sciendo

ORIGINAL ARTICLES

The impact of demographic and clinical characteristics on diabetic painful neuropathy

ANTÓNIO ASSUNÇÃO[1], DINA CAMPOS[1], RUI MARQUES[2], INÊS CUNHA[2], PATRÍCIA SANTOS[3], ADRIANA MARTINS[1], ANA SOFIA GONÇALVES[4], ANA REBELO[5], CAROLINA LIMA[6], CÉSAR MATOS[7], ANA CRISTINA PRATA[3], JOSÉ TIAGO TEIXEIRA[1], LUÍS DUARTE[8], MARIANA BELO[1], PATRÍCIA FIGUEIREDO[3], TIAGO LETRAS ROSA[9]

[1] Family Health Unit (FHU) Viriato, Viseu, Portugal
[2] Department of Internal Medicine, Tondela-Viseu Hospital Center, Viseu, Portugal;
[3] FHU Sobreda, Almada-Seixal, Portugal
[4] FHU Tondela, Tondela, Portugal
[5] FHU Cidade Jardim, Viseu, Portugal
[6] FHU Sº Pedro do Sul, Viseu, Portugal
[7] FHU Azeitão, Azeitão, Portugal
[8] FHU Grão-Vasco, Viseu, Portugal
[9] FHU Vale do Sorraia, Coruche, Portugal

Introduction. Diabetic neuropathy (DN) is one of the most devastating complications of diabetes mellitus; however, in contrast to other countries, there are no scientific studies in Portugal evaluating the impact of demographic and clinical characteristics of this pathological entity. The aim of this study was to evaluate the impact of gender, metabolic control, age of diabetic patients, as well as time of disease progression, the appearance of complaints related to neuropathic pain.

Material and methods. A multicentre study with a non-probabilistic, convenience sample of 359 patients was performed employing the quantitative method, using the Statistical Package for Social Science 24 software. The p-value of $p < 0.05$ was defined to consider a result statistically significant. The Spearman correlation coefficient (r) was determined to determine the relationship between categorical variables.

Results. There was no statistically significant difference in the prevalence of DN between genders ($p = 0.633$ and $r = 0.025$). There was a statistically significant relationship between the value of HbA1c and DN, with $p = 0.010$ and $r = 0.136$. There is a relationship between age and complaints of neuropathic pain, with $p = 0.034$ and $r = 0.112$. The variable, time of disease progression, is also correlated with the appearance of complaints of neuropathic pain with $p = 0.020$ and $r = 0.112$.

Conclusion. The prevalence of neuropathic pain in subjects with diabetes is not negligible and is associated with modifiable risk factors that can be identified, possibly modified and prevented. The correct approach for these patients, which involves screening and early treatment, is decisive improving functionality and quality of life.

Key words: diabetic neuropathy; neuralgia; diabetes mellitus; prevalence; diabetes complications.

INTRODUCTION

Diabetic neuropathy (DN) is the most prevalent microvascular complication of diabetes mellitus (DM). It is a heterogeneous group of entities that can affect different parts of the nervous system, with symmetric distal polyneuropathy and diabetic autonomic neuropathy being the most common [1]. Distal symmetric neuropathy is defined as the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after excluding other causes [2]. The most common nerve injury is the bilateral and symmetrical lesion of the nerves of the lower limbs. This dysfunction mainly affects the sensory nerves and the symptoms may vary depending on the type of fibres involved. It is a devastating complication of DM which can lead to foot ulcers, Charcot foot or even amputation [2, 3].

Neuropathic symptoms can be positive/painful or negative/non-painful. Positive symptoms include burning sensation, stabbing, electric shocks, constriction and allodynia; negative symptoms include itching, tingling, numbness or stinging. In this context, painful diabetic neuropathy (PDN) has a prevalence of around 25–30%. Approximately 80% of PDN patients complain of moderate to severe pain. Concomitantly, negative symptoms prevail in DN. Patients with negative symptoms are at increased risk of foot ulcers due to loss of protective sensitivity [4, 5, 6].

