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REVIEW ARTICLE

Assessment of risk factors and diagnosis for cardiac autonomic neuropathy in diabetic people

Evaluación de factores de riesgo y diagnóstico de neuropatía autonómica cardíaca en personas diabéticas

Avaliação dos fatores de risco e diagnóstico para neuropatia autonômica cardíaca em pessoas diabéticas

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Abstract

The aim was to highlight the publications expressed in the world scientific literature on this topic. This is an integrative literature review study that followed the PICo strategy to identify risk factors and diagnoses associated with diabetic neuropathy. The search for articles was performed in three electronic databases: Medline, BVS and SciELO. The descriptors "Diabetic Neuropathies", "Diseases of the Peripheral Nervous System", "Neuralgia", "Risk Factors", "Diabetes Mellitus" were used, the inclusion criteria are full texts, published from 2011 to 2021, in the language English, Portuguese and Spanish and the Boolean AND operator was used. It resulted in 51 articles. Forty-six articles were selected to be read in full and 7 met the criteria of this review. It is concluded that autonomic neuropathy can be reduced with better blood glucose control, and improved lipid and blood pressure levels, avoidance of smoking and excessive alcohol consumption are already recommended for the prevention of other complications of diabetes. The treatment of symptoms includes the use of tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, gabapentin, pregabalin and opioids.

Descriptors: Diabetic Neuropathies; Peripheral Nervous System Diseases; Neuralgia; Risk Factors; Diabetes Mellitus.

Resumén

El objetivo fue destacar las publicaciones expresadas en la literatura científica mundial sobre este tema. Este es un estudio integrador de revisión de la literatura que siguió la estrategia PICo para identificar factores de riesgo y diagnósticos asociados con la neuropatía diabética. La búsqueda de artículos se realizó en tres bases de datos electrónicas: Medline, BVS y SciELO. Se utilizaron los descriptores "Neuropatías diabéticas", "Enfermedades del Sistema Nervioso Periférico", "Neuralgia", "Factores de Riesgo", "Diabetes Mellitus", los criterios de inclusión son textos completos, publicados de 2011 a 2021, en el idioma inglés, Portugués y español y se utilizó el operador booleano AND. Resultó en 51 artículos. Se seleccionaron 46 artículos para ser leídos en su totalidad y 7 cumplieron con los criterios de esta revisión. Se concluye que la neuropatía autonómica se puede reducir con un mejor control de la glucosa en sangre, y ya se recomiendan mejores niveles de lípidos y presión arterial, evitar el tabaquismo y el consumo excesivo de alcohol para la prevención de otras complicaciones de la diabetes. El tratamiento de los síntomas incluye el uso de antidepresivos tricíclicos, inhibidores de la recaptación de serotonina y noradrenalina, gabapentina, pregabalina y opioides.

Descriptores: Neuropatías Diabéticas; Enfermedades del Sistema Nervioso Periférico; Neuralgia; Factores de Riesgo; Diabetes Mellitus.

Resumo

Objetivou-se evidenciar as publicações expressas na literatura cientifica mundial sobre essa temática. Trata-se de um estudo de revisão integrativa da literatura que seguiu a estratégia PICo para identificar os fatores de risco e diagnósticos associados à neuropatia diabética. A busca dos artigos foi realizada em três bases de dados eletrônicas: Medline, BVS e SciELO. Foram utilizados os descritores "Neuropatias Diabéticas", "Doenças do Sistema Nervoso Periférico", "Neuralgia", "Fatores de Risco", "Diabetes Mellitus", os critérios de inclusão são textos completos, publicados no período de 2011 a 2021, no idioma inglês, português e espanhol e foi usado o operador booleano *AND*. Resultou-se em 51 artigos. Quarenta e seis artigos foram selecionados para serem lidos na íntegra e 7 atenderam aos critérios desta revisão. Conclui-se que a neuropatia autonômica pode ser reduzida com melhor controle da glicose no sangue, e a melhora dos índices de lipídios e pressão arterial, evitar o tabagismo e o consumo excessivo de álcool já são recomendados para a prevenção de outras complicações do diabetes. O tratamento dos sintomas inclui uso de antidepressivos tricíclicos, inibidores da recaptação da serotonina e noradrenalina, gabapentina, pregabalina e opioides.

