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REVIEW

Modulating the Gut-Nerve Axis and Inflammation: A Narrative Review of Dietary Patterns in Diabetic Peripheral Neuropathy

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Abstract: Diabetic peripheral neuropathy (DPN) is a prevalent and debilitating complication of diabetes, arising from a complex interplay of metabolic dysregulation, oxidative stress, and chronic inflammatory pathways. This narrative review synthesizes the core pathophysiology of DPN and critically evaluates the potential role of various dietary patterns in its management. Healthy patterns, such as the Mediterranean, DASH, and plant-based diets, may offer neuroprotective potential by improving systemic metabolic and inflammatory status. Conversely, pro-inflammatory diets remain associated with exacerbated nerve damage. Furthermore, emerging strategies like low-carbohydrate diets and intermittent fasting show promise in preclinical models via mechanisms such as metabolic reprogramming and autophagy, though direct clinical evidence in DPN populations remains emerging. A critical gap persists regarding the lack of large-scale, direct intervention studies in patients with established DPN. Future research must prioritize this population to build a robust evidence base for dietary strategies in secondary prevention and personalized therapy.

Keywords: diabetic peripheral neuropathy, dietary patterns, biomarkers, inflammation, oxidative stress

Introduction

Diabetic peripheral neuropathy (DPN) represents a major global health challenge, affecting approximately 50% of individuals with diabetes during their lifetime.[1,2] As the primary driver of chronic pain and non-traumatic lower-limb amputations, DPN accounts for a staggering economic burden, with annual global healthcare expenditures for diabetes-related complications approaching $1 trillion.[1,3] Clinically, it is essential to distinguish between primary prevention and the management of established DPN.[2] Primary prevention, centered on intensive glycemic control, has demonstrated robust efficacy in type 1 diabetes (T1DM) but offers only modest protection in type 2 diabetes (T2DM).[1,2,4] Conversely, once DPN is clinically established, management pivots toward secondary and tertiary strategies—specifically alleviating neuropathic symptoms and slowing neurovascular degradation to prevent debilitating ulcers—as structural nerve damage is often irreversible.[2,5] Given the limitations of traditional monotherapy, multi-targeted dietary patterns have emerged as a pivotal strategy for both preventing onset and improving clinical outcomes in established cases.[5,6]

Dietary patterns are a key modifiable factor and offer a powerful, multi-target strategy for DPN management. This review summarizes the core pathophysiology of DPN and evaluates the role of various dietary patterns in its development and man-agement. We assess established healthy patterns like the Mediterranean, plant-based, and DASH diets, as well as the detrimental pro-inflammatory diet. We also explore novel strategies such as low-carbohydrate diets and intermittent fasting.

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Search Strategy and Selection Criteria

A comprehensive literature search was performed across PubMed, Web of Science, and Google Scholar databases for articles published from inception to February 2024. The search used combinations of keywords including "diabetic peripheral neuropathy", "dietary patterns," "Mediterranean diet," "DASH diet," "plant-based diet," "ketogenic diet," "intermittent fasting," "inflammation," "oxidative stress," and "gut microbiota." Selection criteria prioritized randomized controlled trials (RCTs), systematic reviews, and meta-analyses focused on DPN or related metabolic markers. Additionally, high-quality mechanistic studies using animal models were included to elucidate potential biochemical pathways connecting nutrition to nerve function. Only peer-reviewed articles published in English were considered.

The Pathogenesis of Diabetic Peripheral Neuropathy

Chronic hyperglycemia, dyslipidemia, and insulin resistance drive DPN pathogenesis by directly inducing neuronal injury and microvascular impairment.[4–6] These primary drivers trigger an interconnected cascade of metabolic disruptions. Specifically, excess glucose overactivates the polyol pathway, causing osmotic stress and depleting cellular antioxidants like glutathione.[7] Simultaneously, the accumulation of advanced glycation end products (AGEs) and the overactivation of the protein kinase C (PKC) pathway collaboratively generate reactive oxygen species (ROS) and activate NF-κB.[8–10] This cascade upregulates pro-inflammatory cytokines and vascular factors, driving Schwann cell demyelination, vascular permeability, and ischemia.[8,11] Subsequently, ROS-induced DNA breaks overactivate the PARP pathway, severely depleting NAD+ and ATP, which culminates in neuronal energy failure and apoptosis.[12,13] Ultimately, these mutually reinforcing pathways converge on mitochondrial dysfunction, sustained oxidative stress, and chronic neuroinflammation.[14,15] Because these core pathogenic mechanisms are intrinsically linked to nutritional status, multi-targeted dietary patterns offer a compelling and logical strategy for DPN management (Figure 1).

Biomarkers Associated with DPN and Their Clinical Significance

The pathogenesis of diabetic peripheral neuropathy (DPN) is complex, with its onset and development resulting from the combined effects of multiple pathophysio-logical changes. Therefore, identifying sensitive and specific biomarkers is not only crucial for the early diagnosis, disease assessment, and prognosis of DPN, but it also provides a window for understanding its intrinsic pathological network. More im-portantly, these biomarkers—which reflect glycemic homeostasis, lipotoxicity, in-flammatory status, and microvascular damage—can largely be modulated by dietary and nutritional interventions. This section aims to systematically review the key bi-omarkers associated with DPN and to reveal their potential to serve as both a bridge connecting dietary interventions with neuropathic improvement and as targets for monitoring. The major biomarkers discussed in this section are summarized in Table 1.

Biomarkers Related to Glycemic Control and Metabolic Dysregulation

Chronic hyperglycemia and its associated metabolic dysregulation are the initi-ating and central factors in the onset and development of DPN. As the "gold standard" for reflecting average blood glucose levels over the past 2–3 months, glycated hemo-globin (HbA1c) is closely correlated with the incidence and severity of DPN. Multiple studies have confirmed that an elevated HbA1c level is an independent risk factor for DPN.[16–19] A systematic review by Casadei also emphasized the potential of HbA1c as a biomarker for peripheral neuropathy in the diabetic foot.[20] Strict glycemic control that maintains HbA1c within the standard range is fundamental to preventing and delaying the progression of DPN. However, research suggests that for established neuropathy, its progression appears difficult to completely reverse despite subsequent improvements in glycemic control,[21] highlighting the importance of early interven-tion.

Time in Range (TIR) is a new indicator for assessing glycemic variability and quality of control that has emerged with the popularization of continuous glucose monitoring technology. A study by Wang Danyu demonstrated that TIR levels in pa-tients with T2DM are negatively correlated with the prevalence of DPN, where lower TIR levels are associated with a higher prevalence of DPN.[22]

The Triglyceride-glucose (TyG) index is a simple and reliable indicator for as-sessing insulin resistance (IR).

