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# Diabetes Mellitus and Diabetic Peripheral Neuropathy

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## Abstract

Diabetes *mellitus* (DM) is considered a major public health problem because of its high prevalence and progressive increase of incidence. DM chronic complications are major causes of morbidity and mortality, among which diabetic neuropathy (DN) stands out, affecting 30% - 50% of DM patients. An appropriate medical approach, involving anamnesis and thorough clinical examination, is extremely important for the early diagnosis of DN and, therefore, to the prevention of its complications, including the amputation of limbs. Despite of the importance of DN prevention and treatment, in order to provide improved quality of life and longevity to DM patients, current therapeutic options are very limited with respect to both symptom control and as effective disease therapies. Intensive glucose control is extremely important in order to prevent and avoid the progression of DN, as demonstrated in two large multicenter studies involving patients with type 1 DM, the DCCT (Diabetes Control and Complications Trial) and the EDIC (Epidemiology of Diabetes Interventions and Complications).

## Keywords

Diabetes *mellitus*, Diabetic Peripheral Neuropathy, Diabetic Foot, Diabetes and Complications

## 1. Introduction

Diabetes *mellitus* (DM) is a highly prevalent disease with a major impact on the quality of life of patients, mainly, because of several complications, both acute and chronic. Given the relevance of the subject, this work aimed at performing a literature review on one of the major complications of diabetes: peripheral

diabetic neuropathy. Emphasis was placed on studies addressing the pathophysiology and diagnosis of diabetic peripheral neuropathy, in order to provide health professionals with the information they need to prevent and treat it, improving the quality of life and the autonomy in routine activities of patients with diabetes.

## 2. Diabetes Mellitus

DM represents a group of metabolic diseases of different etiologies, characterized by hyperglycemia, which can result from deficient insulin secretion by the pancreas beta cells (β), peripheral resistance to insulin action, or both. Among the different types of diabetes, type 1 diabetes *mellitus* (DM1) and type 2 diabetes *mellitus* (DM2) stand out, corresponding to 5% - 10% and 80% - 90% of the cases, respectively [1].

DM can be considered an ongoing epidemic, as the global estimate of the number of affected adults in 1985 was 30 million, increasing to about 135 million in 1995, and an estimate of 300 million in 2030 [2].

DM is responsible for several complications that influence the quality of life and increase the mortality rate. Among the acute complications are hypoglycemia, diabetic ketoacidosis, and hyperosmolar coma. Chronic complications may be associated with microvascular alterations, leading to nephropathy and retinopathy, macrovascular changes, including ischemic heart disease, cerebrovascular disease and peripheral vascular disease, as well as neuropathic changes [3].

## 3. Diabetic Peripheral Neuropathy

### 3.1. Concept and Epidemiology

Diabetic neuropathy (DN) is defined as a neurological damage in patients with DM, after excluding other causes [4]. It is the most prevalent chronic complication affecting 30% - 50% of diabetic patients [4] [5]. DN can affect the peripheral, autonomic, and central nervous systems, exhibiting, therefore, several clinical symptoms [4] [6]. However, about 80% of the cases of DN manifest as distal symmetrical sensorimotor polyneuropathy, which is responsible for cases of chronic pain; impaired sleep quality; 15× increase of the falling risk associated with weakness and ataxia, and a 15 - 40× increase of the risk of extremities amputation. The latter is the leading cause of non-traumatic lower extremity amputations, resulting from initial ulceration and foot gangrene [5] [7] [8] [9].

DN can be prevented by intensive glycemic control and DM prevention [4] [5] [10]. Treatment is aimed at relief or resolution of pain symptoms, quality of life improvement, and prevention of serious complications, but it cannot restore neurological loss [8] [10].

