

DOI: <https://doi.org/10.36489/saudecoletiva.2021v11i67p6923-6936>

# Peripheral diabetic neuropathies as complications of diabetes mellitus: review study

**Neuropatías diabéticas periféricas como complicaciones de la diabetes mellitus: estudio de revisión****Neuropatias diabéticas periféricas como complicações do diabetes mellitus: estudo de revisão****ABSTRACT**

Objective: this study aimed to highlight publications expressed in the worldwide scientific literature on this topic. Methods: this is an integrative review that follows a pico strategy to identify the factors associated with diabetic neuropathy. The search for articles carried out in three electronic databases: medline, virtual health library and scielo. The descriptors "diabetic neuropathies", "neuralgia", "risk factors", "diabetes mellitus" were used, with complete texts, published between 2011 and 2021. Result: 118 articles were found. Fifty-five articles were selected to be read in full and 5 met the criteria of this review. Conclusion: diabetic neuropathy can be reduced with better blood glucose control, and improved lipid and blood pressure levels.

**DESCRIPTORS:** diabetic neuropathies; neuralgia; risk factors; diabetes mellitus.

**RESUMEN**

Objetivo: este estudio tuvo como objetivo destacar las publicaciones en la literatura científica mundial sobre este tema. Métodos: se trata de una revisión integradora que siguió la estrategia pico para identificar los factores asociados a la neuropatía diabética. La búsqueda de los artículos se realizó en bases de datos electrónicas: medline, biblioteca virtual en salud y scielo. Se utilizaron los descriptores "neuropatías diabéticas", "neuralgia", "factores de riesgo", "diabetes mellitus", con textos completos, publicados entre 2011 y 2021. Resultado: se encontraron 118 artículos. Se seleccionaron cincuenta y cinco artículos para ser leídos en su totalidad y cinco cumplieron los criterios de esta revisión. Conclusión: la neuropatía diabética se puede reducir con un mejor control de la glucosa en sangre y mejores niveles de lípidos y presión arterial.

**DESCRIPTORES:** neuropatías diabéticas; neuralgia; factores de riesgo; diabetes mellitus.

**RESUMO**

Objetivo: este estudo objetivou a evidenciar publicações expressas na literatura científica mundial sobre essa temática. Métodos: trata-se de uma revisão integrativa que seguiu a estratégia pico para identificar os fatores associados a neuropatia diabética. A busca dos artigos foi realizada em três bases de dados eletrônicas: medline, biblioteca virtual de saúde e scielo. Foram utilizados os descritores "neuropatias diabéticas", "neuralgia", "fatores de risco", "diabetes mellitus", com textos completos, publicados entre 2011 a 2021. Resultado: foram encontrados 118 artigos. Cinqüenta e cinco artigos foram selecionados para serem lidos na íntegra e 5 atenderam aos critérios desta revisão. Conclusão: a neuropatia diabética pode ser reduzida com melhor controle da glicose no sangue, e a melhora dos índices de lípidos e pressão arterial.

**DESCRIPTORIOS:** neuropatias diabéticas; neuralgia; fatores de risco; diabetes mellitus.

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## INTRODUCTION

**D**iabetes Mellitus Type 1 (DM1) is a chronic autoimmune disease, being in most cases diagnosed in children and adolescents, it is a disease caused by insufficient production or malabsorption of insulin, a hormone that regulates blood glucose and provides energy for the body.<sup>1</sup> Insulin is a hormone that has the function of breaking down glucose molecules, transforming them into energy for the maintenance of our body's cells.<sup>2</sup> Diabetes can cause blood glucose to rise and the high rates can lead to complications in the heart, arteries, eyes, kidneys and nerves.<sup>3</sup> In more severe cases, diabetes can lead to death. In Brazil, according to the Brazilian Society of Diabetes, there are currently more than 13 million people living with the disease, which represents 6,9% of the national population.<sup>4</sup> Prolonged exposure to hyperglycemia leads to the development of microvascular complications; excessive glycolysis leads to increased electron flow in the mitochondrial electron transport chain with increased production of reactive oxygen species, which are chemically unstable, highly reactive molecules that induce cell damage.<sup>5</sup>

Neuropathy is a common complication of type 1 and type 2 diabetes. The prevalence of neuropathy is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease. 1 Sensory-motor neuropathy is marked by pain, paresthesia and sensory loss. The mechanisms involved in different pain sensations are still poorly understood, but there is ample evidence that abnormal discharges from diseased somatosensory neurons are responsible.<sup>3,5</sup>

DM1 has a great impact on morbidity and mortality due to the development of chronic micro and macrovascular complications.<sup>4</sup> Considering the scarcity of studies in the literature on the prevalence of Autonomic Neuropathies (AN) in the Brazilian population with DM1, this study becomes relevant in the early identification of this complication as well as in the determination of possible clinical and laboratory factors related to its presence. In this sense, the aim of this article is to highlight the profile of publications on diabetic neuropathies expressed in the international literature and their impacts on public health.

