by blood pressure, could effectively stratified patients to develop DPN [53]. In addition, patient-reported outcomes—particularly reduced quality-of-life scores and psychological measures such as depression and anxiety—were frequently ranked among important features [34]. These variables may capture early functional, perceptual, and behavioral changes that precede formal neurological diagnosis and are not readily detected by objective testing. In terms of the methods applicability for subclinical DPN detection, these models are feasible primarily because of their reliance on routinely collected, non-invasive variables [34-37].

Deep learning methods

As limitations of traditional machine learning classifiers in capturing high-dimensional and spatially complex data became apparent, researchers increasingly shifted toward deep learning architectures [54]. AI studies employing deep learning architectures have primarily focused on imaging-based modalities [55,56]. Mostly, the images incorporated to the models are derived from high-frequency peripheral nerve ultrasound and corneal confocal microscopy [50, 51, 53]. These modalities are capable to capture structural correlates of neuropathy that are not accessible through routine clinical testing [50,51,53]. These modalities are particularly suited to early neuropathy assessment because they interrogate small-fiber integrity and nerve microarchitecture, which are affected earlier in the disease course than large-fiber conduction parameters [31]. Convolutional neural networks and advanced segmentation models consistently identified features such as nerve cross-sectional area, corneal nerve fiber length, density, branching complexity, and fractal metrics, reflecting axonal loss, impaired regeneration, and disruption of nerve network organization that may precede overt clinical symptoms [50,51,53]. An intriguing instance, as reported by a study, is that reductions in corneal nerve fiber length and density capture diffuse axonal degeneration, whereas alterations in branching patterns and fractal measures reflect loss of network complexity and regenerative capacity [57].

Further, deep learning and AI frameworks have also been applied to non-imaging data sources to support early neuropathy risk assessment. An integrated AI risk-prediction model evaluated asymptomatic individuals with type 2 diabetes using routinely available clinical and biochemical variables, with neuropathy status benchmarked against vibration perception threshold measured by biothesiometer [10]. This approach explicitly targets the pre-symptomatic phase of disease and shifts the role of AI from direct structural detection toward probabilistic risk stratification [58]. The prominence of variables such as age, disease duration, and metabolic burden in these models reinforces convergence between imaging-based and non-imaging AI approaches around shared pathophysiological drivers of early nerve injury [59,60]. The integrated risk-prediction systems enable scalable screening in asymptomatic populations [10]. However, most deep learning models have been trained and validated in cohorts with clinically manifest DPN, and their applicability to subclinical disease remains largely extrapolated.

Challenges and gaps in the literature

Unfortunately, the current evidence base for AI-assisted identification of subclinical DPN remains constrained by several methodological and translational challenges [55]. Most studies rely on small, single-center datasets without standardized acquisition protocols, limiting generalizability and increasing the risk of overfitting. The problem is particularly concerning for deep learning models that require large and diverse training data [61-63]. In addition, the absence of a universally accepted definition of subclinical DPN results in heterogeneous diagnostic thresholds, inclusion criteria, and outcome measures, complicating cross-study comparisons and precluding the establishment of reliable benchmarks. Model validation is frequently retrospective and confined to controlled research settings, raising concerns regarding robustness and performance in real-world clinical practice, where early or mild neuropathic changes are often underrepresented [64,65]. Data imbalance, in which early or subclinical DPN cases constitute a

small minority relative to non-DPN samples, has been shown to reduce model sensitivity for minority outcomes. The application of data-balancing techniques, such as the Synthetic Minority Over-sampling Technique (SMOTE), has been associated with improved recall and F1-scores in imbalanced disease classification tasks [66]. In addition, limited model interpretability constrains clinician trust and clinical adoption, particularly in convolutional neural network–based systems [42,55]. Finally, unresolved issues related to data governance and regulation. Their integration into existing care pathways underscore persistent gaps between technical feasibility and practical implementation [67].

