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ORIGINAL ARTICLE

SEVERITY OF PERIPHERAL NEUROPATHY, IN DIFFERENT DOMAINS, IN TYPE II DIABETIC PATIENTS

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RESUMEN

Introduction: Diabetes mellitus is a chronic degenerative disease that can significantly impact both life expectancy and quality of life among affected populations, primarily by disrupting metabolic control and exacerbating disease complications. **Objective:** To assess the severity of neuropathy across four domains (pain, loss of sensation, postural instability, and depression) in individuals with diabetes mellitus. **Materials and Methods:** This was a cross-sectional, descriptive-correlational, and qualitative study conducted during the authors' professional internship. The study population comprised diabetic individuals attending outpatient clinics for diabetic foot care at Hospital de S. João - Unidade de Valongo and Centro Hospitalar do Alto Ave in Guimarães. Variables included gender, age, type and duration of diabetes, neuropathic characteristics, balance, dependency/independence, and depression. Data analysis was performed using SPSS^® software version 22. **Results:** Regarding neuropathy severity, most diabetic patients exhibited loss of sensation and moderate pain, with no apparent postural instability or depression. However, both instability and depression were observed when neuropathic signs were present. **Conclusions:** The presence of neuropathic signs was associated with increased postural instability, reduced functionality, and a higher prevalence of depressive symptoms. Furthermore, a positive relationship was observed between pain severity and depressive symptomatology.

INTRODUCTION

The developed world has witnessed an increase in the prevalence of diabetes mellitus in recent decades. According to the International Diabetes Federation (IDF), in 2021, approximately 463 million adults were living with diabetes all over the world, with most cases found in high-income countries (IDF Diabetes Atlas, 9th edition). In developed nations such as the United States and countries in Europe, prevalence rates reach alarming levels. For example, in the United States, the Centers for Disease Control and Prevention (CDC) reported that in 2021, more than 34 million people had diabetes, with more than 90% of cases being type 2 diabetes (CDC Diabetes Statistics Report). Additionally, the National Observatory for Diabetes 2020 published the data for the year 2018 and found a very alarming fact, Intermediate Hyperglycaemia in Portugal, 2018, reaches 28.0% of the Portuguese population aged between 20 and 79 years (2.1 million subjects) (Raposo, 2020), further corroborating previous authors

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who mention a higher prevalence when compared with what is found in other European countries.

Peripheral diabetic neuropathy (PDN) is a common and disabling complication of DM that consists of a pathologic progressive process of lesions of peripheral nerves (Pedrosa, 2004). Persistent hyperglycaemia is the principal factor related to DPN (Boulton, 2014). The pathophysiology of diabetic neuropathy is multifactorial and not fully understood. Chronic hyperglycaemia, coupled with other metabolic disturbances such as oxidative stress, advanced glycation end products (AGEs) and altered insulin signalling contribute to nerve damage. Increased glucose flux through the polyol pathway, leading to osmotic stress, is also (Khalid et al., 2022).

The most common form of diabetic neuropathy distal symmetric polyneuropathy is the focus of this Primer, and as such will be referred to as diabetic neuropathy throughout. Distal symmetric polyneuropathy manifests with a 'stocking and glove' distribution, whereby the hands and lower limbs are commonly affected. Other diffuse neuropathies secondary to diabetes can occur and include the constellation of autonomic neuropathies, such as cardiac autonomic neuropathy, gastrointestinal dysmotility and diabetic cystopathy and impotence . Focal neuropathies, although less common, include dysfunction of individual peripheral nerves leading to isolated mononeuropathies, or less commonly to nerve roots leading to radiculopathy or polyradiculopath (Feldman, E. L., et al., 2019).

