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ARTICLE

Ankle-brachial index and diabetic neuropathy: study of 225 patients

Index tornozelo-braquial e neuropatia diabética: estudo de 225 pacientes

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ABSTRACT

Objective: To evaluate neuropathic pain and peripheral vascular disease in diabetics and compare this with the length of time since diagnosis in type 1, and type 2 diabetes. **Methods:** A cross-sectional study with 225 diabetics chosen from their responses on the DN4 questionnaire, who were then evaluated with the ankle-brachial index (ABI), separating type 1 diabetes from type 2 diabetes. **Results:** A higher incidence of neuropathic pain in those over 60 years of age showed an ABI > 1.3. Neuropathic pain was related to an abnormal ABI in 144 patients (64.2%). A statistically significant value was obtained in type 2 diabetes patients with more than 10 years from disease onset, 69 with altered ABI and 25 with normal ABI. There was an altered ABI (< 0.9) observed in 33% of type 1 diabetes patients and in 67% of type 2 diabetes patients. **Conclusion:** The ABI test in type 1 diabetes and type 2 diabetes patients is important even in those who are asymptomatic. A diagnosis of more than 10 years prior, regardless of the presence of neuropathic pain or ischemic signs, altered the ABI.

Keywords: diabetes mellitus; diabetic neuropathies; ankle-brachial index.

RESUMO

Objetivo: Avaliar dor neuropática e doença vascular periférica em diabéticos e comparar com, tempo de diagnóstico de diabetes tipo 1(DM 1) e diabetes tipo 2(DM2). **Métodos:** Estudo de corte transversal onde, 225 diabéticos responderam ao questionário (DN4) sendo submetidos ao índice tornozelo-braquial (ITB). **Resultados:** predomínio de dor neuropática foi em pacientes acima de 60 anos com (DM2), com um ITB > 1,3 nesta população; assim a dor neuropática foi relacionada com o ITB anormal em 144 pacientes, total de 64,2%. Um valor estatisticamente significativo foi com (DM2).Um ITB alterado (< 0,9) em 33% no (DM 1) e em 67% (DM 2). Totalizando 132 indivíduos com alterações no ITB. **Conclusão:** O teste ITB é útil em pacientes com DM 1 e DM 2 quando a dor neuropática é suspeita, mesmo em assintomáticos. E o tempo prolongado de diabetes (> 10 anos), independentemente da presença de dor ou sinais isquêmicos, alterou o ITB.

Palavras-chave: diabetes mellitus; neropatias diabéticas; índice tornozelo-braquial.

According to the International Diabetes Federation (2015), there are more than 415 million people with diabetes worldwide and the prevalence of obesity and sedentary lifestyle will increase this number. The projection of the International Diabetes Federation is that in 2040 this estimate will be 642 million people affected by this disease, and the risk of cardiovascular events and neurological complications is four times that of a non-diabetic[1].

Population-based studies reveal that 50% of patients over 60 years of age develop neuropathy in the early stages of type 2 diabetes, while neurological symptoms in type 1 diabetes are usually manifested later[2].

Diagnoses of diabetic neuropathies rely on the characterization of symptoms and clinical signs, such as pain being the reason for 40% of patients visiting a health service annually, and 20% of these had felt pain for more than six months. Due to its complexity, managing chronic pain is a challenge to the clinician[3].

The diagnosis of diabetic neuropathy is based on the characterization of the most typical symptoms and clinical signs, such as pain and neurological conduction tests[4].

Peripheral arterial disease often affects younger patients and develops in 10% of newly-diagnosed cases of diabetes. For this reason, it is necessary to be able to evaluate arterial disease in a simple and quick way.

The ankle-brachial index (ABI) shows the existence of peripheral arterial disease and is also related to cardiovascular mortality in diabetic patients, even in those with coronary artery disease at an early stage[5].

Chronic complications render many patients unable to work[2]. Population-based studies of diabetics reveal that 50%

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of patients over 60 years of age develop neuropathy, with peripheral diabetic neuropathy[6].

Diabetes mellitus is the leading cause of peripheral neuropathy, commonly manifested as symmetrical and distal polyneuropathy.

A chronic increase of glucose leads to glycosylation of proteins and the final products, which accumulate in the tissues, produce microvascular disease by direct deposition of these proteins in endothelial cells or by generation of oxidative stress[7].