Future directions

Future research should prioritize the development of multicenter, standardized datasets that capture diverse patient populations and employ consistent diagnostic criteria for subclinical DPN. Such datasets would improve reproducibility, enable benchmarking of algorithms, and facilitate external validation. In parallel, explainable AI (XAI) techniques should be increasingly applied to enhance transparency, allowing clinicians to understand which features drive predictions and improving trust in automated systems [68,69]. Integration of AI with wearable technologies and mobile health applications also holds significant promise. Continuous monitoring of gait, plantar pressure, and other functional parameters could provide real-time insights into neuropathic changes, enabling proactive interventions [70]. In this context, wearable sensor–based point-of-care platforms can be used for such monitoring of early neuropathic changes outside traditional clinical settings [30,71]. Further, longitudinal prediction models should be developed to estimate individual risk trajectories over time, supporting personalized diabetes management. Unfortunately, most of the reports on real-time monitoring of DPN or other diabetic complications remain conceptual [72].

Explainable AI (XAI)

XAI techniques aim to address the lack of interpretability in complex models by making the decision-making process more transparent and understandable to clinicians [73]. Methods such as SHapley Additive exPlanations (SHAP), Local Interpretable Model-Agnostic Explanations (LIME), and saliency maps can be used to highlight which features such as HbA1c levels, nerve conduction parameters, or specific regions of an image can contribute most to the model's predictions [56,74]. For example, in a deep learning model trained on corneal confocal microscopy (CCM) images, saliency maps can visually indicate the nerve fibers that drive the classification decision, thereby aligning AI outputs with clinical intuition. Similarly, in structured-data models, SHAP values can rank the most important predictors of subclinical neuropathy, helping clinicians validate whether the model is consistent with established risk factors. XAI not only improves clinician trust but also facilitates regulatory approval and ethical deployment in practice [73].

Wearable and sensor-based AI

Wearable technologies and sensor-based AI approaches provide an innovative, non-invasive avenue for detecting subclinical DPN by continuously monitoring functional outcomes such as gait, balance, and plantar pressure distribution [30,71]. As suggested in non-diabetic contexts, devices like accelerometers, inertial measurement units (IMUs), and pressure-sensitive insoles can capture detailed spatiotemporal gait parameters and subtle deviations in walking patterns that may reflect early sensory or motor nerve dysfunction [75,76]. For example, patients with incipient neuropathy may demonstrate reduced stride variability, asymmetrical pressure distribution across the foot, or impaired postural stability, all of which can be quantified through wearable sensors [71]. Machine learning algorithms can be applied to these datasets to classify patients at risk of DPN, expected outperforming traditional screening tools due to their sensitivity to micro-level biomechanical changes. A key advantage of wearable-based models is their ability to provide continuous, real-world data that reflect daily activity rather than isolated clinical measurements [35]. To develop this emerging research area, the progress will depend on interdisciplinary collaboration among clinicians, engineers, data scientists, and behavioral researchers.

Conclusion

Integration of AI is highly promising for the early identification of subclinical DPN, with the potential to stratify high-risk individuals before irreversible nerve damage occurs. Across diverse methodological approaches, existing studies report encouraging accuracy and sensitivity. However, the evidence base remains fragmented by small sample sizes, heterogeneous definitions of subclinical DPN, and limited validation in real-world settings. To enable meaningful clinical translation, future research should prioritize large, standardized, and multicenter datasets, the systematic incorporation of explainable AI frameworks, and rigorous prospective validation. If these challenges are addressed, the integration of AI-driven models into routine diabetes care may represent a transformative step toward earlier intervention and reduction of the long-term burden of neuropathic complications.

Acknowledgments

The authors have nothing to declare.

Competing interests

The authors declare no competing interests.

Funding

This study received no external funding.

Underlying data

All underlying data have been presented in this article.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

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 - http://doi.org/10.52225/narrarev.v1i3.14.

