

Diabetes & its Complications

From Nerve Conduction to Meaningful Recovery: Palm-Derived Tocotrienols in Diabetic Peripheral Neuropathy, Small-Fiber Injury, Neuroinflammation, and Glycemia-Independent Disease Modification — A Critical Review

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ABSTRACT

Diabetic peripheral neuropathy (DPN) remains among the most common, disabling, and therapeutically unresolved complications of diabetes. Current management can reduce neuropathic pain and improve cardiometabolic risk, but reliable disease-modifying therapy capable of restoring damaged peripheral nerves remains unavailable. Palm-derived tocotrienols represent an intriguing candidate because experimental evidence supports antioxidant, anti-inflammatory, neurotrophic, vascular, and membrane-protective effects, while clinical trials have reported improvements in selected sensory and motor nerve-conduction velocities. These electrophysiological effects, however, have not been accompanied consistently by proportional improvements in glycated hemoglobin, nerve-action-potential amplitudes, pain, or patient-reported outcomes. This critical qualitative literature review synthesizes contemporary evidence published primarily from 2020–2026 to examine this apparent nerve-conduction–clinical-recovery paradox. The analysis distinguishes large-fiber conduction, axonal integrity, small-fiber pathology, Schwann-cell and myelin dysfunction, neuroinflammation, autonomic neuropathy, pain mechanisms, and functional disability. The synthesis proposes a glycemia-independent neuroprotection hypothesis in which tocotrienols may preferentially preserve or improve myelin–Schwann-cell function and neural microenvironment without necessarily regenerating lost axons. It further argues that future trials should abandon single-surrogate efficacy models and combine nerve-conduction studies with corneal confocal microscopy, intraepidermal nerve-fiber density, quantitative sensory testing, autonomic measures, gait, balance, quality of life, falls, and foot-ulcer outcomes. Tocotrienols should presently be viewed as a biologically plausible adjunct requiring phenotype-enriched, longer-duration trials before disease-modifying claims can be justified.

Keywords

Diabetic peripheral neuropathy, Tocotrienols, Palm-derived vitamin E, Nerve conduction velocity, Small-fiber neuropathy, Neuroinflammation, Schwann cells, Oxidative stress, Neuroprotection, Disease modification.

JEL Classification: I10; I12; I14; I18; Q16.

Introduction

Diabetic peripheral neuropathy is not a single neurological disorder but a heterogeneous family of peripheral nerve complications arising within the metabolic, vascular, inflammatory, and

neurodegenerative environment of diabetes mellitus. Distal symmetrical polyneuropathy is the dominant phenotype, but diabetic neuropathy can also involve small sensory fibers, autonomic fibers, focal nerves, radiculoplexus structures, and mixed sensory-motor systems. Its burden extends far beyond tingling or pain. Progressive sensory loss compromises protective sensation, motor impairment alters gait and postural control, autonomic dysfunction increases cardiovascular and systemic risk, and the combination of neuropathy, vascular disease, mechanical stress, and impaired wound healing contributes importantly to diabetic foot ulceration and amputation. Contemporary epidemiological synthesis therefore positions DPN as both a neurological complication and

an important mediator of disability, reduced quality of life, health-care utilization, and premature mortality [1-4].

The therapeutic problem is equally consequential. Modern management of DPN rightly emphasizes optimized glucose control, cardiovascular risk reduction, lifestyle intervention, weight management, foot protection, and treatment of neuropathic pain. Yet most available medications for painful DPN primarily suppress the experience of pain rather than repair the underlying nerve lesion. Antidepressants, gabapentinoids, sodium-channel modulators, topical therapies, and selected interventional approaches may provide clinically useful analgesia, but symptomatic improvement does not establish reversal of demyelination, restoration of axonal number, recovery of small sensory fibers, or normalization of autonomic function. Contemporary expert reviews and guidelines continue to emphasize that dependable disease-modifying treatments for DPN remain lacking [5-11].

This therapeutic gap creates a strong rationale for investigating interventions that act upstream of pain perception by modifying nerve injury itself. Palm-derived tocotrienols are especially interesting in this context. Tocotrienols are unsaturated members of the vitamin E family and occur in particularly relevant concentrations in palm oil and palm-derived tocotrienol-rich fractions. Compared with conventional descriptions of vitamin E as a generic antioxidant, contemporary tocotrienol literature emphasizes a broader range of potential biological effects involving lipid membranes, oxidative signaling, inflammatory pathways, vascular function, transcriptional regulation, cellular survival, and neuroprotection. Reviews of palm-derived tocotrienol-rich fractions have reported plausible activity across experimental neurological and chronic inflammatory models, although translation to human disease remains incomplete and sometimes inconsistent [12-16].

The most provocative evidence comes from trials in diabetic neuropathy itself. An eight-week randomized Phase II trial of a tocotrienol-rich formulation reported significant improvements in conduction velocities of median, sural, and tibial nerves together with increased serum nerve growth factor. A subsequent 12-month randomized trial found improvements particularly in median and sural sensory conduction velocity, as well as a more transient tibial motor effect. Importantly, the electrophysiological improvements were not accompanied by comparable changes in several circulating biomarkers and disappeared after a six-month washout. A 2026 meta-analysis subsequently reported pooled improvements in selected sensory and motor nerve-conduction velocities, whereas action-potential amplitudes and HbA1c remained essentially unchanged [17-19].

This pattern creates a conceptual problem that is more scientifically valuable than a simple question of whether tocotrienols “work”. Nerve-conduction velocity, amplitude, pain intensity, protective sensation, small-fiber density, autonomic function, balance, and quality of life do not measure the same biological phenomenon.

Faster conduction may plausibly reflect improved myelin integrity, Schwann-cell function, membrane physiology, temperature or metabolic conditions, whereas increased amplitude would more directly imply preservation or recruitment of functioning axons. Likewise, pain can be generated by hyperexcitable surviving nociceptors and central sensitization even in the presence of peripheral fiber loss, while painless neuropathy can occur with substantial structural injury. The fundamental research question is therefore whether tocotrienols are producing a clinically meaningful form of neuroprotection that is currently being detected only partially by conventional electrophysiology [9,20,21].

This review develops the proposition that tocotrienols should be evaluated through a **glycemia-independent neuroprotection hypothesis**. Under this hypothesis, tocotrienols may influence peripheral nerve biology through antioxidant, anti-inflammatory, Schwann-cell, neurovascular, mitochondrial, or neurotrophic pathways even when glycemic control remains unchanged. However, a change in nerve-conduction velocity alone cannot be assumed to represent axonal regeneration or disease modification. Disease modification should ultimately require convergent evidence across structural, electrophysiological, sensory, autonomic, functional, and patient-centered domains.

Accordingly, this critical qualitative literature review has four principal objectives. First, it evaluates the contemporary pathobiology of DPN that is relevant to tocotrienol action. Second, it critically examines the clinical evidence for palm-derived tocotrienols and the discordance among nerve-conduction, amplitude, glycemic, biomarker, and symptomatic outcomes. Third, it considers whether current findings are more consistent with preservation of myelin and Schwann-cell function than with true axonal regeneration. Fourth, it develops a phenotype-sensitive outcome framework for future disease-modifying trials, incorporating small-fiber imaging and biopsy, autonomic assessment, gait, balance, quality of life, falls, and diabetic foot outcomes.

Literature Review

DPN beyond the Traditional Hyperglycemia Model

Chronic hyperglycemia remains fundamental to diabetic neural injury, particularly through oxidative stress, advanced glycation processes, altered cellular signaling, mitochondrial overload, and microvascular dysfunction. However, contemporary models of DPN increasingly reject the idea that glucose exposure alone explains the occurrence, severity, and progression of neuropathy. The particularly limited ability of intensive glycemic control to prevent or reverse neuropathy in many patients with type 2 diabetes has strengthened interest in obesity, insulin resistance, dyslipidemia, inflammation, mitochondrial dysfunction, endothelial injury, and altered axon–glia metabolism as parallel or interacting pathogenic mechanisms [3,22-24].

