SCRIPTA SCIENTIA
ISSN: 3134-5824 | Vol. 1 (2026)

Published by
ChauxLab Institute

REVIEW ARTICLE

Phenotypic Characterization of Sarcopenia in Patients With Diabetic Neuropathy: The Role of Pain and Motor Dysfunction

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Received: 1 Jan 2026
Accepted: 11 Jan 2026
Published: 13 Jan 2026

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How to cite this article:

Correa Nogueira J, De Paula Oliveira LV, De Souza Teixeira J, Dos Santos Mendes RR, De Santana TN, De Oliveira Becegato MM, Dinnebier ME, Danielli PT. Phenotypic characterization of sarcopenia in patients with diabetic neuropathy: The role of pain and motor dysfunction. *Scripta Scientia.* 2026;1:e003

DOI:
https://doi.org/10.66201/ss.v1.3

SUMMARY

Introduction: Although diabetic peripheral neuropathy (DPN) is a known risk factor for sarcopenia, the literature has not sufficiently characterized the differential impact of clinical phenotypes, specifically painful versus painless DPN, on muscle function. The aim of this review is to assess and compare the prevalence, underlying pathophysiological mechanisms, and clinical characteristics of sarcopenia and dynapenia (weakness) in patients with painful versus painless DPN.

Methods: A comprehensive integrative review of the scientific literature was conducted (January 2014 to January 2024) using PubMed, Scopus, and Scite.ai. The Whittemore and Knafl framework was applied, and the MMAT and JBI tools were used to assess the methodological quality of observational studies and clinical trials that stratified patients by neuropathic symptomatology.

Results: The pain phenotype is significantly associated with earlier onset of dynapenia and greater clinical severity. This functional impairment is driven by a “biobehavioral vicious cycle” that includes kinesiophobia (avoidance of movement) and a state of systemic neuroinflammation (characterized by elevated levels of TNF-α and IL-6). Furthermore, conventional screening tools, such as the SARC-F questionnaire, have been found to have low sensitivity in this population. Muscle ultrasound, by detecting early qualitative changes such as myosteatosis (fatty infiltration), emerges as a superior screening technique.

Conclusions: Neuropathic pain is an independent catalyst for accelerated motor disability. A high-risk profile is proposed that requires priority screening strategies using dynamometry and advanced imaging techniques. Pain management should be redefined as an essential

intervention for preserving muscle function.

Keywords: Diabetic Neuropathy, Sarcopenia, Dynapenia, Neuropathic Pain, Phenotype, Myosteatosis.

INTRODUCTION

Diabetes mellitus (DM) and sarcopenia together represent two of the most formidable and complex challenges in contemporary public health. This pathological convergence constitutes a “double burden” of metabolic and functional impairment that drastically accelerates the physical decline of middle-aged and elderly patients. The global prevalence of diabetic peripheral neuropathy (DPN) is estimated at 46% according to recent meta-analyses (1), with ranges varying widely between 8% and 59% depending on the population studied and the diagnostic criteria (2,3). Concurrently, the progressive and generalized loss of muscle mass and strength—a clinical entity known as sarcopenia—has emerged as an “invisible” or overlooked complication that significantly exacerbates morbidity, dependence, and the risk of falls and fractures.

From a historical perspective, clinical and research attention to diabetic foot ulcers (DFU) has been almost exclusively focused on preventing its most dramatic complications: diabetic foot ulcers and non-traumatic amputations. In this traditional paradigm, the muscle weakness observed in diabetic patients was frequently, and simplistically, attributed to the natural aging process or general physical deconditioning resulting from a sedentary lifestyle. However, the evidence accumulated in the last decade challenges this notion, strongly suggesting that DFU constitutes an independent and potent risk factor for the development of sarcopenia (4). This link is mediated by complex and multifactorial pathophysiological mechanisms that include chronic low-grade inflammation, insulin resistance in muscle tissue, mitochondrial dysfunction, and the progressive loss of motor units. However, there is critical clinical heterogeneity within the neuropathic population that is often overlooked in general studies: the presentation and evolution of the disease vary drastically between painful and non-painful phenotypes.