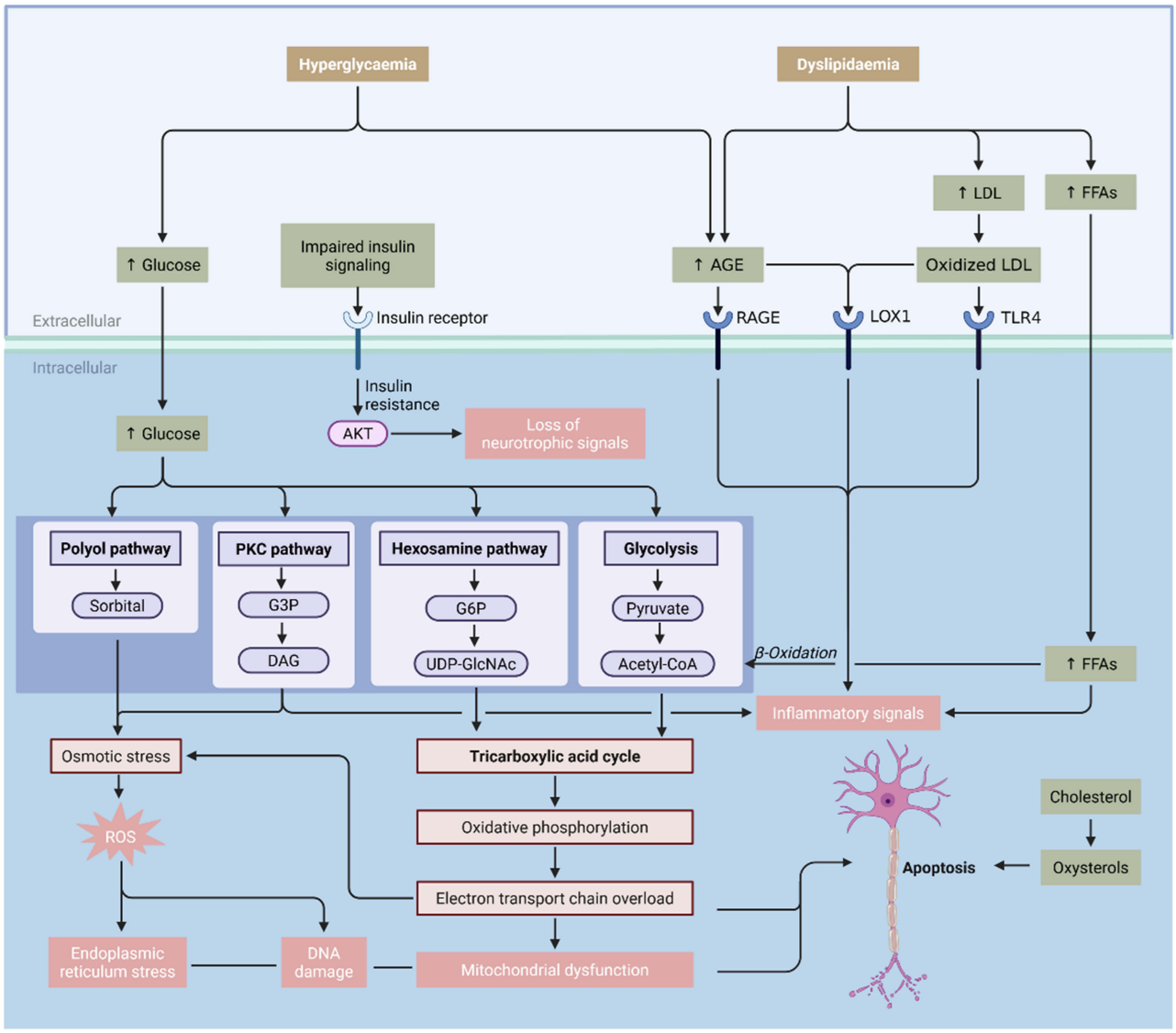

Figure 1 Interplay of Hyperglycaemia and Dyslipidaemia in the Pathogenesis of Diabetic Pe-ripheral Neuropathy.
Abbreviations: LDL, low-density lipoprotein; FFAs, free fatty acids; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; LOX1, lectin-like oxidized low-density lipoprotein receptor-1; TLR4, Toll-like receptor 4; G3P, glycer-aldehyde-3-phosphate; DAG, diacylglycerol; G6P, glucose-6-phosphate; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; Acetyl-CoA, acetyl coenzyme A; ROS, reactive oxygen spe-cies; AKT, protein kinase B; PKC, protein kinase C.

The aforementioned indicators, which reflect long-term glycemic levels, glycemic variability, and insulin resistance, constitute the core monitoring targets for evaluating the efficacy of dietary interventions, such as adjusting the quality and quantity of car-bohydrates and increasing dietary fiber.

Biomarkers Related to Glycemic Control and Metabolic Dysregulation

Dyslipidemia is a recognized risk factor for DPN, and its neurotoxic effects (ie., lipotoxicity) can be evaluated using various biomarkers. Conventional lipid markers have demonstrated an association with DPN. Multiple studies have confirmed that hypertriglyceridemia (high TG) and low high-density lipoprotein cholesterol (HDL-C) are risk factors for DPN.[17–19]

To more comprehensively reflect the integrated effects of lipotoxicity, researchers have further explored the value of composite indices. The TG/HDL-C ratio is the ratio of triglycerides to high-density lipoprotein.

In addition, some molecules directly related to the pathogenic mechanisms of li-pids have also come under investigation. Oxidized low-density lipoprotein (oxLDL) is theoretically considered to be an important pro-

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Table 1 Overview of Major Biomarkers Associated with DPN and Their Clinical Significance

Biomarker Category	Biomarker Name	Summary of Key Association & Findings with DPN	Clinical Validation Level
Glycemic Control	Glycated Hemoglobin (HbA1c)	Elevated levels are associated with DPN risk and severity.	Gold Standard
	Time in Range (TIR)	Decreased levels are associated with DPN risk and symptoms.	High
	Glycemic Variability (CV, SD, MAGE)	Increased levels may be associated with DPN risk.	High
Lipid Metabolism	Triglyceride-glucose Index (TyG Index)	An elevated level is an influential factor for DPN.	Moderate
	TG/HDL-C Ratio	An elevated ratio is a risk factor for DPN in elderly T2DM patients.	Moderate
Inflammation & Immunity	High-sensitivity C-reactive Protein (hs-CRP)/C-reactive Protein (CRP)	An elevated level is an independent risk factor for DPN, associated with severity and pain.	Moderate/ Supportive
	TNF-α, IL-1β, IL-6	Elevated levels are associated with DPN severity; TNF-α and IL-6 are associated with painful DPN.	Emerging/ Mechanistic
Renal Function/ Microvascular	Urinary Albumin-to-Creatinine Ratio (UACR)/Microalbuminuria (MAU)	An elevated level is a risk factor for DPN, associated with abnormal nerve conduction.	High
Neural/Vascular Structure	Intraepidermal Nerve Fiber Density (IENF/ PGP9.5)	A decrease is direct evidence of DPN.	Gold Standard
	Vascular Density (vWF), CGRP:vWF Ratio	Alterations may differentiate between painful and painless DPN.	Emerging/ Mechanistic
Other Systems	Cardiovascular markers (BNP, Homocysteine, etc.)	May predict DPN risk.	Emerging/ Mechanistic

Notes: The "Clinical Validation Level" categorizes biomarkers based on their established diagnostic utility in routine clinical practice versus their emerging role in mechanistic and experimental research.

Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, glycated hemoglobin; TIR, time in range; CV, coefficient of variation; SD, standard deviation; MAGE, mean amplitude of glycemic excursions; TyG, triglyceride-glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin 6; UACR, urinary albumin-to-creatinine ratio; MAU, microalbuminuria; IENF, intraepidermal nerve fiber density; PGP9.5, protein gene product 9.5; vWF, von Willebrand factor; CGRP, calcitonin gene-related peptide; T2DM, type 2 diabetes mellitus.

atherosclerotic and neurotoxic factor. However, a case-control study by Rosales-Hernandez et al found no significant difference in plasma oxLDL levels between DPN patients and control subjects, suggesting that its pathogenic role in human DPN requires further investigation.[23]

Inflammatory and Immune-Related Biomarkers

Chronic low-grade inflammation is a key pathological link connecting metabolic disorders with nerve damage; therefore, biomarkers that assess systemic and local in-flammatory status hold a significant position in DPN research.

As a systemic inflammatory marker, elevated levels of high-sensitivity C-reactive protein (hs-CRP/CRP) are associated with the incidence and severity of DPN.

