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REVIEW ARTICLE

Diabetic Neuropathy, Pain, and Sarcopenia: An Integrative Review of Their Convergent Pathophysiological Mechanisms and Clinical Association

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SUMMARY

Introduction: Diabetes mellitus (DM) is an accelerator of biological aging. Diabetic peripheral neuropathy (DPN) and sarcopenia, traditionally viewed separately, are emerging as prevalent complications that share pathogenic pathways. Evidence suggests a synergistic and bidirectional interaction, where neuropathic pain is an active catalyst for musculoskeletal deterioration and disability.

Methods: A rigorous integrative review (Whittemore and Knafl framework) was performed, synthesizing heterogeneous evidence from PubMed, Scopus, and Google Scholar (2015–2025). Studies that explicitly assessed the clinical, functional, and biomolecular substrates between neuropathy, chronic pain, and muscle function in adults with diabetes were selected.

Results: The synthesis confirms a robust, clinically relevant, bidirectional association. Patients with the painful diabetic foot-and-mouth disease phenotype exhibit a significantly higher prevalence of severe sarcopenia and dynapenia (weakness), a finding that persists after adjusting for age and duration of diabetes. Pain acts as a behavioral disruptor (inducing kinesiophobia and disuse atrophy). Pathophysiologically, the convergence is based on three axes: (1) toxicity from advanced glycation end products (AGEs, such as pentosidine); (2) impaired mitochondrial bioenergetics that generates oxidative stress; and (3) pro-inflammatory neuroimmune crosstalk that perpetuates protein catabolism.

Conclusions: Neuromuscular neuropathy (NDP) is a complex and disabling neuromuscular syndrome. It is imperative to incorporate dynamometric and functional assessments into the routine screening of patients with neuropathic pain in order to intercept irreversible physical disability through early and multimodal interventions.

Keywords: Diabetic Neuropathies, Sarcopenia, Neuralgia, Dynapenia, Advanced Glycation End Products, Neuroimmune Crosstalk.

INTRODUCTION

Diabetes mellitus (DM) represents a paradigmatic challenge for global public health in the 21st century, defined not only by chronic dysglycemia but also by a devastating spectrum of multisystemic complications that precipitate functional decline and increase healthcare costs. Among these complications, diabetic peripheral neuropathy (DPN) stands out as the most prevalent microvascular impairment, substantially impacting the quality of life of up to 50% of patients throughout their lifespan. This condition manifests through a heterogeneous range of symptoms, from debilitating paresthesias to neuropathic ulcers (1).

Historically, research and clinical management of peripheral neuropathy (PN) have focused almost exclusively on sensory and autonomic dysfunction, relegating motor function to a secondary role. However, the integrity of the motor system and the quality of skeletal muscle have emerged in the last decade as critical, though dangerously underestimated, determinants in the natural history of the disease. In this evolving clinical scenario, sarcopenia—reconceptualized not as an inevitable sign of aging, but as a pathological muscle insufficiency characterized by the progressive loss of mass, strength, and function—has been identified as a frequent and aggressive comorbidity in the diabetic population, whose progression is exponentially exacerbated by peripheral denervation (2).

The clinical intersection between PDN and sarcopenia transcends mere geriatric coincidence, suggesting a deeply intertwined pathophysiology. Contemporary epidemiological and mechanistic studies indicate a bidirectional and synergistic association: the prevalence of sarcopenia is significantly higher in patients with painful neuropathy phenotypes compared to those with painless forms or no nerve damage. This finding postulates chronic neuropathic pain as a metabolic and behavioral catalyst for muscle catabolism (3,4). Clinically, this deterioration phenomenon manifests early as dynapenia (loss of intrinsic muscle strength), which correlates directly with the severity and extent of distal symmetric polyneuropathy (5). This creates a “toxic triad”—refractory neuropathic pain, progressive muscle incompetence, and biomechanical instability—which establishes a vicious cycle of forced physical inactivity and secondary atrophy, drastically increasing the risk of falls, fragility fractures, and premature functional dependence (6,7).

However, reducing diabetic muscle atrophy to a mechanical consequence of disuse due to pain would result in a mechanistic reductionism that ignores the underlying biology. Current literature points to a shared and complex molecular etiology. Chronic hyperglycemia promotes the systemic and tissue accumulation of advanced glycation end products (AGEs), such as pentosidine, which compromise nerve ultrastructure and muscle contractile machinery, inducing extracellular matrix stiffness and cell apoptosis (8). In parallel, mitochondrial dysfunction and oxidative stress act as cross-cutting axes that link glucotoxicity with distal axonal degeneration and diabetic myopathy. Additionally, a state of chronic low-grade inflammation, mediated by proinflammatory cytokines, has been described, which simultaneously promotes central and peripheral nociceptive sensitization, as well as the activation of muscle proteolytic pathways.

