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Review Article

Emerging Role of HbA1c trend analysis in the Diagnosis of diabetic neuropathy

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Abstract

Background: Glycated haemoglobin (HbA1c) is used to diagnose diabetes and monitor glycaemic control, but diabetic peripheral neuropathy is still usually recognized only after symptoms appear, well after subclinical nerve injury has begun.

Objective: This review examines whether the longitudinal trend in HbA1c, its cumulative exposure, updated mean, and visit-to-visit variability, predicts diabetic neuropathy more informatively than a single HbA1c value, and how such trend analysis might be integrated with established diagnostic tools.

Methods: We synthesized evidence from major randomized glycaemic-control trials and their long-term follow-ups, large population cohorts, and variability meta-analyses, alongside consensus statements on neuropathy diagnosis and screening.

Findings: Cumulative glycaemic exposure and updated mean HbA1c predict confirmed clinical and electrophysiological neuropathy independently of any single reading, an effect that persists for over a decade after treatment groups' HbA1c values converge. HbA1c variability across visits adds further prognostic information beyond the mean, plausibly through fluctuation-driven oxidative stress.

Conclusions: Longitudinal HbA1c trend analysis, drawn from data already collected in routine care, offers a low-cost, scalable signal for prioritizing patients for earlier neuropathy screening with tools such as the Michigan Neuropathy Screening Instrument, nerve conduction studies, or corneal confocal microscopy, without replacing direct neurological assessment.

Keywords: HbA1c; glycaemic variability; diabetic peripheral neuropathy; glycaemic trend; diabetes complications

1. Introduction

Diabetic peripheral neuropathy affects up to half of all people with diabetes and is the largest identifiable risk factor for foot ulceration, which precedes most non-traumatic lower-limb amputations worldwide [1,2]. Unlike retinopathy and nephropathy, readily detected by fundoscopy and urinary albumin screening, DPN is frequently asymptomatic early on and is missed unless clinicians actively examine for it, so many patients already have measurable nerve dysfunction when diabetes is first diagnosed [3,4]. The result is a persistent diagnostic gap between the biological onset of nerve injury and its clinical recognition.

Glycated haemoglobin has been the cornerstone measure of glycaemic control since it was validated as a marker of average glucose exposure over the preceding two to three months, and it was later adopted as a diagnostic criterion for diabetes once assay standardization made cross-laboratory comparison reliable [5,6]. Its use in the neuropathy literature, however, has historically been limited to a single baseline or most-recent value, discarding information contained in the shape of a patient's glycaemic history. The earliest evidence that sustained control, rather than a single reading, altered neuropathy risk came from the Stockholm Diabetes Intervention Study, where intensified insulin treatment slowed deterioration of nerve conduction velocity over five years relative to standard treatment, tracking the separation in mean HbA1c between arms [7]. Two subsequent landmark trials confirmed this picture. The Diabetes Control and Complications Trial (DCCT) showed that intensive glycaemic control substantially reduced clinical neuropathy incidence over a mean of 6.5 years, and its Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up showed the benefit of early intensive control persisted for over a decade after the groups' HbA1c values converged, a "metabolic memory" also reflected in lower cardiovascular event rates in the same cohort [8,9,10,11]. The United Kingdom Prospective

Diabetes Study (UKPDS) extended this to type 2 diabetes, showing a continuous, near-log-linear relationship between mean HbA1c and microvascular complications with no lower threshold [12,13].

These findings reframed HbA1c from a snapshot into a marker whose trajectory, mean, rate of change, and visit-to-visit variability carry prognostic information a single measurement cannot capture. This review addresses whether longitudinal HbA1c trend predicts neuropathy better than a single value, whether variability adds information beyond the mean, and how trend analysis might integrate with established diagnostic tools to bring forward recognition of neuropathy.

2. Methods

We conducted a narrative synthesis of the literature on glycated haemoglobin, glycaemic variability, and diabetic peripheral and autonomic neuropathy, drawing on landmark randomized trials, their long-term observational extensions, large population cohorts, and subsequent meta-analyses. Search terms combined "HbA1c," "glycaemic variability," "glycaemic trend," "diabetic neuropathy," and "diabetic polyneuropathy," supplemented by hand-searching the reference lists of consensus statements from the American Diabetes Association and the Toronto Diabetic Neuropathy Expert Group [14,2,15]. Priority was given to studies reporting longitudinal HbA1c data, whether serial measurements, area-under-the-curve exposure, or visit-to-visit variability, analyzed against a validated neuropathy endpoint such as confirmed clinical neuropathy, nerve conduction abnormality, the Michigan Neuropathy Screening Instrument, or corneal confocal microscopy [16,17,18,19]. As a narrative rather than systematic review, no formal risk-of-bias scoring or pooling was performed.

