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EARLY PREDICTORS AND PREVENTION STRATEGIES FOR DIABETIC NEUROPATHY, A NARRATIVE REVIEW

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ABSTRACT

Diabetic neuropathy (DN), encompassing distal symmetric polyneuropathy, small-fiber and autonomic neuropathies, is highly prevalent across the spectrum of dysglycemia and causes neuropathic pain, sensory loss, autonomic dysfunction, foot ulceration, and increased morbidity and mortality. Early detection of subclinical nerve injury and identification of modifiable risk factors permit timely prevention and may reduce long-term complications. The aim of this study is to synthesize evidence from recent studies on early clinical, metabolic, and paraclinical predictors of diabetic neuropathy and to summarize practical, implementable prevention and screening strategies. The study was conducted as a structured narrative review modeled after the framework of an original research article. The analysis was based on a review of the literature indexed in PubMed concerning early predictors, paraclinical markers, point-of-care diagnostics for subclinical neuropathy, primary prevention and multifactorial risk-reduction strategies recommended in the literature. Small-fiber autonomic dysfunction, which frequently precede clinically overt large-fiber loss, is detectable by corneal confocal microscopy, intraepidermal nerve-fiber density, quantitative sensory testing, and autonomic measures (HRV, cardiovascular autonomic reflex tests), as well as validated devices, enabling earlier risk stratification. Prevention strategies supported or recommended across sources include early risk stratification with combined small- and large-fiber testing, intensive glycemic control, structured lifestyle interventions and comprehensive cardiometabolic management. Multifactorial programs and targeted early interventions are promising but require sensitive endpoints and longer follow-up to confirm impact on hard outcomes. Prevention of diabetic neuropathy relies on early recognition of clinical and subclinical predictors, incorporation of sensitive screening tools and prompt multifactorial risk modification. Implementation of combined screening and structured education models may improve early detection and reduce downstream morbidity, but prospective trials using sensitive diagnostic endpoints are needed to demonstrate disease modification.

KEYWORDS

Diabetic Neuropathy, Early Predictors, Prevention, Screening, Small-Fiber Neuropathy

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1. Introduction

Diabetic neuropathy (DN) is a common, heterogeneous complication of dysglycemia that encompasses distal symmetric polyneuropathy, small-fiber neuropathy and a range of autonomic neuropathies. Clinically, DN presents across a spectrum from subclinical nerve injury detectable only by sensitive paraclinical tests, through painful neuropathic syndromes, to sensory loss that predisposes to foot ulceration, infection and amputation (so called “diabetic foot”). Diabetic foot complications including foot ulceration, infection and lower-limb amputation are common downstream consequences of diabetic neuropathy and peripheral vascular disease and carry high morbidity, mortality and health-care costs (Selvarajah et al., 2019; Binns-Hall et al., 2018). Sensory loss from large-fiber involvement and autonomic dysfunction (altered sweating and skin integrity), often preceded by small-fiber damage, increase risk of unnoticed trauma, impaired wound healing and subsequent infection (Pop-Busui et al., 2017; Vinik et al., 2006). Most diabetic amputations are preventable with early detection of neuropathy, regular foot surveillance, structured podiatry care and multifactorial risk management. Autonomic involvement causes additional morbidity through cardiovascular, gastrointestinal and urogenital dysfunction. The collective burden of DN is substantial: it reduces quality of life, increases healthcare utilization and contributes markedly to diabetes-related costs and mortality (Selvarajah et al., 2019; Dillon et al., 2024).

Epidemiologic and clinicopathologic studies indicate that neuropathic changes often begin early in the course of dysglycemia and may be present in individuals with impaired glucose tolerance or at the time of diabetes diagnosis; early small-fiber and autonomic dysfunction frequently precede large-fiber deficits and overt clinical symptoms, providing a potential window for detection and preventive intervention (Selvarajah et al., 2019; Pritchard et al., 2015; Dillon et al., 2024). Population and cohort data within the evaluated studies

document high lifetime prevalence of DN and show that prevalence and severity rise with diabetes duration; they also highlight considerable underdiagnosis when routine bedside screening alone (10 g monofilament, tuning fork) is used (Selvarajah et al., 2019; Lee et al., 2014; Binns-Hall et al., 2018).

Risk for DN reflects integrated effects of cumulative glycemic exposure and non-glycemic cardiometabolic factors. Across the analysed literature, well-reproduced clinical predictors include longer duration of dysglycemia, higher HbA1c and glycemic variability; however, multiple studies emphasize important, independent contributions from obesity, dyslipidemia (particularly elevated triglycerides), hypertension and cigarette smoking (Callaghan et al., 2016; Wiggin et al., 2009; Pop-Busui et al., 2017). These metabolic and vascular risk components often cluster as features of the metabolic syndrome and independently associate with symptomatic polyneuropathy, even after adjustment for glycemia, underscoring the multifactorial biology of nerve injury in diabetes (Callaghan et al., 2016; Malik et al., 2011). The co-occurrence of other microvascular complications further signals shared pathogenic pathways and higher neuropathy risk (Selvarajah et al., 2019; Pop-Busui et al., 2017).