## METHOD

This is an integrative literature review. Method that is characterized by gathering and synthesizing research results on a topic, in a systematic and orderly manner. The research question was defined based on the PICO strategy, which provides for the definition of the participant (P), intervention (I), comparison (C) and outcomes (O).

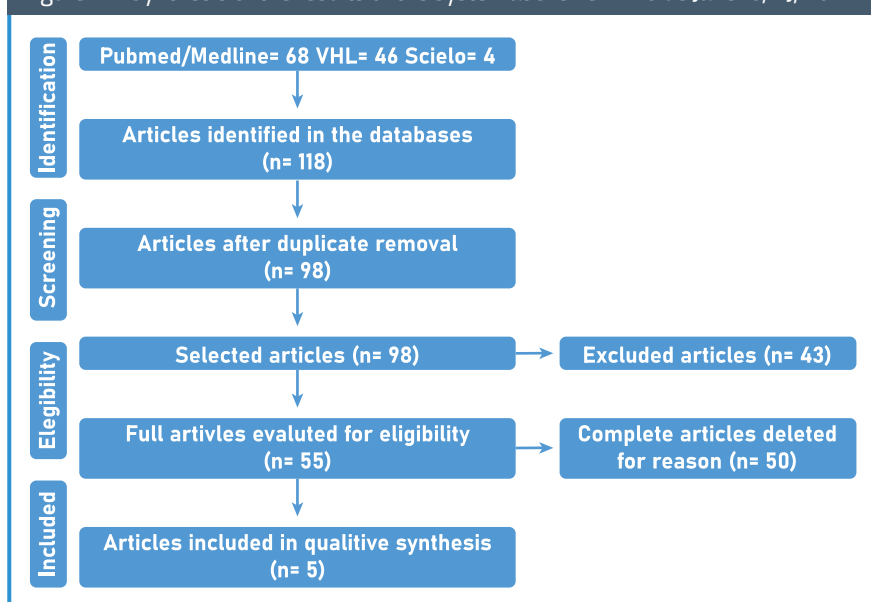
It is intended to answer the guiding question: Which factors identified in the literature (O) are associated with neuropathies (I) in diabetic people (P)? Then the keywords "Neuropatias Diabéticas", "Neuralgia", "Fatores de Risco", "Diabetes Mellitus" were defined from the vocabulary of the Health Sciences Descriptors (DeCS), as it is a common terminology for research. These were combined with each other using the Boolean AND operator in databases and/or electronic libraries: Medical Literature Analysis and Retrieval System Online (MEDLINE), Virtual Health Library (VHL) and Scientific Electronic Library Online (SciELO). The same search strategy was performed in all databases and/or electronic libraries.

Chart 1 - Levels of evidence. Rio de Janeiro, RJ, Brazil, 2021

LEVEL	DEFINITION	IMPLICATIONS
High	There is strong confidence that the true effect is close to that estimated	It is unlikely that further work will change the confidence in the effect estimate.
Moderated	There is moderate confidence in the estimated effect	Future work may change the confidence in the effect estimate, with the possibility of even modifying the estimate
Low	Confidence in the effect is limited	Future work is likely to have a major impact on our confidence in the effect estimate.
Very Low	Reliance on effect estimation is very limited. There is an important degree of uncertainty in the findings.	Any effect estimate is uncertain

Source: The authors, 2021

Figure 1 – Synthesis of the results of the systematic review. Rio de Janeiro, RJ, 2021.



Source: The authors, 2021

The inclusion criteria for the articles for analysis were: population group of diabetic people, published between 2011 and 2021, available in full, in Portuguese, English and Spanish, dealing with the theme of diabetic neuropathies.

Opinion articles, editorials, other reviews, duplicate articles and publications that did not deal with the theme were excluded. The collection period took place from February to March 2021. For data analysis, an analytical framework was built that made it possible to gather and synthesize key information from the studies. The collection instrument gathered the following information: title, author(s)/year of publication/country,

objective, method, main results. The level of evidence identified in the analyzed articles was classified according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, a system considered sensitive for grading the quality of evidence. In this system, the quality of evidence is described at four levels: high, moderate, low and very low (Chart 1).