As an important pro-inflammatory cytokine, Tumor Necrosis Factor-alpha (TNF-α) levels are elevated in DPN patients and are associated with reduced nerve conduction velocity and pain.[24,25] Pro-inflammatory cytokines from the interleukin (IL) family, such as IL-1β and IL-6, are elevated in DPN patients and correlate with the severity of DPN and pain.[26,27] Conversely, anti-inflammatory cytokines like IL-10 may be de-creased in DPN patients.[25]

Biomarkers Related to Renal Function and Microvascular Damage

DPN and diabetic nephropathy (DN) are both microvascular complications that often coexist and share similar pathological foundations. Therefore, indicators reflect-ing renal microvascular damage, such as the urinary albumin-to-creatinine ratio (UACR), also provide indirect clues for DPN risk assessment.

The urinary albumin-to-creatinine ratio (UACR) is a sensitive indicator for early DN and has also been found to be associated with DPN.

Other Relevant Hematological Indicators

Serum uric acid (SUA) is receiving increasing attention due to the relationship between hyperuricemia and DPN. Hyperuricemia is not only related to purine metab-olism but is also closely linked to modern dietary factors such as high-fructose diets, which adds a new dimension to its potential as a target for nutritional intervention.

DPN and Dietary Patterns

Diabetic peripheral neuropathy (DPN) pathogenesis is complex, involving multi-ple links such as hyperglycemia, dyslipidemia, insulin resistance, oxidative stress, chronic inflammation, and microvascular dysfunction. Lifestyle factors, particularly dietary habits, play a crucial role in the management of diabetes and its complications. Compared to studies on single nutrients, analysis of dietary patterns can more com-prehensively reflect an individual's overall dietary structure and its complex relation-ship with health. Therefore, exploring the association between different dietary pat-terns and DPN, along with their potential mechanisms, is of great importance for the prevention and management of DPN (summarized in Table 2).

Table 2 Summary of Dietary Patterns and Their Potential Neuroprotective Mechanisms in DPN

Dietary Pattern	Core Principles & Key Foods	Potential Neuroprotective Mechanisms (Link to Pathophysiology)
Mediterranean (MD) & Nordic (ND) Diets	- MD: Rich in extra virgin olive oil, fruits, nuts, vegetables.	- Anti-inflammatory & Antioxidant: Mitigates oxidative stress and neuroinflammation; may inhibit NF-κB pathway.
	- ND: Rich in rapeseed oil, berries, fatty fish, root vegetables	- Microvascular Health: Improves endothelial function, countering nerve ischemia.
	- Shared: High in plant foods & high-quality fats.	- Metabolic Improvement: Improves insulin resistance and dyslipidemia (e.g., via AMPK signaling).
DASH Diet	- High in fruits, vegetables, whole grains, nuts, and low-fat dairy.	- Insulin Sensitivity: Significantly improves insulin action and reduces fasting insulin.
	- Unique Emphasis: Strict sodium limitation.	- Anti-inflammatory: Reduces systemic inflammation markers like CRP and fibrinogen.
		- Microvascular Protection: Protects the neurovascular unit via its robust blood-pressure-lowering effect.
Healthful Plant-Based Diets (hPDI)	- Emphasizes healthy plant foods (whole grains, fruits, veg, legumes)	- "Gain" Mechanism: High fiber modulates gut microbiota (produces SCFAs); high phytochemicals (DPI) provide antioxidant/anti-inflammatory effects.
	- Limits or excludes all animal products.	- "Harm Reduction" Mechanism: Reduces saturated fat (mitigates lipotoxicity); avoids heme iron (reduces pro-oxidant stress).

(*Continued*)

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Table 2 (Continued).

Dietary Pattern	Core Principles & Key Foods	Potential Neuroprotective Mechanisms (Link to Pathophysiology)
MIND Diet	- A hybrid of the Mediterranean and DASH diets.	- Targeted Neuroprotection: Directly counters neuroinflammation and oxidative stress via high flavonoid content (from berries).
	- Unique Emphasis: Specifically elevates berries and leafy greens.	- Enhanced Neuro-Resilience: May help the nervous system maintain function despite ongoing pathological stress.
Low-Glycemic Index/ Load (Low-GI/GL) Diets	- Chooses carbohydrates that are digested and absorbed slowly, resulting in a gradual and lower postprandial glucose rise.	- Targets Root Cause: Directly minimizes postprandial hyperglycemia and glycemic variability (GV).
		- Reduces Substrate: Systematically reduces the glucose substrate flux into pathological pathways (e.g., Polyol, AGEs).
Low-Carbohydrate (LCD) & Ketogenic (KD) Diets	- Strict restriction of carbohydrate intake (KD typically <50g/day).	- Bypasses Glucose Metabolism: Removes the primary substrate for hyperglycemia, inhibiting pathways like Polyol, AGEs, and PKC.
		- (KD-Specific): Generates ketone bodies (BHB) as an alternative neuronal fuel and a potent anti-inflammatory agent (via NLRP3 inflammasome inhibition).
Microbiota-Targeted Diets	- Utilizes prebiotics (fiber), probiotics (fermented foods, yogurt), and postbiotics (SCFAs) to modulate the gut ecosystem.	- Modulates "Gut-Nerve Axis".
		- Repairs Gut Barrier: Reduces "leaky gut" and metabolic endotoxemia (LPS).
		- Generates Neuroactive Postbiotics: Fiber fermentation produces SCFAs, which can inhibit the NLRP3 inflammasome.
Intermittent Fasting (IF)	- Focuses on when to eat (e.g., Time-Restricted Eating, TRE), rather than what to eat.	- (Unique Mechanism): Potently induces neuronal autophagy, clearing damaged mitochondria and misfolded proteins.
		- Circadian Rhythm: Synchronizes nutrient intake with the biological clock, reducing metabolic stress.
		- Metabolic Improvement: Enhances insulin sensitivity and reduces oxidative stress.
(Detrimental Pattern) Pro-inflammatory Diet	- High in red/processed meats, refined grains, sugary beverages	- (Harmful Mechanism): "Fuel supplier" for DPN pathology.
	- High saturated fat, high exogenous AGEs, high Ultra-Processed Foods (UPFs).	- Exacerbates Gluco/Lipotoxicity: Provides substrates for Polyol, PKC, and AGEs pathways.
		- Induces Dysbiosis: Causes "leaky gut" and metabolic endotoxemia (LPS), fueling systemic inflammation.

Abbreviations: DPN, diabetic peripheral neuropathy; MD, Mediterranean diet; ND, Nordic diet; DASH, Dietary Approaches to Stop Hypertension; hPDI, healthful Plant-Based Diet Index; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; GI, glycemic index; GL, glycemic load; GV, glycemic variability; LCD, low-carbohydrate diet; KD, ketogenic diet; IF, intermittent fasting; TRE, time-restricted eating; NF-κB, nuclear factor-kappa B; AMPK, AMP-activated protein kinase; CRP, C-reactive protein; SCFAs, short-chain fatty acids; DPI, Dietary Phytochemical Index; AGEs, advanced glycation end products; PKC, protein kinase C; BHB, β-hydroxybutyrate; NLRP3, NLR family pyrin domain containing 3; LPS, lipopolysaccharide; UPFs, ultra-processed foods.

The Mediterranean Dietary and Nordic Dietary Pattern

Healthy dietary patterns adapted to regional foods and cultures, such as the Mediterranean and Nordic diets, offer important insights for DPN management. Alt-hough their food components differ—with the former emphasizing olive oil, fruits, and nuts, and the latter featuring rapeseed oil, berries, and fatty fish[28–30]—their under-lying nutritional

principles are highly consistent. Both patterns appear to exert neuro-protective potential by targeting similar core pathological mechanisms.