Vascular pathogens have been postulated and hypoxia and ischemia are also involved in diabetic polyneuropathy. On a macroscopic level, the study of the distribution and fiber loss in diabetic nerves also suggests a vascular disorder[8].

The diagnosis of clinical pain in peripheral diabetic neuropathy is based on the description provided by the patient. The symptoms are distal and symmetric, with frequent nocturnal exacerbation. Symptoms are typically described as pins and needles, deep pain, electric shock, tingling, and burning sensations, and may present as hyperalgesia, allodynia, or both[9].

Painful diabetic neuropathy may affect up to 50% of patients who have been diagnosed for more than 25 years. The associated risk factors include age, genetic predisposition, inflammation, oxidative stress, lipotoxicity, and glucotoxicity[10,11]

Distal sensory polyneuropathy is the most common form in diabetes, and premature symptoms are decreased sensation of vibration, touch, and the ability to feel a needle or monofilament. There is evidence that both symptomatic and asymptomatic lesions may be present in diabetic arterial disease, and these predict cardiovascular lesions[12].

The ABI is used to diagnose peripheral arterial disease, as well as to estimate future progression and severity[13].

In the non-diabetic population, the incidence of ABI changes varied about 8.7%, and the prevalence of 62.2% artery disease was very likely among patients with chronic kidney failure, tobacco use and cardiovascular disease[14].

Normal levels are considered to be an ABI of 0.9 – 1.3; below this there is an arterial insufficiency and high cardiovascular risk. It is recommended that the ABI is performed on all patients older than 50 years of age or any patient with symptoms of pain when walking[2,13,15].

Many individuals with diabetes have few symptoms because, despite extensive loss of vascularized tissue, sensation loss is common due to the distal sensory polyneuropathy. The artery disease mortality and morbidity is a common cause of hospitalization, where the risk of ulceration is 15-25%[16].

The arterial disease, a risk factor irrespective of ulceration and amputation, is present in 50% patients with ulcers, so early detection is of great concern[16].

The International Working Group on the Diabetic Foot Guidelines suggests that, added to the symptoms of neuropathic pain, vascular insufficiency can be evaluated by a manual Doppler and calculated by an ABI of less than 0.9, to assess for possible revascularization. This peripheral arterial involvement is diffuse and particularly severe in the tibial arteries with a high prevalence of occlusion[13,17,18,19].

We believe that this study is of real importance, since through the application of a simple examination, the ABI, along with an examination for neuropathic pain and the DN4 questionnaire, further evidence of the relationship between arterial damage and the presence of neuropathy in diabetics can be found.

METHODS

This cross-sectional study includes a descriptive analysis of a group of patients with diabetes. The group consisted of patients with type 1 diabetes and type 2 diabetes, who had previously been examined and diagnosed by a physician with experience in treating diabetes (the author).

The DN4 questionnaire included 10 objective questions regarding sensitivity symptoms related to painful peripheral neuropathy, requiring direct "yes" or "no" answers. The experts examined patients with chronic, central neurological, or peripheral pain and differentiated them by whether or not they presented with somatic tissue injuries. This differentiation was based on the DN4, which includes pain descriptors and neurological examination[19].

The diagnostic sensitivity of this questionnaire for neuropathic pain is 82.9% and the specificity is 89.9% when patients respond in the affirmative to at least four items[20].

The DN4 interview is discriminatory, suggesting its feasibility for large-scale epidemiological studies, consistent with a major review on neuropathic pain[4].

Routine use of the ABI has been proposed for use in diabetic patients at high risk of arterial disease. The Doppler method is a well-established and non-invasive technique to assess peripheral arterial disease[15].

The ABI should be measured in the supine position after five minutes of rest. The ABI reference scores are: a) > 1.3 = hardened vessels; b) from 0.9–1.3 = normal arterial flow; c) < 0.9 = arterial occlusion. The ABI measurement is recommended for all patients with diabetes over 50 years of age, or those presenting with symptoms of peripheral arterial disease or other cardiovascular risk factors[8,16,17].

Patients' DN4 scores were then subjected to ABI measurement, which was calculated by dividing the highest systolic blood pressure in the lower and upper limbs[17].