3. Results

Cumulative glycaemic exposure predicts confirmed neuropathy

The DCCT randomized 1441 patients with type 1 diabetes

to intensive or conventional insulin therapy and found intensive treatment reduced confirmed clinical neuropathy risk by approximately 60%, tracking the separation in mean HbA1c between arms [8]. When DCCT/EDIC investigators later modelled cumulative exposure directly, as the area under the HbA1c-versus-time curve rather than a single updated mean, this integrated measure explained microvascular and neuropathy risk more completely than any single HbA1c value, establishing glycaemic exposure as a cumulative, dose-dependent process rather than a threshold phenomenon [20]. The EDIC follow-up showed this effect persists: patients originally assigned to intensive therapy still had lower confirmed clinical and electrophysiological neuropathy prevalence 13-14 years after HbA1c values converged with the conventional-therapy group, a durable signature a contemporaneous reading years later would miss entirely [9,10].

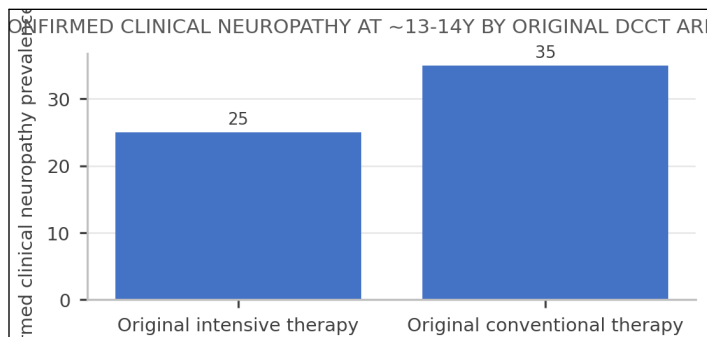


Figure 1: Prevalence of confirmed clinical neuropathy in the DCCT/EDIC cohort roughly 13-14 years after original treatment-group assignment, remaining lower among patients originally randomized to intensive therapy despite subsequent convergence of HbA1c between groups [9,10].

The UKPDS reinforced this at population scale: across more than 4,500 patients followed for a median of ten years, each one-point reduction in updated mean HbA1c was associated with substantially lower microvascular risk, including amputation and neuropathic foot pathology, with no lower threshold [13,12]. Because this dose-response relationship derives from an updated mean across serial visits rather than a single value, it is

itself an early form of trend analysis, establishing the trajectory, not the isolated reading, as the operative exposure variable.

HbA1c variability adds prognostic information beyond the mean

A more recent strand of evidence shows that HbA1c variability across successive visits, quantified as standard deviation or coefficient of variation, predicts microvascular complications independently of the mean. In the Finnish Diabetic Nephropathy (FinnDiane) cohort, Waden and colleagues found higher HbA1c variability predicted incident cardiovascular events, microalbuminuria, and overt nephropathy after adjustment for mean HbA1c, implicating fluctuation as an independent contributor rather than a proxy for poor average control [21]. A subsequent meta-analysis by Gorst and colleagues, pooling data across type 1 and type 2 cohorts, confirmed long-term variability was consistently associated with increased microvascular and macrovascular risk, supporting it as a reproducible signal rather than a cohort-specific artefact [22].

Mechanistic work on shorter-timescale fluctuation offers a plausible pathway linking variability to nerve injury. Monnier and colleagues showed acute glucose fluctuations activate oxidative stress more potently than sustained chronic hyperglycaemia at an equivalent mean, implicating fluctuation itself as a driver of vascular and neural injury [23]. Sartore and colleagues extended this to continuous-monitoring-derived variability and found an association with diabetic retinopathy, a microvascular complication sharing pathogenic mechanisms with neuropathy, lending indirect support to an analogous variability-neuropathy relationship [24]. A full account of glycaemic trend for risk stratification should therefore capture volatility as well as direction and level.