Despite the compelling nature of these recent findings, considerable discrepancies remain in the scientific literature regarding how these molecular domains specifically interact with the patient's clinical phenotype. Therefore, this integrative review aims to synthesize the available evidence on the clinical association between diabetic neuropathy, pain, and sarcopenia, and to elucidate the convergent pathophysiological mechanisms—neurogenic, metabolic, and inflammatory—that underlie this detrimental interaction, to propose new diagnostic and therapeutic approaches.

METHODS

Methodological design and approach

An integrative literature review was conducted, rigorously adopting the five-stage methodological

framework proposed by Whittemore and Knafl: 1) problem identification; 2) literature search; 3) data appraisal; 4) data analysis; and 5) presentation. This design was strategically selected for its inherent capacity to synthesize studies with heterogeneous methodologies (including experimental trials, cohort studies, and cross-sectional studies), allowing for a holistic and multidimensional understanding of complex phenomena such as neuromuscular interaction in the context of chronic diseases.

Search strategy and information sources

The literature review was conducted through systematic and exhaustive searches in high-impact electronic databases: PubMed, Scopus, and Google Scholar. High-sensitivity and high-specificity Boolean search algorithms were designed, combining MeSH (Medical Subject Headings) controlled terms and free vocabulary, structured into three interrelated conceptual domains:

- **Population/clinical condition:** «Diabetic Neuropathies», «Painful Diabetic Neuropathy», «Type 2 Diabetes Mellitus», «Peripheral Nervous System Diseases».
- **Muscular and functional outcome:** «Sarcopenia», «Muscle Atrophy», «Dynapenia», «Muscle Weakness», «Myosteatosis», «Gait Disorders, Neurologic».
- **Mechanisms/pathophysiology:** «Pathophysiology», «Oxidative Stress», «Advanced Glycation End Products», «Mitochondrial Dysfunction», «Inflammation mediators».

Eligibility, selection and rigor criteria

The selection of studies was governed by strict inclusion and exclusion criteria to ensure the internal validity of the review:

- **Inclusion:** 1) studies conducted in adult populations (over 18 years of age) with a confirmed diagnosis of type 1 or 2 diabetes mellitus according to international criteria; 2) research that explicitly evaluated the statistical or biological covariation between neuropathy (painful/painless) and quantitative metrics of muscle health (mass, strength, quality); and 3) availability of the full text in English or Spanish for in-depth analysis.
- **Exclusion:** Single case reports were excluded due to their low level of evidence, as were editorials or expert opinions without empirical data, and studies focused on non-diabetic myopathies, neuropathies of other etiologies (e.g., chemotherapy, alcoholic) or exclusively animal models without a clinical correlate discussed in the manuscript.
- **Temporality:** The publication period 2015–2025 was prioritized to ensure the currency of the pathophysiological and clinical data. However, the selective inclusion of seminal and classic literature (e.g., Young et al., 1993; Davies et al., 2006) was permitted to provide a solid epidemiological context and relevant historical definitions.

Extraction, quality assessment, and synthesis

The extracted data were systematized in an evidence matrix that included design variables, sample size, diagnostic tools, and main results. A critical appraisal of the methodological quality of the primary studies was performed, prioritizing those that controlled for bias through multivariable adjustments (age, HbA1c, duration of diabetes). Due to the heterogeneity of the reported metrics (e.g., different cut-off points for sarcopenia), a thematic narrative synthesis was chosen, grouped into three logical clusters: 1) prevalence and bidirectional clinical association; 2) functional and behavioral impact of neuropathic pain; and 3) convergent pathophysiological mechanisms.

RESULTS

A systematic and critical analysis of the selected literature reveals an unequivocal convergence between peripheral nervous system deterioration and loss of muscular system integrity. The findings, derived from various methodological designs, including large cross-sectional studies and longitudinal follow-ups, delineate an increased risk profile that far exceeds that expected from physiological aging alone.

Prevalence and bidirectional clinical association

Epidemiological evidence confirms a positive, significant, and robust correlation between the presence of diabetic peripheral neuropathy (DPN) and accelerated deterioration of muscle health. Multiple international cohorts corroborate that the prevalence of sarcopenia is notably higher—even doubling in some series—in patients with type 2 diabetes complicated by neuropathy compared to diabetics without nerve involvement. This association remains statistically significant even after rigorous

multivariable adjustments for age, sex, disease duration, renal function, and glycemic control (HbA1c), suggesting a direct pathogenic link.

In this regard, the pivotal study by Oh et al. established that peripheral denervation (PDN) is an independent predictor of low appendicular muscle mass, reporting an odds ratio that demonstrates how the risk of sarcopenia scales proportionally with the severity of neuropathic damage (measured by clinical scales and nerve conduction velocity) (2). This finding is crucial for understanding the disease, as it suggests that motor denervation is not a late or trivial epiphenomenon, but a parallel and aggressive process that decimates lean tissue, predominantly in the lower extremities.