### 3.2. Pathogenesis

Chronic hyperglycemia, the main factor in the pathogenesis of DN, can cause cell damage in several ways, including the activation of the polyol pathway, gen-

eration of reactive oxygen species (ROS) and nitrogen, and through the accumulation of advanced glycation end products (AGE) that activate inflammatory cascades, resulting in cell damage and death [6] [7] [11] [12]. Endothelial nitric oxide (NO), in turn, a powerful vasodilator, becomes less available because it is used in the formation of peroxynitrite, a strong oxidant, toxic to endothelial cells. Furthermore, there is a faulty response to the vasodilatory effect of substance P, bradykinin, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and histamine. Another route possibly involved in the pathogenesis of diabetic peripheral neuropathy, involves the activation of the nuclear enzyme, poly(ADP ribose) polymerase (PARP), that like oxidative stress can lead to cell energy deficit (**Figure 1**) [4] [12].

The state of insulin deficiency associated to DM also favors the development of DN, since insulin possesses neurotrophic effects that influence the growth and survival of neurons [5] [11].

Factors such as DM long duration, ischemia of the peripheral nerves, glycemic variability, and poor glycemic control, are related to a higher risk of DN [4] [6] [7] [10] [11] [12]. The DCCT (Diabetes Control and Complications Trial) and the EDIC (Epidemiology of Diabetes Interventions and Complications), multicenter and randomized studies with DM1patients showed a reduction of up to