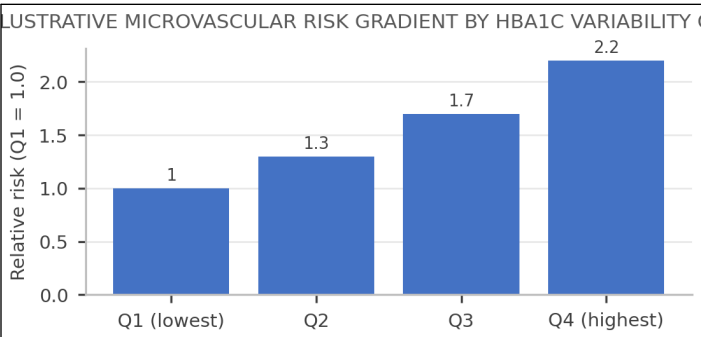


Figure 2: Illustrative gradient of microvascular complication risk across quartiles of visit-to-visit HbA1c variability, consistent with the independent variability effect reported in the FinnDiane cohort and confirmed across cohorts in a subsequent meta-analysis [21,22].

Comparison with established clinical and electrophysiological diagnostic tools

None of the trend-based measures above substitute for direct neurological assessment; the reference standards for DPN remain clinical examination supplemented by electrophysiology. The Michigan Neuropathy Screening Instrument, developed by Feldman and colleagues, combines a questionnaire with a brief foot examination and remains a widely used bedside tool for its practicality in high-volume clinics [16]. Nerve conduction studies remain the most objective measure of large-fibre function and are recommended by the American Academy of Neurology as the reference standard against which simpler tools are validated [17]. For the small-fibre neuropathy that often precedes large-fibre involvement, corneal confocal microscopy, validated by Malik and colleagues as a non-invasive surrogate of nerve fibre damage and repair, offers complementary sensitivity nerve conduction alone can miss [19]. Perkins and colleagues showed that combined simple bedside tests achieve good sensitivity for identifying patients warranting electrophysiological work-up, precisely the triage role trend analysis could extend upstream of the clinic visit [18]. Autonomic neuropathy, sharing the same glycaemic risk factors but requiring a distinct battery of cardiovascular reflex tests, is reviewed by Vinik and colleagues, whose consensus criteria remain the reference framework for any trend-triggered autonomic pathway

[25]. The pathological alterations underlying both forms, segmental demyelination, axonal loss, and endoneurial microvascular injury, were characterized by Dyck and Giannini, underpinning the biological plausibility of a cumulative, dose-dependent glycaemic-nerve-injury relationship [26].

Table 1: Principal clinical and electrophysiological tools for diagnosing diabetic peripheral and autonomic neuropathy, alongside the proposed pre-clinical triage role of HbA1c trend analysis [16,17,19,18,25].

Tool	Fibre type assessed	Setting	Role
Michigan Neuropathy Screening Instrument	Large fibre, mixed	Clinic bedside	Rapid first-line screening [16]
Nerve conduction studies	Large fibre	Electrophysiology lab	Reference standard confirmation [17]
Corneal confocal microscopy	Small fibre	Ophthalmic imaging suite	Early small-fibre detection [19]
Cardiovascular reflex/HRV testing	Autonomic	Clinic or lab	Autonomic neuropathy assessment [25]
HbA1c trend analysis (mean, exposure, variability)	Not fibre-specific	Registry / EHR, no visit required	Pre-clinical risk triage, proposed

HbA1c trend analysis's value is therefore as a pre-clinical triage signal embedded in existing registry data, not a diagnostic substitute. Because HbA1c is measured at nearly every clinic visit, a rising trend or high variability can be flagged automatically, prioritizing patients for MNSI screening, nerve conduction studies, or corneal confocal microscopy before symptoms appear. This mirrors the American Diabetes Association's position statement, which recommends annual foot and neuropathy examination but acknowledges risk-based prioritization is needed where screening resources are constrained [14,27].

Population-scale evidence linking HbA1c trajectory to complication burden

Large population cohorts extend the trend-based

argument beyond trial populations. Selvin and colleagues, studying non-diabetic adults, found HbA1c predicted incident cardiovascular disease and mortality along a continuous gradient even below the diagnostic threshold for diabetes, reinforcing exposure as a graded rather than threshold risk factor [28]. The China Kadoorie Biobank, reported by Bragg and colleagues, similarly linked diabetes and glycaemic control to markedly elevated cause-specific mortality across a large, diverse population, showing trial-derived relationships generalize to real-world settings [29]. Reviews by Callaghan and colleagues, Pop-Busui and colleagues, and Tesfaye and Selvarajah all note the global burden of diabetic neuropathy is rising with diabetes prevalence, making scalable, registry-based tools such as HbA1c trend analysis increasingly relevant where specialist neurology capacity is limited [30,14,31].