Long peripheral axons are metabolically demanding structures whose distal segments are especially vulnerable to impaired

substrate utilization and bioenergetic failure. Hyperglycemia and dyslipidemia can generate excessive reactive oxygen species, damage mitochondria, impair ATP production, alter lipid handling, and compromise axonal transport. These effects occur in neurons as well as in supporting Schwann cells. The resulting injury may propagate through a cycle in which metabolic overload promotes mitochondrial dysfunction, mitochondrial dysfunction amplifies oxidative stress, and damaged cellular organelles activate inflammatory signaling. This framework explains why neuropathy in type 2 diabetes may persist or progress despite improvements in glucose measurements and why cardiometabolic factors beyond HbA1c deserve consideration when assessing therapeutic response [22-25].

Inflammation adds another layer of complexity. Experimental and translational studies implicate cytokine signaling, nuclear factor-kappa B, Toll-like receptors, macrophage activation, inflammasome pathways, and interactions between oxidative stress and innate immune signaling. NLRP3 activation is particularly relevant conceptually because mitochondrial damage can provide signals that activate inflammasome-associated inflammatory cascades. Although the relative clinical importance of each pathway remains uncertain, the broader evidence supports a model in which chronic low-grade inflammation is not merely an epiphenomenon but can reinforce neuronal, Schwann-cell, and microvascular injury [26-28].

Schwann cells are central to this discussion because myelinated peripheral nerve conduction depends on healthy axon-Schwann-cell units. Hyperglycemic stress can induce oxidative injury, inflammatory signaling, endoplasmic-reticulum stress, altered autophagy, apoptosis, and other forms of cell death in Schwann cells. Experimental research also supports necroptotic pathways in diabetic neuropathy. These observations are highly relevant when interpreting a treatment that improves conduction velocity without clearly increasing action-potential amplitude: such a treatment could theoretically improve myelin maintenance or Schwann-cell physiology while leaving the number of viable axons largely unchanged [29,30].

Microvascular disease is similarly intertwined with neuronal degeneration. Endoneurial capillaries must maintain oxygen and nutrient delivery to long peripheral nerves, and endothelial dysfunction, vasoconstriction, oxidative stress, and impaired nitric-oxide biology can contribute to chronic neural ischemia. The vascular and neural compartments should therefore not be separated conceptually. An intervention that improves endothelial redox status or membrane function might enhance nerve physiology even if it does not directly replace lost axons. This possibility is one reason why electrophysiological improvement may occur earlier than structural regeneration.

DPN Phenotypes and the Problem of Endpoint Equivalence

The term DPN often hides important biological heterogeneity. Distal symmetrical polyneuropathy usually progresses length-

dependently and can involve large myelinated fibers, small thinly myelinated fibers, unmyelinated fibers, and motor systems to different degrees. Large-fiber involvement affects vibration, proprioception, reflexes, balance, and conventional nerve-conduction measures. Small-fiber involvement affects pain, temperature detection, autonomic functions, and nociceptive signaling. In early disease, a patient may therefore have clinically meaningful small-fiber pathology while conventional nerve-conduction studies remain relatively preserved [2,20,31].

Painful and painless DPN provide another example of phenotype divergence. Pain is not simply proportional to nerve loss. Some patients with marked fiber loss experience little spontaneous pain, whereas others with painful DPN can demonstrate abnormal peripheral nociceptor excitability, altered sensory profiles, spinal disinhibition, or central nervous-system adaptations. Neuroimaging and spectroscopy studies further indicate that painful DPN is associated with changes in central sensory processing and cerebral energy metabolism. Consequently, a treatment could conceivably improve peripheral conduction while failing to produce an equivalent reduction in pain because part of the pain phenotype has become centrally maintained [20,21].

This distinction is essential for clinical trial design. Pain-relief trials and nerve-restoration trials answer different questions. The OPTION-DM trial, for example, provided valuable information about combinations of amitriptyline, pregabalin, and duloxetine for neuropathic pain, but analgesic efficacy cannot establish reversal of nerve degeneration. Likewise, spinal-cord stimulation can produce substantial and durable analgesia and improvements in quality of life, yet its mechanism and clinical purpose differ fundamentally from a pharmacological intervention intended to preserve Schwann cells, myelin, or axons [32-34].

The distinction between symptomatic treatment and disease modification is therefore not semantic. A credible disease-modifying intervention should ideally alter the trajectory of nerve pathology rather than merely suppress pain perception. This would require evidence that treatment affects one or more underlying disease processes and that those effects lead to sustained structural, physiological, or clinically meaningful improvements. The recent international consensus on diabetic-neuropathy drug development emphasizes precisely this need for better phenotyping and outcome measures capable of detecting clinically meaningful treatment responses [9].

Small Fibers as an Undermeasured Therapeutic Target

Conventional nerve-conduction studies are invaluable for assessing large myelinated sensory and motor fibers, but they do not directly quantify the integrity of the unmyelinated C fibers and thinly myelinated A δ fibers that contribute importantly to pain, temperature sensation, autonomic function, and early neuropathy. This creates a major blind spot in tocotrienol trials that rely primarily on standard electrophysiology.

Skin biopsy with measurement of intraepidermal nerve-fiber density provides a direct structural measure of small-fiber integrity. Corneal confocal microscopy offers a non-invasive alternative that quantifies corneal nerve-fiber parameters and has been investigated extensively as a surrogate marker of peripheral small-fiber loss. A multinational longitudinal cohort demonstrated that reduced corneal nerve-fiber length predicted subsequent development of DPN, supporting the idea that corneal nerves can provide early structural information before advanced clinical neuropathy appears [35].

Nevertheless, small-fiber tests should not be assumed to be interchangeable. Studies directly comparing CCM, skin biopsy, thermal thresholds, and clinical neurophysiology demonstrate incomplete correlations between modalities. In one wide-field CCM study, corneal nerve density did not correlate closely with IENFD or conventional clinical measures. A separate large prospective cohort comparing CCM, IENFD, and cold-detection thresholds found different patterns of sensitivity and specificity, while another study of diabetic polyneuropathy also demonstrated that small-fiber measures do not necessarily track the same underlying component of neuropathy [36-40].

These findings have direct implications for tocotrienol research. If tocotrienols influence oxidative injury, microvascular perfusion, or Schwann-cell biology, the earliest detectable effect may differ by neural compartment. Large-fiber conduction could improve while intraepidermal fiber density remains unchanged; conversely, small-fiber regeneration could occur without a major shift in conventional motor NCV. A future disease-modifying trial should therefore employ a multidomain rather than single-test strategy.

Autonomic Neuropathy as a Neglected Domain

Diabetic autonomic neuropathy is another major evidence gap. Cardiovascular autonomic neuropathy is associated with impaired heart-rate variability, abnormal cardiovascular reflexes, exercise intolerance, arrhythmia risk, and increased mortality. Risk reflects glycemia but also diabetes duration, obesity, blood pressure, insulin resistance, and dyslipidemia, particularly in type 2 diabetes. Recent reviews emphasize the value of earlier autonomic detection because potentially reversible stages may exist before severe autonomic failure becomes established [41,42].

Yet tocotrienol clinical studies have focused primarily on somatic nerve conduction. Whether palm-derived tocotrienols influence cardiac autonomic reflexes, heart-rate variability, sudomotor function, gastrointestinal autonomic pathways, or other autonomic endpoints remains insufficiently investigated. This omission is important because unmyelinated and thinly myelinated fibers contribute substantially to autonomic control, and a putative broad neuroprotective intervention should not be evaluated solely within large somatic nerves.