Descritores: Neuropatias Diabéticas; Doenças do Sistema Nervoso Periférico; Neuralgia; Fatores de Risco; Diabetes Mellitus.

Introduction

Diabetic neuropathy is a common complication estimated to affect 30-50% of individuals with diabetes. Its main risk factor is hyperglycemia. Other risk factors include age, duration of illness, smoking, hypertension, high triglycerides, higher BMI, alcohol consumption[1,2].

Interestingly, between 25 and 62% of patients with idiopathic peripheral neuropathy are reported to have prediabetes; among those 11-25% are thought to have peripheral neuropathy, and 13-21% have neuropathic pain. Population-based studies suggest a gradient for the prevalence of neuropathy, being highest in patients with overt diabetes mellitus, followed by individuals with impaired glucose tolerance, then by individuals with impaired fasting glucose, and finally, at least in those with normoglycemia[3-5].

In general, it is believed that oxidative stress is the main pathological process that induces nerve damage in diabetes. Oxidative stress, possibly triggered by vascular abnormalities and microangiopathy, is a key pathological process that induces nerve damage. Cardiovascular autonomic neuropathy (CAN) is one of the main causes of morbidity and mortality in diabetic patients. NAC results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and eventually lead to abnormalities in cardiovascular dynamics and anatomy. It originates from complex interactions between glycemic control, glycemic fluctuation, duration of diabetes, age-related neuronal deficits, and other cardiovascular risk factors such as hypertension, hyperlipidemia, obesity, and smoking[6-10].

Other diabetic microvascular complications have also been identified as clinical predictors of CAN. This is a common complication in people with type 1 and type 2 diabetes. Its prevalence is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease. Studies show that NAC presents itself as a decrease in heart rate variability (HRV) due to parasympathetic denervation, and thus will progress to NAC that results from the increase or sympathetic denervation, in an average of 5 years[1,4-7,11].

A prospective study demonstrated that during 2 years of follow-up, most HRV indices gradually deteriorated in all patients with type 1 or 2 diabetes who had CAN but no overt cardiovascular disease (ECD). Although several risk factors for the progression of CAN have been established, it is not known whether it is reversible over time, and the characteristics associated with its recovery have not been identified. Glycemic control has a greater effect on preventing diabetic neuropathy in type 1 diabetes compared to type 2 diabetes, suggesting that the underlying mechanism may be different. The scarcity of studies nationwide makes this study relevant to science.[5,6,8,12,13].

Thus, this study aims to describe what the international literature has been producing on this subject, as well as the state of the art of NAC and to determine the risk factors and clinical diagnoses related to it.

Methodology

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 context (o). It is intended to answer the guiding question: What risk factors and diagnoses (C) identified in the literature (O) are associated with neuropathies (I) in diabetic people (P)? Then, the keywords "Diabetic Neuropathies", "Diseases of the Peripheral Nervous System", "Neuralgia", "Risk Factors", "Diabetes Mellitus" were defined from the vocabulary of the Health Sciences Descriptors (DeCS), for being a common research terminology. 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. 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 address the topic 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. Evidence from randomized controlled trials starts at a high level and evidence from observational studies at a low level (Chart 1). Evidence from randomized clinical trials starts at a high level and evidence from observational studies at a low level.