Table 2: Key studies linking longitudinal or cumulative HbA1c metrics to neuropathy or broader microvascular and mortality outcomes [8,20,13,21,28,29].			
Study	Glycaemic metric	Population	Key finding
[8]	Randomized mean HbA1c separation	Type 1 diabetes, n=1441	~60% reduction in confirmed clinical neuropathy with intensive therapy
[20]	Area-under-curve HbA1c exposure	DCCT/EDIC re-analysis	Cumulative exposure outperforms single updated-mean HbA1c
[13]	Updated mean HbA1c	Type 2 diabetes, n>4500	Continuous risk gradient, no lower threshold
[21]	Visit-to-visit HbA1c variability	FinnDiane, type 1 diabetes	Variability predicts complications independent of mean
[28]	Single HbA1c	Non-diabetic adults	Continuous gradient of cardiovascular risk below diagnostic threshold
[29]	Diabetes/glycaemic status	China Kadoorie Biobank	Elevated cause-specific mortality across a large population

4. Discussion

The evidence reviewed supports three linked conclusions. First, cumulative glycaemic exposure, captured as area under the HbA1c-time curve or an updated longitudinal mean, is a stronger, more durable predictor of confirmed neuropathy than any single value, demonstrated directly in DCCT/EDIC and consistent with the UKPDS dose-response relationship [20,9,13]. Second, HbA1c variability across visits carries prognostic information independent of the mean, replicated in FinnDiane and a multi-cohort meta-analysis, and plausibly explained by the oxidative-stress-activating effect of fluctuation demonstrated experimentally [21,22,23]. Third, none of this is currently used systematically at the point of care: HbA1c is measured serially in nearly every clinic yet interpreted almost universally as a single most-recent value.

This gap is a genuine opportunity, because the data needed, serial HbA1c results, already exist in most electronic records at essentially no additional cost. A registry-level algorithm calculating rolling mean, cumulative exposure, and variability could flag patients for earlier MNSI, nerve conduction, or corneal confocal screening well before symptoms prompt a referral [16,17,19]. The metabolic memory phenomenon in EDIC is relevant here: because early trend has effects that outlast the exposure itself, such an algorithm should weight historical trajectory, not only recent values [10].

Limitations temper this optimism. Much of the strongest evidence comes from type 1 cohorts (DCCT/EDIC, FinnDiane) with protocolized measurement schedules not replicated in routine type 2 care, where heterogeneous visit intervals may inflate apparent variability through measurement noise rather than true fluctuation [21,22]. The mechanistic link between HbA1c variability and nerve injury specifically is less directly established than for retinopathy and nephropathy, and the Monnier and Sartore findings, while plausible, were not neuropathy-specific endpoints [23,24]. Trend analysis is

also inherently retrospective, limiting usefulness in newly diagnosed or sparsely attending patients, who are often at highest neuropathy risk [3,4]. Future work should prioritize prospective validation against electrophysiological endpoints in real-world type 2 cohorts, comparison with continuous-glucose-monitoring variability, and pragmatic trials of trend-triggered screening to determine whether earlier detection reduces ulceration and amputation [1,2].

5. Conclusion

A converging body of evidence, from the DCCT and its EDIC follow-up through the UKPDS and FinnDiane to recent variability meta-analyses, demonstrates that HbA1c trajectory, expressed as cumulative exposure, updated mean, or variability, predicts diabetic peripheral neuropathy more completely than any single measurement [8,20,13,21,22]. Trend analysis should not replace validated tools such as the MNSI, nerve conduction studies, or corneal confocal microscopy, but it offers a scalable, near-zero-marginal-cost signal, already latent in existing registry data, for identifying which patients need those assessments earlier than symptom-triggered referral allows [16,17,19,18]. As registries and electronic records mature, incorporating longitudinal HbA1c trend analysis into routine risk stratification is a practical step toward closing the gap between the biological onset of diabetic nerve injury and its clinical recognition.

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