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THERAPEUTIC MANAGEMENT OF DIABETIC POLYNEUROPATHY: FROM GLYCEMIC CONTROL TO PAIN MANAGEMENT

MANEJO TERAPÊUTICO DA POLINEUROPATIA DIABÉTICA: DA GLICEMIA AO CONTROLE DA DOR

MANEJO TERAPÉUTICO DE LA POLINEUROPATÍA DIABÉTICA: DEL CONTROL GLUCÉMICO AL CONTROL DEL DOLOR

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ABSTRACT

Diabetic polyneuropathy (DPN) is the most common chronic complication of Diabetes Mellitus, affecting more than 50% of patients and severely impacting quality of life. This narrative review analyzes recent scientific evidence on the therapeutic management of DPN, ranging from pathophysiology to pain control. The pathogenesis is multifactorial, involving oxidative stress, advanced glycation, and microvascular dysfunction, which result in symmetric distal axonal damage (the “glove-and-stocking” pattern). Diagnosis remains essentially clinical, based on medical history and sensory testing using monofilaments and tuning forks. Therapeutic strategies are based on three pillars: strict metabolic control (glycemic and lipid), pathogenetic interventions (alpha-lipoic acid and benfotiamine), and management of neuropathic pain. For symptomatic relief, first-line agents such as pregabalin, duloxetine, and amitriptyline have demonstrated efficacy, with growing evidence (OPTION-DM study) supporting combination therapies for refractory cases. It is concluded that a multidimensional and individualized approach is essential to delay disease progression and reduce the risk of severe outcomes, such as ulcerations and amputations.

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Keywords: Diabetic Polyneuropathies. Diabetes Mellitus. Neuropathic Pain. Glycemic Control. Pregabalin. Alpha-Lipoic Acid.

RESUMO

A polineuropatia diabética (PD) é a complicação crônica mais comum do Diabetes Mellitus, afetando mais de 50% dos pacientes e impactando severamente a qualidade de vida. Esta revisão narrativa analisa as evidências científicas recentes sobre o manejo terapêutico da PD, abrangendo desde a fisiopatologia até o controle da dor. A patogênese é multifatorial, envolvendo estresse oxidativo, glicação avançada e disfunção microvascular que resultam em dano axonal simétrico distal (padrão em "luvas e botas"). O diagnóstico permanece essencialmente clínico, fundamentado na anamnese e em testes de sensibilidade com monofilamento e diapasão. As estratégias terapêuticas baseiam-se em três pilares: o controle metabólico rigoroso (glicêmico e lipídico), intervenções patogenéticas (ácido alfa-lipoico e benfotiamina) e o manejo da dor neuropática. Para o alívio sintomático, fármacos de primeira linha como pregabalina, duloxetina e amitriptilina demonstram eficácia, com evidências crescentes (estudo OPTION-DM) favorecendo terapias combinadas para casos refratários. Conclui-se que uma abordagem multidimensional e individualizada é indispensável para retardar a progressão da doença e reduzir o risco de desfechos graves, como ulcerações e amputações.

Palavras-chave: Polineuropatias Diabéticas. Diabetes Mellitus. Dor Neuropática. Controle Glicêmico. Pregabalina. Ácido Alfa-Lipoico.

RESUMEN

La polineuropatía diabética (PD) es la complicación crónica más común de la Diabetes Mellitus, afectando a más del 50% de los pacientes y deteriorando significativamente la calidad de vida. Esta revisión narrativa analiza la evidencia científica reciente sobre el manejo terapéutico de la PD, abarcando desde la fisiopatología hasta el control del dolor. La patogénesis es multifactorial e incluye estrés oxidativo, glicación avanzada y disfunción microvascular, lo que da lugar a un daño axonal distal simétrico (patrón en “guante y media”). El diagnóstico sigue siendo esencialmente clínico, basado en la anamnesis y en pruebas de sensibilidad con monofilamento y diapasón. Las estrategias terapéuticas se sustentan en tres pilares: control metabólico estricto (glucémico y lipídico), intervenciones patogenéticas (ácido alfa-lipoico y benfotiamina) y manejo del dolor neuropático. Para el alivio sintomático, fármacos de primera línea como pregabalina, duloxetina y amitriptilina han demostrado eficacia, con evidencia creciente (estudio OPTION-DM) que respalda las terapias combinadas en casos refractarios. Se concluye que un enfoque multidimensional e individualizado es indispensable para retrasar la progresión de la enfermedad y reducir el riesgo de desenlaces graves, como ulceraciones y amputaciones.