Evidence from randomized controlled trials starts at a high level and evidence from observational studies at a low level. In this review, based on the classification adopted (GRADE system) to assess the quality of evidence, the risk of bias of randomized clinical trials of product te-

chnologies in relation to methodological limitations regarding the design or execution of individual studies was considered. Evidence from randomized clinical trials can be downgraded by lack of allocation confidentiality, lack of blinding, incomplete follow-up, selective reporting of outcomes and other limitations, such as early interruption of the study for benefit and insufficient information to assess whether there is a significant risk of bias. For each of these domains, the risk of bias is assessed, being classified as high risk, uncertain and low risk of bias.

## RESULTS

A total of 118 studies were identified in these databases, as illustrated in (Figure 1), which followed the PRISMA recommendations to describe the literature search process. Of these, 20 duplicate articles were excluded, leaving 98 unique articles. Then, titles and abstracts were read, observing the inclusion and exclusion criteria. As a result of this process, 43 articles were excluded and another 55 articles met the eligibility criteria. Then, the full and in-depth reading of these studies by two researchers began, independently.

Any disagreements between the evaluators that emerged during this stage were worked out and resolved by consensus, which resulted in a final sample of 5 articles. The articles included in this synthesis (Table 1) were developed in six different countries: Brazil (n= 1), United States (n= 2), Taiwan (n= 1), Africa (n=

1) As for the method, the majority of the researchers used the qualitative and quantitative approach (n=5) to describe and analyze, in depth, the different dimensions in which diabetic neuropathy occurs.

## DISCUSSION

Several very distinct syndromes of diabetic neuropathy have been delineated. <sup>6</sup> The most common, as noted, is a distal, symmetrical, mainly sensory polyneuropathy, which affects the feet

and legs chronically and slowly progressively. <sup>7</sup> The others are as follows: acute ophthalmoplegia affecting the third, and less frequently the sixth cranial nerve on one side; acute mononeuropathy of limbs or trunk including a painful thoracolumbar radiculopathy; <sup>8</sup> an acute or subacu-

Table 1 – Summary of published studies, Rio de Janeiro, RJ, 2021.

TITLE	AUTHOR(S), COUNTRY/ YEAR	OBJECTIVE	METHOD	RESULTS	EVIDENCE LEVEL
Diabetic polyneuropathy with/out neuropathic pain in Mali: A cross-sectional study in two reference diabetes treatment centers in Bamako (Mali)	Maiga, Y. et al. Africa (2020)	Determine the prevalence of diabetic polyneuropathy.	Descriptive cross-sectional study	The prevalence of healthcare-based diabetic polyneuropathy with or without neuropathic pain was high in our cohort 69,8% (176/252).	Low
Prevalence and biochemical risk factors of diabetic peripheral neuropathy with or without neuropathic pain in Taiwanese adults with type 2 diabetes mellitus	Pai, Y. wei, Taiwan (2018)	To investigate the prevalence and risk factors for diabetic peripheral neuropathy with or without neuropathic pain in Taiwanese.	Cross-sectional observational study	The risk of diabetic peripheral neuropathy with neuropathic pain should be considered for people with advanced age, high glycated hemoglobin, low high density lipoprotein cholesterol	Low
Factors associated with altered tactile sensory perception in the feet of patients with diabetes mellitus	Noronha, J. A. F. Brazil (2019)	To analyze signs, symptoms and etiological factors of the change in tactile sensory perception in patients with diabetes mellitus	Quantitative cross-sectional study	There was a high prevalence of change in tactile sensory perception among diabetics	Moderated
Treatment-induced neuropathy of diabetes: An acute, iatrogenic complication of diabetes	Gibbons, C., Freeman, R. USA (2015)	Identifying the prevalence and risk factors for this disorder are not known..	Qualitative Transversal	Treatment-induced diabetes neuropathy is an underestimated iatrogenic disorder associated with diffuse microvascular complications. Rapid glycemic change in patients with uncontrolled diabetes increases the risk of this complication.	Moderated
Sensory phenotype and risk factors for painful diabetic neuropathy: A cross-sectional observational study	Raputova, J. et al. USA (2016)	To characterize the sensory phenotypes of patients with painful and painless diabetic neuropathy and assess demographic parameters.	Observational cross-sectional study	Neuropathic pain was positively correlated with neuropathy severity and thermal hyposensitivity	High