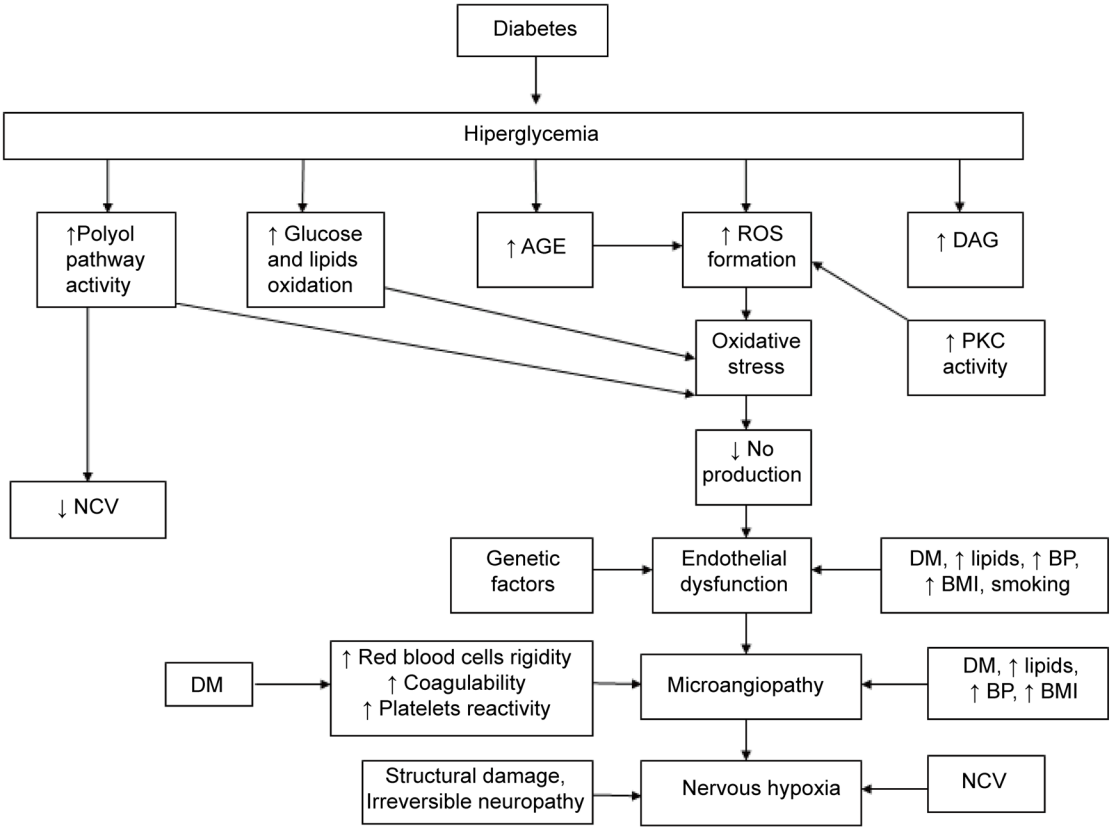


**Figure 1.** Pathogenesis of diabetic neuropathy. Source: BOULTON; PEDROSA, 2013; SHAKHER; STEVENS, 2011 [12] [13]. Adapted. Legend: DM = diabetes mellitus; ↑ = increase; ↓ = decrease; AGE = advanced glycation end products; PKC = protein kinase C; ROS = reactive oxygen species; NO = nitric oxide; BP = blood pressure; BMI = body mass index; NCV = nerve conduction velocity; DAG = diacylglycerol.

70% in the incidence of this complication in patients of the intensive glycemic control group [11] [14]. With respect to DM2, the impact of isolated intensive glycemic control in preventing DN is controversial, showing a protection of only 5% - 7% in recent studies, probably due to longer hyperglycemia exposure before diagnosis and to important associations with other metabolic risk factors, especially dyslipidemia [4] [5] [11].

Additional factors probably also involved in the pathogenesis of DN are dyslipidemia, age, systemic arterial hypertension (SAH), obesity, and smoking [4] [5] [8] [11].

## 3.3. Diagnosis

### 3.3.1. Pain Assessment

ND diagnosis should be based on a careful anamnesis and neurological examination, focused on the detection of specific organs affected by diabetes [9].

The 1992 conference of the American Academy of Neurology and the San Antonio Conference on Diabetic Neuropathy held in 1998recommended the assessment of at least one parameter of the following five categories, in order to classify DN: Symptoms profile; neurological examination; QST (Quantitative Sensory Testing); nerve conduction, and autonomic function tests.

The QST is a measure of the psychophysiological perception in response to external stimuli of controlled intensity. This parameter is able to evaluate positive phenomena, such as allodynia and hyperalgesia [15].

Another useful tool in the neuropathy screening is the Michigan Neuropathy Screening Instrument (MNSI), a questionnaire of 15 items, which characterizes an individual with a score ≥ 8 as neuropathic [9] [16].

Other useful methods in the evaluation and monitoring of pain are the visual analogue scale (VAS) and the Likert numerical scale. A reduction of 50% - 70% of the pain level is considered very good, since full relief of pain is not always possible [12]. It is also important to address sleep quality and the impact of pain on the individual's daily activities [8] [11].

### 3.3.2. Neurological Assessment

Neurological assessment should be performed bilaterally to determine the sensitivity, reflexes, and muscular strength. DN annual screening should be performed starting from the diagnosis moment, in the case of DM2, and after 5 years in the case of DM1. It is important to note that DN is a diagnosis of exclusion and, therefore, other peripheral causes must be excluded [12].

The 10 g Semmes-Weinstein monofilament (SWM) is recommended in the evaluation of the tactile sensitivity (protopathic), which allows assessing the risk of ulceration. This test has a low cost, it is easy to apply, and has a high sensitivity. [15]. Nevertheless, a normal SWM test does not rule out other forms of DN [11] [17].

The vibration sensitivity can be qualitatively tested with a 128 Hz tuning fork. This test is considered abnormal when the perception of the vibration intensity in the lower limbs is reduced relative to other prominences. This is compared

with the perception time of the examiner while holding the tuning fork [11] [12] [17].

The biothesiometer quantitatively evaluates, by measuring the vibration sensitivity threshold (VST), a7x larger risk of ulceration when the VST is greater than 25 volts [12].

Sensitivity to cold or hot can be assessed with the tuning fork cable itself (heating with hot water or cooling with alcohol or cold water) in the patient's legs and on the dorsal side of both halluces [12]. Similarly, the inability to perceive a needlestick injury and the absence of Achilles reflex is associated with an increased risk of ulceration [11] [17].