Palabras clave: Polineuropatías Diabéticas. Diabetes Mellitus. Dolor Neuropático. Control Glucémico. Pregabalina. Ácido Alfa-Lipoico.

1 INTRODUCTION

Diabetes mellitus is a major public health challenge worldwide, affecting more than 500 million people. Among its chronic complications, diabetic polyneuropathy is the most common, occurring in up to 50% of patients with type 2 diabetes after 10 years and at least 20% of patients with type 1 diabetes after 20 years. In addition, DPN may be present in approximately 20–25% of patients newly diagnosed with type 2 diabetes. Although the vast majority of patients with peripheral diabetic neuropathy (PDON) do not present with pain, painful PDO affects about 15–30% of all patients with diabetes (Chang, M. C.; Yang, S.). This condition is associated with pain, sensory loss, foot ulcers, and an increased risk of lower limb amputations.

Diabetic polyneuropathy (PD) is one of the most prevalent and debilitating chronic complications of Diabetes Mellitus (DM), along with diabetic eye complications, diabetic foot, and diabetic cardiovascular complications, with an estimated prevalence that exceeds 50% throughout the life of patients (Dillon et al., 2024; ZHU, J. et al., 2024). Clinically, the most common form is symmetrical distal sensorimotor polyneuropathy (PSDS), which manifests through a length-dependent axonal loss, resulting in the classic "gloves and boots" pattern of distribution (Chang and Yang, 2023; Ziegler et al., 2022).

The most common manifestation of DPN is distal symmetrical numbness of the limbs with loss of sensation, and about 20% of people with diabetes may also develop neuropathic pain due to PDN. Common types of pain include stabbing, electrical, and sharp pain, followed by itching, hyperalgesia, and provoked pain. In addition, the combination of hyperglycemia and metabolic disorders impairs the body's immune system and immune function, and this unconscious and insidious wound can eventually become infected and lead to severe limb damage. Current studies consider peripheral diabetic neuropathy (PND) to be the most common cause of non-traumatic lower limb amputation in most high-income countries (Zhu, J. et al., 2024).

The clinical relevance of this condition lies in the high morbidity associated with neuropathic pain, which affects between 15% and 30% of patients, with a significantly higher incidence in females and in individuals with obesity (Jang and Oh, 2023). Another determining factor is the poor prognosis associated with the increased risk of foot ulcerations, amputations, and higher mortality rates (Dillon et al., 2024; Zhu et al., 2024).

The pathogenesis of PD is multifactorial, being driven by chronic hyperglycemia, dyslipidemia, and insulin resistance, which trigger a cascade of oxidative, inflammatory,

and metabolic damage in the peripheral nervous system (Zhu et al., 2024; Yang et al., 2022). Despite advances in the understanding of these mechanisms, therapeutic management remains a challenge, requiring an approach that ranges from strict control of metabolic risk factors to symptomatic pain relief (Ziegler et al., 2022). The present study aims to discuss the current evidence on the diagnosis and therapeutic strategies for diabetic polyneuropathy, integrating glycemic control and pharmacological interventions.

2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to the therapeutic management of diabetic polyneuropathy. The search was carried out in the PubMed database, using the descriptors "Diabetic Polyneuropathies", "Treatment" and "Diagnosis", combined using the Boolean operators AND and OR, according to the terminology of Medical Subject Headings (MeSH). Articles published in the last five years, available in full and written in English, that directly addressed the topic were included. Studies that did not have a direct relationship with the central theme, duplicate publications, narrative reviews with low methodological rigor, and articles not indexed in the database used were excluded. The selection of studies was conducted in two stages: screening of titles and abstracts, followed by the evaluation of full texts to confirm relevance. The information extracted was organized in a descriptive way.