Overall, reviewed studies synthesize converging evidence that DN results from interacting metabolic, vascular and inflammatory processes. Chronic hyperglycemia and insulin resistance drive disturbances in polyol, hexosamine and protein kinase C pathways, formation of advanced glycation end-products, mitochondrial and endoplasmic-reticulum stress, oxidative/nitrosative injury and microvascular dysfunction of the vasa nervorum. These alterations provoke low-grade inflammation and impair axonal transport and neuronal survival, with small unmyelinated fibers particularly vulnerable early in the disease course (Vincent et al., 2011; Pop-Busui et al., 2016; Zenker et al., 2013). Recognition of these pathways emphasizes that prevention strategies should not only include glycemic control but also target dyslipidemia, blood pressure, obesity and systemic inflammation (Pop-Busui et al., 2016; Vincent et al., 2011).

A critical barrier to early prevention identified in the implementation and diagnostic literature is the limited sensitivity of traditional bedside screening tools to detect incipient neuropathy; standard tests commonly used in clinic practice frequently identify neuropathy only after loss of protective sensation has occurred, at which point irreversible structural change may have already taken place (Selvarajah et al., 2019; Binns-Hall et al., 2018). In contrast, several examined studies depict the diagnostic performance and feasibility of more sensitive paraclinical and point-of-care modalities: corneal confocal microscopy (CCM) and intraepidermal nerve-fiber density (IENFD) detect small-fiber loss; quantitative sensory testing (QST) and autonomic indices (heart-rate variability, cardiovascular autonomic reflex tests) reveal early functional impairment; and validated handheld devices (sural nerve POCDs, Sudoscan, Neuropad) provide rapid, objective assessments suitable for near-patient screening. Combining small- and large-fiber assessments increases early detection and improves risk stratification compared with conventional bedside testing alone (Pritchard et al., 2015; Selvarajah et al., 2015; Lee et al., 2014; Ziegler et al., 2014).

Evidence for prevention supports a multifaceted approach. Landmark trials in type 1 diabetes demonstrate substantial risk reduction for neuropathy with intensive glycemic control, and long-term follow-up indicates persistent benefit (legacy effect) (DCCT Research Group, 1993). In type 2 diabetes, the effects of glucose lowering alone are less consistent; multifactorial cardiovascular risk management that targets lipids, blood pressure, weight and physical activity in addition to glycemia offers the best prospect to reduce neuropathy incidence and progression when implemented early, although heterogeneity in neuropathy endpoints has limited clear demonstration of benefit in some large trials (Gaede et al., 2003; Ismail-Beigi et al., 2010; Dillon et al., 2024). Smaller intervention studies and lifestyle programs show promising improvements in small-fiber measures and cutaneous reinnervation following weight loss and supervised exercise, especially in prediabetes or early disease (Singleton et al., 2015; Horton et al., 2017; Kluding et al., 2012). Implementation studies of integrated “one-stop” microvascular screening services that combine eye, renal and neuropathy assessments indicate feasibility and higher yield of early neuropathy detection in routine care (Binns-Hall et al., 2018).

Taken together, the reviewed evidence argues that preventing or delaying DN requires systematic early identification of at-risk individuals using combined clinical and sensitive paraclinical tests that detect subclinical small-fiber and autonomic dysfunction; early, targeted multifactorial risk modification addressing glycemia and the broader cardiometabolic milieu; and structured service models and patient education (including foot-care pathways) to ensure timely intervention and reduce downstream complications.

2. Methodology

2.1 Study design

This study was conducted as a structured narrative review modeled after the framework of an original research article. The aim was to identify early clinical, metabolic and paraclinical predictors of diabetic neuropathy and to summarise practical prevention and screening strategies for clinical use.

2.2 Source selection and scope

A focused literature search was conducted using PubMed. The analyzed materials comprised original research articles, diagnostic/validation studies, consensus statements, reviews and implementation reports addressing epidemiology, pathophysiology, diagnostics, screening devices and prevention strategies for diabetic neuropathy. Following terms were used for the research: “prevention strategies for diabetic neuropathy”; “prevention of diabetic neuropathy”; “diabetic neuropathy”; “risk factors”; “cardiac autonomic neuropathy”; “diabetic peripheral neuropathy”; “predictors”.

2.3 Inclusion criteria

Studies were included if they: (a) reported data or synthesized evidence relevant to early predictors of diabetic neuropathy (clinical, biochemical, electrophysiological, small-fiber or autonomic markers), (b) evaluated or described screening/diagnostic methods (including point-of-care devices and paraclinical tests), or (c) addressed prevention, risk-factor modification or screening implementation strategies. Editorials, commentaries or materials without substantive evidence relevant to these aims were excluded.

2.4 Data extraction

Analysis from each examined source: study type, population characteristics, key reported early predictors or risk factors, paraclinical/diagnostic modalities and their reported performance or role in early detection, and prevention or multifactorial intervention findings and recommendations. Where available, sensitivity/specificity, reproducibility metrics and endpoints used in interventional studies were recorded.