Tocotrienol Biology Relevant to DPN

Tocotrienols share the chromanol ring structure of vitamin E

compounds but contain an unsaturated isoprenoid side chain that distinguishes them from tocopherols. Palm oil is an important natural source of tocotrienols, and palm-derived tocotrienol-rich fractions commonly contain combinations of tocotrienol isoforms together with smaller proportions of tocopherols. Experimental literature has suggested that tocotrienols can integrate efficiently into lipid environments and influence oxidative, inflammatory, signaling, and survival pathways relevant to neuronal injury [12,14,16].

Antioxidant activity represents the most familiar mechanism. Peripheral nerves contain abundant lipid-rich membranes and myelin structures that are vulnerable to oxidative damage. Reactive oxygen species can oxidize membrane lipids, mitochondrial components, proteins, and nucleic acids. Tocotrienol-mediated interruption of lipid peroxidation is therefore biologically plausible as a means of stabilizing neuronal and Schwann-cell membranes. However, human biomarker evidence should be interpreted cautiously. A meta-analysis of randomized trials found inconsistent effects of tocotrienol supplementation on several circulating inflammatory and oxidative markers; reductions in specific markers were not uniformly reproduced across preparations and populations [43].

Anti-inflammatory effects provide another mechanistic pathway. Tocotrienols have been reported to modulate NF- κ B-related signaling and downstream inflammatory mediators in experimental systems. Because NF- κ B intersects with cytokine production, cell survival, oxidative stress, and immune activation, modulation of this pathway could theoretically reduce inflammatory amplification of nerve injury. Yet evidence from molecular models cannot be equated automatically with clinical suppression of intraneural inflammation. The stronger conclusion is that tocotrienol pharmacology overlaps plausibly with pathways implicated in DPN and therefore warrants mechanistically designed trials rather than assumption of therapeutic efficacy [13,26,27].

Neurotrophic signaling is also relevant. In the eight-week Tocovid trial, increased serum nerve growth factor accompanied improved nerve-conduction velocities. NGF has important biological roles in sensory-neuron survival and maintenance, but circulating NGF is not a direct measure of peripheral axonal regeneration. The finding is therefore best interpreted as a potentially supportive mechanistic signal rather than proof that new axons were generated [17].

Overall, the tocotrienol literature supports a multi-target neuroprotective hypothesis involving oxidative stress, inflammatory signaling, membrane protection, vascular biology, neurotrophic support, and potentially myelin-related processes. Nevertheless, the translation from biochemical plausibility to clinically meaningful neural recovery remains the critical unresolved step [12,14,15].

Method

This study employed a **critical qualitative literature review** rather

than a systematic literature review or meta-analysis. The purpose was interpretive synthesis: to integrate contemporary clinical, mechanistic, diagnostic, and translational evidence in order to explain contradictory or apparently discordant outcomes in the tocotrienol-DPN literature. The review was therefore structured around concepts and explanatory themes rather than a PRISMA-style exhaustive enumeration of all records.

Literature published primarily between January 2020 and September 2026 was prioritized. Searches were conceptually organized around the terms *diabetic peripheral neuropathy*, *distal symmetrical polyneuropathy*, *painful diabetic neuropathy*, *small-fiber neuropathy*, *autonomic neuropathy*, *tocotrienol*, *tocotrienol-rich fraction*, *palm-derived vitamin E*, *nerve conduction velocity*, *nerve action potential*, *Schwann cell*, *myelin*, *neuroinflammation*, *NF- κ B*, *oxidative stress*, *nerve growth factor*, *corneal confocal microscopy*, *intraepidermal nerve fiber density*, *gait*, *balance*, *falls*, and *diabetic foot ulcer*. Priority was given to peer-reviewed articles indexed in major biomedical databases and to high-quality randomized trials, cohort studies, consensus statements, clinical guidelines, systematic syntheses used as background evidence, and mechanistically important reviews.

The qualitative synthesis proceeded through iterative thematic coding. Evidence was grouped into six domains: (1) DPN pathogenesis; (2) clinical phenotype; (3) tocotrienol pharmacobiology; (4) neurophysiological outcomes; (5) structural and small-fiber outcomes; and (6) patient-centered and functional outcomes. Contradictory findings were not averaged conceptually but treated as analytically informative. Particular attention was paid to instances in which one endpoint improved while another did not, because such discordance can reveal which neural compartment or physiological process is most likely being modified.

The review also distinguished **mechanistic plausibility**, **biomarker response**, **surrogate physiological response**, and **clinically meaningful disease modification**. Experimental antioxidant or anti-inflammatory effects were not treated as equivalent to human nerve regeneration. Likewise, improvements in NCV were interpreted separately from changes in sensory nerve-action-potential or compound motor-action-potential amplitude, pain, structural small-fiber measures, autonomic function, gait, quality of life, falls, or ulceration.

No formal risk-of-bias score or pooled quantitative effect estimate was generated because those procedures would transform the article toward an SLR or meta-analysis design. Instead, methodological strength was considered qualitatively according to randomization, blinding, sample size, follow-up duration, phenotype definition, endpoint specificity, and correspondence between the claimed therapeutic mechanism and the outcome measured. Contemporary expert guidance on DPN trial design, diagnosis, and treatment informed this interpretive framework [9,31].

Results: Thematic Synthesis

DPN Remains Predominantly Symptom-Managed Rather Than Disease-Modified

The contemporary treatment landscape demonstrates the distinction between pain control and nerve restoration particularly clearly. Pharmacological guidelines support several classes of medications for painful DPN, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids, and sodium-channel blockers. These therapies can reduce pain, and combination strategies can benefit patients who respond incompletely to monotherapy. However, these recommendations are primarily directed toward symptom control rather than regeneration of damaged nerves [6,44,45].

Clinical trials illustrate both the value and limitations of this symptomatic paradigm. OPTION-DM demonstrated that commonly recommended pathways involving amitriptyline, pregabalin, and duloxetine can provide meaningful pain reduction, while neuromodulation studies have demonstrated substantial analgesia in treatment-refractory disease. Psychological interventions, including cognitive-behavioral or mindfulness-based strategies, can also improve pain-related outcomes and quality of life. These approaches are clinically important, but a reduction in pain does not necessarily indicate that peripheral nerve degeneration has slowed or reversed [32,33,46,47].

The unmet need is therefore a therapy that modifies biological injury and ultimately changes the natural history of neuropathy. That goal is especially urgent because neuropathy affects walking, balance, psychosocial well-being, protective sensation, and risk of foot complications. Quality-of-life studies show substantial disease-specific burden, while gait and balance literature demonstrates that DPN affects sensory feedback and motor control in ways that increase fall risk [48-51].

These observations change the standard by which tocotrienols should be evaluated. If they are proposed as disease-modifying agents, it is insufficient to ask whether they reduce pain scores or improve one electrophysiological parameter. The relevant question is whether they alter the progression of nerve injury and whether that alteration produces durable benefits in sensation, movement, independence, and complication prevention.

Tocotrienol Trials Reveal a Reproducible but Incomplete Neurophysiological Signal

The 2020 Phase II Tocovid trial represents a major transition in the clinical tocotrienol literature because it focused on objective nerve-conduction outcomes. Participants received 200 mg of Tocovid twice daily for eight weeks. Compared with placebo, the intervention improved conduction velocity in median, sural, and tibial nerves and was associated with an increase in serum NGF. These findings suggested that the intervention could affect peripheral nerve physiology over a relatively short period [17].

The subsequent 12-month randomized study strengthened the

electrophysiological signal. Tocovid at 400 mg/day improved median and sural sensory conduction velocity after 12 months, while improvement in tibial motor conduction was most evident earlier in treatment. The reported between-group effects were modest in absolute magnitude but internally consistent enough to suggest more than random fluctuation. Importantly, however, several circulating biomarkers did not show parallel improvement, and after six months without supplementation, the nerve-conduction advantages were no longer evident [18].

The washout finding is scientifically important. If tocotrienols had produced robust and permanent structural regeneration of previously lost axons, one might expect at least some residual electrophysiological benefit after supplementation stopped. The disappearance of the group difference does not disprove structural benefit, because regenerated or preserved tissue could still be vulnerable to the continuing diabetic environment. Nevertheless, the washout result is also compatible with a reversible improvement in membrane properties, metabolic support, endothelial function, or myelin physiology that requires continued treatment.