Sampling

The study population included 225 patients with diabetes, recruited through the Diabetics Association, who were then separated into groups of type 1 diabetes (n = 75) and type 2 diabetes (n = 150). Forty-six men and 29 women had type 1 diabetes, and 47 men and 103 women had type 2 diabetes.

For patients younger than 60 years, there were 60 patients in the type 1 group, and 37 in the type 2 group, totaling 97 patients.

For those over 60 years of age, 15 had type 1 and 113 had type 2 diabetes, totaling 128 participants, randomly selected from the endocrinology outpatient clinic of the Diabetes Association.

According to the responses obtained on the DN4, when four responses were positive, the patients were assessed by their ABI scores. Patients with less than four positive responses were excluded; as well as smokers and those with renal disease.

The prevalence of neuropathy was considered when calculating the sample size of 225 patients, yielding a sample power of 0.9 with a sample error of 0.05.

This study was approved by the Hospital Research Ethics Committee under protocol number 451.639.

Statistical analyses

Statistics were analyzed using the Stata 9.2 software. The variables for analyses were obtained from the DN4 questionnaire applied in this study. The percentage of results obtained in the DN4 and ABI were determined in the two groups of diabetics. The two groups were compared through RxC contingency or ANOVA tables, as indicated.

Chi-square, Fisher's exact test, student's t tests, and the Mann-Whitney tests were used to assess the statistical significance of data. Differences between the two groups were described in terms of odds ratios, and adjustments of ABI and DN4 interpretation correlations based on the variables, using logistic regression models specifically designed to meet the aims of the analyses. Differences with p-values less than 0.05 were considered statistically significant.

RESULTS

As shown in Table 1, an ABI < 0.9 was associated with 43 type 1 patients and 89 type 2 diabetic patients.

On the other hand, an ABI > 1.3 in two type 1 diabetic patients, and one type 2 diabetic patients was associated with a higher cardiovascular risk.

A normal ABI was found in 30 patients with type 1 diabetes and 51 patients with type 2 diabetes.

Table 2 shows that altered ABI scores were observed in 58 individuals below 59 years of age and in 86 individuals above 60 years of age. Normal ABI scores were observed in 39 patients with diabetes who were below 59 years of age and in 42 patients with diabetes who were above 60 years of age.

Scores corresponding to positive responses on the DN4 were combined with the altered or normal ABI scores accordingly.

Table 3 shows the ABI results allowing the classification of two possible situations, which included individuals diagnosed with type 1 diabetes for either more, or less, than 10 years. A non-significant statistical correlation was obtained for this group, with a p-value of 0.263.

Table 4 shows patients with type 2 diabetes who presented with altered ABI scores, which is in agreement with the observed variations in the duration of time since the diagnosis.

On the other hand, normal ABI scores were obtained by 21 patients who had been diagnosed for less than 10 years and for 25 patients who had been diagnosed for more than 10 years. Comparison of these groups yielded a statistically significant correlation, with a p-value of 0.014.

DISCUSSION

Previous literature indicated that neurological symptoms are reported by 38% of women compared to 31% of men. However, fewer women presented with peripheral diabetic neuropathy confirmed by neurological examination, and the risk of developing symptoms associated with neurological pain remained 50% higher in women than in men[20].

A similar gender relationship was not observed in type 1 diabetes, contrary to the positive responses observed from men with type 2 diabetes (46 men; 29 women). However, a higher incidence of neuropathic pain was observed among individuals > 60 years of age (113 in type 2; 15 in type 1 diabetes) according to the DN4 questionnaire. This is consistent with other literature that reported a higher number of complications with increases in the duration from diagnosis, and age, of patients[19].

Table 1. ABI and diabetes.

ABI	Type 1 diabetes	Type 2 diabetes	Total
< 0.9	43	89	132
0.9–1.3	30	51	81
> 1.3	2	10	12

Normal range for ABI = 0.9 - 1.3; Risk of obstructive arterial disease < 0.9 and >1.3. ABI: ankle-brachial index.

Table 2. ABI score and age.

Age	Altered ABI	Normal ABI	Total
< 59 years	58	39	97
> 60 years	86	42	128

Altered and normal ABI values according to the age of participants with diabetes. ABI: ankle-brachial index.

Table 3. ABI and Type 1 diabetes disease duration.