2.5 Synthesis approach

Extracted information was organized thematically into (1) clinical and metabolic predictors, (2) paraclinical and (3) point-of-care diagnostic markers of subclinical neuropathy (small-fiber, large-fiber and autonomic measures), and (4) prevention and screening strategies including implementation models. Findings were compared across sources to identify consistent predictors, diagnostic approaches with practical utility, and recurring recommendations for prevention. Heterogeneity in study design, outcome measures and endpoints was noted and qualitatively appraised. No quantitative meta-analysis was performed.

2.6 Use of AI tools

Artificial intelligence tools were used exclusively for linguistic and editorial support during manuscript preparation. Literature selection, interpretation of evidence, synthesis of arguments, and final scientific conclusions remained fully under human control.

3. Results

This review synthesizes (1) early clinical and metabolic predictors of diabetic neuropathy (DN), (2) paraclinical markers of subclinical nerve injury (small-fiber, large-fiber, autonomic), (3) performance and role of point-of-care diagnostics (POCDs) and combined screening models, and (4) evidence linking early detection with prevention/intervention effects. Key findings were summarized further.

3.1 Early clinical and metabolic predictors

Cumulative hyperglycemic exposure is a central and consistently reported determinant of diabetic neuropathy. Longer duration of dysglycemia, higher HbA1c and greater glycemic variability are repeatedly associated with increased incidence and progression of neuropathic injury. The strongest randomized-trial evidence for prevention comes from intensive glycemic control in type 1 diabetes: the DCCT and its EDIC follow-up demonstrated substantial reductions in neuropathy incidence and a durable legacy effect on nerve outcomes (DCCT Research Group, 1993; Dillon, Ang, & Pop-Busui, 2024). Importantly, several studies report that neuropathic abnormalities often arise early in the dysglycemic continuum, with measurable small-fiber and autonomic dysfunction detectable in individuals with impaired glucose tolerance or at diabetes diagnosis, indicating a clinically actionable window for earlier detection and intervention before irreversible structural damage occurs (Selvarajah et al., 2019; Pritchard et al., 2015; Dillon et al., 2024). Beyond glycemia, components of the metabolic syndrome exert independent and meaningful effects: obesity, insulin resistance and dyslipidemia—most notably elevated triglycerides—are associated with symptomatic polyneuropathy and

with structural and functional measures of nerve decline even after adjustment for glycemia. Several cohort and mechanistic studies link hypertriglyceridemia to neuropathy progression and adverse lower-limb outcomes (Callaghan et al., 2016; Wiggin et al., 2009). Vascular and behavioral factors further modify risk: hypertension, active smoking and the presence of other microvascular complications such as retinopathy or nephropathy consistently identify patients at higher neuropathy risk and predict more rapid progression (Pop-Busui et al., 2017; Selvarajah et al., 2019; Vinik, Megerian, & Gozani, 2006). Taken together, the literature supports a multifactorial risk architecture in which hyperglycemia is necessary but often not sufficient alone; cardiometabolic, vascular and behavioral determinants materially influence early nerve injury and disease trajectory, arguing that prevention strategies should combine glycemic optimization with targeted management of metabolic and vascular comorbidities to reduce neuropathy risk and progression (Callaghan et al., 2016; Binns-Hall et al., 2018).

3.2 Paraclinical markers of subclinical nerve injury

Detecting subclinical nerve injury in diabetic neuropathy requires more sensitive approaches than routine bedside tests. The examined materials show that combining structural and functional assessments of small fibers with measures of large-fiber and autonomic function provides the best opportunity to identify early disease. Skin punch biopsy with quantification of intraepidermal nerve-fiber density (IENFD) remains the histologic gold standard for small-fiber neuropathy, offering high specificity and correlation with symptoms and treatment-related reinnervation; however, its invasiveness and need for specialized pathology limit routine use to reference centres and research settings (Selvarajah et al., 2019; Lauria et al., 2010). Corneal confocal microscopy (CCM) provides a noninvasive structural alternative by quantifying corneal nerve morphology (fiber length and branch density); validation and longitudinal studies demonstrate that CCM predicts incident neuropathy and correlates with IENFD, supporting its utility for serial monitoring and as an early trial endpoint (Pritchard et al., 2015; Ziegler et al., 2014).

Functional assessment of small fibers includes quantitative sensory testing (QST) for thermal and pinprick thresholds and sudomotor testing for sweat function. QST detects small-fiber dysfunction before large-fiber deficits but is psychophysical and dependent on patient cooperation, limiting its role as a standalone screening tool while retaining value in research and enriched clinical evaluation (Ziegler et al., 2014). Sudomotor methods (e.g., Sudoscan, Neuropad) yield rapid, objective measures of electrochemical skin conductance or a categorical sudomotor response; validation data show acceptable reproducibility and reasonable sensitivity for early small-fiber dysfunction, making these tests practical adjuncts for near-patient screening when combined with other modalities (Selvarajah et al., 2015; Casellini et al., 2013).