To begin with, a key advantage of these dietary patterns is their potent an-ti-inflammatory and antioxidant capacity, which directly counteracts critical drivers of DPN. The Mediterranean diet (MD) is rich in polyphenols and antioxidants from extra virgin olive oil, fruits, and vegetables, which can mitigate oxidative stress and neu-roinflammation.[28] Similarly, the Nordic diet (ND) provides strong antioxidant support through its high content of berries and root vegetables. Clinical evidence supports this: a randomized controlled trial showed that the ND significantly im-proved markers of inflammation in individuals with impaired glucose metabolism.[30] Another study found that adherence to core ND components was associated with lower concentrations of high-sensitivity C-reactive protein (hs-CRP),[31] a key bi-omarker for DPN severity. By mitigating systemic inflammation, both diets may inhibit the activation of pro-inflammatory cascades, such as the NF-κB pathway, thereby protecting neurons from damage.

Furthermore, both patterns can effectively protect microvascular health, which is crucial for alleviating the nerve damage caused by ischemia and hypoxia. Endothelial dysfunction is a central event in the course of DPN. A randomized controlled trial by de Mello et al explicitly reported that the ND improved markers of endothelial func-tion.[30] This finding is supported by large cohort data; the EPIC-Potsdam study, for instance, found that ND adherence was associated with a possible reduced risk of car-diovascular events like myocardial infarction and stroke.[32] While direct evidence for the MD on DPN is still evolving,[33–35] its robust, well-documented benefits for re-ducing systemic cardiovascular risk are undisputed, which indirectly supports its po-tential benefits for the neurovascular unit.

Additionally, these diets address the upstream metabolic disturbances that initiate neuropathy, and their effects are now traceable through specific biomarkers. Insulin resistance and dyslipidemia are primary drivers of DPN. The MD, with its high fiber and MUFA content, is effective in improving these metabolic markers.[27,28] Research on the ND provides even more detailed evidence at the molecular level. An interven-tion study by Fritzen et al found that the ND improves overall metabolism by acti-vating AMPK signaling in adipose tissue,[26] a master regulator that enhances insulin sensitivity. Furthermore, metabolomics studies have identified biomarkers like pipe-colic acid betaine, which is linked to whole grain intake. The level of this compound is inversely associated with fasting insulin and unfavorable lipid profiles,[36] providing strong evidence for how the ND precisely regulates metabolic pathways.

Finally, these fiber-rich dietary patterns are closely linked to the gut microbiota, a frontier that opens new possibilities for personalized nutrition. The gut microbiome is a key hub connecting diet and host health. Interestingly, a 6-month trial by Roager et al found that while the ND did not cause major shifts in the overall microbiota, the par-ticipants' baseline microbial signature (specifically the Prevotella-to-Bacteroides ratio) predicted their metabolic response to the diet, such as changes in plasma cholesterol.[37] This suggests that the benefits of healthy diets may not be uniform and could be influenced by an individual's enterotype. This finding points to a new direction for DPN management, where analyzing a patient's gut microbiota could help tailor the most effective dietary interventions for them.

In conclusion, although direct clinical evidence for using MD or ND to treat DPN is still accumulating and can be inconsistent,[35,38] the mechanistic evidence is strong and convergent. The diets' abilities to act simultaneously on inflammation, vascular health, metabolism, and the microbiota demonstrate their significant neuroprotective potential. The fact that these distinct regional diets achieve similar benefits underscores a crucial point: for managing diabetic complications, adhering to the principles of a diet rich in plant foods, high-quality fats, and antioxidants is likely more important than following a specific food list.

The DASH Dietary Pattern

The Dietary Approaches to Stop Hypertension (DASH) diet is another well-researched, plant-forward dietary pattern.[39] Initially developed to lower blood pressure, the DASH diet emphasizes a high intake of fruits, vegetables, whole grains, and nuts. Unlike the Mediterranean and Nordic diets, it specifically promotes low-fat dairy products and places a stronger emphasis on strict sodium limitation.[39] Its nu-trient-rich composition provides a strong foundation for improving overall metabolic health.

The relevance of the DASH diet to DPN lies in its proven ability to improve insulin sensitivity and glycemic control. A key randomized controlled trial by Ard et al showed that adding the DASH diet to a lifestyle intervention significantly

enhanced insulin action, an effect not seen with lifestyle changes alone.[40] A meta-analysis further supports this, finding that the DASH diet can significantly reduce fasting insu-lin levels.[41] More recent research has begun to identify the specific glucose homeo-stasis pathways improved by DASH, suggesting the benefits likely arise from its plant-based components.[42] Furthermore, long-term adherence to the DASH diet is associated with a lower risk of developing a metabolically unhealthy phenotype, which is a major upstream risk factor for the development of DPN.[43] For patients with type 2 diabetes, following the DASH diet has been shown to yield comprehensive benefits. These include significant reductions in glycated hemoglobin (A1C), fasting blood glu-cose, LDL cholesterol, and blood pressure.[44] These metabolic improvements directly counteract the hyperglycemic and dyslipidemic states that fuel the core pathological pathways of DPN.

Furthermore, the DASH diet directly targets the chronic inflammation and vas-cular dysfunction central to DPN's pathogenesis. A clinical trial by Azadbakht et al demonstrated that the DASH diet significantly reduced levels of C-reactive protein (CRP) and fibrinogen in diabetic individuals.[45] This anti-inflammatory effect is consistent with other findings linking the DASH diet to lower hs-CRP levels.[46] No-tably, the key biomarkers improved by the DASH diet—such as A1C and triglycer-ides—are the same factors identified in recent studies as strong predictors for the de-velopment and severity of neuropathy.[47] The diet's strong, well-established effect on lowering blood pressure also helps protect the microvasculature, potentially improving nerve blood supply and reducing ischemic damage.[44,48]

In conclusion, the DASH diet offers a multi-faceted intervention that addresses the complex pathology of DPN. It simultaneously improves metabolic control, enhances insulin sensitivity, and reduces inflammation.[40,41,44–46] Its well-documented effects on blood pressure also suggest a distinct benefit for protecting the microvasculature that supports nerve health.[44,48] By acting on several key pathological pathways at once, the DASH diet represents a robust strategy for the prevention and management of diabetic peripheral neuropathy.

Plant-Based Dietary Patterns

Plant-based dietary patterns are defined by an emphasis on foods derived from plants, such as fruits, vegetables, legumes, whole grains, nuts, and seeds, while dis-couraging or completely excluding most or all animal products.[49] Recent global health initiatives, such as the EAT-Lancet Commission report, also advocate for a predominantly plant-based "planetary health diet" to simultaneously promote human health and environmental sustainability.[50] For more precise research, indices like the healthful Plant-Based Diet Index (hPDI) have been developed. The hPDI distinguishes between healthy plant foods (eg., whole grains, fruits, vegetables) and less healthy ones (eg., refined grains, sugary drinks).[51] Broadly, greater adherence to healthy plant-based diets is associated with a lower risk of major chronic diseases, including type 2 diabetes.[52]

Strong evidence supports the benefits of plant-based diets for improving key metabolic markers relevant to DPN. Recent meta-analyses of randomized controlled trials (RCTs) show that vegetarian and vegan diets significantly reduce both glycated hemoglobin (A1C) and body mass index (BMI) in patients with type 2 diabetes.[53,54] Data from large prospective cohorts, such as the UK Biobank, further confirm that adherence to plant-based diets is associated with a lower risk of incident type 2 dia-betes, thereby reducing the foundational risk for DPN.[55] Most critically, a direct link to neuropathy has been established. A case-control study by Asadi et al found that a higher Dietary Phytochemical Index (DPI), reflecting a diet rich in plant-derived bio-active compounds, was associated with a 75% reduced odds of having diabetic sen-sorimotor polyneuropathy (DSPN) after adjusting for confounders.[56]

