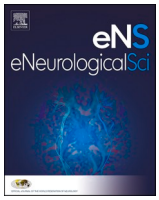
eNeurologicalSci 38 (2025) 100542

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci



Neuropathy and the metabolic syndrome

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ARTICLE INFO

Keywords:
Diabetes
Dyslipidemia
Metabolic syndrome
Neuropathy
Obesity
Prediabetes

ABSTRACT

Obesity and the metabolic syndrome (MetS) are major global health challenges that contribute significantly to the rising prevalence of type 2 diabetes (T2D) and neuropathy. Neuropathy, a common and disabling complication of T2D, is characterized by progressive distal-to-proximal axonal degeneration, driven in part by mitochondrial dysfunction in both neurons and axons. Recent evidence points to the toxic effects of saturated fatty acids on peripheral nerve health, with studies demonstrating that these fats impair mitochondrial function and bioenergetics, leading to distal axonal loss. Conversely, monounsaturated fatty acids are found to be neuroprotective, restoring mitochondrial function and preventing neuropathy. These findings suggest that dietary factors play a crucial role in the pathogenesis of neuropathy associated with metabolic dysregulation and emphasize the need for lifestyle interventions and therapies that target these newly identified mechanisms.

1. Introduction

Obesity is a global epidemic, affecting over 980 million adults worldwide [1], with incidence steadily on the rise due to sedentary lifestyles, Westernized diets, and an aging population [2]. In the Americas (North, Central, and South), 32 % of men and 37 % of women are considered obese, while 20 % of men and 30 % of women in the Eastern Mediterranean Region and 26 % of men and 28 % of women in Europe are considered obese [1]. Projections suggest that if these trends continue, the majority of the global population will be overweight or obese by 2030 [3]. The significant global prevalence of obesity also imposes a substantial financial burden on both healthcare systems and national economies, with the global economic impact of high BMI levels estimated to be approximately 1.96 trillion USD in 2020 [1]. Critically, obesity drives development of the metabolic syndrome (MetS).[4] MetS is characterized by central obesity, elevated blood pressure, insulin resistance, and dyslipidemia and significantly increases the risk of heart disease, stroke, and type 2 diabetes (T2D) [4]. The increased prevalence of MetS, and its constellation of metabolic impairments, driven by the growing rates of obesity, has led to an escalating global pandemic of T2D, which currently affects more than 537 million individuals worldwide [5].

Studies continue to demonstrate that obesity, MetS, and diabetes (both type 1 and T2D) cause profound changes in the peripheral nervous system (PNS) that often lead to the development of neuropathy [6]. Indeed, approximately 50 % of individuals with diabetes develop neuropathy, characterized by progressive length-dependent damage to peripheral nerves, at some point during the disease [7]. Although knowledge regrading neuropathy associated with metabolic dysregulation has significantly advanced over the last decade, the specific pathophysiological mechanisms remain unclear. As the global burden of obesity, MetS, and diabetes increases, identifying and addressing the underlying mechanisms of neuropathy associated with metabolic dysregulation is, therefore, critical to mitigating its rising prevalence.

Abbreviations: CNS, central nervous system; DRG, dorsal root ganglia; HDL, high-density lipoprotein; IENFD, intraepidermal nerve fiber densities; LDL, low-density lipoprotein; MetS, metabolic syndrome; PNS, peripheral nervous system; SCs, Schwann cells; T1D, type 1 diabetes; T2D, type 2 diabetes.

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[4] Abbreviations: CNS, central nervous system; DRG, dorsal root ganglia; HDL, high-density lipoprotein; IENFD, intraepidermal nerve fiber densities; LDL, low-density lipoprotein; MetS, metabolic syndrome; PNS, peripheral nervous system; SCs, Schwann cells; T1D, type 1 diabetes; T2D, type 2 diabetes.

https://doi.org/10.1016/j.ensci.2024.100542
Received 23 October 2024; Accepted 25 November 2024
Available online 28 November 2024

This review explores the pathogenesis of neuropathy within the framework of PNS anatomy, identifying specific drivers of neuropathy associated with MetS. We examine the underlying molecular mechanisms that contribute to neuropathy associated with metabolic dysregulation and their intricate relationship with dietary factors, particularly dyslipidemia. Finally, we highlight evidence suggesting that improvements in metabolic parameters through dietary modifications or exercise may prevent or alleviate neuropathy in at-risk individuals.