The evaluation of muscle strength is also very important, although assessed in more advanced stages of the disease. The strength of the peroneal and tibialis anterior groups can be evaluated by observing the patient walking, first on tiptoes, and then on heels. Although the limitation of walking on heels exhibits low sensitivity, the positive predictive value is high for DN. Thus, no other diagnostic procedure is required in patients with this degree of motor dysfunction. Atrophy of the interosseous muscles of the feet, causingtoe-overlapping (hammertoes) and the shortening of the Achilles tendon (horse foot), are also possible DN manifestations [11].

In cases of advanced disease, with sensory denervation and chronic proprioceptive, the patient may develop Charcot arthropathy with theresulting increase of recurrent ulceration risk and eventual amputation [4] [11] [17].

Distal pulses (posterior tibial and dorsalis pedis) must be recordedto assess peripheral arterial disease and intermittent claudication [12].

From a clinical point of view, the Brazilian Diabetes Society (SBD), the Latin American Diabetes Association (ALAD), the American Diabetes Association (ADA), and the American Association of Clinical Endocrinologists (AACE) recommend the assessment of the loss of protective sensitivity, using a 10 g monofilament properly calibrated, and another test for vibration or painful sensitivity, or Achilles reflex. These combined tests have a sensitivity of 87% for the positive screening of DN, with emphasis on the neuropathic risk of ulceration [12].

Neurological damages can also be assessed by nerve conduction velocity (NCV) measurement and skin biopsyto test for small fibers [9] [12].

### 3.4. Treatment

For an effective therapeutic approach, general measures, such as adequate metabolic control and lifestyle changes, should first be considered. Establishinga better glycemic control is critical to the management of patients with DN [4] [5] [11] [12].

Patients with feet sensitivity problems should be instructed to take special care. The following recommendations should be followed: 1) use of comfortable shoes (orthotic sandals); 2) use of white cotton socks and seamless (which should be changed daily); 3) nail cutting care; 4) proper drying, inspection of the feet, and 5) application of urea-based creams [10] [11] [18].

#### 3.4.1. Symptomatic Treatment of Painful Neuropathy

The symptomatic treatment of painful neuropathy is based on drugs that act upon pathogenic mechanisms and drugs that relieve neuropathic symptoms [4] [12]. However, available drugs have limited efficacy and the association of more than one class of drugs is often necessary to achieve therapeutic success. The treatment is considered significant if pain reduction, evaluated by analogical or numerical scales is superior to 50% [11] [12].

The adoption of an optimistic approach by the physician when a pain relief medication is started is also important, since the placebo effect can reach up to 30% relief [8] [11].

First-line drugs are tricyclic antidepressants (Amitriptyline, and Imipramine), calcium channel anticonvulsants modulators, alpha-2-delta subunit binders (gabapentin and pregabalin), and selective serotonin and noradrenalin reuptake inhibitors (Duloxetine). When the expected analgesia is not achieved, association of two drugs among these three medication classes can be made [5] [11] [12].

Opioids are second-line drugs and are an alternative upon total or partial failure of the latter three medication classes [11] [12]. Topical agents (capsaicin) are indicated in the case of localized pain [8] [11] [12]. In the case of compressive neuropathies non-hormonal anti-inflammatory drugs should be used with care and during short periods of time, due to the possibility of aggravation of a pre-existent renal damage [12] [19].

#### 3.4.2. Pathogenesis-Based Treatment of Diabetic Neuropathy

The thioctic acid, also called alpha lipoic acid, stands out in pathogenesis-based treatments of DN, being a powerful antioxidant that inhibits the formation of free radicals and acts as coenzyme in mitochondrial multienzyme complexes. When used intravenously, it contributes to a cellular oxidative stress reduction, nerve conduction improvement, and a significant reduction of pain [12] [20]. In Brazil, however, it is only available in oral form. The recommended dose is 600 mg/day in the morning underfasting conditions, showing good tolerability. It should be stressed that hypoglycemia may occur during the treatment. In Brazilit is available as 600 mg Thioctacid® [11].