Source: The authors, 2021

te, asymmetric, predominantly motor painful multiple neuropathy affecting the upper lumbar roots and proximal leg muscles (diabetic amyotrophy); a proximal motor weakness usually painless and with variable sensory loss,<sup>9</sup> following a subacute or chronic course, and an autonomic neuropathy involving bowel, bladder, sweating and circulatory reflexes.<sup>10</sup>

These forms of neuropathy often co-exist or overlap, particularly the symmetrical autonomic and distal types and the subacute proximal neuropathies.<sup>10,11</sup> Distal sensory diabetic polyneuropathy is the most common presentation of neuropathy in diabetes, and up to 50% of patients may experience symptoms more frequently such as burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia, and deep pain.<sup>12</sup> These symptoms often worsen at night and disturb sleep. Along with painful symptoms during the day, this often leads to a reduction in the individual's ability to carry out daily activities.<sup>13</sup>

Muscle weakness is usually mild, but in some patients a distal sensory neuropathy is combined with proximal weakness and atrophy.<sup>7,14</sup> Cranial neuropathy in diabetic patients most commonly involves the oculomotor nerve, followed by the trochlear and facial nerves in order of frequency.<sup>15</sup> Pupil-sparing third nerve palsy is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction. Rarely is an upper extremity nerve affected.<sup>16</sup> In these cases, nerve entrapment appears to be more common than nerve infarction.<sup>17</sup> Mononeuropathies often arise during transition periods in diabetic disease, for example, after an episode of hyper- or hypoglycemia, when insulin treatment is started or adjusted, or when rapid weight loss occurs.<sup>18</sup> Multiple mononeuropathies and diabetic radiculopathies A syndrome of painful unilateral or asymmetric multiple neuropathies tends to occur in older patients with relatively mild or even unrecognized diabetes.<sup>4,5,7</sup>

Lumbosacral radiculoplexus diabetic neuropathy occurs in approximately 1%

of diabetic patients and is probably the form of diabetic neuropathy that causes the greatest morbidity.<sup>2,5</sup> It has been known by different names, including diabetic amyotrophy, Bruns-Garland syndrome, diabetic mononeuritis multiplex, diabetic polyradiculopathy, proximal diabetic neuropathy, and others.<sup>2,5,6,19</sup> Diabetic thoracic radiculopathies are a rare but important complication of diabetes mellitus.<sup>3</sup> These typically present with severe pain and dysesthesia along the trunk, chest, or abdominal wall, and often require extensive testing for underlying thoracic or abdominal pathology.<sup>4,8</sup> They can be symmetrical and can involve multiple dermatomes. Although diabetic lumbosacral radiculoplexus neuropathy is a much more familiar branch of the spectrum of radiculoplexus neuropathy, the cervical segment may also be involved, but this is very rare.<sup>17</sup>

Diabetic autonomic neuropathy is a generalized disorder of cholinergic, adrenergic, and peptidergic autonomic fibers

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in the context of diabetes without other causes. It is characterized by a subclinical form detectable only by examinations, and a clinical form with the presence of signs and symptoms.<sup>14,15</sup> Cardiovascular Autonomic Neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system.<sup>20</sup> In diabetes, CAN is the result of complex interactions between the degree of glycemic control, disease duration, age-related neuronal wasting, and systolic and diastolic blood pressure.<sup>19</sup>

Hyperglycemia plays a fundamental role in the activation of several biochemical pathways related to the metabolic and/or redox state of the cell, which, together with impaired nerve perfusion, contributes to the development and progression of diabetic neuropathies.<sup>12</sup> As neuropathy is seen first in the longer fibers, the first manifestations of autonomic neuropathy in diabetes tend to be associated with parasympathetic denervation, with a consequent early increase in sympathetic tone.<sup>19</sup> Clinical symptoms of autonomic dysfunction may not appear until long after the onset of diabetes.<sup>2</sup> However, subclinical CAN can be detected within 1 year of diagnosis in type 2 diabetes and within 2 years of diagnosis in type 1 diabetes.<sup>16</sup> Signs of this disease are decreased heart rate variability, resting tachycardia, exercise intolerance, abnormal blood pressure regulation, and orthostatic hypotension.<sup>12</sup> NAC is significantly associated with mortality, such as silent myocardial ischemia, coronary artery disease, stroke, progression of diabetic nephropathy, and perioperative morbidity.<sup>9</sup>