The 2026 meta-analysis provides the clearest quantitative synthesis. Across eligible randomized trials, vitamin E/tocotrienol-rich interventions improved selected sural sensory, median sensory, and tibial motor conduction velocities. In contrast, nerve-action-potential amplitudes and HbA1c were not significantly altered. The authors interpreted this profile as more compatible with preservation or remyelination than with unequivocal axonal regeneration [19].

This interpretation should be treated as a mechanistic hypothesis rather than a proven histological conclusion. Conduction velocity

is affected strongly by myelination and saltatory conduction, whereas action-potential amplitude depends more on the number and synchrony of functioning axons. A preferential increase in velocity without amplitude recovery therefore fits a model in which surviving fibers conduct more efficiently without a major expansion in functioning axonal mass.

The NCV–Amplitude Dissociation May Be the Key to Mechanism

The distinction between conduction velocity and amplitude deserves central importance because it determines what can legitimately be inferred from current tocotrienol evidence. In demyelinating conditions, slowing of conduction can be prominent even when axons remain anatomically present. Conversely, advanced axonal degeneration may cause reduced amplitudes that cannot be corrected simply by improving myelin around surviving fibers. DPN commonly contains both axonal and myelin-related abnormalities, and their relative contribution can differ by stage and phenotype.

Tocotrienol-induced NCV improvement with little corresponding amplitude change therefore suggests several possibilities. The first is preservation or partial restoration of Schwann-cell or myelin function. The second is improved axonal membrane excitability or ion-channel function in surviving fibers. The third is improved neural microvascular perfusion, resulting in more efficient conduction. The fourth is reduction in oxidative or inflammatory interference with the function of viable nerves. These mechanisms are not mutually exclusive.

Schwann-cell evidence strengthens the first interpretation. Diabetes exposes Schwann cells to oxidative, inflammatory,

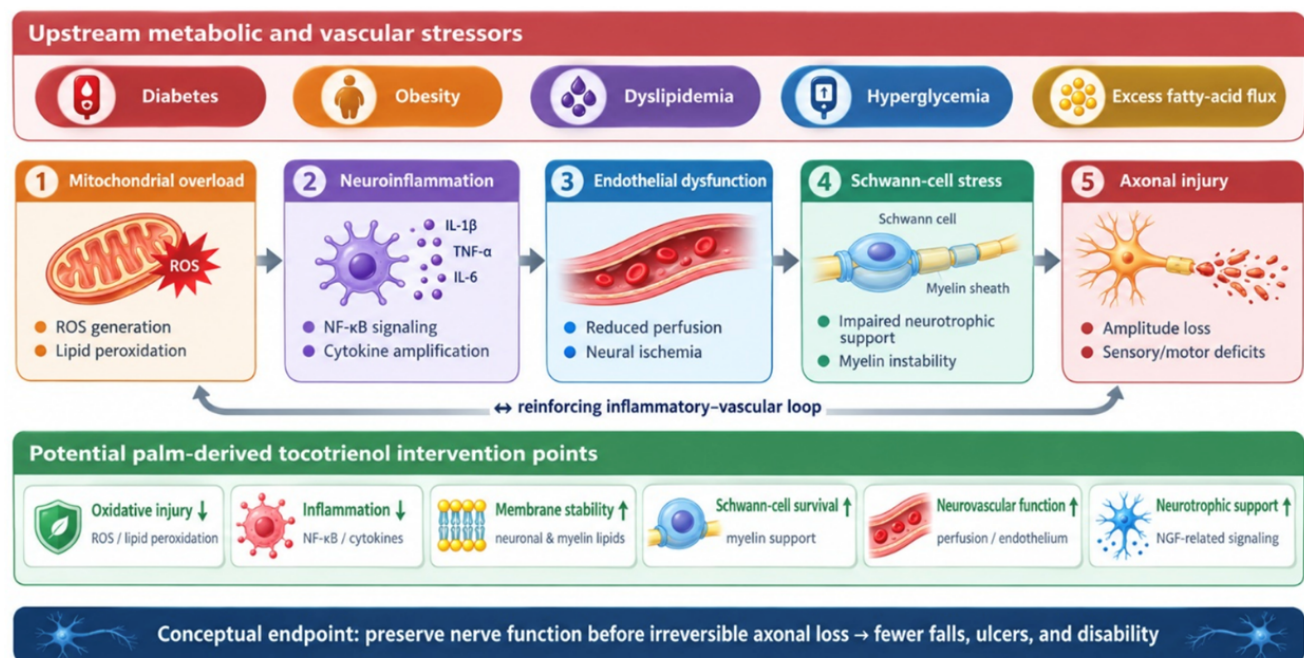


Figure 1: Proposed Mechanistic Pathway from Diabetic Metabolic Stress to Tocotrienol-Sensitive Neural Dysfunction.

and endoplasmic-reticulum stress and can activate apoptotic or necroptotic pathways. Since Schwann cells provide metabolic support and myelination for peripheral axons, an intervention that reduces cellular stress could improve conduction without recreating previously lost axons [29,30].

This is also consistent with broader contemporary pathophysiological thinking. DPN is increasingly conceptualized as metabolic and bioenergetic failure of the peripheral nerve unit rather than isolated neuronal death. Dyslipidemia, mitochondrial dysfunction, inflammation, and disturbed axon–glia interactions can impair neural function before irreversible structural loss occurs. Thus, a therapeutic window may exist during which conduction abnormalities remain partly reversible [3,22].

Figure 1 illustrates that DPN should be regarded as a convergent metabolic–vascular–inflammatory neuropathy rather than a direct linear consequence of hyperglycemia alone. Tocotrienols could theoretically act at several points upstream of irreversible axonal loss, which provides a mechanistic explanation for electrophysiological improvement even when HbA1c remains unchanged.

Figure 1 shows that the most important distinction in the figure is between potentially reversible dysfunction and irreversible structural loss. Oxidative stress, inflammation, endothelial dysfunction, and Schwann-cell impairment may slow conduction before extensive axonal disappearance has occurred. If tocotrienols preferentially improve this earlier compartment, increased NCV without restored action-potential amplitude becomes biologically plausible. The model therefore predicts stronger responsiveness in early or intermediate neuropathy than in advanced disease characterized by severe axonal depletion.

Small-Fiber Injury Is the Largest Structural Blind Spot in Tocotrienol Trials

The existing clinical tocotrienol literature cannot determine whether treatment influences small-fiber degeneration because the principal endpoints were conventional nerve-conduction parameters. This is a major limitation if the objective is disease modification. Small-fiber damage may occur early, contributes importantly to neuropathic pain and thermal sensory loss, and may evolve differently from large-fiber disease.

Corneal confocal microscopy is particularly attractive for repeated clinical trials because it is non-invasive and can quantify corneal nerve-fiber density, length, and branching. Longitudinal evidence indicates that corneal nerve measures can identify individuals at increased risk of developing clinically defined DPN. This makes CCM potentially useful both for enrichment of early-disease cohorts and for monitoring change during intervention [35,39].

Skin biopsy offers a complementary advantage: direct quantification of intraepidermal nerve fibers in the tissue affected by length-dependent neuropathy. It is invasive compared with CCM but provides a structural endpoint closely related to peripheral small-fiber pathology. The key lesson from comparative studies is that CCM and IENFD are related conceptually but not interchangeable empirically. A treatment trial that includes both modalities could determine whether structural improvement occurs consistently across different small-fiber compartments [36-38].

Figure 2 emphasizes why a single electrophysiological test cannot provide a comprehensive measure of neural recovery. Conventional NCS primarily interrogates large fibers, whereas clinically important small-fiber and central pain processes require different methods.