3 RESULTS AND DISCUSSION

3.1 PATHOPHYSIOLOGY AND MECHANISMS OF NERVE DAMAGE

The pathophysiology of diabetic neuropathy results from the complex interaction between metabolic disorders, microvascular dysfunction, and neuroinflammatory processes that culminate in progressive damage to peripheral nerve fibers. Chronic hyperglycemia and the accumulation of free fatty acids promote metabolic overload in Schwann cells and neurons, leading to mitochondrial dysfunction, reduced ATP production, and increased generation of reactive oxygen species (ROS), configuring a state of persistent oxidative stress (Chang and Yang, 2023; Elafros et al., 2023).

Concomitantly, activation of deleterious metabolic pathways, including the polyol pathway, the formation of advanced glycation end products (AGEs), the protein kinase C (PKC) pathway, and the hexosamine pathway, results in osmotic changes, modification

of structural proteins, and activation of pro-nociceptive inflammatory cascades (Zhu et al., 2024; Yang et al., 2022; Elafros et al., 2023). These mechanisms contribute to chronic low-grade inflammation, loss of glial neurotrophic support, and increased neuronal apoptosis and Schwann cells, impairing axonal regeneration (Zhu et al., 2024; Feldman et al., 2022).

In parallel, microvascular involvement of the *vasa nervorum*, characterized by basement membrane thickening, endothelial dysfunction, and reduced blood flow, leads to neural hypoxia and exacerbates distal axonal degeneration in a length-dependent pattern typical of DN (Elafros et al., 2023; Zhu et al., 2024). Interestingly, while hyperglycemia is the main driver in type 1 DM, dyslipidemia appears to play a preponderant role in type 2 DM (Chang and Yang, 2023).

In addition to oxidative stress, low-grade systemic inflammation mediated by proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, has emerged as a central component of the pathogenesis of diabetic polyneuropathy. These mediators promote nociceptive sensitization, endothelial dysfunction, and direct damage to peripheral nerve fibers, connecting the concept of immunometabolism to diabetic neurodegeneration. Such an understanding broadens the rationale for therapies targeting inflammation and insulin resistance as future therapeutic targets (Zhu et al., 2024; Elafros et al., 2022).

3.2 DIAGNOSIS IN CLINICAL PRACTICE

The diagnosis of diabetic polyneuropathy is essentially clinical and exclusionary, requiring a detailed anamnesis and careful physical examination (Dillon et al., 2024; Chang and Yang, 2023). Clinical symptoms are predominantly characterized by symmetrical pain in the limbs, accompanied by tingling sensation and numbness, especially in the distal extremities, configuring the "glove and sock" pattern. Neuropathic pain is described as burning, painful cold, twinges or stings similar to electric shock, as well as dull or stabbing pain, with intensity ranging from mild to severe, often worse at night and in situations of tiredness or stress, which compromises daily activities, quality of sleep and life (Chang and Yang, 2023; Ziegler et al., 2022).

In addition to pain, non-painful neuropathic symptoms are frequent, such as paresthesias (tingling or stinging sensations), dysesthesias (abnormal and unpleasant sensations, spontaneous or provoked), sensory ataxia and the sensation of "walking on thick socks" or being "wrapped in wool". Neuropathic pain may be associated with

hyperalgesia (exacerbated response to painful stimuli) and allodynia (pain caused by normally non-painful stimuli, such as contact with socks, shoes, or bedding), and in advanced stages of DPN, weakness, loss of balance, and instability may appear. Neuropathic symptoms have a potentially heterogeneous course over time and may reflect different pathophysiological mechanisms, so that manifestations such as pain and paresthesias do not always have a linear relationship with the degree of structural damage to nerve fibers, and may also result from compensatory regeneration processes.(Chang and Yang, 2023; Ziegler et al., 2022).

Even if the patient's clinical condition is suggestive of diabetic polyneuropathy, it is essential to keep other pathologies that may coexist in the diabetic patient on the differential diagnosis list, often with treatment that can reverse the clinical condition. Pathologies that should be considered are neuropathies secondary to kidney disease, alcohol abuse, thyroid gland dysfunction or other micronutrients such as vitamin B12, medications, demyelinating polyneuropathies, infectious or inflammatory diseases (Dillon et al., 2024).