Benfotiamine also demonstrated the ability to improve neuropathic symptoms, by reducing AGE in tissues. Benfotiamine is a soluble precursor of thiamine (vitamin B1), which emerged as a therapeutic agent to counteract oxidative stress, reducing AGE in tissues and preventing vascular endothelial dysfunction [12] [21] [22]. Additional drugs that also showed improvements in the DN symptoms, either in clinical practice or in laboratory studies, include: L-acetylcarnitine, which stimulates the neuronal growth factor enhancement and corrects electrophysiological deficits through modulation of its activity; ACE inhibitors, which increase the synthesis of nitric oxide and acetylcholine-mediated vascular relaxation; PARP inhibitors; sildenafil; neuronal growth factor and neurotrophin-3, C-peptide; aldose reductase inhibitors, and prostaglandins analogues and flavonoids [13] [22]-[27].

## 4. Discussion and Results

DM is a multifactorial metabolic disease whose prevalence is increasing every day, especially DM2, because of current poor eating habits and sedentary lifestyle, which increases the rate of obesity, in addition to an increased life expectancy, leading to a general population aging. DM can lead to complications associated with microvascular (diabetic nephropathy and retinopathy) and macrovascular (ischemic heart disease, cerebrovascular diseases, and peripheral vascular disease) alterations, as well as with neuropathies (diabetic peripheral and autonomic neuropathy).

DN is the most prevalent complication of diabetes, affecting 30% - 50% of patients, the majority corresponding to diabetic peripheral neuropathy. The pathogenesis of DN is directly related to chronic hyperglycemia, which can lead to cell damage, either by the increased formation of free radicals or the formation of AGE, activating inflammatory cascades that culminate in cell damage and death. The importance of intensive glycemic control in the prevention of DN was demonstrated in studies such as the DCCT and EDIC, with a reduction of up to 70% of DN in the intensive glycemic group, compared with the control group. However, other factors are also involved, such as dyslipidemia, smoking, hypertension, obesity, and age.

DN diagnosis should be founded on a careful anamnesis, where specific questionnaires can be applied, such as the MNSI, and pain scales, such as the Likert numerical scale and VAS, and on a careful physical examination with neurological assessment focused on the detection of specific parts of the nervous system affected by diabetes. For tactile sensitivity evaluation, a 10 g SWM is recommended; the vibration sensitivity can be tested with a 128 Hz tuning fork; sensitivity to hot or cold can be assessed with the tuning fork cable itself (heating with hot water or cooling with alcohol or cold water). Reflexes and muscle strength evaluation are also very importance in the clinical neurological examination of DM patients. Neurological damages can also be evaluated with recourse to NCV measurement and skin biopsy to test for small fibers.

The treatment of diabetic peripheral neuropathy is based on the adoption of general procedures, such a cardiovascular and metabolic adequate control; lifestyle changes, involving regular physical activity practices and smoking and alcohol consumption cessation; feet care, including the use of appropriate shoes and socks, and nail cutting in square shape, the use of moisturizers, and daily feet inspection in order to identify calluses and ulcer areas. The pharmacological approach may be divided into drugs that act on the pathogenic mechanisms and those, which act on the ease of symptoms, improving quality of life, but without interfering in the pathogenesis of the disease.

## 5. Conclusions

Diabetes mellitus is a highly prevalent disease, considered a global epidemic in progress, with about 300 million affected adults expected in 2030, implying about 183 million people suffering from diabetic peripheral neuropathy, a number

that will significantly affect health services and society.

It is extremely important to perform a detailed medical analysis, involving careful anamnesis and clinical examination, in order to early diagnose DN and start and the prevention and treatment of its complications such as intractable pain and amputation of limbs.

Because of the complex pathogenesis of DN, a therapeutic approach based on different procedures is required, and in many cases, effective treatment involves the association of two or more drugs in order to achieve symptomatic relief. Nonetheless, on several cases, complete resolution of the neuropathic symptoms cannot be attained due to neurological damage, and unfortunately, there is not a therapeutic universally accepted and included in the recommendations for the DN treatment.