DN affects approximately 50% of the elderly with diabetes or with the disease evolving over a

DOI: 10.2478/rjim-2019-0019

long period of time, defined in the literature as a progression of over 15–20 years. DN is present at the time of diagnosis in about 10% of individuals with type 2 diabetes mellitus (DM2), generally appearing 5 to 10 years after diagnosis of type 1 diabetes 1 [1, 3].

Approximately 50% of DN cases may be asymptomatic and these individuals are at risk of foot injuries, since only about 80% of amputations are preceded by an ulcer [1, 6].

In approaching DN, the following risk factors should be taken into account: level and duration of hyperglycaemia, age, height, male gender, hypertension, smoking and dyslipidaemia. Non-diabetic causes of symptomatic polyneuropathy should also be taken into account, among which the following stand out: metabolic causes (e.g., hypothyroidism, porphyria), toxic causes (e.g., alcohol), vitamin B deficiency, infection (e.g., acquired immunodeficiency virus, leprosy), malignancy (e.g., paraneoplastic syndrome), iatrogenic causes (e.g., isoniazid, vincristine alkaloids, post-chemotherapy), non-pharmacological iatrogenic causes (e.g., post-surgery) and genetic causes (e.g., familial amyloidosis). All of these variables make DN a first diagnosis of exclusion, based on clinical history and objective examination [7, 8, 9].

Neuropathic pain is caused by a primary dysfunction of the nervous system, which may have several etiologies [10, 11] and cause about 5% of neuropathic syndromes in subjects with diabetes that are due to other etiologies than diabetes [12,13].

Early detection of DN as well as its correct approach is important for several reasons related to the fact that there are a number of treatment options. It provides the possibility of an early approach to the increased risk of foot ulceration, which these patients face, since sensorimotor neuropathy and peripheral sympathetic neuropathy are the major risk factors for foot ulceration [14, 15].

Early recognition and appropriate treatment of neuropathy in patients with diabetes are important for a number of reasons. (DN) is a diagnosis of exclusion, since non-diabetic neuropathies may be present in patients with diabetes and can be treated by specific measures [16].

MATERIAL AND METHODS

This study was approved by all directors off all heath units. The aim of this study is to evaluate the prevalence of neuropathic pain diagnosis in subjects with diabetes followed by Portuguese Health Care System and to investigate correlations between this diagnosis and the demographic and clinical characteristics of diabetics.

The following questions were posed in order to perform the research:

- Question 1: Does sex condition the onset of complaints of neuropathic pain?
- Question 2: Is the value of glycated haemoglobin (HbA1c) related to complaints of neuropathic pain?
- Question 3: Is the diabetic's age related to complaints of neuropathic pain?
- Question 4: Does the time of disease progression affect the appearance of complaints of neuropathic pain?

In order to track and evaluate the prevalence of neuropathic pain, the Douleur Neuropathique 4 (DN4) questionnaire, translated and validated for the Portuguese population, was applied because it is one of the simplest and briefest, favouring its practical applicability in the research context in this area, in the context of a consultation [24]. A neuropathic pain compatible screening is admissible when at least 4 positive-response lines are present [24].

The dependent variable was defined by the existence of neuropathic pain in subjects with diabetes and the independent variables were defined as age, sex, HbA1c level and time of disease progression. We attempted to operationalize the variables as quantitative, so that: [1] sex would define the number of subjects with diabetes who were female or male; [2] age would define the number of subjects with diabetes aged 65 years or older or under 65 years, since the age over 64 years is the most consensual to define the elderly; [3] the HbA1c level would define the number of subjects with diabetes with HbA1c greater than or equal to 7.0% or less than 7.0%; [4] the time of disease progression would define the number of subjects with diabetes who had the disease for less than 10 years since diagnosis of diabetes, or 10 or more years since diagnosis of the disease.