The neuroprotective potential of plant-based diets stems from a dual "gain and harm reduction" mechanism.[49] The "gain" mechanism arises from a high intake of beneficial components. Abundant dietary fiber promotes a healthy gut microbiota, which in turn produces beneficial metabolites like short-chain fatty acids (SCFAs) that modulate systemic inflammation and improve metabolic health.[57] The high intake of phytochemicals provides direct antioxidant and anti-inflammatory effects. This is supported by the DPI study[56] and other research linking the hPDI to lower levels of hs-CRP.[46]

Simultaneously, a "harm reduction" mechanism works by limiting deleterious components. The exclusion or reduction of animal products lowers the intake of satu-rated fats, which mitigates the lipotoxicity that drives mitochondrial

dysfunction in neurons. The avoidance of red and processed meat is particularly important, as their consumption is linked to increased inflammation and a higher risk of T2D.[58] It also significantly reduces the intake of heme iron. Excess heme iron is a potent pro-oxidant that can generate reactive oxygen species, directly contributing to the oxidative stress central to DPN's pathogenesis.[59] Furthermore, plant-based diets often have a lower energy density, which aids in weight management. Evidence from a two-year RCT by Turner-McGrievy et al confirmed that a vegan diet was more effective for weight loss than a moderate low-fat diet.[60] This indirect benefit of weight control can compre-hensively improve insulin resistance and the overall metabolic environment.

Looking forward, the distinction between different qualities of plant-based diets is crucial. The foundational work by Satija et al demonstrated that while an hPDI was associated with a substantially lower risk of T2D, an unhealthful plant-based diet (uPDI) rich in refined grains and sugary drinks was associated with a higher risk.[51] This highlights that simply avoiding animal products is not enough. Future research on DPN should therefore use these indices to differentiate diet quality and provide more precise and effective dietary recommendations.

The Mediterranean, Nordic, DASH, and healthy Plant-Based diets, despite their different geographical origins and specific food lists, converge on a core set of princi-ples that collectively target the complex pathophysiology of DPN. Their shared foun-dation is a high intake of whole, minimally processed plant foods—including fruits, vegetables, whole grains, and legumes—and a limitation of red and processed meats, refined grains, and sugar-sweetened beverages.

This common core results in a multi-pronged mechanistic attack on DPN. First, by emphasizing high-fiber, unrefined carbohydrates, all four patterns are typically lower in glycemic index and load, directly counteracting the primary driver of DPN: hyper-glycemia and its associated glucotoxicity. Second, their richness in phytochemicals, vitamins, and minerals provides a powerful antioxidant and anti-inflammatory de-fense. A systematic review of RCTs confirmed that adherence to such healthy, plant-rich patterns is indeed associated with a reduction in biomarkers of inflamma-tion.[61] Third, by favoring unsaturated fats (from olive oil, rapeseed oil, or nuts) over saturated fats, these diets improve lipid profiles and endothelial function, thereby mitigating the lipotoxicity and microvascular damage that contribute to nerve ische-mia.

However, their subtle differences offer unique, complementary benefits. The DASH diet's explicit focus on sodium restriction and high potassium and magnesium intake provides a distinct advantage for blood pressure control and vascular health. The complete exclusion of heme iron in vegan diets offers the most potent strategy for reducing this specific source of oxidative stress. The Mediterranean and Nordic diets, with their emphasis on specific high-quality oils, robustly target lipotoxicity.

The MIND Dietary Pattern

The MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet is a dietary pattern designed specifically to promote brain health. It is a hybrid of the Mediterranean (MD) and DASH diets. The MIND diet adopts the core principles of these two patterns but has a unique focus. It specifically highlights 10 brain-healthy food groups, such as leafy greens and berries, and 5 food groups to limit, including red meat, sweets, and fried foods.[62]

Although the MIND diet was created to prevent Alzheimer's disease, its benefits also apply to the key risk factors for DPN. A key prospective study was the first to show that adherence to the MIND diet is associated with a lower risk of developing type 2 diabetes.[63] Another study found that following the MIND diet helps reduce the risk of developing a metabolically unhealthy phenotype, which is closely linked to insulin resistance and systemic inflammation.[43] These findings show that the MIND diet can address the upstream drivers of DPN.

The diet's neuroprotective mechanisms are linked to its emphasis on specific nu-trients and bioactive compounds. The MIND diet places special importance on the in-take of berries and leafy greens.[62] Berries are an excellent source of flavonoids. A large prospective study by Devore et al confirmed that a high intake of flavonoids, particularly from berries, is associated with slower cognitive decline.[64] Similarly, a study by Morris et al found that daily consumption of leafy green vegetables was linked to a significant slowing of cognitive decline.[65] These foods are rich in anti-oxidants and anti-inflammatory compounds. They can directly counter oxidative stress and neuroinflammation, which are core pathological mechanisms in DPN. This is supported by research showing that a MIND-like diet can protect the brain from the damage caused by environmental pollutants.[66]

The MIND diet may also enhance neuro-resilience, or the nervous system's ability to withstand damage. A unique study by Dhana et al found that adherence to the MIND diet was associated with better cognitive function, even in the presence of Alz-heimer's disease pathology.[67] This suggests the diet's benefits go beyond just pre-venting damage and may help the nervous system maintain function despite ongoing stress. This mechanism is highly relevant to DPN, where peripheral nerves are under constant metabolic pressure.

When compared to the Mediterranean and DASH diets, all three patterns share a common foundation. They are all plant-forward and recommend limiting red meat, saturated fats, and added sugars. All three can positively influence the biomarkers and pathophysiological processes of DPN by improving insulin sensitivity, lipid profiles, and inflammation. The key innovation of the MIND diet, however, is its specificity. Unlike the broad recommendations for fruits and vegetables in the MD and DASH diets, the MIND diet precisely elevates berries and leafy greens to a central role because of their strong, specific evidence for neuroprotection.[64,65] Therefore, the MIND diet can be seen as a refined version of the MD and DASH diets, optimized to maximize benefits for the nervous system. In summary, the MIND diet is a highly promising strategy for the prevention and management of diabetic peripheral neuropathy due to its proven effects on metabolic health and its targeted neuroprotective mechanisms.