For patients who have had type 1 diabetes mellitus for 5 years or more and those who have diabetes mellitus 2, the guidelines recommend annual evaluation through at least two tests that evaluate functions of small fibers (such as thermal or pain sensitivity) and large fibers (such as vibratory sensitivity with a tuning fork of 128 Hz or pressure with a 10g monofilament) (Dillon et al., 2024). Although monofilament is widely used to screen for ulcer risk, it alone is not sensitive enough to identify the disease in early stages, requiring combination with vibration tests and Achilles reflexes (Chang and Yang, 2023; Ziegler et al., 2022). Still considering the tests that assess nerve electrical function, the use of electrodiagnosis should be considered in the face of atypical clinical findings (Dillon et al., 2024).

Recent evidence indicates that diabetic polyneuropathy may begin predominantly as a small-fiber neuropathy, preceding changes detectable in traditional nerve conduction tests. This initial phenotype is associated with disproportionate pain, autonomic dysfunctions, and normal neurological examinations, which reinforces the need for more sensitive diagnostic strategies, such as quantitative sensory testing and skin biopsy to assess intraepidermal fiber density. Early identification of this subtype may allow for early and potentially disease-progression-modifying interventions (Ziegler et al., 2022; Feldman et al., 2019).

Recent advances point to the use of serum and metabolic biomarkers, such as circulating advanced glycation end products, microRNAs, and markers of mitochondrial dysfunction, as potential tools for risk stratification and monitoring of diabetic neuropathy progression. Although not yet incorporated into routine clinical practice, these biomarkers represent a promising prospect for treatment personalization and objective assessment of therapeutic response (Dillon et al., 2024; Zhu et al., 2024).

3.3 THERAPEUTIC STRATEGIES

The management of diabetic polyneuropathy is based on three fundamental pillars: metabolic control, pathogenesis-oriented treatment, and symptomatic pain relief (Ziegler et al., 2022).

- **Glycemic Control and Lifestyle:** Intensive glycemic control has been shown to significantly reduce the incidence of PD in patients with type 1 DM (78% risk reduction), however its effect is less pronounced in type 2 DM, where multifactorial and lifestyle interventions are crucial (Dillon et al., 2024; Zhu et al., 2024). However, there is consensus that optimizing glycemic control is critical to preventing or slowing the progression of peripheral diabetic neuropathy (PND) in individuals with type 1 and type 2 diabetes mellitus (Ziegler et al., 2022).

Dyslipidemia can contribute to the increase in the levels of oxidized LDL cholesterol and free fatty acids, favoring the elevation of inflammatory mediators and the intensification of systemic inflammatory responses. These mechanisms promote damage to neurons, glial cells, and vascular endothelial cells, culminating in the development of DPN. Thus, the control of dyslipidemia becomes a fundamental strategy in the management of these patients (CHANG, M. C.; YANG, S, 2023).

- **Pathogenetic Treatment:** Substances such as alpha-lipoic acid (antioxidant) and benfotiamine (thiamine derivative) are approved in several countries to influence underlying metabolic processes, demonstrating efficacy in reducing neurological symptoms and deficits (Ziegler et al., 2022; Yang et al., 2022).
- **Neuropathic Pain Control:** For pain relief, first-line classes include anticonvulsants (pregabalin and gabapentin), tricyclic antidepressants (amitriptyline), and serotonin and norepinephrine reuptake inhibitors (duloxetine) (Dillon et al., 2024; Tesfaye et al., 2022).

- **Exercise and Rehabilitation:** Nonpharmacologic interventions, including supervised physical exercise, sensorineural physical therapy, and foot self-care education, have demonstrated additional benefits in the management of diabetic polyneuropathy. Aerobic and resistance exercise improves neural perfusion, reduces systemic inflammation, and can attenuate neuropathic symptoms, in addition to contributing to overall metabolic control. These strategies complement pharmacological treatment and are fundamental in preventing complications, such as falls and ulcerations (Jang and Oh, 2023; Ziegler et al., 2022).

Serotonin and norepinephrine reuptake inhibitors (SNRIs), especially duloxetine, are widely recommended due to their efficacy and safety profile. Tricyclic antidepressants, such as amitriptyline, are also effective, but their use is limited by anticholinergic side effects (Tesfaye et al., 2011).