The study population consisted of patients enrolled in the patient lists of the researchers involved in this project. They belong to several primary health care units (PHC) in Portugal, as well as the diabetes consultation of a national hospital. The sample was represented by 60% subjects with diabetes belonging to the population mentioned above, corresponding to 359 patients who were part of this research design (306 patients

followed in PHC and 53 in the hospital visit). This is a multicentre study, with a non-probabilistic, convenience sample. This type of sampling is very common in research and consists of selecting a sample of the population that is accessible. Thus, the patients included in this study were not selected by randomization, but rather because they stated they were willing to participate.

Patients who presented any of the following pathologies or clinical conditions when the questionnaire was applied were excluded: sequelae of cerebrovascular accident, spinal cord injury, multiple sclerosis, radiculopathies, nerve damage, traumatic or postoperative injuries. Patients who were taking the following medication were also excluded: amitriptyline, carbamazepine, duloxetine, gabapentin, imipramine, lidocaine plaster, nortriptyline, pregabalin, tramadol, tapentadol or venlafaxine.

The quantitative method was employed with the Statistical Package for Social Sciences 24 (SPSS) being used for the statistical treatment of data, with the aim of contributing to the development and validation of knowledge, thus offering the possibility of generalizing the results, as well as predicting them. The p value defined for statistical significance result was $p < 0.05$. Later, the qualitative method was also used to analyse and interpret the results. To determine the relationship between categorical variables, the Spearman correlation coefficient (r) was determined.

RESULTS

359 questionnaires were applied, of which DN4 was an integral part. In a first analysis, 89.14% of the diabetic patients consulted did not meet criteria for the diagnosis of neuropathic pain, since they did not present a score on the DN4 of at least 4 points. The remainder 10.86% met the positive criteria for neuropathic pain.

Description of the sample: as shown in Table 1, we found that 54.87% of the subjects with diabetes are male and 45.13% are female. It was possible to verify that 30.08% of subjects with diabetes are less than 65 years old, with 69.92% being 65 years of age or older. We also observed that 60.73% of diabetic patients had been diagnosed with the disease less than 10 years prior to the study and 39.27% of subjects with diabetes had 10 or more years of disease progression since the diagnosis of the disease. Finally, when the questionnaires were applied, 62.40% of the subjects with diabetes were found to have an HbA1c value of less than 7.0% and, 37.60% of the subjects with diabetes had an HbA1c greater than or equal to 7.0%.

Table 1

Description of sample

CHARACTERIZATION OF SAMPLE	NO. OF PATIENTS	PERCENTAGE OF PATIENTS
DN4 ≥ 4	39	10.86%
DN < 4	320	89.14%
MALES	197	54.87%
FEMALES	162	45.13%
< 65 YEARS	108	30.08%
≥ 65 YEARS	251	69.92%
DIAGNOSIS < 10 YEARS	218	60.73%
DIAGNOSIS ≥ 10 YEARS	141	39.27%
HBA1C < 7.0%	224	62.40%
HBA1C ≥ 7.0%	135	37.60%

At the physical examination, we verified that 7.80% of subjects with diabetes have hypoesthesia at the sting in the region where the pain is located and 7.52% have hypoesthesia by touching and, also in the painful area. We also observed that in 4.18% of subjects with diabetes, the pain is caused by mild friction.

The symptom mentioned most often by the patients was numbness, present in 21.72% of subjects with diabetes, followed by paraesthesia and stinging, with 16.71% and 15.56% respectively. These data can be observed in more detail in Table 2.

Statistical inference: We intended to study whether there was a relationship between the female or male sex and the emergence of complaints of neuropathic pain. It was found that 48.7% of the patients with neuropathic pain were women (11.7% of the total women) and the remaining 51.3% were men (10.2% of all men). There was no statistically significant difference between the sexes ($p = 0.633$, $r = 0.025$).