Pro-Inflammatory Dietary Pattern

In contrast to healthy dietary patterns, a diet characterized by a high intake of red and processed meats, refined grains, and sugar-sweetened beverages is widely recog-nized as pro-inflammatory. Its nutritional profile—high in saturated fats, exogenous advanced glycation end products (AGEs), and low in fiber—contributes to this effect.[68] To quantify this inflammatory potential, researchers have developed tools such as the Dietary Inflammatory Index (DII).[69] A core feature of this pattern is the high consumption of ultra-processed foods (UPFs), which are industrial formulations con-taining numerous additives.[70]

Substantial evidence links this dietary pattern to negative neurological outcomes. In human populations, adherence to a pro-inflammatory diet is significantly associated with an increased risk of developing type 2 diabetes,[71] while high consumption of UPFs also elevates T2D risk.[72] Animal models provide more direct evidence of nerve damage. High-fat diets have been shown to induce neuronal inflammation[73] and can produce peripheral nerve damage similar to that seen in diabetes, even in the ab-sence of overt hyperglycemia.[74] This suggests that dyslipidemia itself is a critical factor in nerve injury. Furthermore, a "cafeteria diet," which models this eating pattern, has been shown to cause nerve dysfunction even in a prediabetic state, highlighting the direct detrimental effect of the diet itself.[75]

Mechanistically, this pro-inflammatory dietary pattern acts as a "fuel supplier" for the pathological network of DPN, simultaneously igniting multiple damaging path-ways. First, the high load of sugar and saturated fat provides the substrate for core metabolic disturbances. This directly exacerbates hyperglycemia and lipotoxicity, thereby overloading the polyol, protein kinase C (PKC), and AGEs pathways.[76] The role of saturated fatty acids is particularly detrimental. The animal study by Rumora et al clearly demonstrated that a diet rich in saturated fats induces neuropathy through mechanisms involving mitochondrial dysfunction and neuronal lipotoxicity.[27] Ad-ditionally, foods like processed meats, which are often cooked at high temperatures, are a major source of exogenous AGEs. These compounds activate their receptor (RAGE), directly triggering oxidative stress and inflammatory responses.[8]

Second, this dietary pattern acts as a "disruptor" of the gut microbiota, exacer-bating nerve damage via the gut-nerve axis. The high-fat, low-fiber structure disrupts the balance of intestinal microorganisms, leading to dysbiosis.[77] The study by Guo et al directly linked these diet-induced changes in the gut microbiota to peripheral neu-ropathy phenotypes and to the expression of genes in the nerve related to inflammation, lipid metabolism, and antioxidant defense.[78] A deeper mechanism involves the impairment of intestinal barrier integrity, leading to a "leaky gut." This allows bacterial endotoxins like lipopolysaccharide (LPS) to translocate into the bloodstream, a condi-tion known as metabolic endotox-emia. This process fuels a chronic, low-grade systemic inflammatory state that persistently activates the immune system and intensifies neu-roinflammation.[79,80]

In summary, the pro-inflammatory dietary pattern provides a continuous patho-logical drive for the development and progression of DPN. It achieves this by directly activating multiple metabolic damage pathways and indirectly by

disrupting gut ho-meostasis. Therefore, a foundational strategy in the nutritional intervention for pa-tients with DPN is the strict avoidance of this dietary pattern.

Low-Glycemic Index/Load Diets

The glycemic index (GI) and glycemic load (GL) are key metrics for assessing the quality, rather than the quantity, of carbohydrates.[81] The GI ranks carbohy-drate-containing foods based on their effect on postprandial blood glucose levels, while the GL accounts for both the GI and the amount of carbohydrate consumed. The core principle of a low-GI/GL diet is to choose foods that are digested and absorbed slowly, resulting in a gradual and lower rise in blood glucose and insulin.[76] This principle is a shared, underlying component of many healthy dietary patterns, including the Mediterranean, DASH, and healthy plant-based diets.

A large body of high-level evidence confirms that low-GI/GL diets effectively improve key metabolic markers in individuals with diabetes.[82,83] Multiple system-atic reviews and meta-analyses of randomized controlled trials (RCTs) consistently show that low-GI/GL diets significantly reduce glycated hemoglobin (A1C) compared to high-GI/GL diets. Importantly, these diets also address glycemic variability.[84] A dedicated meta-analysis found that a low-GI diet significantly improves measures of glucose fluctuations in patients with type 2 diabetes.[85] This is a critical point, as re-search by Pai et al has directly identified high glycemic variability as an independent risk factor for the development of painful diabetic peripheral neuropathy (PDPN).[86]

Mechanistically, the neuroprotective potential of a low-GI/GL diet lies in its ability to target the root cause of DPN: hyperglycemia and its fluctuations.[87] Postprandial glucose spikes are potent triggers of oxidative stress, a primary driver of diabetic complications.[88] Research has even shown that acute glucose fluctuations can gener-ate a more intense oxidative stress response than sustained chronic hyperglyce-mia.[89] By creating a smoother postprandial glucose profile, a low-GI/GL diet sys-tematically reduces the substrate flux into multiple, well-established pathological pathways.

This concept is further supported by pharmacological evidence. Al-pha-glucosidase inhibitors, such as acarbose, function by slowing intestinal carbohy-drate absorption, effectively mimicking the physiological effect of a low-GI meal.[90] In the UKPDS 44 trial, acarbose was shown to improve glycemic control over three years, providing a proof of principle for this mechanism.

In summary, a low-GI/GL diet is a foundational intervention that directly targets the initial steps of DPN pathogen-esis. By minimizing postprandial hyperglycemia and glycemic variability, it systematically inhibits multiple interconnected pathological pathways. This reduces glucotoxicity, oxidative stress, and neuroinflammation. Therefore, incorporating low-GI/GL principles into daily eating is a core and effective strategy for the prevention and management of DPN.

Low-Carbohydrate and Ketogenic Diets

Low-carbohydrate diets (LCDs) are a class of dietary patterns that alter macro-nutrient distribution by restricting carbohydrate intake. This restriction exists on a spectrum, from moderate LCDs (<45% of energy from carbohydrates) to very-low-carbohydrate ketogenic diets (KDs), which typically limit carbohydrates to less than 50 grams per day.[91]

Accumulating evidence suggests potential short-term benefits of LCDs on glycemic control. Multiple systematic reviews and meta-analyses indicate that in patients with type 2 diabetes, LCDs may be associated with a greater reduction in glycated hemoglobin (A1C) at 6 months compared to high-carbohydrate diets.[92,93] More encouragingly, preclinical studies suggest an emerging neuroprotective potential. In a type 1 diabetic mouse model, Enders et al reported that a KD might help mitigate and potentially reverse mechanical allodynia and improve epidermal nerve fiber density.[94] Another study in diabetic rats observed that a KD could alleviate neuropathic pain.[95]

Mechanistically, the primary neuroprotective potential of LCDs stems from their ability to bypass glucose metabo-lism. By drastically reducing carbohydrate influx, LCDs remove the primary substrate for hyperglycemia, thereby directly inhibiting the flux through damaging pathological pathways like the polyol, AGEs, and PKC path-ways.[88]

The ketogenic diet introduces a unique and deeper layer of mechanisms. In a state of carbohydrate restriction, the liver produces ketone bodies, primarily β-hydroxybutyrate (BHB). Ketones serve as a highly efficient alternative fuel source for neurons, which is particularly beneficial when glucose metabolism is impaired.[96] More importantly, ketone

bodies also function as signaling molecules.[97] First, BHB exerts direct anti-inflammatory effects. Groundbreaking work by Youm et al demon-strated that BHB specifically blocks the activation of the NLRP3 inflammasome, thereby inhibiting the release of pro-inflammatory cytokines like IL-1β and directly countering neuroinflammation.[98] Second, BHB is an endogenous histone deacety-lase (HDAC) inhibitor. By inhibiting HDACs, BHB can epigenetically modify gene expression, leading to the upregulation of antioxidant genes and enhancing cellular defenses against oxidative stress.[99]

Despite the promising mechanisms and short-term benefits, significant contro-versies regarding the long-term application of LCDs must be critically addressed. First, the pronounced initial advantage in glycemic control appears to attenuate over time. Both major meta-analyses and a two-year RCT have shown that the difference in A1C reduction between LCDs and other diets is often no longer statistically significant at 12 to 24 months.[92,100,101] This is likely due to challenges with long-term dietary adherence, as highly restrictive diets can be difficult to sustain amidst social and cultural food environments.[101]

Second, cardiometabolic safety, particularly regarding dyslipidemia, remains a primary concern. While many individuals on LCDs see improvements in triglycerides and HDL cholesterol, a significant portion experiences an increase in low-density lip-oprotein cholesterol (LDL-C).[102] Although some evidence suggests this may be a shift towards larger, less atherogenic LDL particles, the National Lipid Association advises caution, emphasizing that elevated LDL-C remains a risk factor for cardio-vascular disease regardless of particle size.[102] The long-term cardiovascular impact, especially in diets high in saturated fats, is not yet fully understood and requires careful monitoring.