2. Anatomy of the peripheral nervous system

The pathophysiology of neuropathy is highly complex and influenced by the unique anatomy and metabolic demands of the PNS. The PNS is composed of a sophisticated network of spinal and cranial nerves, along with supportive Schwann cells (SCs), vasculature-related cells, and connective tissue [6], all of which are essential for maintaining its proper functioning. Efferent motor neurons convey signals from the central nervous system (CNS) to muscles and glands, with their cell bodies residing within the protected environment of the ventral horn of the spinal cord, safe-guarded by the blood-brain barrier from systemic metabolic insults. In contrast, afferent sensory neurons relay information from sensory receptors to the CNS, and their cell bodies are situated in the dorsal root ganglia (DRG), outside the blood-nerve barrier. This exposes them to circulating metabolic byproducts, such as high glucose and fatty acids, making sensory neurons more susceptible to damage due to metabolic dysregulation. To effectively innervate or respond to peripheral targets or stimuli, motor and sensory neurons extend exceptionally long axons, with some axons reaching several feet in length [8]. The distal nature of these axons, combined with their high energy demands, makes them particularly vulnerable to metabolic stressors [8].

Neuronal axons within the PNS can be further classified based on their diameter and myelination status. Large, myelinated axons are responsible for transmitting rapid vibratory and proprioceptive sensations, ensuring the swift relay of information about body position and movement. Smaller-diameter, myelinated axons primarily convey mechanical pressure [9]. In contrast, the most abundant axons in the PNS are C-fibers, small unmyelinated axons less than 1 μm in diameter, which transmit signals related to pain and temperature [8]. The absence of myelin leads to slower impulse conduction and increased susceptibility to metabolic insult, as well as a lack of essential nutrients normally provided by SCs [8].

At its simplest, neuropathy is defined as progressive axonal degeneration [8]. For neuropathy associated with metabolic dysregulation, metabolic insult drives the progressive axonal degeneration of all classes of nerve fiber types over time, though earliest changes are often observed in the abundant, unmyelinated C-fibers [6,8]. Axonal degeneration or loss typically begins at the most distal parts of the neuron (the longest axons), such as the nerves in the feet and hands, and progressively moves toward more proximal regions, closer to the nerve cell body. Clinically, patients often present with a “stocking-and-glove” distribution of sensory loss, meaning that sensory deficits occur in the feet and then the hands, before gradually moving upward as the disease progresses [10]. Negative symptoms include loss of sensation, such as numbness, tingling, and decreased proprioception, which can impair balance and coordination. Upon examination, these patients often have diminished or absent sensation to light touch, pinprick, or vibration in the distal extremities. Patients may also report positive symptoms like burning, shooting pain, or electric shock-like sensations [10]. Together, the complex sensory deficits and pain associated with neuropathy contribute to a wide range of functional impairments that significantly impact quality of life.

3. MetS components drive neuropathy

Clinical evidence clearly demonstrates that MetS is a key driver of neuropathy development [11–13]. While hyperglycemia is a critical risk factor for diabetic neuropathy in type 1 diabetes (T1D) [14,15], intervention trials targeting glucose control in T2D demonstrated only modest reductions in neuropathy risk [16–18]. This suggests that other components of MetS contribute significantly to the pathophysiology of neuropathy associated with metabolic dysregulation. For instance, an observational study comparing obese patients to lean controls found a high prevalence of neuropathy in obese participants, even those with normoglycemia [13]. Additionally, waist circumference and high-density lipoprotein (HDL) cholesterol were strongly associated with neuropathy in a cohort of over 2000 older individuals aged 70–79 [12]. This study also showed that the presence of multiple MetS components, regardless of glycemic status, associated with neuropathy [12]. Another set of studies examining Danish individuals with T2D found, again, that waist circumference, low HDL, and high low-density lipoprotein (LDL) cholesterol increased the risk of diabetic neuropathy [19,20]. In a population-based survey, age, diabetes status, and weight were key predictors of neuropathy [11]. Of note, while MetS components are more common in T2D, they also increase the risk of diabetic neuropathy in individuals with T1D [21,22]. Together, these findings highlight the pivotal role of central obesity and dyslipidemia, independent of hyperglycemia, in both the development and progression of neuropathy in individuals with obesity, MetS, or T2D.