Table 2

Description of the symptoms according to the DN4 questionnaire

SYMPTOMS	NO. OF PATIENTS	PERCENTAGE OF PATIENTS
BURNING	31	8.64%
FEELING OF PAINFUL COLD	17	4.74%
ELECTRIC SHOCK	19	5.29%
PARAESTHESIA	60	16.71%
STINGING	56	15.56%
NUMBNESS	78	21.72%
ITCHING	48	13.37%
HYPOAESTHESIA TO THE TOUCH	27	7.52%
HYPOESTHESIA TO THE STING	28	7.80%
PAIN CAUSED BY LIGHT FRICTION	15	4.18%
TOTAL PATIENTS	**The same subject with diabetes may refer more than one symptom. These results regard the application of the ND4 questionnaire to the studied sample, consisting of 359 patients.**	

On the other hand, neuropathic pain was observed to be was significantly more prevalent in individuals with HbA1c greater than or equal to 7% than in those with lower values (16.3% vs. 7.6%, $p = 0.010$, $r = 0.136$). Of the total number of patients with neuropathic pain (n = 39), 56.4% had HbA1C greater than or equal to 7%. The HbA1c value seems to be related to complaints of neuropathic pain.

Regarding the relationship between the age of subjects with diabetes and complaints of neuropathic pain, it was found that these were significantly more prevalent in individuals aged 65 years or older (13.1%) than in individuals under 65 (5.6%), with $p = 0.034$ and $r = 0.112$. In fact, of the total number of patients with neuropathic pain, 84.6% was 65 years or older.

Finally, there was a higher prevalence of neuropathic pain in patients with 10 or more years of disease progression compared to those with a duration of less than 10 years (15.6% vs 7.8%, $p = 0.020$, $r = 0.112$). Of the total number of patients with neuropathic pain, 56.4% had had the disease for 10 years or more.

We realised that 38.1% of men and 40.7% of women had been diagnosed with diabetes 10 or more years ago, and there was no statistically significant relationship between sex and the disease duration ($r = 0.027$ and $p = 0.606$). There was also no statistically significant relationship between sex and HbA1c values, with 37.1% for men and 38.3% for women with HbA1C values equal or greater to 7% ($r = 0.012$, $p = 0.813$).

Table 3

Statistical inference applied to the study variables

	Variable: sex		**Variable: HbA1c**		**Variable: age**		**Variable: disease progression**	
	man	woman	≥ 7%	< 7%	≥ 65	< 65	≥ 10	< 10
% with neuropathic pain (n = 39)	51.3% **(n = 20/39)**	48.7% **(n = 19/39)**	56.4% **(n = 22/39)**	43.6% **(n = 17/39)**	84.6% **(n = 33/39)**	15.4% **(n = 6/39)**	56.4% **(n = 22/39)**	43.6% **(n = 17/39)**
Total proportion of patients	10.2% **(n = 20/197)**	11.7% **(n = 19/162)**	16.3% **(n = 22/224)**	7.6% **(n = 17/135)**	13.1% **(n = 33/251)**	5.6% **(n = 6/108)**	15.6% **(n = 22/141)**	7.8% **(n = 17/218)**
p-value	0.633		0.010		0.034		0.020	
Spearman correlation (r)	0.025		0.136		0.112		0.112	

DISCUSSION

This research demonstrates the importance of early diagnosis of DN, but above all, it aims to raise awareness of the need to incorporate DN screening and assessment methods in order to act upon their natural history and thus gain health gains.

In the more recent literature, males are defined as a risk factor for the development of DN, and there are some documented statistical correlations, such as the fact that stature also conditions DN, in the sense that taller subjects with diabetes have a higher prevalence of DN. Their percentiles of taller stature may, in part, justify the fact that males are at higher risk of developing ND [7, 9]. On the other hand, previous studies have shown that there is a relationship between male and DN, directed at complaints of sexual dysfunction, a variable that is

not addressed in the data collection instrument. The authors of this study chose to evaluate whether there is a statistical relationship between females and DN. This was not found, so the null hypothesis prevails, that is, the female sex does not condition the appearance of DN. It should be noted that the statistical data presented do not allow us to discern the relation between male sex and DN as a conditioning factor, despite the fact that their relationship is already established, but taking variables such as sexual dysfunction or height into account.