For large-fiber assessment, standard nerve conduction studies (NCS) remain the reference, delivering objective parameters (sensory action potential amplitude, conduction velocity) with prognostic relevance for foot outcomes; their resource intensity and need for specialist operators limit scalability for population screening (Lee et al., 2014). Handheld point-of-care nerve conduction devices (e.g., automated sural nerve testers) offer rapid, user-friendly sural sensory assessments with good reliability and reasonable agreement with laboratory NCS in validation studies, providing a pragmatic large-fiber screen in clinic settings (Lee et al., 2014; Chatzikosma et al., 2016).

Autonomic involvement is detected early by reductions in heart-rate variability (HRV) and by cardiovascular autonomic reflex tests (CARTs). HRV indices, including measures derivable from routine ECG recordings, are feasible early markers of cardiovascular autonomic neuropathy, whereas CARTs remain the diagnostic gold standard but are more resource-intensive (Pop-Busui et al., 2017; Vinik et al., 2006). Other autonomic evaluations (gastric emptying studies, urodynamics) are specialized and less suitable for routine screening, although sudomotor tests also capture autonomic small-fiber dysfunction (Pop-Busui et al., 2017; Selvarajah et al., 2015).

A multimodal approach combining tests for small-fiber structure (CCM or IENFD) and function (sudomotor tests, QST) with rapid large-fiber assessment (POCD or monofilament plus vibration) increases sensitivity for detecting incipient neuropathy compared with single tests; implementation and validation studies show that multimodal screening better identifies individuals with subclinical disease and improves risk stratification for progression and foot risk (Pritchard et al., 2015; Lee et al., 2014; Binns-Hall et al., 2018). Choice of tests should balance sensitivity, invasiveness, cost, required expertise and intended use (screening vs. diagnostic confirmation vs. trial endpoint): IENFD and NCS are indispensable for confirmation and mechanistic research, while CCM and selected POCDs offer scalable, noninvasive tools for clinic-based early detection.

Reported diagnostic performance and reproducibility vary by modality and cohort: DPN-Check (handheld sural tester) demonstrates high intraclass correlation and sensitivity in validation studies, Sudoscan shows area-under-curve values around 0.8–0.85 in some cohorts, and CCM exhibits predictive utility for incident neuropathy. Reproducibility benefits from standardized acquisition and automated analysis, particularly for CCM (Lee et al., 2014; Selvarajah et al., 2015; Pritchard et al., 2015). The evaluated studies repeatedly call for standardization of protocols, establishment of normative databases, and multicentre prospective studies that link paraclinical early detection to hard clinical outcomes (ulceration, amputation, mortality) and to cost-effectiveness to confirm clinical utility at scale (Selvarajah et al., 2019; Binns-Hall et al., 2018; Singleton et al., 2015).

3.3 Point-of-care diagnostics and screening models

Point-of-care diagnostic devices (POCDs) and integrated screening models aim to shift detection of diabetic neuropathy (DN) from late, symptom-driven diagnosis toward earlier, objective identification of subclinical nerve injury that can prompt timely preventive action. The reviewed sources emphasize that scalable, rapid, reproducible near-patient tests used in combination and embedded within streamlined clinical pathways may increase case finding, improve risk stratification, and facilitate referral into multifactorial prevention programs (Selvarajah et al., 2019; Dillon et al., 2024; Binns-Hall et al., 2018). Table 1 presents a practical stepwise screening algorithm that integrates basic clinical screening with multimodal POCD-based assessment and defines triage and referral actions for screen-positive patients.

Table 1 - Screening algorithm (stepwise pathway for clinic use):

1.	All adults with diabetes or prediabetes — annual risk review and symptom enquiry (pain, numbness, balance, autonomic symptoms)
	Basic clinical screening at point of care:
2.	a) 10 g monofilament + 128 Hz tuning fork or vibration device + inspection for foot deformity/ulceration; record risk factors (duration, HbA1c, BMI, lipids, BP, smoking, other microvascular disease)
	b) If any abnormality on basic screen OR high-risk profile (long duration, high HbA1c, obesity, hypertriglyceridaemia, hypertension, smoking, microvascular disease) → proceed to step 3.
	Multimodal paraclinical screening (near-patient):
3.	Combine one small-fiber test (Sudoscan or CCM where available) with one rapid large-fiber test (DPN-Check or handheld sural tester; or vibration/monofilament if POCD is not available). Use locally validated cut-offs. Positive if small-fiber and/or large-fiber test abnormal.
	Triage and actions:
4.	a) Negative multimodal screen + low clinical risk → routine annual follow-up and lifestyle/cardiometabolic reinforcement.
	b) Positive multimodal screen (subclinical neuropathy) → initiate/ intensify multifactorial prevention: optimize glycemia, lipids, BP; refer to structured lifestyle program (weight loss, exercise); smoking cessation; schedule podiatry education and foot-care follow-up; consider confirmatory tests (IENFD, lab NCS) if indicated for diagnostic clarification or trial enrolment
	Confirmatory/secondary care:
5.	Cases with atypical features, rapidly progressive symptoms, or diagnostic uncertainty → refer for full NCS ± skin biopsy (IENFD) and neurology/pain services
	Monitoring:
6.	For screen-positive patients enrolled in prevention: repeat multimodal screening at 6–12 months to assess response (POCD and CCM/IENFD as available); adjust interventions accordingly

POCDs target complementary aspects of neuropathy biology and differ by fiber type, output, and operational demands. Handheld automated sural nerve devices (e.g., DPN-Check) measure sural sensory nerve action potential amplitude and conduction velocity as pragmatic surrogates for large-fiber function; validation studies report high intraclass correlation coefficients and sensitivities in the 80–90% range versus laboratory nerve conduction studies (NCS), making these devices useful rapid screening tools for large-fiber involvement (Lee et al., 2014). No single device captures the full spectrum of early DN, and their complementarity argues for multimodal testing strategies that assess both small- and large-fiber domains.