Furthermore, a review of the literature reveals a pathological bidirectionality: skeletal muscle, being the primary target organ for insulin-mediated glucose uptake, plays a crucial metabolic role. Sarcopenia, by reducing this glucose “sink,” perpetuates hyperglycemia and insulin resistance, creating a negative feedback loop that accelerates neurotoxicity and neurodegeneration.

Functional impact of neuropathic pain

The symptomatic dimension of neuropathy introduces a critical variable that drastically modifies the patient's functional prognosis: neuropathic pain. With an estimated global prevalence between 21% and 54% in the diabetic population (3,4), pain transcends its nociceptive nature to become a potent biomechanical and psychosocial disruptor.

The synthesis of the data indicates that patients with painful phenotypes (painful PPN) are consistently associated with worse skeletal muscle mass indices and functional physical performance compared to those with silent or hypoesthetic neuropathies. The mechanism underlying this discrepancy involves a complex maladaptive behavioral component: “kinesiophobia,” or an irrational fear of movement that exacerbates or triggers pain. This psychological phenomenon precipitates severe sedentary behavior and avoidance behaviors, inevitably leading to secondary disuse muscle atrophy (6).

Functionally, this deterioration presents clinically as dynapenia (loss of strength) long before muscle volume loss is evident upon inspection. Almurdhi et al. demonstrated, using computerized dynamometry, a significant reduction in isometric strength and contractile quality of the knee extensor and flexor groups, which was inversely correlated with the Toronto Clinical Neuropathy Score (5). This proximal weakness, combined with the distal proprioceptive deficit characteristic of neuropathy, severely compromises gait pattern and postural control, exponentially increasing the risk of falls, hip fractures, and subsequent institutionalization (7).

Convergent pathophysiological mechanisms

Beyond physical inactivity secondary to pain, the review identifies three fundamental molecular axes that explain the synchronicity of injury in the nerve and muscle, suggesting a shared pathogenesis, presented below.

Chronic hyperglycemia acts as the primary driver catalyzing the formation of advanced glycation end products (AGEs) through the Maillard reaction. Zhang et al. demonstrated in a clinical cohort that elevated serum pentosidine levels (a specific and stable biomarker of AGEs) are independently associated with a high prevalence of sarcopenia in diabetic patients (8). At the tissue level, AGEs induce aberrant cross-linking of collagen fibers in the epimysium and endomysium of muscle, increasing passive muscle stiffness and reducing the mechanical efficiency of contraction. Simultaneously, these toxic compounds accumulate in nervous tissue, perpetuating oxidative stress in Schwann cells and compromising endoneural microcirculation, proposing a shared toxicity mechanism (9).

The mitochondria is positioned as the central organelle in this dual pathology. Recent studies, such as those by Xie et al. and Vincent et al., highlight that mitochondrial dysfunction in dorsal root ganglion neurons not only sustains peripheral nociceptive sensitization (the cause of pain) but is also phenotypically replicated in the myocyte (10,11). The inability of diabetic mitochondria to efficiently oxidize excess energy substrates generates a massive electron leak and the production of reactive oxygen species (ROS). These ROS activate apoptotic signaling cascades mediated by caspases and cytochrome c, both in distal axons (neurodegeneration) and in muscle fibers (myopathy), validating the theory of “failed bioenergetics” as the dual driving force of the disease.

Finally, there is a low-grade systemic inflammatory state that biologically links pain to accelerated proteolysis. Pro-inflammatory cytokines such as TNF-alpha and IL-6, which are elevated systemically

in patients with painful neuropathy, act in a biphasic and deleterious manner: on the one hand, they sensitize peripheral nociceptors, lowering their firing threshold (hyperalgesia/allodynia), and on the other hand, they potently stimulate the ubiquitin-proteasome pathway and the expression of atrogenes (MuRF1, Atrogin-1) in skeletal muscle (12). Ji et al. suggest that this “neuroimmune crosstalk” creates a hostile catabolic environment where the inflammatory response, originally intended to repair nerve damage, ends up accelerating muscle protein degradation, consolidating the sarcopenic-neuropathic phenotype (13).

DISCUSSION

This integrative review synthesizes and contrasts critical evidence that redefines diabetic peripheral neuropathy (DPN) not as an isolated entity, but as a central component in the pathophysiology of musculoskeletal deterioration. Unlike previous reviews focused exclusively on glycemic control, the findings presented here demonstrate that the coexistence of DPN, pain, and sarcopenia is due to a robust mechanistic convergence, validated by specific clinical and molecular markers.