As mentioned in this investigation, the symptom numbness was the one most mentioned by subjects with diabetes, when filling the DN4 questionnaire, with 21.72%, followed by the paraesthesia and stinging, with 16.71% and 15.56% respectively. The design of the investigation does not allow us to infer about the correlation of these symptoms and the diagnosis of DN, if these symptoms precede diagnosis, if they function as a marker of risk or if they are highlighted because patients better perceive the symptoms. It would, however, be interesting to ascertain these relationships in future studies.

Recent studies have shown a high prevalence of altered oral glucose tolerance in patients with peripheral sensory neuropathy [16, 17], which is consistent with the fact that the relationship between HbA1c equal to or greater than 7% and DN is statistically significant. It is consensual that the increase of glycaemia leads to the increase of its degradation products, such as sorbitol, leading to an increase in oxidative stress and to the flow of sodium and water to nerve cells, compromising their normal activity. This alteration in oral glucose tolerance may be responsible for the decrease in the density of intraepidermal nerve fibres in diabetic neuropathic pain [18, 19].

DN affects about 50% of people with long-term diabetes, specifically subjects with diabetes with more than 15 years of disease progression. On the other hand, we know that DN is present at the time of the diagnosis of DM2 in about 10% of people with diabetes [20, 21]. These data, taken as a whole, may help to characterize the statistical significance between the variables “age greater than or equal to 65 years” and “more than 10 years of DM2 progression” with the appearance of DN.

A long progression of the disease, defined in this study as over 10 years, when associated with an absence of adequate metabolic control, leads to the accumulation of homocysteine and sorbitol, with a consequent decrease in nitric oxide levels, causing endothelial and nerve cell lesions [22, 23]. We also know that studies in this area document the decrease in the density of intraepidermal nerve fibres in painful neuropathy, explained by the decrease in the physiological response to algic modulators, such as serotonin but, above all, prostaglandins. This corroborates the results obtained in this investigation at the pathophysiological level, since a statistically significant relationship between the length of disease progression of DM2 and DN was observed. It was found that 84.6% of patients with neuropathic pain were 65 years of age or older, which testifies to the synergy of the variables age and length of disease progression, that is, older patients are also those who accumulate higher metabolic disease burden and which consequently translates into symptoms.

As mentioned previously, in the physical examination of subjects with diabetes, we observed that 7.8% of these had hyposthesia to the sting in the region where the pain is located and, 7.52% have hyposthesia to the touch, also in the painful region, results that are consistent with sensitive peripheral neuropathy due to poor metabolic control leading to intra-epidermal nerve fiber dysfunction, nerve cell death, and resistance to painkillers such as serotonin and prostaglandins.

Rigorous metabolic control is crucial from the initial phase of DM, since only then can it be possible to modify the progression of the disease, and to avoid the nerve lesions observed in patients, either with inadequate metabolic control, or with a disease progression over 10 years.

CONCLUSION

This study is the first in Portugal to address the problem of DN, a degenerative and debilitating disease, with an impact on patients’ quality of life. It is a pathology that is poorly diagnosed and treated, and its approach must be initiated in PHC and be transversal to the specialities involved in diabetic foot consultation.

When a patient with a clinical context suggestive of DN is approached, careful and systematized anamnesis is essential in order to investigate symptoms consistent with other causes of pain or neuropathy. It is important to address the risk factors of DN, with special attention to the variables studied: level of HbA1c, duration of hyperglycaemia and age. Other risk factors are equally important, such as height, male gender, hypertension, smoking, and

dyslipidaemia. Thus, treatment and clinical approach should address not only the patient's metabolic control, but also the correction of modifiable risk factors.

Other lines of research are pertinent, such as studying the relationship between vitamin B complex levels and the emergence of DN. We know that DM can be considered a thiamine-deficient state due to the accelerated metabolism of glucose in non-insulin dependent tissues, such as the vessel wall. Moreover, pyridoxine, essential for the synthesis of neurotransmitters, reduction of pain intensity and dormancy, and cyanocobalamin, which promotes myelin sheath regeneration and relief of paraesthesia, are decreased in patients with DM. These phenomena appear not only in the biochemical context of the diabetic, with increased levels of homocysteine and methylmalonic acid, which in turn increase resistance to these vitamins, but also by the action of metformin, due to its effects on intestinal dynamics.