The pain associated with PDN is a complex process involving not only sensitive but also cognitive and emotional mechanisms (Tesfaye & Selvarajah, 2012). Neuropathic pain has a great influence on the quality of life of these patients being an important factor for depression (Ziegler, 2008; Jensen 2002). Peripheral diabetic neuropathy also compromises postural stability as the integrity of the proprioceptive system is affected, making difficult postural control, with falls and lesions associated (Cimbiz & Cakir, 2005). Neuropathic diabetic patients often report postural instability as a factor affecting their daily activities, even resulting in depression (Anandhanarayanan et al., 2022).

The main object of the present study is to assess the severity of neuropathy in four domains: pain, loss of sensitivity, postural instability, and depression, in a Portuguese sample of diabetic patients. We also compare the characteristics of diabetic neuropathy, instability, functionality, and depression according to age and sex.

MATERIAL AND METHODS

The present study is a cross-sectional, descriptive correlational, and qualitative one. The population included in this study consisted of diabetic patients with peripheral neuropathy who attended the outpatient clinic of Diabetic Foot at S. João Hospital, E.P.E., in Valongo and at Hospital Centre of Alto Ave, E.P.E., in Guimarães, both in Portugal. The final sample consisted of 60 diabetic patients, older than 18 years, who have shown no exclusion criteria. All the patients signed the informed consent. The study had the approval of the ethical committee of the hospitals involved.

Exclusion criteria of this study were defined as: individuals diagnosed with non-diabetic neurological pathology; individuals with cognitive impairment, diagnosed or evident; individuals diagnosed with critical pain taking non-steroidal anti-inflammatory drugs (NSAIDs) and/or opiates, and who have taken on that day; individuals with nondiabetic symptomatic polyneuropathy.

Each patient filled out a questionnaire for data collection related to socio-demographic characteristics. The instrument used for the neuropathic signs and symptoms was the publication of the State Department of Health, Federal District, concerning the Guidelines of the Brazilian Society of Diabetes to evaluate diabetic neuropathy (Pedrosa et al 2014). We applied the Berg Scale (Berg et al 1992), with 14 items to assess balance. To assess the functionality of the patient, the questionnaire of Lawton and Brody (Lawton & Brody 1969) was used, and finally, the Beck Scale (Beck et al 1996), containing 21 questions, was conducted to evaluate depression. The intensity of pain was evaluated by the analogic visual scale (AVS), considered a reliable and sensible scale for the evaluation of pain (Wodd, 2004).

The Statistical Package for Social Sciences-version 26.0 (SPSS Statistics 26.0, Chicago, USA) was used for the statistical treatment of data. The significance level for rejecting the null hypothesis in all statistical tests was set at $\alpha = 0{:}05$ (95% confidence interval). The main statistical tests applied were; the Shapiro-Wilk test, the student's t-test, the Chi-square test, the Main-Whitney test, and the Spearman test.

RESULTS

In this chapter, we will present the results obtained in this research, from the sample characterization data, as well as the results that aimed to answer the proposed objectives.

Characterization of the sample

Of the 60 patients, 32 (53.3%) were females, and 28 were males (46.7%). The mean age of the patients was 67.3 years (minimum 47 and maximum 83) and 48 patients (80%) were retired. Type 2 diabetes mellitus was present in 54 patients (93.1%) and 30 patients (50%) the disease was present for more than 20 years. Concerning concomitant diseases, 48 patients (80%) suffered from hypertension, 12 (20%) had a diagnosis of cardiac pathology and 36 (53.3%) had dyslipidaemia.

The severity of neuropathy concerns loss of sensitivity, pain, postural instability, and depression

The severity of neuropathy was evaluated by inspection, presence of deformities, loss of protective sensitivity, presence of neuropathic signs and symptoms, and pain.