Duration	Altered ABI	Normal ABI	p
< 10 years	12	5	
> 10 years	27	22	0.263

ABI values and duration of type 1 diabetes, statistical significance. ABI: ankle-brachial index.

Table 4. ABI and Type 2 diabetes disease duration.

Duration	Altered ABI	Normal ABI	p
< 10 years	23	21	
> 10 years	69	25	0.014

ABI values and duration of type 2 diabetes, statistical significance. Significant p value. ABI: ankle-brachial index.

In participants aged > 60 years, an ABI ≥ 1.3 was observed as a result of arterial hardening. These scores were obtained in 10 patients with type 2 diabetes and in two in the same age group with type 1 diabetes. This suggested a correlation between ABI scores indicative of health complications and advancing age.

The group was diagnosed with sensory neuropathy, and peripheral arterial disease was detected in almost 40% of the patients. Arterial calcification also develops in other conditions associated with peripheral diabetic neuropathy, although it does not increase at the same rate as it does in patients with diabetes[20,21].

Diabetic arteriopathy involves the most distal vessels of the lower limbs, such as the tibioperoneal, posterior tibial, and dorsalis pedis arteries[17,18].

Neuropathic pain (as assessed in the DN4 questionnaire) directly correlated with altered ABI scores, and was observed in the majority of our population (i.e., in 144 individuals; 64.2%).

Previous studies indicate that some symptoms are preferentially manifested in neuropathic pain. In particular, paresthesia and dysesthesia are highly specific, and are used as diagnostic indicators[22,23].

Diagnosis becomes difficult when peripheral arterial disease is associated with peripheral diabetic neuropathy, since the latter could mask claudication and pain at rest induced by severe ischemia, with the consequent prevalence of neuropathic pain diagnoses. It is also known that only one third of patients with diabetes present with intermittent claudication[24].

However, the sensitivity of this ABI threshold (0.9–1.3) seems to be lower in complicated type 2 diabetes, particularly in the presence of peripheral diabetic neuropathy; 13.6% of patients with type 2 diabetes present with peripheral arterial disease compared to 4% in the general population[15].

Altered ABI scores were observed in 27 patients with type 1 diabetes for over 10 years, whereas normal ABI scores were observed in 22 patients in this group.

Altered ABI scores were observed in 12 patients with type 1 diabetes for less than 10 years, whereas normal ABI scores were observed in five patients in this group. A p-value of 0.263 did not indicate a statistically significant difference.

A strong correlation between the time of diagnosis and the prevalence of altered ABI scores was observed in our sample, when comparing diabetes diagnoses of more than 10 years.

The incidence of neuropathy and peripheral arterial disease increased by 5% per year (on an average) in type 1 diabetes patients who had been diagnosed between 20 and 25 years. The risks of these complications are much higher 20 years after diagnosis, increasing two- to three-fold beyond this period[25].

The role of improved glycemic control in the prevention of macrovascular disease in diabetes is still uncertain. Premature death of these patients, as well as cardiovascular, cerebrovascular, and peripheral arterial disease, limit the design of these studies in both patients with type 1 and type 2 diabetes. Over the past 20 years, large-scale studies, such as the Diabetes Control and Complication Trial for type 1 diabetes and the United Kingdom Prospective Diabetes Study for type 2 diabetes, have reported premature deaths in these populations, caused by diabetic arterial disease[26].

When evaluating the disease duration in type 2 diabetes, 23 patients who had had the disease for less that 10 years had an abnormal ABI and 21 patients had a normal ABI. In patients with type 2 diabetes for longer than 10 years, 69 patients had low ABI scores and the ABI score was normal in 25 patients.

Previous studies have also compared the prevalence of cardiovascular disease in patients with or without types 1 and 2 diabetes. In the same age group, cardiovascular disease occurred in 44% of patients with type 1 and 51% of patients with type 2 diabetes[26].

We observed that 23 patients with type 2 diabetes diagnosed for less than 10 years presented with an altered ABI. Normal ABI scores were found in 21 individuals. In patients with type 2 diabetes for longer than 10 years, 69 patients had altered ABI scores, whereas 25 had a normal ABI. By comparing patients diagnosed with type 2 diabetes for longer than 10 years, a p-value of 0.014 was obtained, indicating a positive correlation (Table 4).