4. Dyslipidemia and bioenergetic failure within the nerve

As noted in Section 2, the PNS is characterized by exceptionally long axons, which necessitate the transport of energy-producing mitochondria from the neuronal cell body to the distal axon terminals [8]. This mitochondrial trafficking is essential for maintaining proper axonal function, but also imposes a significant energy demand on neurons [10]. Under conditions of metabolic dysregulation, such as obesity, MetS, or T2D, mitochondrial function becomes compromised. Dysfunctional mitochondria are unable to meet the energy requirements necessary for both axonal maintenance and mitochondrial transport, ultimately impairing axonal health and function at the terminal ends.

Glucose and lipids are the primary energy substrates used by mitochondria for ATP production, making diet a critical factor in supporting the metabolic needs of the PNS. Dysregulation or an excess of these substrates can disrupt nerve bioenergetics, leading to nerve damage and degeneration. The type of dietary fats consumed plays a particularly crucial role in maintaining PNS bioenergetics and overall nerve health. For example, mice fed a high-fat diet rich in saturated fatty acids develop prediabetes and neuropathy resembling human peripheral neuropathy [23–25]. Interestingly, supplementing their diets with unsaturated fatty acids improves neuropathy, independent of reductions in body fat mass or improvements in systemic insulin resistance [26]. At the cellular level, the impact of fatty acids is stark: treatment with the saturated fatty acid palmitate significantly reduces the number and velocity of motile mitochondria in DRG axons, ultimately leading to neuronal death [27,28]. In contrast, treatment with the monounsaturated fat oleate has no detrimental effect on mitochondrial motility or ATP production [26]. In fact, oleate restores mitochondrial trafficking and function in palmitate-treated DRG [26].

The differential effects of saturated and unsaturated fatty acids on PNS health are linked to their structural properties and metabolic behavior. Unsaturated fatty acids, which contain one or more double bounds, are already partially oxidized, allowing for more efficient oxidation and energy production [29]. In contrast, saturated fatty acids, which lack double bonds, are metabolized less efficiently, leading to substrate accumulation and the production of reactive oxygen species. This results in inflammation, impaired mitochondrial trafficking, distal bioenergetic failure, and ultimately neuropathy when saturated fats are the primary energy source. Additionally, unsaturated fatty acids form lipid droplets that encapsulate harmful saturated fatty acids, preventing their toxic effects on nerve cells [26,28]. Thus, dyslipidemia resulting from a diet rich in saturated fatty acids impairs mitochondrial function

and trafficking, causing energetic failure at the distal axonal termini, distal to proximal loss of axonal function, and ultimately neuropathy (Fig. 1).

5. Diet and exercise for metabolic neuropathy

As noted in Section 3, for patients with T1D, tight glucose control targeting normal glycemia does decrease the incidence of diabetic neuropathy [30]. However, for neuropathy associated with metabolic dysregulation, the American Diabetes Association recommends lifestyle interventions, which include diet, exercise, or addressing hypertension, dyslipidemia, and glucose control [31]. It is well-established that dietary changes and exercise improve systemic metabolic health in individuals with obesity, MetS, and T2D [32–34]. Growing evidence also suggests that by correcting metabolic dysregulation, these interventions can also prevent or alleviate neuropathy [35]. For example, a randomized control trial divided individuals with prediabetes or newly diagnosed diabetes into two groups: one group underwent a lifestyle intervention consisting of diet modification and increased physical activity, while the control group received standard care [36]. Results from the study showed that the lifestyle intervention group experienced significant improvements in cutaneous reinnervation, neuropathy symptoms, and nerve function compared to the control group. Specifically, intraepidermal nerve fiber densities (IENFDs) were higher, nerve conduction velocities were faster, and patients reported reductions in pain and discomfort associated with neuropathy. The study concluded that early diet and lifestyle interventions focusing on diet and exercise could play a critical role in preventing the progression of prediabetic neuropathy. Similar results were also observed in later clinical studies, where exercise increased IENFDs in distal and proximal lower extremity skin biopsies of patients with MetS or diabetes, suggesting that exercise enhances cutaneous regenerative capacity [37–39].

Regarding dietary interventions, following a Mediterranean diet, which is rich in fruits, vegetables, whole grains, and olive oil, is associated with a lowered incidence of neuropathy in patients with T1D or T2D [40]. Additionally, a 20-week pilot study reported that adherence to a low-fat, plant-based diet, with weekly support classes, and vitamin B12 supplementation improved electrochemical skin conductance in feet and pain measures in individuals with T2D and painful diabetic neuropathy [41]. Thus, diet and lifestyle interventions are effective ways to improve metabolic dysregulation and promote peripheral nerve health to prevent or improve neuropathy. However, additional studies are needed to identify the exact molecular mechanisms underlying the neuroprotective benefits of diet and exercise and to directly compare the effectiveness of each intervention, alone or in combination.