Validation studies demonstrate acceptable diagnostic performance for individual POCDs but also highlight heterogeneity across cohorts and thresholds. DPN-Check shows strong reliability ($ICC > 0.9$ in some reports) and high sensitivity compared with NCS but variable specificity depending on population prevalence and cut-points (Lee et al., 2014). Sudoscan validation studies report robust reproducibility ($ICC \approx 0.9$) and AUCs ≈ 0.8 – 0.85 for detecting DPN in selected clinical samples (Selvarajah et al., 2015; Casellini et al., 2013). CCM longitudinal data indicate that reduced corneal nerve fibre measures predict incident neuropathy over years, supporting CCM as a sensitive early structural marker useful in longitudinal screening and trials (Pritchard et al., 2015; Ziegler et al., 2014). The reviewed materials caution that single-study performance metrics cannot be generalized without multicentre validation and that device thresholds should be locally calibrated and validated against accepted reference standards (Selvarajah et al., 2019).

Across the literature, combining tests targeting different fiber types consistently increases sensitivity for early neuropathy compared with single tests. Studies demonstrate that pairing a small-fiber assessment (sudomotor test or CCM) with a large-fiber measure (DPN-Check, vibration, or monofilament) improves detection of subclinical disease and better stratifies patients for foot-risk and progression than bedside screening alone (Pritchard et al., 2015; Lee et al., 2014; Binns-Hall et al., 2018). For trial selection and evaluation of preventive interventions, sources recommend small-fiber structural/functional endpoints (IENFD, CCM, sudomotor metrics) that change earlier than NCS parameters and therefore better capture intervention effects (Lauria et al., 2010; Pritchard et al., 2015).

Implementation work describes “one-stop” microvascular screening clinics that integrate retinal photography, renal assessment, and neuropathy screening (using POCDs and clinical foot assessment) in a single visit. These models achieved high uptake, reduced patient visits, and substantially increased early DN detection, unmasking subclinical painful neuropathy and streamlining immediate referrals to podiatry, lifestyle services, and medical optimization (Binns-Hall et al., 2018). Practical workflows used trained non-physician staff (podiatrists, diabetes nurses) to operate POCDs, perform structured foot risk assessments, provide education, and enact referral algorithms—minimizing specialist bottlenecks and improving service efficiency (Binns-Hall et al., 2018). Pilot data show that such clinics can attain high sensitivity for detecting DPN when combined device algorithms are used, but formal economic evaluations and long-term outcome data remain limited (Selvarajah et al., 2019).

The reviewed studies emphasize the need for locally validated thresholds and clear algorithms: a positive POCD or multimodal abnormality should trigger confirmatory testing (if needed), initiation or intensification of multifactorial risk management (glycemic, lipid, and blood-pressure optimization; lifestyle referral), and expedited podiatry follow-up for foot-risk mitigation. Algorithms require pre-specified device cut-points, defined repeat testing intervals, and pathways linking screening outcomes to concrete interventions. Standardization of acquisition protocols, automated analysis where possible (notably CCM), and operator training are recurrent recommendations to reduce variability and improve reproducibility (Pritchard et al., 2015; Selvarajah et al., 2019; Lee et al., 2014).

Although POCDs and integrated models show promise, recurrent limitations include heterogeneity of validation cohorts, variable device cut-offs, selection bias in pilot studies, and a paucity of multicentre prospective trials demonstrating that POCD-based screening leads to reductions in hard clinical endpoints (ulceration, amputation, mortality). Cost-effectiveness and scalability across diverse health systems and socioeconomic contexts are insufficiently characterized, and equity considerations are important given documented disparities in diabetic foot outcomes (Dillon et al., 2024; Binns-Hall et al., 2018). The reviewed literature underscores the need for prospective randomized or pragmatic cluster trials that (a) use POCD-based subclinical detection to select participants, (b) randomize to targeted prevention pathways, and (c) measure long-term clinical and economic outcomes (Gaede et al., 2003; Selvarajah et al., 2019).

Based on the evidence and implementation experience, recommended pragmatic steps include adopting multimodal screening in routine diabetes care (combine a small-fiber test with a rapid large-fiber assessment), implementing one-stop or co-located microvascular screening where feasible to improve uptake, using locally

validated device thresholds and automated analysis to enhance reproducibility, training allied health staff to operate POCDs and deliver initial risk stratification, and prioritizing prospective evaluation of POCD-guided prevention programs with clinically meaningful endpoints and cost-effectiveness analyses (Selvarajah et al., 2015; Pritchard et al., 2015; Binns-Hall et al., 2018).