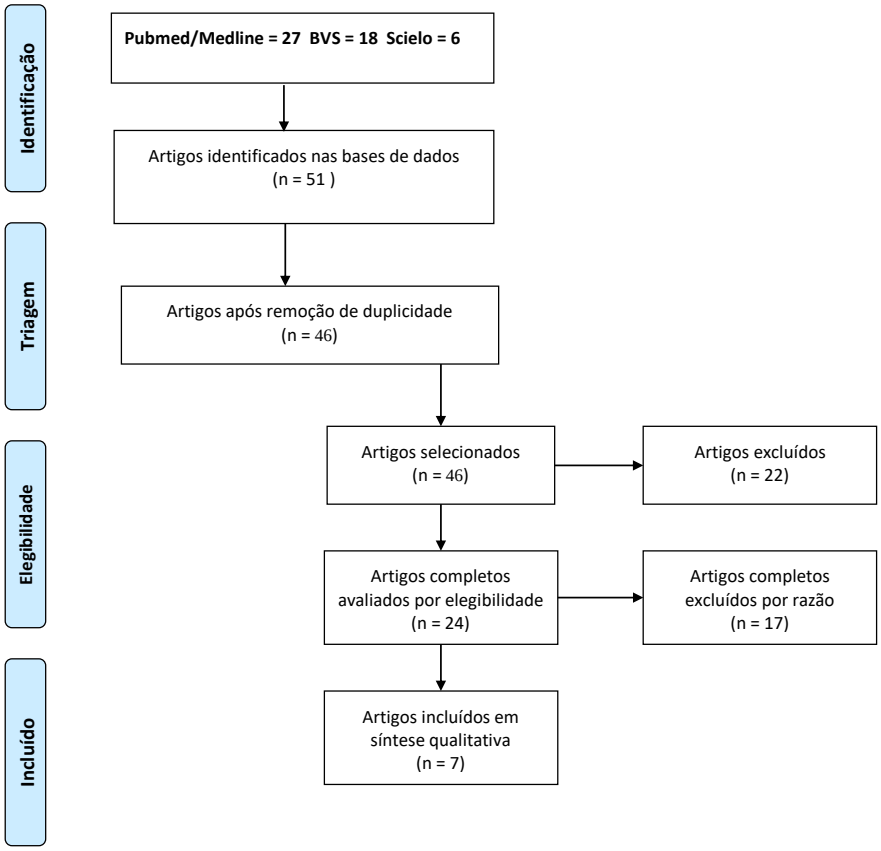
Chart 1. Levels of evidence. Rio de Janeiro, RJ, Brazil, 2021

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

Moderate	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

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 technologies 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.

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



Results

A total of 51 studies were identified in these databases, as illustrated in (Figure 1), which followed the PRISMA recommendations. to describe the literature search process. Of these, 5 duplicate articles were excluded, leaving 46 unique articles. Then, titles and abstracts were read, observing the inclusion and exclusion criteria. As a result of this process, 39 articles were excluded, and another 7 articles met the eligibility criteria. Then, the full and in-depth reading of these studies by two reviewers, independently, began. Any disagreements between the evaluators that emerged during this stage were worked on and resolved by consensus, which resulted in a final sample of 7 articles[14].

The articles included in this synthesis (Chart 2) were developed in six different countries: Brazil (n= 2), United States (n= 3), Taiwan (n= 1), Africa (n= 1) As for the method, most of the researchers used the qualitative and quantitative approach (n=7) to describe and analyze, in depth, the different dimensions in which diabetic neuropathy occurs.

Chart 2. Summary of published studies. Rio de Janeiro, RJ, Brazil, 2021

Titles	Author(s), Country/ Year	Objective	Method	Results	Level of Evidence
Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies	Vinik, TuchmanSafirstein. Estados Unidos (2017)	To assess the efficacy and tolerability of lamotrigine in pain associated with diabetic neuropathy	Clinical Trial	Compared with placebo, lamotrigine (300 and 400 mg daily) was inconsistently effective for pain associated with diabetic neuropathy, but was generally safe and well tolerated	Moderate
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
Fatores associados a alteração da percepção sensorial tátil nos pés de pacientes com diabetes mellitus TT - Factors associated with altered tactile sensory perception in the feet of patients with diabetes mellitus	Noronha, J. A. F. Brasil (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	Moderate
Treatment-induced neuropathy of diabetes: An acute, iatrogenic complication of diabetes	Gibbons, C., Freeman, R. Estados Unidos (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	Moderate
Sensory phenotype and risk factors for painful diabetic neuropathy: A cross-sectional observational study	Raputova, J. et al. República Tcheca (2018)	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
Degree of risk for foot ulcer due to diabetes: nursing assessment	Lucoveis; Gamba; Paula. Brasil (2018)	Rate the risk level for foot ulcers in people with diabetes	Exploratory, descriptive study	Of this total analyzed, 96% had never had their feet examined with the Semmes-Weinstein monofilament	Moderate