The phenotype of painful diabetic neuropathy (PDN), which affects a significant proportion—approximately 25–50%—of patients with established neuropathy (5,6), introduces a critical variable into the equation of muscle health: chronic nociception. Unlike painless neuropathy, where the clinical risk lies primarily in the lack of protective sensory feedback (leading to unnoticed injury), patients with PDN experience a vicious and debilitating cycle of avoidance behavior and antalgic gait. This behavior, instinctively adopted to minimize pain, accelerates disuse muscle atrophy. Recent studies indicate a worrying inverse correlation: the intensity of neuropathic pain is directly associated with a decrease in gait speed and handgrip strength (7), suggesting that pain acts not only as a symptom but also as an active catalyst for dynapenia (loss of strength).

Despite these substantial phenotypic differences, current clinical practice guidelines rarely stratify the risk of sarcopenia based on the presence or severity of painful symptoms. Therefore, there is a pressing need to characterize these phenotypes more precisely to design and implement early screening strategies before motor disability becomes irreversible. The central aim of this integrative review is to critically assess the prevalence, elucidate the shared pathophysiological mechanisms, and describe the distinctive clinical features of sarcopenia and dynapenia in patients with painful versus non-painful diabetic neuropathy. The ultimate goal is to propose a clinical risk profile to guide medical practice.

METHODS

Studio design

An integrative literature review was conducted, rigorously following the methodological framework proposed by Whittemore and Knafl (2005) (8). This specific design was deliberately selected for its versatility and unique ability to combine data from diverse empirical literature (quantitative, qualitative, and mixed methods) with theoretical perspectives. This allows for a more holistic and in-depth

understanding of complex phenomena such as neuromuscular interaction in diabetes, where biological and behavioral factors are intertwined. The final review report adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, specifically adapted to ensure the transparency, rigor, and reproducibility of the study selection and synthesis process.

Search strategy

The systematic and exhaustive search was conducted using three high-impact and biomedically relevant electronic databases: PubMed/MEDLINE, Scopus, and Scite.ai. The search window covered the period from January 2014 to January 2024. This 10-year time frame was strategically established to ensure the inclusion of studies that used contemporary and consensus definitions of sarcopenia (such as the 2019 EWGSOP2 criteria) and updated diagnostic criteria for neuropathy, thus guaranteeing the currency of the findings.

An iterative and responsive Boolean search strategy was designed, using a combination of MeSH (Medical Subject Headings) terms and free-text keywords to capture all possible terminological variations. The base search string was structured as follows:

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("Diabetic Neuropathies"[MeSH] OR "Diabetic Neuropathy" OR "Painful Diabetic Neuropathy" OR "Diabetic Polyneuropathy") AND ("Sarcopenia"[MeSH] OR "Muscle Weakness" OR "Dynapenia" OR "Muscle Atrophy" OR "Skeletal Muscle Mass") AND ("Pain" OR "Phenotype" OR "Screening" OR "Diagnosis").
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Additionally, a secondary manual search was conducted using the "snowball" technique in the reference lists of the included primary studies, to identify relevant grey literature or key articles that may not have been initially indexed.

Eligibility criteria

To ensure the relevance and homogeneity of the evidence, the following inclusion and exclusion criteria were applied:

- **Population:** Studies were included that were conducted in adults (>18 years) with a confirmed diagnosis of diabetes mellitus (either type 1 or type 2) and the documented presence of peripheral neuropathy (PDN).
- **Interest:** The main focus was on studies that quantitatively assessed parameters of sarcopenia (such as appendicular muscle mass, skeletal muscle mass index) or dynapenia (handgrip strength, walking speed, chair stand test) and that, crucially, allowed differentiation or comparison between painful and non-painful phenotypes of neuropathy.
- **Context:** Research conducted in primary care settings, specialized diabetic foot clinics, endocrinology units, or rehabilitation centers was considered.
- **Designs:** Analytical observational studies (cross-sectional, prospective or retrospective cohort, case-control), as well as clinical trials (using their baseline data) and diagnostic validation studies of screening tools were included.
- **Exclusion:** Studies conducted in animal models, single case reports, opinion editorials, narrative reviews without systematic methodology, and studies focused exclusively on non-diabetic myopathies or polyneuropathies of other origin (e.g., chemotherapy-induced, alcoholic, or hereditary) were systematically excluded.

Evaluation of methodological quality

The methodological quality and risk of bias of the included studies were assessed independently using standardized tools. The Mixed Methods Appraisal Tool (MMAT) 2018 was used for qualitative and mixed-methods studies, while the Joanna Briggs Institute (JBI) critical appraisal tools were used for cross-sectional and cohort studies. During this process, priority was given to assessing the control of confounding biases (specifically, statistical adjustment for age, sex, duration of diabetes, and HbA1c levels) and the validity of measurement biases (use of internationally validated instruments such as the DN4 questionnaire for neuropathic pain and hydraulic dynamometry for muscle strength).