This research also intends to convey the importance of addressing DN in diabetes surveillance consultations, since it has been shown that the prevalence of neuropathic pain in patients with diabetes is not negligible, suggesting the particular relevance of conducting the DN4 questionnaire to screen for neuropathic pain. This is especially important in patients aged 65 or over, 10 or more years of disease progression and HbA1C values greater than or equal to 7%, because if DN goes undiagnosed, it is not possible to apply its treatment, aimed at improving quality of life, physical and emotional function, as well as pain relief. The importance of an early diagnosis makes pharmacological treatment possible, which must also be started early.

Introducere. *Neuropatia diabetică (DN) este una dintre cele mai devastatoare complicații ale diabetului zaharat, În Portugalia nu sunt încă studii care să evalueze impactul său demografic și caracteristicile sale clinice. Scopul acestui studiu a fost de a evalua impactul genului, al controlului metabolic, al vârstei, precum și al progresului bolii asupra durerii neuropate.*

Materiale și metode. *A fost realizat un studiu multicentric cu o populație de 359 de pacienți la care s-a folosit softul SPSS versiunea 24. Valorea lui p sub 0,05 a fost considerată relevantă statistic. Coeficientul Speraman a fost folosit pentru a corela variabilele.*

Rezultate. *Nu a existat nicio diferență semnificativă statistic între prevalențele DN la ambele sexe (p = 0,633 și r = 0,025). A fost stabilită o asociere semnificativă statistic între valoarea HbA1c și DN (r = 0,136 cu p = 0,01). S-a găsit o corelație pozitivă între vârstă și durerea neuropată (r = 0,112, p = 0,034). Progresia bolii a fost și ea corelată cu apariția manifestărilor durerii neuropate (p = 0,02 și r = 0,112).*

Concluzii. *Prevalența DN nu este neglijabilă în cadrul populației cu diabet zaharat și este asociată cu factori de risc modificabili ce pot fi preveniți și identificați. Pentru îmbunătățirea calității vieții sunt imperios necesare screening-ul și tratamentul cât mai precoce.*

Correspondence to: António Assunção, M.D, Family Health Unit (FHU) Viriato, Viseu, Portugal.
E-mail: ajsassuncao@gmail.com
Mobile phone: 00351917312316

Conflict of interest disclosure: The authors declare that there are not conflicts of interest.

REFERENCES

1. BURSON LK, SCHANK CH. *Charcot neuroarthropathy of the foot and ankle*. Home healthcare now. 2016 Mar; 34(3):135–9.
2. FOSSE S, HARTEMANN-HEURTIER A, JACQUEMINET S, HA VAN G, GRIMALDI A, FAGOT-CAMPAGNA A. *Incidence and characteristics of lower limb amputations in people with diabetes*. Diabet Med. 2009 Apr; 26(4):391–6.
3. BECKMAN JA, CREAGER MA. *Vascular complications of diabetes*. Circulation Research. 2016 May 27; 118(11):1771–85.
4. POP-BUSUI R, BOULTON AJM, FELDMAN EL, BRIL V, FREEMAN R, MALIK RA, *et al. Diabetic neuropathy: a position statement by the American Diabetes Association*. Diabetes Care. 2017 Jan; 40 (1):136–154.