References

1. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Sci Rep 2024;7(3):e2004.
2. Tavakoli M, Klingelhöfer D, Fadavi H, *et al*. The landscape of global research on diabetic neuropathy. Frontiers Endocrinol 2023;14:1220896.
3. Pan Q, Fei S, Zhang L, *et al*. How does diabetic peripheral neuropathy impact patients' burden of illness and the economy? A retrospective study in Beijing, China. Front Public Health 2023;11:1164536.
4. Ang L, Mizokami-Stout K, Eid SA, *et al*. The conundrum of diabetic neuropathies—past, present, and future. J Diabetes Complications 2022;36(11):108334.
5. Burgess J, Frank B, Marshall A, *et al*. Early Detection of Diabetic Peripheral Neuropathy: A Focus on Small Nerve Fibres. Diagnostics 2021;11(2):165.
6. Alhejaily AG. Artificial intelligence in healthcare (review). Biomed Rep 2025;22(1):11.
7. Kong M, Song SJ. Artificial intelligence applications in diabetic retinopathy: What we have now and what to expect in the future. Endocrinol Metab 2024;39(3):416-424.
8. Irlik K, Aldosari H, Hendel M, *et al*. Artificial intelligence-enhanced electrocardiogram analysis for identifying cardiac autonomic neuropathy in patients with diabetes. Diabetes Obes Metab 2024;26(7):2624-2633.