Third, the long-term effects on renal function are another area of debate. While studies in individuals with normal kidney function have not shown adverse effects, there is a theoretical concern that a sustained high-protein intake could increase glo-merular hyperfiltration. Therefore, caution is advised when applying LCDs in patients with pre-existing chronic kidney disease.[103] Other potential long-term issues include the risk of micronutrient deficiencies if the diet is not well-formulated and the potential for loss of lean body mass if protein intake is inadequate.[101]

In conclusion, low-carbohydrate and ketogenic diets represent emerging dietary strategies with multi-faceted mechanistic potential, demonstrating initial short-term efficacy in improving overall glycemic control and suggesting a theoretical basis for neuroprotection.However, given the challenges with long-term adherence, the attenuation of effects over time, and unresolved safety questions, they should be considered as a medical nutrition therapy to be implemented under clinical supervision, rather than a universal, lifelong recommendation for all individuals.[104]

Microbiota-Targeted Diets

As the understanding of the gut microbiota's central role in host health deepens, nutritional research is shifting from broad dietary patterns to more specific "microbi-ota-targeted diets".[105] This approach is not a fixed menu but rather a strategy de-signed to actively shape the structure and function of the gut microbial community through precise nutritional inputs. The core tools of this strategy include several key components designed to modulate the gut ecosystem. These include prebiotics, which are typically non-digestible dietary fibers like fructooligosaccharides and inulin that selectively promote the growth of beneficial bacteria;[106] and probiotics, which are live microorganisms commonly found in yogurt and fermented foods that confer a health benefit to the host when consumed in adequate amounts.[107] A combination of these is known as synbiotics. Furthermore, the approach considers postbiotics, which are the beneficial metabolites produced by microorganisms, such as short-chain fatty acids (SCFAs).[105]

A growing body of evidence indicates that gut dysbiosis is a key component in the pathophysiology of DPN. An animal model study by Guo et al directly demonstrated that the peripheral neuropathy induced by a high-fat diet was associated with specific gut microbiota signatures, nerve lipid profiles, and nerve gene expression pathways related to inflammation and antioxidant defense.[78] Another study found that ginger, a food rich in phytochemicals, could alleviate neuropathic pain in diabetic rats by beneficially modulating the gut microbiome.[108] These findings provide a strong rationale for intervening in DPN by targeting the gut microbiota.

Microbiota-targeted diets exert their effects on DPN through multiple mechanisms, centrally involving the modulation of the gut-nerve axis. First, these diets work to re-store gut barrier integrity and reduce metabolic endotoxemia. An unhealthy diet can compromise the tight junctions of the intestinal epithelium, leading to a "leaky gut" that allows bacterial endotoxins like lipopolysaccharide (LPS) to enter the bloodstream and cause systemic low-grade

inflammation.[79] Prebiotics and probiotics can enhance gut barrier function by nourishing intestinal cells and producing metabolites like butyrate, thereby reducing this primary inflammatory trigger from the source.[105]

Second, microbiota-targeted diets can directly modulate the host's immune and inflammatory responses. Wastyk et al found that a diet rich in fermented foods (a source of probiotics) was more effective than a high-fiber diet at reducing multiple in-flammatory markers, including interleukin-6 (IL-6).[109] This is highly relevant, as inflammation is a central mechanism of nerve damage in DPN. Furthermore, SCFAs produced from prebiotic fermentation, particularly butyrate, have been shown to in-hibit the NLRP3 inflammasome,[98] a mechanism of inflammation control that par-allels the action of ketones.

Most importantly, these diets exert their effects by producing neuroactive postbi-otics, primarily SCFAs. When beneficial bacteria ferment dietary fibers (prebiotics), they produce large amounts of SCFAs like butyrate, propionate, and acetate.[110] These molecules not only serve as energy for intestinal cells but also enter the circula-tion and can influence the nervous system through various pathways.[111,112] A critical animal study by Sheval et al provided direct evidence for this, showing that prebiotics (galactooligosaccharides and resistant starch) effectively protected against high-fat diet-induced peripheral neuropathy and mechanical hypersensitivity.[113] This suggests that promoting endogenous SCFA production through prebiotics is a key neuroprotective mechanism of microbiota-targeted diets.

The effects of these interventions can be monitored through biomarkers. In addi-tion to traditional inflammatory markers like hs-CRP and IL-6, circulating levels of SCFAs are emerging as a promising biomarker. Research by Müller et al indicates that circulating, rather than fecal, SCFA levels are closely related to metabolic markers like insulin sensitivity.[114]

In summary, microbiota-targeted diets represent a sophisticated, mecha-nism-based intervention. By using prebiotics, probiotics, and fermented foods to op-timize the gut ecosystem, this strategy can systematically improve gut barrier function, reduce systemic inflammation, and generate neuroprotective metabolites, offering a precise and promising new avenue for the prevention and management of DPN.[115,116]

Intermittent Fasting

Intermittent fasting (IF) is a unique dietary intervention that focuses on when to eat, rather than what to eat. It creates regular, cyclical periods of fasting, with common approaches including time-restricted eating (TRE) and alternate-day fasting.[117] This strategy does not prescribe specific foods but instead aims to reset metabolic and cel-lular repair processes by altering the timing of nutrient intake.

A growing body of evidence points toward potential metabolic benefits of IF. Several randomized controlled trials (RCTs) in humans have indicated that TRE may improve insulin sensitivity, lower blood pressure, and reduce oxidative stress, even without weight loss.[118] Other RCTs have confirmed its effectiveness for weight loss and for improving cardiometabolic markers in adults with obesity.[119] For pa-tients with type 2 diabetes, systematic reviews and meta-analyses provide high-level evidence that IF effectively improves glucose, lipids, and insulin resistance.[120,121] While direct clinical trials on DPN are still in their infancy, these findings are highly relevant, as improving these upstream metabolic drivers is a foundational strategy for mitigating nerve damage.

The neuroprotective potential of IF extends beyond metabolic improvement, with its most compelling and unique mechanism being the potent induction of autophagy. Autophagy is a critical intracellular process for clearing and recycling damaged com-ponents, such as dysfunctional mitochondria and misfolded proteins.[122] In the pathogenesis of DPN, neurons are burdened by these damaged elements due to glu-cotoxicity and oxidative stress. A groundbreaking study by Alirezaei et al was the first to demonstrate that even short-term fasting induces profound autophagy in neurons.[123] By activating this process, IF may help neurons clear harmful metabolic by-products and repair damaged mitochondria, thereby promoting cellular repair and enhancing neuronal survival.[124]

Furthermore, IF, particularly TRE, helps synchronize nutrient intake with the body's internal circadian rhythms. Metabolism is tightly regulated by the biological clock, and eating at misaligned times can disrupt this rhythm and exacerbate metabolic stress.[125,126] A study by Jamshed et al directly linked early time-restricted feeding to improved 24-hour glucose levels and beneficial changes in markers of the circadian clock, autophagy, and inflammation.[127] Furthermore, preclinical evidence suggests that fasting has the potential to promote the regeneration of peripheral nerves