5. YAGIHASHI S, MIZUKAMI H. *Diabetic neuropathy*. In: Diabetes and Aging-related Complications. 2017 Jun 15; 8(6):249–269.
6. BOOYA F, BANDARIAN F, LARIJANI B, PAJOUHI M, NOORAEI M, LOTFI J. *Potential risk factors for diabetic neuropathy: A case control study.* BMC Neurol. 2005 Dec 10; 5:24.
7. SMITH AG, SINGLETON JR. *Obesity and hyperlipidemia are risk factors for early diabetic neuropathy.* J Diabetes Complications. 2013 Sep–Oct; 27(5):436–42.
8. ASLAM A, SINGH J, RAJBHANDARI S. *Pathogenesis of painful diabetic neuropathy*. Pain Research and Treatment. 2014 (4 i):412041.
9. JAVED S, PETROPOULOS IN, ALAM U, MALIK RA. *Treatment of painful diabetic neuropathy.* Therapeutic Advances in Chronic Disease. 2015 Jan; 6(1):15–28.
10. PODWALL D, GOOCH C. *Diabetic neuropathy: Clinical features, etiology, and therapy.* Current Neurology and Neuroscience Reports. 2004 Jan; 4(1):55–61.
11. LOZERON P, NAHUM L, LACROIX C, ROPERT A, GUGLIELMI JM, SAID G. *Symptomatic diabetic and non-diabetic neuropathies in a series of 100 diabetic patients*. J Neurol. 2002 May; 249(5):569–75.
12. DOBRETSOV M, ROMANOVSKY D, STIMERS JR. *Early diabetic neuropathy: Triggers and mechanisms*. World Journal of Gastroenterology. 2007 Jan 14; 13(2):175–191.
13. WON JC, PARK TS. *Recent Advances in Diagnostic Strategies for Diabetic Peripheral Neuropathy.* Endocrinol Metab. 2016 Jun; 31(2):230–8.
14. FELDMAN EL, STEVENS MJ, THOMAS PK, BROWN MB, CANAL N, GREENE DA. *A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy.* Diabetes Care. 1994 Nov; 17(11):1281–9.
15. BOULTON AJM, VINIK AI, AREZZO JC, BRIL V, FELDMAN EL, FREEMAN R, *et al. Diabetic neuropathies: A statement by the American Diabetes Association.* Diabetes Care. 2005 Apr; 28(4):956–62.
16. PAPANAS N, VINIK AI, ZIEGLER D. *Neuropathy in prediabetes: Does the clock start ticking early?* Nature Reviews Endocrinology. 2011 Jul 12; 7(11):682–90.
17. SINGLETON JR, SMITH AG, BROMBERG MB. *Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy.* Diabetes Care. 2001 Aug; 24(8):1448–53.
18. KHOSHNOODI MA, TRUELOVE S, BURAKGAZI A, HOKE A, MAMMEN AL, POLYDEFKIS M. *Longitudinal assessment of small fiber neuropathy: Evidence of a non-length-dependent distal axonopathy.* JAMA Neurol. 2016 Jun 1; 73(6):684–90.
19. POURHAMIDI K, DAHLIN LB, ENGLUND E, ROLANDSSON O. *No difference in small or large nerve fiber function between individuals with normal glucose tolerance and impaired glucose tolerance.* Diabetes Care. 2013 Apr;36(4):962–4.
20. KAUR S, PANDHI P, DUTTA P. *Painful diabetic neuropathy: An update.* Ann Neurosci. 2011 Oct; 18(4):168–175.
21. SNYDER MJ, GIBBS LM, LINDSAY TJ. *Treating painful diabetic peripheral neuropathy: An update.* Am Fam Physician. Aug 1; 94(3):227–34.
22. MIRANDA-MASSARI JR. B, GONZALEZ MJ. D, JIMENEZ FJ., ALLENDE-VIGO MZ., DUCONGE J. *Metabolic correction in the management of diabetic peripheral neuropathy: Improving clinical results beyond symptom control.* Curr Clin Pharmacol. 2011 Nov; 6(4):260–73.
23. GRISOLD A, CALLAGHAN BC, FELDMAN EL. *Mediators of diabetic neuropathy.* Curr Opin Endocrinol Diabetes Obes. 2017 Apr; 24(2):103–111.
24. DIREÇÃO GERAL DE SAÚDE. *Tratamento farmacológico da dor neuropática no adulto e idoso.* Número 043/2011, atualizada a 13/07/2017. 2017

Received 27th May 2019