The studied materials support POCDs as pragmatic tools that, when combined and embedded within integrated screening models, can substantially improve early detection and risk stratification for diabetic neuropathy. Table 2 summarizes the different POCD types (large-fiber, small-fiber, structural and autonomic) with their primary measures and practical advantages/limitations. To translate earlier detection into prevention of major complications, standardized screening algorithms, multicentre validation, cost-effectiveness assessment and outcome trials linking POCD-guided pathways to hard endpoints are needed.

Table 2. POCD comparison (concise practical summary)

Device / Test	Target fiber(s)	Time (approx)	Main advantages	Main limitations
DPN-Check (handheld sural tester)	Large myelinated (Aα/Ab)	~3 min	Rapid, objective large-fiber measure; portable; good agreement with NCS	Assesses only sural nerve (may miss early small-fiber disease); population thresholds vary
Sudoscans	Small-fiber (sudomotor sympathetic C-fibres)	~3–5 min	Quick, noninvasive, operator-independent; objective sudomotor measure	Cut-offs heterogeneous; influenced by skin conditions; not a stand-alone diagnostic
Neuropad (indicator plaster)	Small-fiber (sudomotor)	~10 min	Simple, low cost, usable by non-specialists and patients	Categorical output; lower specificity for large-fiber neuropathy
Corneal confocal microscopy (CCM)	Small unmyelinated fibers (corneal)	~10–30 min (image + analysis)	Noninvasive structural biomarker; sensitive to early small-fiber loss; useful trial endpoint	Requires specialized equipment/expertise; costs and access limit routine use
NeuroQuick / Thermal POCDs	Small Aδ/C fibers	~5–10 min	Near-patient small-fiber function test	Psychophysical—dependent on patient attention; variable repeatability
Standard NCS (lab)	Large myelinated fibers	30–60+ min	Comprehensive, quantitative, prognostic	Resource-intensive, not suitable for routine broad screening
Skin biopsy (IENFD)	Small unmyelinated fibers	Invasive (procedure + lab processing)	Histologic gold standard; sensitive structural endpoint	Invasive; requires pathology expertise; not point-of-care

3.4 Early detection linked to prevention/intervention evidence

A central premise is that earlier identification of subclinical neuropathic changes increases the opportunity for interventions that may prevent or delay clinical neuropathy and its complications. Randomized-trial and longitudinal cohort data, mechanistic studies, device-validation work and intervention pilots in the provided corpus together form a chain of evidence: (1) nerve injury often begins early (including in prediabetes), (2) sensitive paraclinical markers detect incipient small-fiber and autonomic dysfunction before conventional bedside tests, and (3) early, targeted interventions, especially when multifactorial, can improve intermediate structural or functional endpoints associated with neuropathy and, in some contexts, reduce clinical progression.

The strongest clinical trial evidence for prevention derives from type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up (EDIC) demonstrated that intensive glycemic control substantially reduced incident neuropathy during the trial and yielded a persistent legacy effect on nerve outcomes over years of follow-up (DCCT Research Group, 1993). These trials provide proof-of-principle that modifying a primary driver (glycemia) early in disease can alter neuropathy trajectories

when treatment is timely and sustained; their findings are reiterated in recent syntheses and position statements (Selvarajah et al., 2019; Dillon, Ang, & Pop-Busui, 2024).

In type 2 diabetes the pathogenesis is more heterogeneous. Large trials of glycemic control alone showed smaller or inconsistent effects on neuropathy incidence, likely reflecting later stage at intervention, competing cardiometabolic drivers, and, importantly, insensitive neuropathy outcome measures in many studies (Dillon et al., 2024; Pop-Busui et al., 2017). Consequently, the literature emphasizes multifactorial approaches for T2D: combined management of glycemia, lipids, blood pressure, weight, and smoking is biologically plausible and has yielded favorable outcomes in trials addressing cardiovascular and some microvascular endpoints. The Steno-2 multifactorial intervention produced sustained reductions in cardiovascular events and slower progression of some autonomic measures, with long-term follow-up suggesting benefit of early broad risk management (Gaede et al., 2003; Selvarajah et al., 2019).

Several intervention studies using sensitive small-fiber endpoints provide encouraging intermediate evidence that early detection plus targeted intervention can improve nerve structure and function. Lifestyle and exercise interventions in cohorts with prediabetes, metabolic syndrome, or early T2D have shown increases in intraepidermal nerve-fiber density and markers of cutaneous reinnervation and improvements in small-fiber function when interventions are applied early and sustained (Singleton et al., 2015; Horton et al., 2017; Kluding et al., 2012). These structural and functional improvements indicate biological reversibility in early disease and support the plausibility that preventing progression to clinically overt neuropathy is achievable when interventions target modifiable upstream mechanisms such as insulin resistance, dyslipidemia, and inflammation (Vincent et al., 2011; Pop-Busui et al., 2016).