Thus, the CAN assessment can be used for cardiovascular risk stratification in patients with and without established cardiovascular disease.<sup>6,19</sup> Gastrointestinal Autonomic Neuropathy Gastrointestinal motor, sensory and secretory functions are modulated by the interaction of the autonomic (sympathetic and parasympathetic) and enteric nervous systems with underlying rhythmicity generated by the interstitial cells

of Cajal located within smooth muscle.<sup>8</sup> The assessment of gastrointestinal autonomic function is difficult in humans, and the diagnosis of gastrointestinal autonomic neuropathy is usually one of exclusion.<sup>5</sup> Diabetes is associated with gastrointestinal symptoms such as nausea, abdominal distension, abdominal pain, diarrhea, constipation and delayed gastric emptying with concomitant reduced absorption of oral drugs, poor glycemic control, malnutrition, abnormal postprandial blood pressure regulation, poor quality of life and high rate of hospitalization.<sup>9,11</sup>

Up to 75% of patients with diabetes can experience these symptoms. Erectile dysfunction (ED) affects 30-40% of diabetic men and occurs as a result of endothelial dysfunction and autonomic neuropathy.<sup>6</sup> A estreita associação com a disfunção endotelial significa que a DE é um marcador precoce de risco cardiovascular.<sup>9</sup> Although there are some effective treatments for ED, managing this condition is sometimes extremely difficult.<sup>18</sup> It is recommended to be part of a diabetes care service.<sup>2</sup> It is recommended to be part of a diabetes care service.<sup>7</sup>

Estimates of the prevalence of bladder dysfunction are 43-87% of type 1 diabetic patients and 25% of type 2 diabetic patients.<sup>9</sup> The cause of bladder dysfunction in diabetes mellitus is mainly peripheral and autonomic neuropathy.<sup>10</sup> Animal and human studies have revealed that diabetic cystopathy develops as a result of polyneuropathy, which predominantly affects sensory and auto-

mic nerve fibers.<sup>6</sup> Patients often remain asymptomatic in the early stages despite the demonstrable bladder abnormality. Impaired bladder sensation is usually the first manifestation of lower urinary tract involvement.<sup>9</sup> The urination reflexes are delayed due to decreased bladder sensation with increases in bladder capacity and urinary retention that usually occur asymptotically.<sup>5,19</sup>

Patients are often unaware of bladder dysfunction until they have a urinary tract infection secondary to increased residual urine volume. Common symptoms are straining, hesitation and weakness of flow.<sup>3,4</sup> Diabetic cystopathy is characterized by an impaired sensation of bladder fullness, which causes the bladder to become hyperextended, reduced bladder contractility, increased residual urine, and impaired uro flow.<sup>8,19</sup> Diabetic autonomic neuropathy initially results in a loss of thermoregulatory sweating in a distribution that may extend to the upper limbs and anterior abdomen.<sup>14</sup>

Ultimately, this process results in global anhidrosis that often accompanies severe autonomic neuropathy. Diabetic autonomic neuropathy can also cause hyperhidrosis.<sup>20</sup> Excessive sweating can occur as a compensatory process, involving proximal regions such as the head and trunk, which are spared in an agonizing neuropathy.<sup>21</sup> Gustatory sweating, an abnormal production of sweat that appears on the face, head, neck, shoulders and chest after consuming unseasoned foods, occurs in occasional cases.<sup>22</sup> A limitation of this study was the lack of

research related to the topic, even though it is a subject that should be treated with utmost importance and urgency, as it is a problem that affects a large portion of the population. It is recommended that more field research be carried out so that we have a greater dimension of the problem and thus devise strategies to mitigate the damage and benefit the community.

## CONCLUSION

Sensory-motor and cardiovascular neuropathies are common in diabetic patients. In addition to strict glycemic control, no other therapeutic approach exists to prevent this phenomenon. The reasons why only a few patients with nerve damage develop neuropathic pain are still unknown. Risk factors such as age, sex, smoking are predisposed to the disease. The intensity of pain before and after the injury and emotional and cognitive characteristics indicate that there are several factors in addition to the nerve damage that contribute to the manifestation of chronic pain. Diagnosis and symptomatic treatment are essential for these patients, as painful sensorimotor neuropathies are associated with poor quality of life and autonomic neuropathies are associated with increased cardiovascular mortality. Intensive diabetes therapy, intensive multifactorial cardiovascular risk reduction, and lifestyle intervention are recommended in patients with CAN. Symptomatic treatment of sensory symptoms includes TCAs, SNRIs, gabapentin, pregabalin, and opioids. ■

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