Gabapentin and pregabalin are α2δ calcium channel ligands, acting to reduce neuronal excitability. Pregabalin is approved by the Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain and has strong scientific backing (DWORKIN et al., 2007).

Opioids, including tramadol, are considered second- or third-line options because of the risk of addiction. Topical agents, such as the 8% capsaicin patch and lidocaine, are useful for localized pain and have a favorable safety profile (Attal; Boumedjouti, 2015).

Recent evidence from the OPTION-DM study indicates that amitriptyline, duloxetine, and pregabalin have similar analgesic efficacy as monotherapy (Tesfaye et al., 2022). In addition, the study demonstrated that therapeutic combinations are well tolerated and superior to monotherapy in patients with inadequate pain control, allowing the use of lower doses and reducing side effects (Tesfaye et al., 2022; Chang and Yang, 2023).

Diabetic neuropathic pain is strongly associated with depression, anxiety, sleep disturbances, and reduced functionality, requiring a patient-centered approach. Integrated care models, which combine pharmacological pain management, psychological support, and health education, demonstrate better outcomes in quality of life and treatment adherence, reinforcing that diabetic polyneuropathy should be understood beyond isolated neurological damage (Tesfaye et al., 2022; Jang and Oh, 2023).

A therapy that emerges as a valuable alternative for patients with localized pain or who cannot tolerate systemic medications is topical therapy with 8% capsaicin patch (Jang and Oh, 2023; Ziegler et al., 2022; Yang et al., 2022). Capsaicin, an alkaloid derived from red peppers, acts as a nociceptive receptor agonist. Its action promotes the massive release and subsequent depletion of substance P in nerve endings, resulting in a state of functional desensitization and analgesia, being an efficient option in the treatment of localized diabetic neuropathy (Jang and Oh, 2023; Ziegler et al., 2022; Yang et al., 2022).

New therapeutic approaches are under investigation, including ion channel modulators, gene therapies, recombinant neurotrophic factors, and mitochondrial dysfunction-targeting agents. Although still experimental, these strategies reflect the transition to a precision medicine model, in which treatment is adapted to the patient's metabolic, inflammatory, and phenotypic profile, overcoming the exclusively symptomatic approach (Yang et al., 2022; Feldman et al., 2019).

4 CONCLUSION

Diabetic polyneuropathy represents one of the most prevalent and disabling chronic complications of diabetes mellitus, with a significant impact on quality of life and the risk of serious outcomes, such as ulcerations and amputations. Its pathophysiology is complex and multifactorial, involving chronic hyperglycemia, dyslipidemia, insulin resistance, oxidative stress, inflammation, and microvascular dysfunction, which culminate in progressive damage to peripheral nerve fibers. The diagnosis is predominantly clinical, based on the identification of characteristic signs and symptoms and the exclusion of other causes of neuropathies, and requires periodic evaluation with tests that include small and large nerve fibers, being essential for the early detection and prevention of debilitating complications.

Therapeutic management should be integrated and individualized, based on three pillars: 1) Strict metabolic control, especially glycemic and lipid, focusing on lifestyle changes, 2) Pathogenetic interventions, such as the use of antioxidants and thiamine derivatives, which show promise in acting on the underlying mechanisms of neural injury, and 3) Effective treatment of neuropathic pain, which can be done through first-line drugs, such as anticonvulsants (pregabalin and gabapentin), tricyclic antidepressants (amitriptyline) and serotonin and norepinephrine reuptake inhibitors (duloxetine) or, in the

case of patients with localized pain and/or who cannot tolerate systemic medications, topical options, such as capsaicin at 8%, expand the therapeutic alternatives.

From the point of view of public health, diabetic polyneuropathy represents an important factor in the increase of care costs, hospitalizations and functional disability. Systematic screening, early diagnosis, and multidimensional treatment strategies have been shown to be cost-effective in reducing amputations, prolonged hospitalizations, and loss of productivity. Thus, the incorporation of these measures into diabetes care policies is essential to mitigate the socioeconomic impact of the disease (Callaghan et al., 2012; Dillon et al., 2024).

Only with a multidimensional and continuous approach is it possible to tackle diabetic polyneuropathy, slowing the progression of the disease, relieving symptoms, and improving the prognosis of patients.

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