The analyzed results consistently confirm the hypothesis of a bidirectional association. The observation by Oh et al. (2), who reported that neuropathy severity independently predicts sarcopenia, is consistent with recent meta-analysis findings such as those by Wannarong et al. (14), which identify neuropathy as one of the most potent risk factors for muscle wasting, even surpassing nephropathy in some studies. This evidence challenges the traditional paradigm that considered sarcopenia in diabetes simply as an effect of aging. On the contrary, Nomura et al. suggest that diabetes induces "accelerated muscle aging" (15), and our findings indicate that denervation is the primary driver of this process. Clinically, this implies that muscle assessment in neuropathic patients is not optional, but imperative.

A critical point of debate in the literature is the timing: what comes first, the loss of strength or muscle mass? Our review strongly supports the findings of Almurdhi et al. (5), who detected strength deficits (dynapenia) in patients with early-stage neuropathy who still retained their muscle volume. This is physiologically explained by the preferential loss of large, fast-twitch (type II) motor units, which are the first to undergo denervation in diabetic neuropathy, affecting power before overall muscle structure. This muscle “quality failure,” exacerbated by fatty infiltration or mysteatosis, indicates that screening based solely on mass (e.g., calf circumference) is insufficient and too late; hand or quadriceps dynamometry should be the gold standard in diabetological clinical practice.

The interaction between pain and sarcopenia is complex. While Attia & Hamdan (3) document the high prevalence of this comorbidity, it is Yang et al. (6) who illuminate the behavioral mechanism: kinesiophobia. However, we should not attribute everything to disuse. Reviewed mechanistic studies indicate that chronic pain elevates markers of systemic stress (cortisol, catecholamines) that are inherently catabolic. Therefore, as Basit et al. (4) argue, neuropathic pain is a continuous biological stressor. Analgesic treatment, then, not only seeks symptomatic relief but also the disruption of this catabolic state, allowing for physical reactivation, which is, to date, the only proven anabolic agent for this population.

Our review strengthens the theory of*Common Soil* (common floor) initially proposed for microvascular complications, extending it to muscle.

- **Axis of the AGEs:** The correlation found by Zhang et al. (8) between pentosidine and sarcopenia provides the missing molecular link. It is not simply that the nerve dies and the muscle atrophies; it is that both tissues become "caramelized" and stiffened simultaneously. This agrees with Mori et al. (9), who describe the same process in Schwann cells.
- **Mitochondrial axis:** Recent evidence from Xie et al. (10) on bioenergetic dysfunction in dorsal root ganglia offers an elegant explanation for the fatigue and weakness reported by these patients, beyond atrophy. Consistent with Vincent et al. (11), we propose that the mitochondria is the shared “Achilles’ heel” where neurotoxicity and myotoxicity converge.
- **Inflammatory axis:** The “neuroimmune crosstalk” described by Ji et al. (13) and Bian et al. (12) completes the circle, demonstrating that inflammation is not a spectator but an active executioner that degrades muscle proteins through the ubiquitin-proteasome system, stimulated by the same cytokines that cause hyperalgesia.

As a limitation of this review, we must acknowledge that most of the included studies, such as that by Oh

et al., are cross-sectional, which prevents us from establishing definitive causality. Furthermore, the heterogeneity in sarcopenia criteria (EWGSOP vs. AWGS) introduces variability in the reported prevalence rates. However, the strength of this review lies in its integrative approach, combining clinical findings on strength and pain with cutting-edge molecular mechanisms (mitochondria/AGEs), thus providing a solid theoretical foundation for future clinical trials.

Based on the robustness of the evidence discussed, we propose the following imperative-level recommendations:

- **Dual screening:** All patients with NDP, especially those with pain, should be evaluated for dynapenia (grip strength) annually.
- **Aggressive pain management:** Pain management should be considered a “muscle-sparing” intervention.
- **Exercise prescription:** Given the evidence of mitochondrial dysfunction, resistance exercise is not optional, but rather part of the etiological treatment to improve tissue bioenergetics.

In conclusion, painful diabetic neuropathy and sarcopenia are interdependent pathological entities that share a common pathophysiological substrate—characterized by AGE toxicity, mitochondrial bioenergetic failure, and chronic inflammation—and are mutually potentiated through pain-induced physical inactivity (antalgic vicious cycle). Dynapenia stands out as an early warning clinical sign with high prognostic value, temporally preceding evident anatomical atrophy. Consequently, the clinical management of diabetic neuropathy must evolve from a purely symptomatic and pharmacological approach toward a comprehensive functional preservation model. The systematic and protocol-based inclusion of muscle strength assessment in the follow-up of patients with neuropathy is recommended, considering that early intervention on the pain-muscle nexus is the only effective way to interrupt the progression to disability and dependence in this vulnerable population.

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Conflicts of interest

The authors declare no commercial conflicts of interest.

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