Intensive glycemic control is a proven prevention factor influencing the disease's progression, since it interrupts the development of microvascular complications and cell toxicity caused by the production of hyperglycemia-associated agents.

## References

[1] Renan Jr., M.M., *et al*. (2013) Diabetes Mellitus: Classificação e Diagnóstico. In: Vilar, L., Ed., *Endocrinologia Clínica*, Guanabara Koogan, Rio de Janeiro, cap. 50, 617-632.

[2] Wild, S., Roglic, G., Green, A., Sicree, R. and King, H. (2004) Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030. *Diabetes Care*, **27**, 1047-1053.http://care.diabetesjournals.org/content/27/5/1047.full

[3] Santos, I.C.R.V., de Carvalho, E.F., de Souza, W.V., de Medeiros, M.C.W.C., de Lira Nóbrega, M.G. and Lima, P.M.S. (2008) Complicações crônicas dos diabéticos tipo 2 atendidos nas Unidades de Saúde da Família, Recife, Pernambuco, Brasil. *Revista Brasileira de Saúde Materno Infantil*, **8**, 427-433. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1519-38292008000400008

[4] Boulton, A.J.M., Malik, R.A., Arezzo, J.C. and Sosenko, J.M. (2004) Diabetic Somatic Neuropayhies. *Diabetes Care*, **27**, 1458-1486. http://care.diabetesjournals.org/content/27/6/1458.full

[5] Callaghan, B.C., Cheng, H., Stables, C.L., Smith, A.L. and Feldman, E.L. (2012) Diabetic Neuropathy: Clinical Manifestations and Current Treatments. *The Lancet Neurology*, **11**, 521-534. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254767/

[6] Tesfaye, S., Boulton, A.J., Dyck, P.J., Freeman, R., Horowitz, M., Kempler, P., *et al.* (2010) Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. *Diabetes Care*, **33**, 2285-2293. http://www.ncbi.nlm.nih.gov/pubmed/20876709

[7] Jack, M.M. and Wright, D.E. (2012) The Role of Advanced Glycation Endproducts and Glyoxalase I in Diabetic Peripheral Sensory Neuropathy. *Translational Research*, **159**, 355-365. http://www.ncbi.nlm.nih.gov/pubmed/22500508

[8] Vinik, A.I. and Casellini, C.M. (2013) Guidelines in the Management of Diabetic Nerve Pain: Clinical Utility of Pregabalin. *Diabetes, Metabolic Syndrome and Obesity*, **6**, 57-78. http://www.ncbi.nlm.nih.gov/pubmed/23467255

[9] Brownlee, M., *et al*. (2010) Complicações Do Diabetes Melito. In: Kronenberg, H.M., *et al*., Eds., *Williams Tratado de Endocrinologia*, 11th Edition, Elsevier, Rio de Janeiro, cap. 32, 1124-1189.

[10] American Diabetes Association (2014) Standards of Medical Care in Diabetes—2014. *Diabetes Care*, **37**, S14-S80. http://care.diabetesjournals.org/content/37/Supplement_1/S14.full

[11] Costenaro, F., *et al.* (2015) Neuropatia Diabética. In: Silveiro, S.P. and Satler, F. Eds., *Rotinas em Endocrinologia*, Chap. 4, Artmed, Porto Alegre, 23-34.

[12] Boulton, A.J.M. and Pedrosa, H.C. (2013) Manuseio da Neuropatia Diabética. In: Vilar, L., Ed., *Endocrinologia Clínica*, Chap. 59, Guanabara Koogan, Rio de Janeiro, 741-763.