By inspection we saw that 48 patients (80.0%) had dry skin or cracks, 44 patients (73.3%) presented ringworm nails, in 38 (63.3%) we found calluses and dilated dorsal vessels in 32

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(53.3%), hairs were present in 32 patients (53.3%). On the other hand, 46 patients (76.7%) had normal skin colour and 52 (86.7%) wore proper shoes. Concerning deformities, hollow foot was present in 18 (30%) patients and flat feet was also present in 18 patients (30,0%). Lateral compression and claw toes were less frequent (26.7% and 23.3%, respectively). As far as neuropathic signs and symptoms are concerned, 34 patients (56.7%) showed serious neuropathic symptoms and 16 (26.7%) moderate ones. We also found in 34 patients (56.7%) moderate neuropathic signs. In 32 patients (53.3%), we found loss of sensitivity evaluated by monofilament, mainly in the 3rd and 5th metatarsus.

Concerning pain, 48 patients (80%) presented a painful PDN (≥5 neuropathic symptoms and ≥3 neuropathic signs) and 38 patients (63.3%) presented PDN with a risk of ulceration (≥3 neuropathic signs). In 16 patients (26.7%) we found a serious asymptomatic PDN (≥5 neuropathic symptoms or pain ≥40 mm in the AVS) and 56 (93.3%) presented neuropathic pain (≥7 neuropathic signs). Using the Berg scale for the evaluation of postural instability, 32 patients (53.4%) presented a high to moderate risk of falls. The evaluation of functionality by the Lawton & Brody scale revealed that most of the patients, 52 (86.7%), presented a slight grade of dependence or were independent. Concerning depression, evaluated by the Beck scale, we found that 38 patients (63.4%) had a symptomatology of depression.

Comparison of the severity of neuropathy, postural instability, functionality, and depression among sexes

We found statistically significant differences between sexes concerning the intensity of pain, postural instability, and depression, with females presenting higher pain intensity (p=0.002), worse results on the Berg scale (p=0.018), and higher scores on the scale of depression (p=0.026).

On the other hand, we did not find statistically significant differences between sexes concerning loss of sensibility (p=0.282) and the number of neuropathic signs and symptoms, evaluated using the Lawton & Brody scale (p=0.056).

Comparison of the severity of neuropathy, instability, functionality, and depression with age

We found a statistically significant difference between the mean age of patients with and without loss of sensitivity (p=0.018). The mean age of patients with loss of protective sensibility was 71.3 years (+/-8.22) while patients without loss of protective sensibility presented a mean age of 62.8 (+/-10.42). We did not find any significant association between age and the presence of signs and symptoms and intensity of pain of the neuropathy.

It was possible to establish a negative association between age and postural instability (p=0.002) and functionality (p<0.001), that is, the older the patient, the worse stability and functionality. We also found a positive association between age and depression (p=0.011), which means that older patients presented more frequently with depressive symptomatology.

Association between the severity of neuropathy and postural instability, functionality, and depression

Concerning loss of sensitivity, we did not find statistically significant differences between instability, functionality, and depression between patients with or without loss of protective sensitivity.

Also, we did not find a significant association between the presence of neuropathic symptoms and instability, functionality, and depression. Nevertheless, we found a negative association between neuropathic signs and instability and functionality, being a higher number of neuropathic signs associated with worse instability (p=0.017) and functionality (p=0.020). We found a positive association between the number of neuropathic signs and the presence of depressive symptomatology (p=0.035).

As far as pain results are concerned, we found that the intensity of pain is not associated with instability or functionality but there was a positive association between the intensity of pain and depression (p=0.023), that is, a higher intensity of pain is associated with the presence of more severe depressive symptomatology.

DISCUSSION

After analyzing the results obtained, we find that type 2 diabetes mellitus patients corresponded to the great majority of the sample (93.1%) and that in 50% of the sample the disease was present for more than 20 years. Other studies also found that in Portugal diabetic neuropathy has a greater prevalence in type 2 diabetes (Serra, 2008) and increases with the time of the pathology (Bibbo et al. 2006), affecting patients with diabetes mellitus for more than 10 years (Boulton et al. 2005).

Concerning associated pathologies, we found hypertension and dyslipidaemias in most of the patients. This is also in agreement with what was found by other authors that pointed out these as important independent factors for the development of complications in diabetic patients, namely, peripheral diabetic neuropathy (Tesfaye et al. 2005, Wiggin et al. 2009).