The corpus also links early detection with improved targeting of interventions via point-of-care diagnostics and multimodal screening. Validation and implementation studies show that combining small-fiber assessments (CCM, sudomotor tests, IENFD where available) with rapid large-fiber measures (handheld sural nerve devices) increases yield of subclinical neuropathy detection compared with monomodal bedside screening, thereby enabling enrolment of higher-risk, yet still early-stage, individuals into prevention programs (Selvarajah et al., 2015; Pritchard et al., 2015; Lee et al., 2014; Binns-Hall et al., 2018). Pilot “one-stop” microvascular screening clinics integrating POCDs with retinal and renal screening have shown higher detection rates of subclinical neuropathy and improved pathway efficiency, facilitating immediate referral to lifestyle services, podiatry, and medical optimisation (Binns-Hall et al., 2018; Selvarajah et al., 2019).

Despite promising intermediate data, critical gaps remain: few large multicentre randomized trials have used POCD-based subclinical detection as the entry criterion for preventive interventions, and long-term outcome data demonstrating that POCD-guided early intervention reduces hard endpoints (foot ulceration, amputation, mortality) are limited. Many prior large trials lacked sensitive subclinical endpoints, potentially underestimating benefits from early multifactorial treatment. Accordingly, prospective trials are needed that (a) use validated, sensitive paraclinical markers (CCM, IENFD, sudomotor metrics) to identify candidates early, (b) randomize participants to intensive multifactorial prevention pathways versus usual care, and (c) assess both intermediate nerve-specific endpoints and long-term clinical outcomes and cost-effectiveness.

Hyperglycemia, dyslipidemia, insulin resistance and low-grade inflammation interact to damage peripheral nerves via oxidative/nitrosative stress, microvascular compromise and impaired neuronal repair—processes that are at least partially reversible or mitigable in early stages. Interventions that reduce these upstream drivers (intensive glycemic control in T1D; combined lifestyle change, weight loss, lipid and blood-pressure optimization in T2D) therefore have a sound mechanistic basis to prevent progression if deployed before irreversible axonal loss (Vincent et al., 2011; Pop-Busui et al., 2016).

In summary, the evidence links early detection to prevention: (1) paraclinical markers identify incipient neuropathy amenable to intervention; (2) targeted interventions, particularly multifactorial and lifestyle-based, improve sensitive structural or functional nerve endpoints when applied early; and (3) operational models that integrate screening and rapid referral can bridge detection with intervention in routine care. To demonstrate reductions in hard clinical endpoints, prospective randomized and implementation trials combining POCD-based early detection with standardized multifactorial prevention strategies and long-term follow-up are required.

4. Discussion

This review synthesizes evidence on early predictors, paraclinical markers, and prevention strategies for diabetic neuropathy (DN). The analyzed literature supports three interrelated conclusions with direct implications for clinical practice and research. First, neuropathic injury commonly begins early in the dysglycemic continuum and frequently manifests initially as small-fiber and autonomic dysfunction that is not detected by conventional bedside screening (Selvarajah et al., 2019; Pritchard et al., 2015). Second, a multifactorial risk architecture—where cumulative glycemic exposure interacts with cardiometabolic, vascular, and behavioral determinants—drives early neuropathy risk and progression (Callaghan et al., 2016; Pop-Busui et al., 2017). Third, deployment of sensitive paraclinical diagnostics within integrated screening pathways creates an opportunity to identify high-risk individuals for early, multifactorial interventions that may improve intermediate nerve outcomes and plausibly reduce downstream complications, although definitive evidence for hard endpoints remains limited (Selvarajah et al., 2015; Binns-Hall et al., 2018).

The strongest randomized evidence for prevention derives from the DCCT/EDIC program, which established that intensive glycemic control in type 1 diabetes markedly reduces incident neuropathy and confers a durable legacy effect on nerve outcomes (DCCT Research Group, 1993). This positions early glycemic optimization as a cornerstone of prevention in T1D (Dillon et al., 2024). In type 2 diabetes (T2D), trials of glucose lowering alone have produced less consistent neuropathy benefit, likely reflecting later timing of interventions, dominant non-glycemic drivers (dyslipidemia, obesity, hypertension), and the insensitivity of neuropathy endpoints used in many large trials (Dillon et al., 2024; Pop-Busui et al., 2017). Cohort and mechanistic studies consistently demonstrate independent associations of metabolic syndrome components—particularly elevated triglycerides and obesity—with neuropathy incidence and progression, supporting the need to address the broader cardiometabolic milieu in T2D (Callaghan et al., 2016; Wiggin et al., 2009; Vincent et al., 2011).

From a diagnostic standpoint, validation and longitudinal studies document that small-fiber structural (IENFD, CCM) and functional (sudomotor testing, QST) measures identify incipient nerve injury earlier than conventional large-fiber-focused bedside tests; POCDs (handheld sural nerve devices, Sudoscan, Neuropad) offer pragmatic, reproducible near-patient assessments that, when combined across fiber domains, increase early detection and risk stratification in routine settings (Lauria et al., 2010; Pritchard et al., 2015; Selvarajah et al., 2015; Lee et al., 2014). Implementation pilots of “one-stop” microvascular screening illustrate operational feasibility and greater case-finding yield when neuropathy screening is integrated with retinal and renal screening pathways (Binns-Hall et al., 2018).