Data from the literature confirm the high prevalence of cardiovascular complications, such as peripheral arterial disease, evolving in type 2 diabetes patients with a duration of longer than 10 years. Our data are consistent with these findings. We found that increased age of patients with type 2 diabetes, as well as a diagnosis for more than 10 years, were considered risk factors[17,18].

Therefore, the history of neuropathic pain and vascular insufficiency, which can be evaluated by the Doppler method measuring the ABI, allows the International Working Group on the Diabetic Foot Guidelines to be interpreted such that persons with peripheral arterial disease symptoms and ABI scores < 0.9 should be assessed for possible revascularization[13,14,17].

Although ABI scores > 1.3 have no correlation with an accurate evaluation of ischemia, they are associated with high cardiovascular risk, as calcification may occur with normal ABI scores in the absence of clinical signs of peripheral arterial disease. However, an ABI score < 0.9 indicates peripheral arterial disease, which should be carefully confirmed by other complementary examinations[27].

Our data suggests that the populations with type 1 diabetes and type 2 diabetes might increase if the DN4 questionnaire were administered after clinical assessment of sensory-motor neuropathy. Our study participants had paresthesia and burning pain symptoms, although claudication, tingling, and prickling sensations, as well as changes to cold perception, were almost non-existent, thus hindering the minimum score of four positive responses on the DN4.

We hypothesize that a clinical evaluation by measuring ABI, followed by the DN4 would alter our results.

This study aimed to show that neuropathic pain and peripheral diabetic neuropathy occurs in patients with type 1 diabetes and type 2 diabetes, in combination with peripheral arterial disease. This association was confirmed by the DN4 questionnaire, in which altered ABI scores were observed in most of the patients who responded positively. Very often, lower limb pain is attributed to peripheral neuropathy, while the possibility of peripheral vascular disease is not investigated.

CONCLUSION

The present study emphasizes the appropriate clinical and semiological evaluation of patients with diabetes, especially those who have been diagnosed for longer than 10 years. Moreover, it aimed to apply the DN4 questionnaire in all patients with type 1 diabetes and type 2 diabetes, even when the diagnoses occurred less than 10 years prior, and to manually measure ABI scores in these patients once a year, using the Doppler method (8 mHZ).

Our findings suggest that ABI measurement is necessary in all patients with type 1 diabetes and type 2 diabetes when peripheral diabetic neuropathy is suspected, but also in asymptomatic patients diagnosed for longer than 10 years, regardless of neuropathic pain or indicators of ischemia.

Neuropathic pain often occurs in the absence of any abnormalities in physical examinations, such as hypoesthesia/anesthesia[28].

The present study is clinically relevant because it investigates the ankle-brachial index, in combination with a neurological examination and the presence of neuropathic pain. This combination will contribute to the diagnosis of peripheral neuropathy and the search for further evidence correlating arterial damage and neuropathy in patients with diabetes.