RESULTS

A systematic literature review identified and synthesized clear patterns linking diabetic neuropathy to accelerated muscle deterioration. The findings are presented below, structured narratively

to accurately differentiate the specific and disproportionate impact of neuropathic pain.

Phenotypic divergence: dynapenia precedes sarcopenia

The compiled evidence unequivocally demonstrates that diabetic neuropathy functions not only as a comorbidity but also as an independent accelerator of musculoskeletal deterioration. Although the overall prevalence of sarcopenia in patients with diabetic neuropathy varies significantly between 17% and 45% depending on the population (4)—figures that far exceed those observed in diabetic controls without neuropathy—stratified analysis reveals a critical temporal and qualitative distinction between clinical subgroups.

The pain phenotype (NDD) is distinctively characterized by a premature loss of muscle quality and functional strength, a condition known as dynapenia, which chronologically precedes the massive loss of muscle volume detectable by conventional anthropometry or DXA. This clinical observation is supported by recent and rigorous studies, such as that by Hary et al. (7), who reported significant and robust negative correlations between pain severity scores (measured by DN4 or visual analog scales) and handgrip strength ($r = -0.45$, $P < 0.01$). This finding is fundamental, as it indicates that pain intensity is a direct predictor of reduced functional capacity, regardless of whether total muscle mass is preserved. Pain, therefore, acts as an acute functional limiter; reduced walking speed and altered gait patterns are evident even in early stages where severe atrophy is not yet macroscopically visible.

In stark contrast, the painless phenotype exhibits a more insidious, slow, and silent pattern of muscle atrophy. This process is pathophysiologically linked to long-standing chronic motor denervation and the progressive loss of protective sensation. While these patients experience a significant reduction in long-term muscle volume, particularly in the intrinsic muscles of the foot and calf (9), their initial explosive strength and functional capacity are often better preserved compared to the severe pain group. This is primarily due to the absence of acute reflex motor inhibition mediated by nociception.

Convergent pathophysiology: from nerve to muscle

A detailed synthesis of the literature allows us to outline a dual and synergistic pathophysiological architecture that explains the greater clinical severity observed in the pain group.

Initially, a behavioral loop of motor inhibition is identified, frequently described in the rehabilitation literature as kinesiophobia or irrational fear of movement. Since neuropathic pain is usually characterized by mechanical allodynia (pain in response to non-painful stimuli) and is exacerbated by physical activity or even the simple touch of clothing, patients consciously or unconsciously adopt drastic avoidance behaviors. This forced and sustained immobility activates potent catabolic cascades of disuse that disproportionately affect type II (fast-twitch) muscle fibers, which are metabolically more susceptible to inactivity and essential for reactive balance and fall prevention (10).

Alongside the behavioral mechanism, there is a shared molecular toxicity between the damaged peripheral nerve and skeletal muscle tissue. The reviewed studies consistently report a systemic elevation of proinflammatory cytokines, specifically TNF-α, IL-6, and IL-1β, in patients with severe pain phenotypes. These inflammatory markers act as a “dual agent”: on the one hand, they sensitize peripheral nociceptors, generating peripheral and central hyperalgesia, and on the other hand, they block the mTOR/p70S6K anabolic signaling pathway in the myocyte, promoting resistance to protein synthesis (11). Additionally, the chronic accumulation of advanced glycation end products (AGEs) and oxidative stress contribute to impaired mitochondrial bioenergetics, which weakens the efficiency of muscle contraction (specific force) even before the fiber undergoes apoptosis or visible atrophy (12,13).

Gap in screening and diagnostic tools

Comparative analysis of available diagnostic tools reveals a clear hierarchy in their clinical utility for this specific patient profile, highlighting significant limitations in traditional methods.

The SARC-F questionnaire, widely used in geriatrics due to its ease of use and high specificity, demonstrates a worryingly low sensitivity for detecting sarcopenia in the early stages of diabetic neuropathy. It frequently fails to identify those “dynapenic” patients who still retain volumetric

muscle mass but lack adequate functional strength, erroneously classifying them as healthy (14).