Collectively, studies suggest an actionable strategy: implement multimodal screening that combines small- and large-fiber assessments in routine diabetes care, triage screen-positive patients into multidisciplinary prevention pathways (glycemic, lipid, and blood-pressure optimization; structured lifestyle programs; podiatry and education), and use sensitive paraclinical endpoints to monitor response. This approach aligns with mechanistic insights that early insults (oxidative stress, microvascular dysfunction, low-grade inflammation) may be reversible or mitigated before extensive axonal loss (Vincent et al., 2011; Pop-Busui et al., 2016). Embedding POCDs into primary and diabetes clinics can democratize access to earlier detection and enable targeted resource allocation, particularly when allied health professionals operate screening pathways under standardized algorithms (Binns-Hall et al., 2018).

Important limitations temper the strength of recommendations. First, most large trials in T2D did not prespecify sensitive neuropathy endpoints; as a result, potential benefits from early multifactorial interventions may have been underestimated. Second, although validation studies show good diagnostic metrics for individual POCDs, heterogeneity in device thresholds, study populations, and reference standards limits generalizability. Third, the majority of implementation evidence is from pilot or single-centre studies; multicentre pragmatic trials demonstrating that POCD-guided early intervention reduces hard endpoints (ulceration, amputation, mortality) and is cost-effective are lacking. Fourth, many mechanistic and intervention studies are small or short-term; while they show improvement in structural or functional surrogates (IENFD, CCM, sudomotor measures), extrapolation to long-term clinical benefit requires confirmation (Gaede et al., 2003; Ismail-Beigi et al., 2010).

Epidemiologic reports highlight disparities in neuropathy outcomes associated with socioeconomic and racial/ethnic factors; implementation of advanced screening and prevention models must therefore include equity-focused planning—ensuring accessible screening locations, culturally tailored education, and measures to overcome social determinants that impede engagement with prevention programs (Dillon et al., 2024;

Binns-Hall et al., 2018). Workforce training, device cost and maintenance, and integration into existing care pathways are practical barriers requiring local solutions and economic evaluation before widespread rollout.

The analyzed literature indicates clear research priorities: prospective, multicentre trials that (a) use validated paraclinical markers (CCM, IENFD, sudomotor metrics) or POCD algorithms to identify subclinical neuropathy for enrolment, (b) randomize participants to standardized multifactorial prevention pathways versus usual care, and (c) measure both intermediate nerve-specific endpoints and long-term clinical outcomes including ulceration, amputation, quality of life, and cost-effectiveness. Related priorities include establishing normative databases and standardized acquisition/analysis protocols for CCM and POCDs, validating device thresholds across diverse populations, and evaluating scalable one-stop screening models with implementation science methods to determine best practices for different health systems (Singleton et al., 2015; Horton et al., 2017; Kluding et al., 2012).

A strength of this review is that it synthesizes evidence enabling integration of validation, mechanistic and implementation data, ensuring the discussion and recommendations are traceable to the supplied corpus. The principal limitation is that restricting sources to the provided materials may omit other relevant studies; heterogeneity within the reviewed literature constrains formal quantitative synthesis.

The evidence supports early, multimodal detection of subclinical neuropathy and early multifactorial intervention as a coherent strategy to prevent or delay progression of DN. Intensive glycemic control remains essential in T1D; in T2D, integrated cardiometabolic risk management combined with structured lifestyle programs and targeted early enrolment via POCD-based screening offers the most promising prevention approach. To move from plausibility to proof, multicentre, pragmatic trials that test POCD-guided prevention pathways against hard clinical endpoints and rigorously evaluate feasibility, equity, and cost-effectiveness are required.

5. Conclusions

Evidence indicates that diabetic neuropathy often begins early in the dysglycemic continuum, manifesting as subclinical small-fiber and autonomic dysfunction that is frequently missed by conventional bedside screening. Early detection using sensitive paraclinical markers (CCM, IENFD, sudomotor tests, QST) and pragmatic point-of-care devices (handheld sural testers, Sudoscan, Neuropad), especially when applied in multimodal screening algorithms, enables identification of high-risk individuals before irreversible large-fiber loss and foot-risk develop. Intensive glycemic control provides clear preventive benefit in type 1 diabetes, while in type 2 diabetes prevention is most plausibly achieved through early, multifactorial strategies that combine glycemic optimization with aggressive management of dyslipidemia, hypertension, obesity and smoking, and with structured lifestyle interventions. Implementation models that integrate POCD-based neuropathy screening into one-stop microvascular clinics facilitate earlier detection and rapid linkage to multidisciplinary prevention pathways and podiatry care.

Key gaps remain: multicentre, clinical trials are needed that use validated subclinical diagnostics to select participants and test whether POCD-guided, multifactorial prevention reduces hard clinical endpoints (ulceration, amputation, mortality) and is cost-effective and equitable across populations. Meanwhile, pragmatic approach should focus on multimodal screening with locally validated thresholds, standardized acquisition and automated analysis where possible, training of allied health staff, and clear referral algorithms to ensure that earlier detection is rapidly translated into effective preventive care.

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