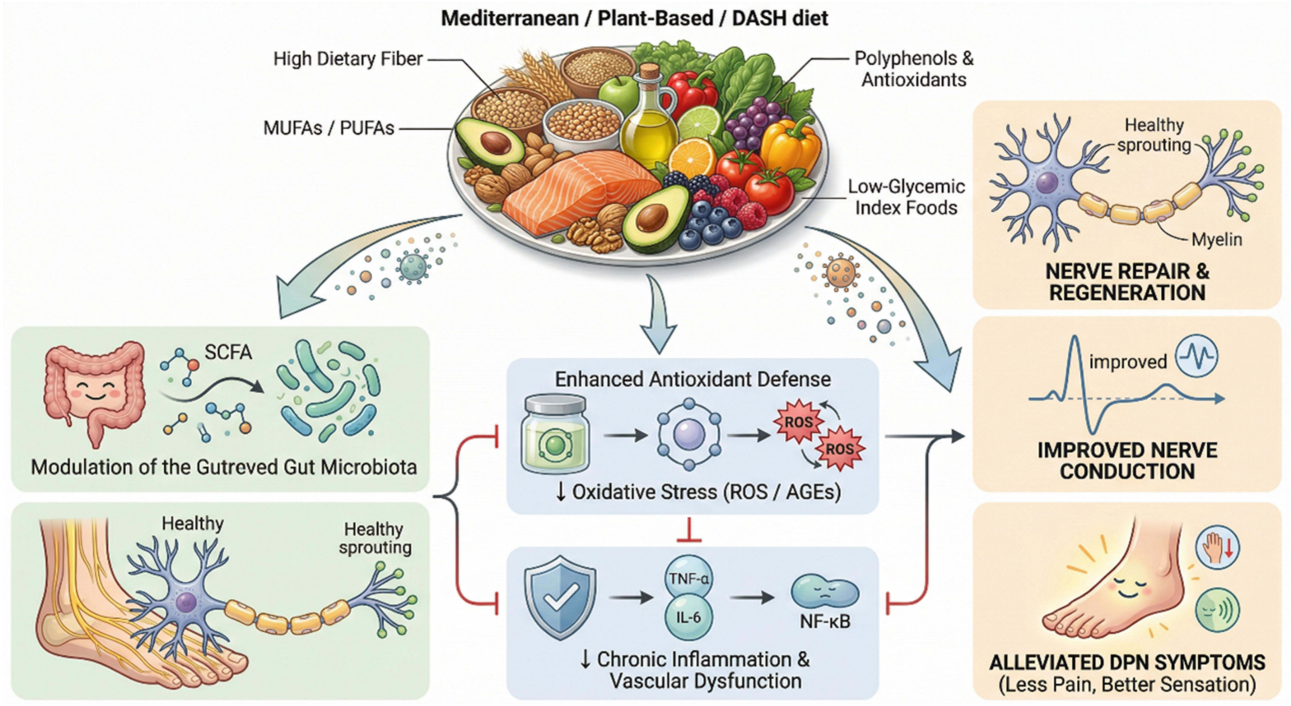

Figure 2 Neuroprotective mechanisms of healthy dietary patterns in DPN. Healthy dietary patterns (e.g., Mediterranean, DASH, plant-based) modulate the gut-nerve axis and promote SCFA production via bioactive nutrients like fiber and antioxidants. These interventions inhibit neuroinflammation and oxidative stress (e.g., ROS and AGEs), facilitating nerve fiber regeneration and improving nerve conduction velocity (NCV), ultimately alleviating neuropathic pain and sensory symptoms.
Abbreviations: DPN, diabetic peripheral neuropathy; SCFA, short-chain fatty acids; ROS, reactive oxygen species; AGEs, advanced glycation end products; NCV, nerve conduction velocity.

and may upregulate levels of neurotrophic factors[128] and increase levels of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which is essential for neuronal survival, growth, and plasticity.[129]

In conclusion, intermittent fasting is an intriguing conceptual intervention that may target DPN through multiple, potentially synergistic pathways. Its hypothesized ability to stimulate neuronal autophagy offers a novel theoretical angle for nerve repair that is less prominent in other dietary patterns. However, research in this area is still in its early stages. Well-designed RCTs are urgently needed to evaluate the efficacy and safety of IF in patients with established diabetic peripheral neuropathy[130,131] (Figure 2).

Discussion

The pathogenesis of diabetic peripheral neuropathy (DPN) is driven by a complex network of interconnected metabolic, oxidative, and inflammatory pathways.[4–6] This review establishes that dietary patterns are a pivotal, modifiable factor capable of influencing these core mechanisms. Healthy dietary patterns, such as the Mediterra-nean and plant-based diets, appear to confer neuroprotection by targeting multiple pathways simultaneously.[33,56] Their rich composition of antiox-idants and an-ti-inflammatory compounds counteracts the damage from oxidative stress and chronic inflammation, which is reflected in the improvement of relevant biomarkers.[132] Conversely, the Western dietary pattern, high in saturated fats and refined carbohy-drates, likely exacerbates DPN by fueling these detrimental pathways.[73,74,133]

Despite compelling mechanistic evidence, a critical gap exists in the literature: the profound lack of high-quality intervention studies targeting patients already diag-nosed with DPN. Most research focuses on primary prevention, leaving it unclear whether dietary modification can serve as a therapeutic strategy to slow progression or alleviate symptoms in those already suffering from neuropathy. Therefore, there is an urgent need to shift the research focus toward this population. Well-designed randomized controlled trials are required to build an evidence base for dietary inter-ventions as a form of secondary prevention and to develop more precise, personalized nutritional therapies.

Abbreviations

The following abbreviations are used in this article: AGEs, Advanced Glycation End Products; AR, Aldose Reductase; CGRP, Calcitonin Gene-Related Peptide; DAG, Diacylglycerol; DN, Diabetic Nephropathy; DPN, Diabetic Peripheral Neuropathy; DSPN, Diabetic Sensorimotor Polyneuropathy; GSH, Reduced Glutathione; HBP, Hexosamine Biosynthesis Pathway; HDL-C, High-Density Lipoprotein Cholesterol; hs-CRP, High-Sensitivity C-Reactive Protein; IENF, Intraepidermal Nerve Fiber Density; IL, Interleukin; IR, Insulin Resistance; IRS, Insulin Receptor Substrate; Lp(a), Lipoprotein(a); MD, Mediterranean Diet; MUFA, Monounsaturated Fatty Acids; NAD+, Nicotinamide Adenine Dinucleotide; NADPH, Reduced Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, Nuclear Factor-κB; NLR, Neutrophil-to-Lymphocyte Ratio; O-GlcNAc, O-linked N-acetylglucosamine; oxLDL, Oxidized Low-Density Lipoprotein; PAI-1, Plasminogen Activator Inhibitor-1; PARP, Poly(ADP-ribose) Polymerase; PKC, Protein Kinase C; RAGE, Receptor for Advanced Glycation End Products; ROS, Reactive Oxygen Species; SAA, Serum Amyloid A; Scr, Serum Creatinine; SDH, Sorbitol Dehydrogenase; SFA, Saturated Fatty Acids; SUA, Serum Uric Acid; T2DM, Type 2 Diabetes Mellitus; TCSS, Toronto Clinical Scoring System; TG, Triglycerides; TGF-β, Transforming Growth Factor-β; TIR, Time in Range; TNF-α, Tumor Necrosis Factor-alpha; TSH, Thyroid-Stimulating Hormone; TyG, Triglyceride-glucose; UACR, Urinary Albumin-to-Creatinine Ratio; UDP-GlcNAc, Uridine Diphosphate N-acetylglucosamine; VEGF, Vascular Endothelial Growth Factor; WMR, White Blood Cell Count to Mean Platelet Volume Ratio.

Data Sharing Statement

Data sharing is not applicable to this article as new data were created.

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