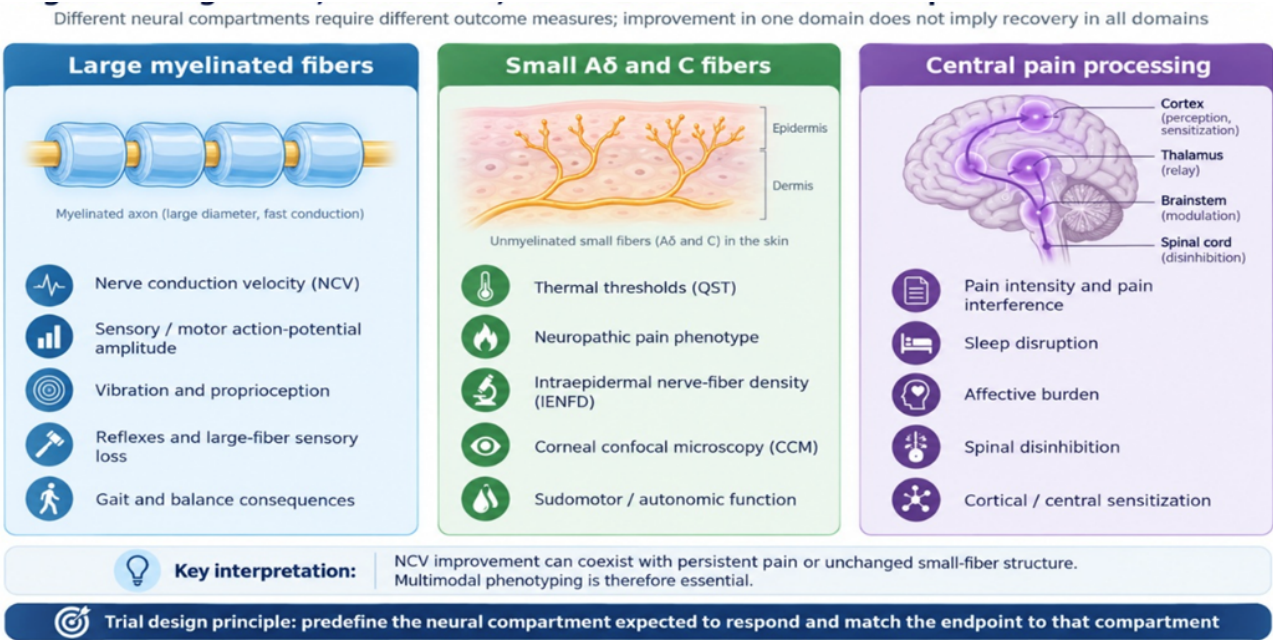


Figure 2: Large-Fiber, Small-Fiber, and Central Pain Outcome Map for Tocotrienol Trials.

Figure 2 explains that a tocotrienol trial could produce divergent outcomes across the three compartments shown. Improvement in large-fiber conduction might occur without a reduction in neuropathic pain if small-fiber or central sensitization persists. Conversely, structural small-fiber regeneration could occur without large changes in motor NCV. An adequately designed disease-modification trial should therefore predefine the neural compartment it expects to modify and select endpoints accordingly.

Pain and Neurophysiological Recovery Are Partly Independent

Painful DPN is frequently used as the clinically visible face of diabetic neuropathy, yet pain intensity is an imperfect proxy for nerve damage. Patients with painful and painless DPN can differ in small-fiber structure, sensory gain and loss, ion-channel behavior, central nervous-system processing, and psychological context. The lack of proportional pain improvement after an intervention does not therefore necessarily mean that peripheral nerve biology has remained unchanged.

This concept is supported by evidence from central nervous-system studies. Increased energy utilization in the somatosensory cortex has been demonstrated in painful compared with painless DPN, and cortical bioenergetic measurements correlated with pain severity. Such findings indicate that once chronic neuropathic pain is established, the clinical phenotype involves more than peripheral conduction alone [21].

Symptomatic trials further demonstrate that substantial pain reduction can occur without necessarily restoring peripheral nerve structure. Pharmacotherapy, psychological interventions, and neuromodulation can all improve the lived experience of pain

through different pathways [32,33,47,52].

The reverse scenario is equally plausible: peripheral conduction may improve while pain remains relatively unchanged. Tocotrienol research should therefore avoid using analgesia as the sole validation of neuroprotection. Instead, pain should be treated as one patient-centered domain within a wider disease-modification framework.

Glycemic Neutrality May Support, Rather Than Refute, a Neuroprotective Mechanism

The absence of a substantial HbA1c effect in tocotrienol neuropathy studies might initially appear disappointing, particularly if DPN is conceptualized principally as a consequence of hyperglycemia. Under a broader metabolic-neurovascular model, however, the dissociation between glycemic and electrophysiological outcomes becomes mechanistically informative.

If NCV improves while HbA1c remains stable, then any true treatment effect is unlikely to be explained primarily by improved chronic glucose exposure. This supports the possibility of direct or indirect neural actions involving oxidative stress, Schwann cells, membrane biology, microvascular function, or inflammatory signaling. Such an interpretation is consistent with current understanding that DPN progression in type 2 diabetes is influenced by several nonglycemic pathways [22,24].

Nevertheless, the glycemia-independent hypothesis must not be misinterpreted as an argument that glucose control is unimportant. Glycemic optimization remains fundamental to diabetes management, particularly in type 1 diabetes, and cardiometabolic

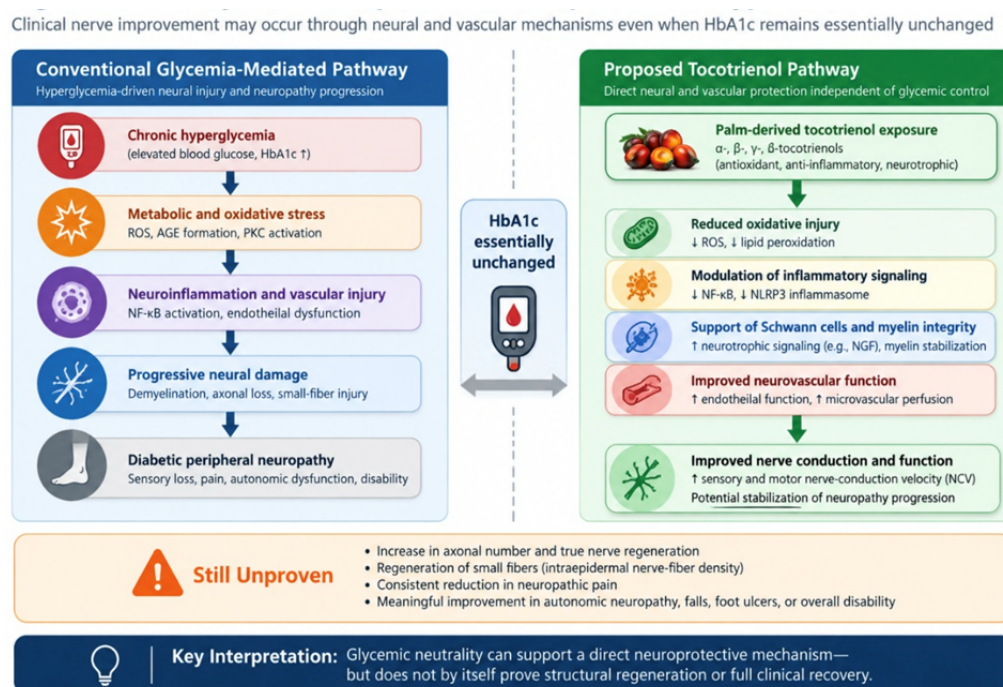


Figure 3: The Glycemia-Independent Neuroprotection Hypothesis.

risk reduction remains central in type 2 diabetes. Tocotrienols, if eventually demonstrated to be useful, would therefore be adjunctive rather than substitutive therapy [31,53].