[13] Shakher, J. and Stevens, M.J. (2011) Update on the Management of Diabetic Polyneuropathies. *Diabetes, Metabolic Syndrome and Obesity*, **4**, 289-305. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3160854/

[14] Martin, C.L., Albers, J.W. and Pop-Busui, R., DCCT/EDIC Research Group (2014) Neuropathy and Related Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care*, **37**, 31-38. http://www.ncbi.nlm.nih.gov/pubmed/24356595

[15] Cruccu, G., *et al.* (2010) EFNS Guidelines on Neuropathic Pain Assessment: Revised 2009. *European Journal of Neurology*, **17**, 1010-1018. http://www.ncbi.nlm.nih.gov/pubmed/20298428

[16] Fortaleza, A.C. de S., *et al.* (2010) Avaliação Clínica Da Sensibilidade Em Indivíduos Com Diabetes Melito. *Colloquium Vitae*, **2**, 44-49.

[17] Boulton, A.J.M., *et al.* (2008) Comprehensive Foot Examination and Risk Assessment: A Report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with Endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care*, **31**, 1679-1685. https://doi.org/10.2337/dc08-9021

[18] Sociedade Brasileira De Diabetes (2014) Diretrizes da Sociedade Brasileira de Diabetes: 2013-2014. AC Farmacêutica, São Paulo. http://www.diabetes.org.br/sbdonline/images/pdf/diabetes-tipo-1/015-Diretrizes-SBD-Diretrizes-Para-Educacao-pg257.pdf

[19] Franco, L.C., Souza, L.A.F., da Costa Pessoa, A.P. and Pereira, L.V. (2011) Terapias não farmacológicas no alívio da dor neuropática diabética: Uma revisão bibliográfica. *Acta Paulista de Enfermagem*, **24**, 284-288. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-21002011000200020

[20] Mijnhout, G.S., Kollen, B.J., Alkhalaf, A., Kleefstra, N. and Bilo, H.J. (2012) Alpha lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials. *International Journal of Endocrinology*, **2012**, Article ID: 456279. http://www.ncbi.nlm.nih.gov/pubmed/22331979

[21] Stirban, A., *et al.* (2014) Benfotiamine: Commentary and Update on Recent Studies. *Diabetes, Stoffwechsel und Herz*, **23**, 203-206. https://www.researchgate.net/publication/274180185_Benfotiamine_Commentary_and_Update_on_Recent_Studies

[22] dos Santos Rua, A.S. (2013) Tratamento da Neuropatia Periférica—Fármacos modifica-dores de doença. Tese (Mestrado Integrado em Medicina). Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto. https://repositorio-aberto.up.pt/bitstream/10216/71789/2/92785.pdf

[23] Li, F., Drel, V.R., Szabó, C., Stevens, M.J. and Obrosova, I.G. (2005) Low-Dose Poly (ADP-Ribose) Polymerase Inhibitor-Containing Combination Therapies Reverse Early Peripheral Diabetic Neuropathy. *Diabetes*, **54**, 1514-1522. http://www.ncbi.nlm.nih.gov/pubmed/15855340

[24] Ilnytska, O., *et al.* (2006) Poly(ADP-Ribose) Polymerase Inhibition Alleviates Experimental Diabetic Sensory Neuropathy. *Diabetes*, **55**, 1686-1694. http://www.ncbi.nlm.nih.gov/pubmed/16731831

[25] Wang, L., *et al.* (2011) Phosphodiesterase-5 Is a Therapeutic Target for Peripheral Neuropathy in Diabetic Mice. *Neuroscience*, **193**, 399-410. http://www.ncbi.nlm.nih.gov/pubmed/21820491

[26] Gagliardi, A.R.T. (2003) Neuropatia Diabética Periférica. *Jornal Vascular Brasileiro*, **2**, 67-74. http://docplayer.com.br/1728512-Neuropatia-diabetica-periferica.html

[27] Sima, A.A., Zhang, W., Li, Z.G., Murakawa, Y. and Pierson, C.R. (2004) Molecular Alterations Underlie Nodal and Paranodal Degeneration in Type 1 Diabetic Neuropathy and Are Prevented by C-Peptide. *Diabetes*, **53**, 1556-1563. http://www.ncbi.nlm.nih.gov/pubmed/15161761