Discussion

It has been previously shown that prediabetes can also be associated with neuropathy. Based on recent ADA guidelines, diabetes can be diagnosed based on results of HgbA1c, fasting plasma glucose, or 2-hour postprandial glucose levels. This statement recommended the use of the A1c test to diagnose diabetes, with a threshold of ≥6.5%. The established glucose criteria for diagnosing diabetes (fasting plasma glucose ≥7 mmol / l or 2-hour postprandial glucose ≥ 11.1 mmol / l) also remained valid. Pre-diabetes can be defined as having altered fasting glucose (fasting plasma glucose levels 5.6-6.9 mmol/l) or impaired glucose tolerance (2-hour postprandial glucose values on the glucose tolerance test oral glucose of 7.8-11.0 mmol / l). It should be noted that the World Health Organization and several other diabetes organizations set the cutoff point for altered fasting glucose at 110 mg/dl (6.1 mmol/l). Therefore, it is reasonable to consider an A1c range of 5.7-6.4% to identify individuals at high risk for future diabetes, a state that can be referred to as pre-diabetes. As with glucose measurements, risk

continuity is curvilinear - as A1c rises, the risk of diabetes rises disproportionately. Consequently, interventions should be more intense and follow-up particularly vigilant for those with A1c>6.0%, who should be considered at high risk[8,9]. Lifestyle and healthcare standards can also be found in this guideline[8-10,13,15-19].

The diagnosis of sensorimotor neuropathy is the most common presentation of neuropathy in diabetes, up to 50% of patients may have symptoms - most often burning pain, electrical sensations or stinging, paresthesia, hyperesthesia, and deep pain. 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. Lower limb examination usually reveals sensory loss of vibration, pressure, pain, and temperature perception (mediated by small and large fibers) as well as absent ankle reflexes. Muscle weakness is usually mild, but in some patients a distal sensory neuropathy is combined with proximal weakness and atrophy. Interestingly, as up to half of patients can be asymptomatic, the diagnosis can only be made on physical examination or, in some cases, when the patient has a painless foot ulcer[10,13,17-22].

For the diagnosis of Peripheral Diabetic Neuropathy (PDN), bedside examination should include assessment of muscle strength, pinprick sensations, joint position, touch, and temperature. The vibration test must be done by a 128 Hz tuning fork. For touch sensation, 10 g monofilament is recommended. Several questionnaires have been developed to help physicians diagnose neuropathic pain. The DN4 questionnaire is of particular interest as it can be completed quickly, is easy to use and has a good diagnostic performance: for a score of ≥4/10, it has a sensitivity of 83% and a specificity of 90% for the diagnosis of pain neuropathic. The main advantage of screening tools is to identify potential patients with neuropathy, mainly by non-specialists. However, these tools fail to identify 10-20% of patients with physician-diagnosed neuropathy, showing that they cannot replace careful clinical judgment[19-26].

Diabetic patients with features of cardiac autonomic dysfunction, such as unexplained tachycardia, orthostatic hypotension, and poor exercise tolerance, or with other symptoms of autonomic dysfunction, should be evaluated for the presence of CAN. Its screening should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at increased risk for CAN due to a history of poor glycemic control, cardiovascular risk factors, PDN, and microangiopathic diabetic complications. The diagnosis of CAN is based on the use of cardiovascular autonomic reflex tests for the heart rate response to deep breathing, standing, and Valsalva maneuver, as well as for the blood pressure response to standing[13,17,20-22,27,28].

Based on the etiology of diabetic neuropathy, several agents have been tested to halt its progression (after the onset of subjective symptoms, only palliative treatments are currently available), thus improving the clinical outcome. A review of the literature on experimental peripheral diabetic neuropathy suggests that, to date, all pharmacological agents that counteract one or several manifestations of painful or insensitive neuropathy are also effective against nerve conduction velocity deficit. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are widely used in diabetic patients to control blood pressure and prevent or treat cardiovascular disease and nephropathy. Large-scale studies have not been performed on the effects of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, although some small studies and prospective evaluations have been performed with a positive impact on neuropathy[4,7,10,16,19,22-24,29].

Conclusion

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, pain intensity before and after the injury, and emotional and cognitive characteristics indicate that there are several factors, in addition to the nerve damage itself, 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. These data demonstrate the importance of researching autonomic alterations in type 1 diabetics. A limitation of this study was the low concentration of studies on this topic in Brazil.

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