Figure 3 summarizes the central proposition of this review: an intervention can plausibly modify neural physiology without materially altering HbA1c. The clinical tocotrienol data are therefore compatible with glycemia-independent neuroprotection, but the current evidence is insufficient to equate such neuroprotection with structural regeneration.

Figure 3 explains that the lower portion of the figure is deliberately separated from the mechanistically plausible pathway. Existing trials demonstrate an electrophysiological signal, not a complete chain from molecular action to patient-level benefit. Future studies must establish whether the intermediate mechanisms shown translate into structural and functional recovery.

The Most Plausible Responder May Have Early, Functionally Reversible Neuropathy

A major reason for failed DPN trials may be inclusion of patients at disease stages where structural damage is no longer reversible. Once substantial axonal loss has occurred, an intervention that reduces oxidative stress or improves Schwann-cell metabolism may preserve remaining function but cannot necessarily reconstruct the original neural architecture.

The tocotrienol NCV–amplitude pattern suggests that patients with preserved axonal reserve but impaired conduction could be particularly informative. Such individuals may have early or moderate DPN characterized by slowed conduction, metabolic stress, and potentially reversible myelin or Schwann-cell dysfunction before major reductions in amplitude become established.

This produces a testable **responder phenotype hypothesis**: the greatest tocotrienol effect may occur in patients with early DPN, measurable conduction slowing, relatively preserved sensory or motor amplitudes, substantial cardiometabolic risk, and evidence of oxidative/inflammatory or small-fiber abnormalities. Patients with severe longstanding neuropathy and marked axonal depletion may exhibit smaller electrophysiological gains.

Disease-stage stratification should therefore become a core design feature rather than a post hoc subgroup analysis. Baseline NCS, symptom phenotype, CCM or IENFD, thermal testing, cardiometabolic profiles, and disease duration could be combined to define biologically meaningful enrollment strata. This approach aligns with contemporary calls for precision phenotyping in diabetic-neuropathy research [9,20].

Autonomic Neuropathy Is an Untested Opportunity

A disease-modifying intervention should not be assumed to act only on the peripheral nerves most convenient to test electrophysiologically. Cardiovascular autonomic neuropathy

and sudomotor dysfunction are clinically important components of diabetic neural injury, and autonomic fibers share several metabolic and oxidative vulnerabilities with somatic nerves.

Future tocotrienol studies could therefore include standardized heart-rate variability, cardiovascular reflex tests, orthostatic responses, and sudomotor measurements. Improvements in these measures would greatly strengthen evidence that tocotrienol neuroprotection is not confined to a narrow large-fiber electrophysiological phenomenon [41,42].

Meaningful Recovery Requires Functional and Hard Clinical Outcomes

Ultimately, nerve protection matters because neuropathy changes what patients can feel and do. Loss of proprioception and plantar sensory feedback can impair gait, reduce balance, increase fear of falling, and contribute to activity restriction. Physical rehabilitation studies demonstrate that balance can be improved in some DPN populations, but fall risk remains an important clinical problem [49,50].

Diabetic foot disease provides an even harder clinical endpoint. Neuropathy reduces protective sensation, allowing repetitive pressure or trauma to go unnoticed, while motor, vascular, and biomechanical abnormalities further increase ulcer risk. Diabetic foot ulcers are strongly associated with infection, hospitalization, amputation, and mortality. A treatment that truly modifies the natural history of neuropathy should eventually be evaluated for its ability to reduce these downstream complications, even if such trials require longer follow-up [54].

Quality of life should also be integrated explicitly. Pain, sleep disruption, mobility loss, fear of falling, concern about amputation, and depression can amplify disability independently of a laboratory measure of conduction. Patient-reported outcomes therefore remain essential even when the primary hypothesis concerns biological neuroprotection [48,51].

Figure 4 proposes a hierarchy for judging disease modification. Current tocotrienol evidence is strongest at Level 3, with mechanistic plausibility at Levels 1–2, but evidence becomes progressively thinner at Levels 4–6.

Figure 4 explains that a future trial program should seek convergence across adjacent levels rather than relying on a single surrogate. For example, improved NCV accompanied by better CCM or IENFD, improved thermal detection, better balance, and fewer foot complications would provide substantially stronger evidence of disease modification than NCV improvement alone.

Discussion and Analysis

Resolving the Nerve-Conduction Paradox

The central paradox identified in this review is not that tocotrienol studies are contradictory, but that their endpoints are measuring different layers of neuropathy. A treatment can plausibly improve

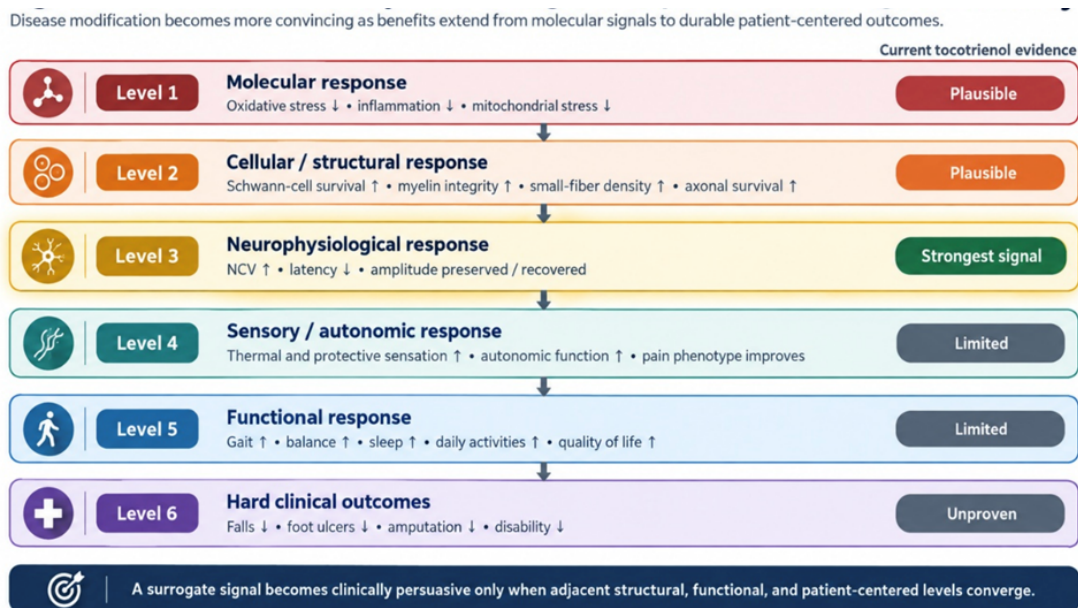


Figure 4: A Six-Level Hierarchy from Biological Response to Meaningful Recovery.

conduction without restoring axonal number; it can improve peripheral nerve physiology without abolishing centrally maintained pain; and it can influence oxidative stress without changing HbA1c.

The current evidence therefore supports a more nuanced interpretation than either enthusiasm or dismissal. The randomized clinical evidence is sufficiently consistent to suggest that tocotrienol-rich supplementation can affect selected nerve-conduction parameters. This signal has been observed over different durations and reinforced quantitatively in the 2026 meta-analysis. It should not be ignored as clinically meaningless simply because HbA1c does not change [17-19].

At the same time, the evidence is not sufficient to use the language of “nerve regeneration” without qualification. Regeneration would be supported more convincingly by increased action-potential amplitude, structural small-fiber regrowth, reproducible neuroimaging or histological measures, recovery after washout, or functional improvement attributable to restored neural integrity. These outcomes have not yet been demonstrated consistently.

A more defensible interpretation is therefore **functional neuroprotection with a possible myelin/Schwann-cell component**. This model fits both the conduction-velocity improvement and the weak amplitude signal. It also fits the biological literature demonstrating that diabetic Schwann cells are vulnerable to oxidative and inflammatory injury and that preservation of their function could theoretically improve saltatory conduction.

Tocotrienols as Multimodal Rather Than Merely Antioxidant Agents

Describing tocotrienols exclusively as antioxidants is too narrow.