9. Li Y, Zhou S, Ren B, *et al*. The application of artificial intelligence models in predicting the risk of diabetic foot: a multicenter study. BioData Min 2025;18(1):57.
10. Sartore G, Ragazzi E, Pegoraro F, *et al*. Artificial Intelligence Algorithm to Screen for Diabetic Neuropathy: A Pilot Study. Biomedicines 2025;13(5):1075.
11. Jensen TS. The pathogenesis of painful diabetic neuropathy and clinical presentation. Diabetes Res Clin Pract 2023;206:110753.
12. Gao L, Qin J, Chen Y, *et al*. Risk factors for subclinical diabetic peripheral neuropathy in type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2024;17:417-426.
13. Unmar Y, Zafar MI, Gao F. Factors associated with peripheral neuropathy in type 2 diabetes: Subclinical versus confirmed neuropathy. J Huazhong Univ Sci Technolog Med Sci 2017;37(3):337-342.
14. Elliott J, Sloan G, Stevens L, *et al*. Female sex is a risk factor for painful diabetic peripheral neuropathy: The EURODIAB prospective diabetes complications study. Diabetologia 2024;67(1):190-198.
15. Elafros MA, Andersen H, Bennett DL, *et al*. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. Lancet Neurol 2022;21(10):922-936.
16. Cheng Y, Chen Y, Li K, *et al*. How inflammation dictates diabetic peripheral neuropathy: An enlightening review. CNS Neurosci Ther 2024;30(4):e14477.
17. Goldney J, Sargeant JA, Davies MJ. Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy. Diabetologia 2023;66(10):1832-1845.
18. Zhu J, Hu Z, Luo Y, *et al*. Diabetic peripheral neuropathy: Pathogenetic mechanisms and treatment. Front Endocrinol 2024;14:12265372.
19. Chen S-P, Li R-Y, Hong J, *et al*. Association between intraneural blood flow of the sciatic nerve, peripheral neuropathies, and foot ulcers in patients with diabetes. Quant Imaging Med Surg 2025;15(7).
20. Dhanapalaratnam R, Issar T, Poynten AM, *et al*. Impact of glucagon-like peptide-1 receptor agonists on axonal function in diabetic peripheral neuropathy. J Neurophysiol 2025;133(1):14-21.
21. Galiero R, Caturano A, Vetrano E, *et al*. Peripheral neuropathy in diabetes mellitus: Pathogenetic mechanisms and diagnostic options. Int J Mol Sci 2023;24(4):3554.
22. Sharma K. N S, Kumar H A. Assessment of the diagnostic accuracy of vibrasense compared to a biothesiometer and nerve conduction study for screening diabetic peripheral neuropathy. J Foot Ankle Res 2023;16(1):65.
23. Hazari A, Mishra V, Kumar P, *et al*. The accuracy of 10 g monofilament use for clinical screening of diabetes peripheral neuropathy among Indian population. PLoS One 2024;19(2):e0297110.
24. Karlsson P. Skin biopsy analysis in diabetic neuropathy. In: Tavakoli M, editor. Diabetic Neuropathy. Amsterdam: Elsevier; 2022.
25. Lauria G, Faber CG, Cornblath DR. Skin biopsy and small fibre neuropathies: Facts and thoughts 30 years later. J Neurol Neurosurg Psychiatry 2022;93(9):915.
26. Cosmo E, Midena G, Frizziero L, *et al*. Corneal confocal microscopy as a quantitative imaging biomarker of diabetic peripheral neuropathy: A review. J Clin Med 2022;11(17):5130.
27. Newlin Lew K, Arnold T, Cantelmo C, *et al*. Diabetes distal peripheral neuropathy: Subtypes and diagnostic and screening technologies. J Diabetes Sci Technol 2022;16(2):295-320.
28. Yang Z, Zhang Y, Chen R, *et al*. Simple tests to screen for diabetic peripheral neuropathy. Cochrane Database Syst Rev 2018;2018(7).
29. Albers JW, Herman WH, Pop-Busui R, *et al*. Subclinical neuropathy among diabetes control and complications trial participants without diagnosable neuropathy at trial completion: Possible predictors of incident neuropathy? Diabetes Care 2007;30(10):2613-2618.
30. Hayashi Y, Himeno T, Shibata Y, *et al*. Simplified electrophysiological approach combining a point-of-care nerve conduction device and an electrocardiogram produces an accurate diagnosis of diabetic polyneuropathy. J Diabetes Investig 2024;15(6):736-742.
31. Ma Y, Wang Z, Yao Z, *et al*. Machine learning in the prediction of diabetic peripheral neuropathy: A systematic review. BMC Med Inform Decis Mak 2025;25(1):344.
32. Salahouddin T, Petropoulos IN, Ferdousi M, *et al*. Artificial intelligence–based classification of diabetic peripheral neuropathy from corneal confocal microscopy images. Diabetes Care 2021;44(7):e151.
33. Siré Langa A, Lázaro-Martínez JL, Tardáguila-García A, *et al*. Advanced AI-driven thermographic analysis for diagnosing diabetic peripheral neuropathy and peripheral arterial disease. Appl Sci 2025;15(11):5886.