6. Conclusions

To conclude, while maintaining glucose control is essential for managing neuropathy in patients with T1D, metabolic dysregulation has emerged as the primary clinical target for preventing and managing neuropathy in patients with obesity, MetS, and T2D. A key contributor to the development of neuropathy associated with metabolic dysregulation is mitochondrial dysfunction in neurons and axons due to the toxic effect of saturated fatty acids. These findings underscore the critical role of diet in damaging the PNS, as poor dietary choices are central to the development of MetS. In contrast, monounsaturated fatty acids have been shown to protect and support nerve health. Given the rising prevalence of obesity, MetS, and diabetes, it is crucial that future studies focus on these underlying mechanisms and explore early interventions that address them. Without such efforts, the burden of neuropathy driven by obesity, MetS, and T2D will continue to grow, placing an even greater strain on public health.

Funding

This work was supported by the National Institutes of Health [grant numbers R01DK130913 to E.L.F.]; the Dr. John H. Doran Neuropathy Research Fund [E.L.F.]; the NeuroNetwork for Emerging Therapies at the University of Michigan [E.L.F.]; the School of Superior Studies

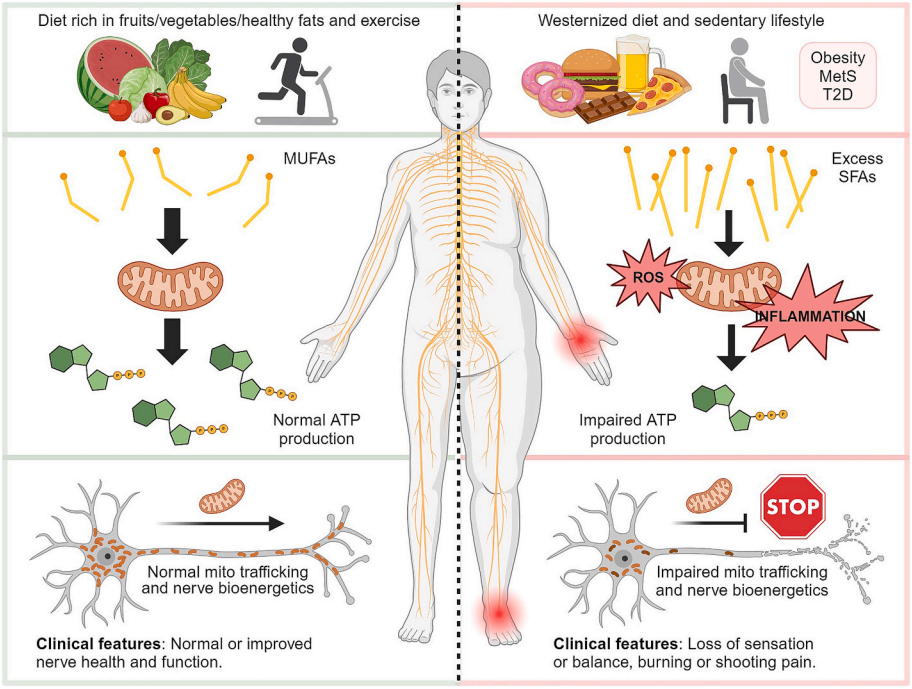

Fig. 1. Nerve and metabolic health. Diets rich in fruits, vegetables, and health fats, particularly monounsaturated fatty acids (MUFAs), along with exercise, support normal mitochondrial (mito) ATP production, energetics, and trafficking, which in turn promote healthy nerve function. In contrast, excess saturated fatty acids (SFAs) from a Westernized diet compromise mito function, leading to impaired mito trafficking, distal energetic failure, and peripheral nerve degeneration. ATP, adenosine triphosphate; MetS, metabolic syndrome; ROS, reactive oxygen species; T2D, type 2 diabetes. Image was created using BioRender.com.

"Ferdinando Rossi" of the University of Turin [N.P.]; the William Demant Foundation [A.W.]; the Danish Diabetes Association [A.W.]; the Hede Nielsen Family Foundation [A.W.]; and the Dagmar Marshalls Foundation [A.W.].

CRediT authorship contribution statement

Nicoló Piccolo: Writing – original draft, Writing – review & editing. **Astrid Wiggers:** Writing – original draft, Writing – review & editing. **Emily J. Koubek:** Writing – original draft, Writing – review & editing. **Eva L. Feldman:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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