Oxidative activity is important, particularly because lipid-rich neural membranes and myelin are highly susceptible to peroxidation, but tocotrienol biology intersects with inflammatory signaling, membrane dynamics, vascular function, and neurotrophic pathways.

Nevertheless, the strength of evidence differs across mechanisms. Experimental studies provide convincing biological plausibility for NF-κB modulation and related inflammatory effects, but clinical biomarker meta-analysis demonstrates that tocotrienols do not uniformly reduce circulating inflammatory or oxidative markers. This discrepancy is a useful warning against assuming that a pathway demonstrated in cells necessarily dominates treatment effects in humans [13,43].

The more appropriate translational model is therefore pleiotropic. A small change across several pathological mechanisms might improve neural physiology even when no single circulating biomarker changes dramatically. Peripheral nerves exist within a tissue environment involving neurons, Schwann cells, microvessels, immune cells, extracellular matrix, and metabolic substrates. A multicomponent intervention could plausibly improve the aggregate function of this system while producing only subtle systemic biomarker shifts.

Glycemia-Independent Neuroprotection as a Testable Hypothesis

The glycemia-independent neuroprotection concept represents the principal theoretical contribution of this review. It should be understood as a hypothesis generated from the pattern of existing evidence rather than as an established clinical fact.

The hypothesis predicts that tocotrienol exposure should improve selected neural outcomes after adjustment for or in the absence

of meaningful changes in HbA1c. It further predicts that the magnitude of benefit should correlate more strongly with markers of oxidative, inflammatory, myelin, microvascular, or neurotrophic status than with changes in glycemia. Finally, if the effect is truly neural rather than statistical, it should be observable across more than one domain.

Future trials can test this directly. Participants could be maintained under stable diabetes management while randomized to a standardized tocotrienol preparation or placebo. HbA1c and continuous glucose metrics would verify comparable glycemic exposure. Meanwhile, NCV, amplitude, CCM, IENFD, thermal thresholds, autonomic measures, and functional outcomes would assess nerve response. Biomarker panels could include measures of lipid peroxidation, inflammation, endothelial function, and neurotrophic signaling.

If neural improvement occurs without between-group differences in glycemia, the glycemia-independent hypothesis would be strengthened. If no structural or functional neural outcomes improve despite NCV changes, the interpretation should shift toward transient physiological optimization rather than disease modification.

Why Small-Fiber Outcomes May Change the Interpretation of the Entire Field

One of the strongest recommendations arising from this review is to incorporate small-fiber outcomes into future tocotrienol research. The absence of small-fiber measures is currently preventing strong conclusions in either direction.

If future studies demonstrate increased IENFD or improved corneal nerve parameters together with electrophysiological improvement, the case for structural neuroprotection would become considerably stronger. Conversely, if large-fiber NCV improves repeatedly while small-fiber structure remains unchanged, the treatment could be characterized more specifically as a modulator of large-fiber or myelin physiology.

CCM is especially attractive for longitudinal trials because repeated assessments are feasible and non-invasive. However, comparative evidence showing incomplete agreement between CCM and skin biopsy means that CCM should not become a new single “gold standard”. Where feasible, a nested subgroup with skin biopsy could validate whether corneal changes reflect parallel peripheral small-fiber regeneration.

The design should also distinguish structural small-fiber recovery from symptomatic pain relief. Improved IENFD need not immediately reduce pain; regenerating fibers can themselves be associated with abnormal sensations, and central sensitization may persist after peripheral improvement. This further reinforces the need for separate outcome domains.

Phenotype-Enriched Trials Are More Rational Than Broad DPN Recruitment

Traditional DPN trials often enroll heterogeneous participants under a single diagnostic label. This can dilute treatment effects when the intervention targets a mechanism present only in a subset of patients.

For tocotrienols, a phenotype-enriched strategy is particularly logical. The putative mechanisms—oxidative stress reduction, membrane stabilization, Schwann-cell preservation, and vascular support—are most likely to produce detectable improvement when viable neural tissue remains. Patients with severe axonal loss may simply have too little recoverable substrate.

A future trial could therefore define three strata. The first would include early DPN with small-fiber abnormality but preserved conventional NCS. The second would include moderate DPN with slowed conduction but relatively preserved amplitude. The third would include advanced axonal neuropathy with low amplitudes and major sensory loss. Differential response across these strata would directly test the proposed responder phenotype.

Painful and painless participants should also be phenotyped separately. Pain status should not be treated merely as a baseline symptom score because it may reflect different peripheral and central mechanisms. Quantitative sensory testing, pain descriptors, small-fiber structure, and central sensitization measures could identify subgroups in whom a neuroprotective intervention is more or less likely to alter pain.

Redesigning the Outcome Framework

The current DPN field increasingly recognizes that outcome selection is not a technical afterthought but a determinant of whether a clinical trial can detect disease modification. The 2025 international consensus emphasizes robust outcomes that capture clinically meaningful change across relevant neuropathy phenotypes [9-11].

For tocotrienol trials, the primary endpoint should depend on the proposed mechanism and disease stage. In moderate large-fiber DPN, a composite electrophysiological endpoint incorporating both NCV and amplitude could be appropriate. In early small-fiber disease, CCM, IENFD, or validated thermal measures may be more sensitive. In autonomic disease, heart-rate variability and cardiovascular reflex tests could be prioritized.

Secondary outcomes should then connect physiology with function. These could include gait speed, postural sway, balance tests, falls, sleep, quality of life, pain interference, and foot-ulcer incidence. Such outcomes are clinically meaningful because DPN affects mobility, confidence, social functioning, mental health, and independence [48,49,51].

Figure 5 provides a practical trial architecture capable of testing whether tocotrienols modify disease rather than merely improve

a surrogate marker. It links baseline phenotyping and disease-stage stratification with a standardized intervention, multidomain outcomes, meaningful recovery measures, and post-treatment follow-up.

Figure 5 explains that there are three features that distinguish this design from earlier studies. First, participants are stratified by phenotype and disease stage before treatment. Second, structural, neurophysiological, and functional outcomes are assessed in parallel. Third, post-treatment follow-up tests durability. Persistent structural and functional improvements after treatment cessation would provide stronger evidence of disease modification than a reversible NCV change during active supplementation.

Duration, Dose, Formulation, and Washout

Treatment duration is another unresolved issue. Eight-week improvement suggests that tocotrienols may exert relatively rapid physiological effects, whereas the 12-month trial indicates that sensory conduction may continue to respond during prolonged treatment. The loss of benefit after washout raises questions about whether continual exposure is necessary.

Future studies should therefore distinguish **on-treatment efficacy** from **persistent modification of disease trajectory**. A treatment may be clinically valuable even if benefits require continued administration; many chronic therapies work this way. However, such a treatment should not automatically be described as regenerating nerves permanently.

Formulation also matters. “Vitamin E” is not a pharmacologically uniform intervention. Tocopherols and tocotrienols differ, as do α -, β -, γ -, and δ -tocotrienol isoforms. Palm-derived tocotrienol-rich fractions contain mixtures whose biological availability may depend on preparation, dose, food intake, formulation technology,

and interactions with transport proteins. Reviews of tocotrienol neurobiology emphasize this heterogeneity as a barrier to direct comparison among studies [12,15,16].

Trials should therefore report exact isoform composition, total dose, formulation technology, plasma concentrations where feasible, adherence, and concomitant vitamin supplementation. Without this information, a negative or positive study cannot easily be generalized to other tocotrienol preparations.

From Palm-Derived Nutraceutical to Precision Neuroprotective Intervention

Palm-derived tocotrienols also present a wider translational opportunity. Palm oil is often discussed primarily in the contexts of edible oil, trade, biofuel, and sustainability, but fractionation of high-value bioactive compounds creates a different pathway for downstream utilization.