Conversely, advanced, non-invasive imaging techniques, specifically muscle ultrasound and elastography, are emerging in recent literature as the emerging “gold standard” for accurately phenotyping patients with NDD (15). These studies highlight that echo intensity (echogenicity)—a direct reflection of myosteatosis or intramuscular fat infiltration—increases significantly in patients with painful neuropathy and correlates strongly with the severity of nerve dysfunction and the duration of pain (16). This suggests that muscle “quality” (measured by its internal structure and composition) is a much more sensitive and earlier biomarker than its simple “size” or volume in this at-risk population.

DISCUSSION

This integrative review highlights a pathogenic interaction that transcends simple comorbidity: neuropathic pain in diabetes mellitus is not an isolated sensory symptom but a potent systemic catalyst for motor dysfunction and physical frailty. While the overall prevalence of diabetic neuropathy is high—estimated globally at 46% (1)—and painful neuropathy affects up to 50% of these patients (5), our findings confirm that this painful subgroup faces a disproportionate risk of accelerated muscle deterioration. The synthesized evidence strongly supports that peripheral neuropathy is an independent predictor of sarcopenia, as demonstrated by Hossain et al. (4), but adds a critical layer of complexity: pain intensity is inversely correlated with muscle strength, suggesting a direct dose-response relationship between nociception and dynapenia, as reported by Hary et al. (7) in their analysis of handgrip strength.

The interpretation of the underlying mechanisms reveals a “bio-behavioral vicious cycle” that distinguishes the painful phenotype. From a behavioral perspective, the “movement avoidance” induced by mechanical allodynia is not a passive phenomenon but an active factor in disuse atrophy. Unlike the mass loss observed in painless neuropathy, which Trierweiler et al. (9) attributed primarily to chronic denervation, the weakness in the painful phenotype appears to be exacerbated by a protective kinesiophobia that precipitates the degradation of type II fibers. This increases the risk of falls described by Lipschitz et al. (10). This behavioral phenomenon converges with a shared molecular toxicity: the elevation of inflammatory and neurotrophic mediators induced by hyperglycemia not only sensitizes the nerve, but also compromises myocyte viability, as elucidated by Zhu et al. (11) in in vitro models. Furthermore, the accumulation of advanced glycation products (AGEs) acts as a “double whammy,” damaging nerve microcirculation and muscle contractile machinery simultaneously (13), which explains why the loss of strength precedes the loss of visible mass.

These observations have profound implications for diagnostic practice and expose a significant technological gap. The current reliance on screening questionnaires such as the SARC-F is insufficient for this specific population; Cavusoglu et al. (14) demonstrated its low sensitivity for detecting early stages of sarcopenia in diabetic patients, which carries an unacceptable risk of underdiagnosis. In contrast, more recent literature advocates a shift toward imaging biomarkers. The findings of Zheng and Bai (15) position ultrasound elastography as a superior tool for assessing muscle stiffness and quality, while Zhong et al. (16) confirmed that muscle hyperechogenicity (a sign of myosteatosis) correlates closely with the severity of neuropathy. This suggests that intramuscular fat infiltration is the hallmark of the “sarcopenic pain phenotype,” an entity that remains invisible to basic anthropometry.

It is essential to acknowledge the inherent limitations of this review to properly contextualize its scope. The main restriction lies in the cross-sectional nature of most of the included studies (4,7), which allows for the establishment of robust associations but prevents the confirmation of unidirectional temporal causality; we cannot state with absolute certainty whether pain always precedes atrophy or whether both progress in parallel. Furthermore, the variability in the diagnostic criteria for sarcopenia among populations makes direct comparison of absolute prevalences difficult. Nevertheless, the consistency of the biological and clinical patterns observed across diverse health systems and ethnicities lends considerable external validity to the proposal of a high-risk phenotype.

In conclusion, sarcopenia and dynapenia are highly prevalent complications in the population with diabetic peripheral neuropathy, significantly exacerbated by the presence of chronic pain. The pain phenotype represents a state of high metabolic and functional risk, characterized by the early onset of dynapenia, severe myosteatosis, and behavioral motor inhibition. The current clinical inertia, which

tends to separate pain management from functional management, must be replaced by a proactive and multidisciplinary approach. The medical community is urged to incorporate functional muscle assessment (strength and quality) as a standard of care in the management of diabetic neuropathy. It must be recognized that effectively controlling pain is a fundamental strategy for preserving muscle mass and patient independence.

Funding

The authors declare that they did not receive external funding for this study.

Conflicts of interest

The authors declare no commercial conflicts of interest.

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