34. Baskozos G, Themistocleous AC, Hebert HL, *et al*. Classification of painful or painless diabetic peripheral neuropathy and identification of the most powerful predictors using machine learning models in large cross-sectional cohorts. BMC Med Inform Dec Mak 2022;22(1):144.
35. Zhang X, Sun Y, Ma Z, *et al*. Machine learning models for diabetic neuropathy diagnosis using microcirculatory parameters in type 2 diabetes patients. Int Angiol 2023;42(3):191-200.
36. Jiang A, Li J, Wang L, *et al*. Multi-feature, Chinese–Western medicine-integrated prediction model for diabetic peripheral neuropathy based on machine learning and SHAP. Diabetes Metab Res Rev 2024;40(4):e3801.
37. Wu Y, Dong D, Zhu L, *et al*. Interpretable machine learning models for detecting peripheral neuropathy and lower extremity arterial disease in diabetics: An analysis of critical shared and unique risk factors. BMC Med Inform Decis Mak 2024;24(1):200.
38. Ganie SM, Pramanik PKD, Bashir Malik M, *et al*. An ensemble learning approach for diabetes prediction using boosting techniques. Front Genet 2023;14:1252159.
39. Oliullah K, Rasel MH, Islam MM, *et al*. A stacked ensemble machine learning approach for the prediction of diabetes. J Diabet Metab Disord 2024;23(1):603-617.
40. Dutta A, Hasan MK, Ahmad M, *et al*. Early prediction of diabetes using an ensemble of machine learning models. Int J Environ Res Public Health 2022;19(19):12378.
41. Banchhor M, Singh P. Comparative study of ensemble learning algorithms on early stage diabetes risk prediction. In: Proceedings of the 2nd International Conference for Emerging Technology (INCET). IEEE; 2021.
42. Zaferani N, Afrash MR, Moulaei K. Predicting and classifying type 2 diabetes using a transparent ensemble model combining random forest, k-nearest neighbor, and neural networks. Sci Rep 2025.
43. Dubé M-C, Tremblay A, Lavoie C, *et al*. Effect of exercise on food consumption and appetite sensations in subjects with diabetes. Appetite 2013;71:403-410.
44. Mahesh T, Kumar D, Vinoth Kumar V, *et al*. Blended ensemble learning prediction model for strengthening diagnosis and treatment of chronic diabetes disease. Comput Intell Neurosci 2022;2022(1):4451792.
45. Lian X, Qi J, Yuan M, *et al*. Study on risk factors of diabetic peripheral neuropathy and establishment of a prediction model by machine learning. BMC Med Inform Decis Mak 2023;23(1):146.
46. Adili A, Aikemu M, Rana KS, *et al*. Development and validation of a predictive model for diabetic peripheral neuropathy with type 2 diabetes mellitus in Xinjiang, China. Sci Rep 2025;15(1):36202.
47. Zhang H, Yang S, Wang H, *et al*. Assessing the diagnostic utility of urinary albumin-to-creatinine ratio as a potential biomarker for diabetic peripheral neuropathy in type 2 diabetes mellitus patients. Sci Rep 2024;14(1):27198.
48. Kanbour S, Harris C, Lalani B, *et al*. Machine learning models for prediction of diabetic microvascular complications. J Diabetes Sci Technol 2024;18(2):273-286.
49. Wang J, Song X, Xia Z, *et al*. Serum biomarkers for predicting microvascular complications of diabetes mellitus. Expert Rev Mol Diagn 2024;24(8):703-713.
50. Williams BM, Borroni D, Liu R, *et al*. An artificial intelligence-based deep learning algorithm for the diagnosis of diabetic neuropathy using corneal confocal microscopy: A development and validation study. Diabetologia 2020;63(2):419-430.
51. Qiao Q, Cao J, Xue W, *et al*. Deep learning-based automated tool for diagnosing diabetic peripheral neuropathy. Digit Health 2024;10:20552076241307573.
52. Abdalrada AS, Abawajy J, Al-Quraishi T, *et al*. Prediction of cardiac autonomic neuropathy using a machine learning model in patients with diabetes. Ther Adv Endocrinol Metab 2022;13:20420188221086693.
53. Liu X, Chen D, Fu H, *et al*. Development and validation of a risk prediction model for early diabetic peripheral neuropathy based on a systematic review and meta-analysis. Front Public Health 2023;11:1128069.
54. Afsaneh E, Sharifdini A, Ghazzaghi H, *et al*. Recent applications of machine learning and deep learning models in the prediction, diagnosis, and management of diabetes: A comprehensive review. Diabetol Metab Syndr 2022;14(1):196.
55. Pan L, Sun W, Wan W, *et al*. Research progress of diabetic disease prediction model in deep learning. J Theor Pract Eng Sci 2023;3(12):15-21.
56. Chen Y, Sun Z, Zhong H, *et al*. Diabetic tibial neuropathy prediction: Improving interpretability of various machine-learning models based on multimodal-ultrasound features using SHAP methodology. Ultrasound Med Biol 2025;51(10):1744-1753.
57. Gao C, Tong W, Liu S, *et al*. Dual–plasticizing strategy for an enhanced performance of degradable chitosan-based triboelectric nanogenerators. ACS Appl Electron Mater 2024;6(3):1982-1991.