For medical translation, however, agricultural origin should not lower evidentiary standards. The central question is not whether a compound is “natural”, but whether its identity, dose, pharmacokinetics, target engagement, efficacy, and safety can be demonstrated reproducibly. A palm-derived tocotrienol intervention intended for DPN should ultimately be evaluated with the same rigor expected of other disease-modifying candidates.

This would represent an important shift from generalized nutraceutical claims toward **precision metabolic neuroprotection**. Rather than recommending tocotrienols indiscriminately to all people with diabetes, research would identify which neuropathy phenotype, disease stage, dose, and neural endpoint are most responsive. That model is scientifically stronger and more clinically useful.

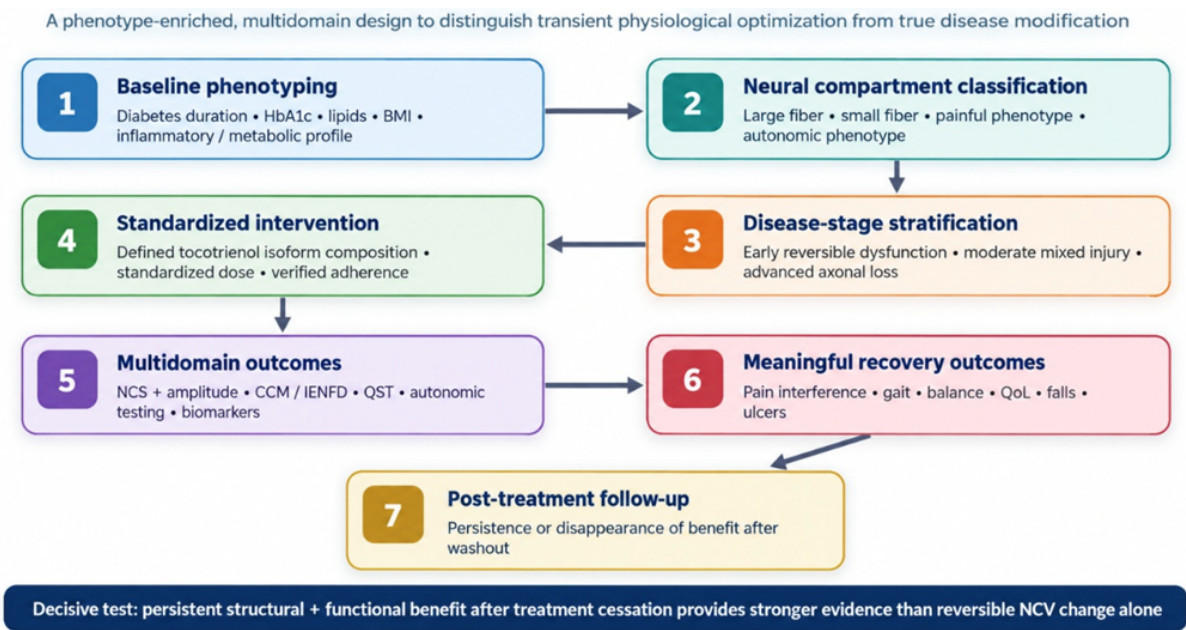


Figure 5: Proposed Precision Trial Architecture for Palm-Derived Tocotrienols.

Linking Neuroprotection to Foot and Mobility Outcomes

One of the most important translational questions is whether modest changes in nerve physiology eventually prevent complications. DPN contributes to altered gait, instability, and falls through loss of proprioception, distal muscle weakness, and impaired sensory feedback. These outcomes are measurable and could therefore become intermediate functional endpoints in longer trials [49,50].

Foot ulceration is a harder but highly meaningful endpoint. Neuropathic loss of protective sensation permits repetitive trauma to occur without warning, and ulcers frequently become portals for infection and pathways toward amputation. Armstrong et al. [54] emphasize the major global burden and clinical consequences of diabetic foot ulceration. A sufficiently large and long-term disease-modification trial could therefore examine whether preservation of sensory function reduces ulcer incidence.

The timescale required for these endpoints will be longer than that required to detect a change in NCV. This creates a staged research strategy: early trials establish biological target engagement; intermediate trials establish structural and functional neural benefit; pragmatic long-term studies determine whether these benefits translate into fewer falls, ulcers, hospitalizations, or amputations.

Clinical Interpretation of Current Evidence

At present, tocotrienols should not be presented as an established replacement for conventional DPN management. Glycemic optimization, cardiovascular risk management, exercise, foot care, and evidence-based treatment of neuropathic pain remain standard clinical priorities [8,31,53].

The evidence does, however, justify continued investigation. The repeated conduction-velocity signal is biologically coherent, appears at least partly independent of HbA1c, and aligns with plausible mechanisms involving oxidative stress, inflammation, membranes, Schwann cells, and neurotrophic signaling. The most accurate current description is therefore **promising adjunctive neuroprotection with unproven disease modification**.

This position avoids two common errors. The first is to dismiss tocotrienols because they do not improve every endpoint simultaneously. The second is to infer regeneration from a single surrogate. A rigorous translational approach accepts that different endpoints may change at different rates but requires eventual convergence before making clinically strong claims.

Limitations of the Existing Evidence

Several limitations constrain interpretation. First, the number of dedicated tocotrienol DPN randomized trials remains small relative to the heterogeneity of the disease. Second, sample sizes are modest and the duration of treatment has generally not exceeded 12 months. Third, electrophysiological outcomes dominate the evidence, while small-fiber structure, autonomic function, gait, falls, and ulceration remain largely untested.

Fourth, differences in tocotrienol formulations and isoform composition complicate generalization. Fifth, circulating biomarkers may inadequately reflect biochemical changes within peripheral nerves, meaning that negative systemic biomarker findings cannot definitively exclude local effects. Sixth, many DPN studies recruit heterogeneous populations without sufficient stratification by large-fiber, small-fiber, painful, autonomic, or disease-stage phenotype.

Seventh, the clinical relevance of relatively small increases in NCV remains uncertain unless they predict preservation of sensation or functional ability. Finally, the disappearance of electrophysiological benefit after washout suggests that continued supplementation may be required, though the biological interpretation of this finding remains unresolved.

These limitations are consistent with broader challenges in diabetic-neuropathy drug development, where the field has repeatedly struggled to translate compelling experimental mechanisms into successful clinical interventions.^{3,9} This broader context reinforces the need to avoid inferring disease modification from surrogate outcomes alone.

Conclusion

Palm-derived tocotrienols occupy a scientifically interesting position in diabetic peripheral neuropathy because they sit at the intersection of a major therapeutic need, biologically plausible neuroprotective mechanisms, and an unusual pattern of clinical evidence. Randomized studies indicate that selected nerve-conduction velocities can improve during tocotrienol-rich supplementation, yet these changes are not accompanied consistently by improved HbA1c, nerve-action-potential amplitudes, pain, or demonstrated long-term functional recovery.

The most defensible interpretation is therefore neither therapeutic failure nor proven nerve regeneration. Current evidence is more consistent with a **glycemia-independent neuroprotective effect that may involve preservation or improvement of Schwann-cell, myelin, membrane, or neurovascular function in surviving nerve fibers**. Whether that effect can slow axonal loss, regenerate small fibers, improve autonomic function, reduce pain disability, restore gait and balance, or prevent foot ulceration remains unknown.

The next generation of trials should move beyond broad DPN recruitment and single-surrogate endpoints. Participants should be phenotyped according to disease stage, large- versus small-fiber involvement, pain phenotype, autonomic involvement, and preserved axonal reserve. Trials should combine nerve-conduction velocity with action-potential amplitude, corneal confocal microscopy, intraepidermal nerve-fiber density, quantitative sensory testing, autonomic measurements, gait, balance, quality of life, falls, and long-term foot outcomes.

Such a program would test whether tocotrienols merely optimize

nerve physiology during active exposure or genuinely alter the natural history of diabetic neuropathy. Until that evidence is available, palm-derived tocotrienols should be viewed as a promising adjunctive candidate for precision metabolic neuroprotection rather than an established disease-modifying therapy.

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