References

1. Standards of Medical Care in Diabetes-2016: summary of revisions. Diabetes Care. 2016;39 Suppl 1:S4-5. https://doi.org/10.2337/dc16-S003
2. American Diabetes Association. Executive summary: standards of medical care in diabetes-2012. Diabetes Care. 2012;35(Supp 1):S4-10. https://doi.org/10.2337/dc12-s004
3. American Diabetes Association. Economic costs of diabetes in the USA in 2007. Diabetes Care. 2008;31(3):596-615. https://doi.org/10.2337/dc08-9017
4. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285-93. https://doi.org/10.2337/dc10-1303
5. Mills JL, Armstrong DG, Lavery L. Evaluation and management of peripheral arterial disease. In: Armstrong DG, Lavery L. Clinical care in diabetic foot. 2nd ed. New York: American Diabetes Association; 2005. p. 99-106.
6. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2007;27(5):1047-53. https://doi.org/10.2337/diacare.27.5.1047
7. Vlassara H, Striker GE. Advanced glycation endproducts in diabetes and diabetic complications. Endocrin Metab Clin N Am. 2013;42(4):697-719. https://doi.org/10.1016/j.ecl.2013.07.005
8. Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ. Diabetic neuropathy part 1: overview and symmetric phenotypes. Neurol Clin. 2013;31(2):425-45. https://doi.org/10.1016/j.ncl.2013.02.004
9. Schestatsky P, Nascimento OJ. What do general neurologists need to know about neuropathic pain?. Arq Neuropsiquiatr. 2009;67(3A):741-9. https://doi.org/10.1590/S0004-282X2009000400039
10. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. Endocrinol Metab Clin N Am. 2013;42(4):747-87. https://doi.org/10.1016/j.ecl.2013.06.001
11. Spallone V, Morganti R, D'Amato C, Cacciotti L, Fedele T, Maiello MR et al. Clinical correlates of painful diabetic neuropathy and relationship of neuropathic pain with sensorimotor and autonomic nerve function. Eur J Pain. 2011;15(2):153-60. https://doi.org/10.1016/j.ejpain.2010.06.011
12. Drummond JP, Marques JO, Nascimento OJM. Dor neuropática: fisiopatologia, clínica e terapêutica. São Paulo: Âmbito; 2007.
13. Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. Eur J Vasc Endovasc Surg. 2011;41(1):110-6. https://doi.org/10.1016/j.ejvs.2010.09.020
14. Triches C, Schaan BD, Gross JL, Azevedo MJ. [Macrovascular diabetic complications: clinical characteristics, diagnosis and management]. Arq Bras Endocrinol Metabol. 2009;53(6):698-708. Portuguese. https://doi.org/10.1590/S0004-27302009000600002
15. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J Vasc Surg. 2008;48(5):1197-203. https://doi.org/10.1016/j.jvs.2008.06.005
16. Vamos EP, Bottle A, Edmonds ME, Valabhjl J Majeed A, Millett C. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care. 2010;33(12):2593-7. https://doi.org/10.2337/dc10-0989
17. Holman N, Young RJ, Jeffcoate WJ. Variations of recorded incidence of amputation of the lower limbs. Diabetologia. 2012;55(7):1919-25. https://doi.org/10.1007/s00125-012-2468-6
18. Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence based management of PAD and the diabetic foot. Eur J Vas Endovasc Surg. 2013;45(6):673-81. https://doi.org/10.1016/j.ejvs.2013.02.014
19. Bakker K, Schaper NC. The development of global consensus guidelines on the management and prevention of the Diabetic Foot 2011. Diabetes Metab Res Rev. 2012;28 Suppl 1:116-8. https://doi.org/10.1002/dmrr.2254
20. Backonja MM, Krause SJ Neuropathic pain questionnaire: short form. Clin J Pain. 2003;19(5):315-6. https://doi.org/10.1097/00002508-200309000-00005
21. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J et al.Comparison of pain syndrome associated with nervous or somatic lesions and development of new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36. https://doi.org/10.1016/j.pain.2004.12.010
22. Resende MA, Nascimento OJ, Rios AA, Quintanilha G, Ceballos LE, Araújo FP et al. Neuropathic pain profile: the basic neurological exam of 33 patients. Rev Bras Anestesiol. 2010;60(2):144-53. https://doi.org/10.1590/S0034-70942010000200006

23. Abbott CA, Malik RA, Ross ER, Kulkarni J, Boulton AJ. Prevalence and character of painful diabetic neuropathy in a large community-based in population in the UK. Diabetes Care. 2011;34(10):2220-4. https://doi.org/10.2337/dc11-1108

24. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev. 2011;27(7):620-8. https://doi.org/10.1002/dmrr.1226

25. Jeffcoate WJ, Rasmussen LM, Hofbauer LC, Game FL. Medial arterial calcification in diabetes and relationship to neuropathy. Diabetologia. 2009;52(12):2478-88. https://doi.org/10.1007/s00125-009-1521-6

26. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M et al. Glycemic Control and Macrovascular disease in type 1 and type 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J. 2006;152(1):27-38. https://doi.org/10.1016/j.ahj.2005.09.015

27. Holland-Letz T, Endres HG, Biedermann S, Mahn M, Kunert J, Groh S et al. Reproducibility and reability of the ankle braquial index as assessed by vascular experts, family physicians and nurses. Vasc Med. 2007;12(2):105-12. https://doi.org/10.1177/1358863X07077281

28. Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropatic pain in the general population: a systematic review of epidemiological studies. Pain. 2014;155(4):654-62. https://doi.org/10.1016/j.pain.2013.11.013