58. Subramani A, Periasamy P, Gunasekaran S. A Comparative analysis of diagnostic accuracy: Vibration perception threshold vs. diabetic neuropathy examination for diabetic neuropathy. J Pharm Bioallied Sci 2024;16(Suppl 5):S4536-S4539.
59. Wee BF, Sivakumar S, Lim KH, *et al*. Diabetes detection based on machine learning and deep learning approaches. Multimed Tools Appl 2024;83(8):24153-24185.
60. Hua Y-j, Zhang Y, Wu R-R, *et al*. Metabolome profiling by untargeted metabolomics and biomarker panel selection using machine-learning for patients in different stages of peripheral neuropathy induced by oxaliplatin. Front Oncol 2025;15:1617207.
61. Alipour M, Alipour A. Algorithmic bias in AI-based diabetes care: Systematic review of model performance, equity reporting, and physiological label bias. InfoScience Trends 2025;2(5):33-46.
62. Rashid MM, Askari MR, Chen C, *et al*. Artificial intelligence algorithms for treatment of diabetes. Algorithms 2022;15(9):299.
63. Bhimavarapu U. Bias in AI-driven diabetes prediction models: Challenges, impacts, and mitigation strategies. In: Kulkarni S, Gochhait S, editors. AI-powered systems for healthcare diagnostics and treatment. Pennsylvania: IGI Global Scientific Publishing; 2025.
64. Chun J-W, Kim H-S. The present and future of artificial intelligence-based medical image in diabetes mellitus: Focus on analytical methods and limitations of clinical use. J Korean Med Sci 2023;38(31):e253.
65. Knevel R, Liao KP. From real-world electronic health record data to real-world results using artificial intelligence. Ann Rheum Dis 2023;82(3):306-311.
66. Salmi M, Atif D, Oliva D, *et al*. Handling imbalanced medical datasets: Review of a decade of research. Artif Intell Rev 2024;57(10):273.
67. Guan Z, Li H, Liu R, *et al*. Artificial intelligence in diabetes management: advancements, opportunities, and challenges. Cell Rep Med 2023;4(10).
68. Hossain MI, Zamzmi G, Mouton PR, *et al*. Explainable AI for medical data: Current methods, limitations, and future directions. ACM Comput Surv 2025;57(6):1-46.
69. Payrovnaziri SN, Chen Z, Rengifo-Moreno P, *et al*. Explainable artificial intelligence models using real-world electronic health record data: A systematic scoping review. J Am Med Inform Assoc 2020;27(7):1173-1185.
70. Ellahham S. Artificial intelligence: The future for diabetes care. Am J Med 2020;133(8):895-900.
71. Golledge J, Fernando M, Lazzarini P, *et al*. The potential role of sensors, wearables and telehealth in the remote management of diabetes-related foot disease. Sensors 2020;20(16):4527.
72. Sathya R, Bharathi VC, Ananthi S, *et al*. Real time prediction of diabetes by using artificial intelligence. In: 2nd International Conference on Self Sustainable Artificial Intelligence Systems (ICSSAS); 2024.
73. Misir A. Artificial intelligence and machine learning in diabetic foot ulcer care: Advances in diagnosis, treatment, prognosis, and novel therapeutic strategies. J Diabetes Sci Technol 2025:19322968251363632.
74. Srinivasu PN, Ahmed S, Hassaballah M, *et al*. An explainable Artificial Intelligence software system for predicting diabetes. Heliyon 2024;10(16).
75. Subramaniam S, Majumder S, Faisal AI, *et al*. Insole-based systems for health monitoring: Current solutions and research challenges. Sensors 2022;22(2):438.
76. Nassajpour M, Seifallahi M, Rosenfeld A, *et al*. Comparison of wearable and depth-sensing technologies with electronic walkway for comprehensive gait analysis. Sensors 2025;25(17):5501.