Regarding the assessment of diabetic neuropathy, by inspection, we verified the presence of all frequent signals of the pathology, with dry skin with cracks being the change that has the highest percentage. These results were also found by Boulton (2004). Concerning deformities, we found hollow feet and flat feet with the same percentage (30%). According to Abbot et al. (2005), Boulton, et al. (2008), and Perez, et al. (2010), neuropathic deformities such as the metatarsal heads and prominent bow are important components for the evaluation of diabetic neuropathy.

Most of the patients had loss of sensitivity. This is very important because the loss of protective plantar sensitivity, assessed by the 10-gram monofilament, is an alternative for a positive clinical diagnosis of peripheral diabetic neuropathy (Serra, 2008). Loss of sensitivity seems to be a key factor for the development of ulcers and greater susceptibility to trauma, for example, falls, (Chung, M. L., Widdel, et al., 2022).

Concerning neuropathic symptoms, we found that in most of the patients they were severe, unlike neuropathic signs that were

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moderate. These results suggest that there is difficulty in describing the neuropathic symptoms as they differ with the severity of neuropathy (Boulton, 2014). Neuropathic symptoms may change throughout the day and can be aggravated and more painful at night, producing insomnia, fatigue, muscle cramps, ascending from distally to proximally slowly. When the patients were asked to quantify pain by a visual analog scale, they may not fit severe symptoms to moderate pain, presented in 40% of the cases (Schestatsky, 2008). Patients with diabetic neuropathic pain report multiple and complex complaints and there is a clear difficulty in verbal description to characterize this type of pain.

When we compare the variables of the study between sexes, the results agree with what was found by other authors, reporting that females have more pain (Oliveira & Gabbor, 1998) and greater instability (Fried et al. 2000). Women have less lean mass capacity and muscle strength, what make them more susceptible to falls due to postural imbalance with increasing age, (Falsarella, G.R., et al., 2014). Concerning depression, we found that females also had more depressive symptoms.

When comparing the age with the characteristics of diabetic neuropathy, postural instability, functionality, and depression we observed that with increasing age, worse stability and functionality were present. The ability to maintain postural equilibrium decreases with increasing age due to loss of sensory reception, slow cognitive processing, and difficulty in performing the required motor response (Andrade et al. 2001). With age, patients become more vulnerable to situations that can lead to a loss of autonomy and independence (Paschoal, 1996). It was also found that the greater the age, the greater the presence of depressive symptoms. (Zimmerman, 2000).

Finally, we found that the higher the number of neuropathic signs, the worse stability and functionality and more depressive symptoms. These data fit with what was found by other authors, which stated that sensory integration is the process by which the central nervous system directs and organizes sensory information to promote adaptive and appropriate responses (Roy, 1999). The somatosensory system automates sensory information about touch, position, pain, and temperature. Receptors involved in conducting these sensations are mechanoreceptors (of touch and proprioception), thermoreceptors (temperature), and nociceptors (for pain or noxious stimuli) (Costanzo, 2014). Chronic sensorimotor polyneuropathy, although it affects the motor part, is predominantly sensory, initially affecting the distal portion of the long limbs, thus reducing the tactile, thermal, pain, and vibration sensitivity, which can lead to complete elimination of deep reflections (Moreira et al. 2005).

Symptoms and signs of these patients essentially vary according to the nerve fibers involved. The achievement of thin nerve fibers produces decreased feeling of pain and temperature, while the damage of the thick sensory fibers produces decreased sensation to light touch, vibration, and position, and decreased deep tendon reflexes (Schmid et al. 2003). The loss of sensation in the lower limbs is one of the main factors contributing to the reduction of afferent motor coordination and therefore to the regulation of postural control (Cimbiz & Cakir, 2005). Diabetic neuropathy may compromise postural stability as the integrity of the proprioceptive system is affected, making it difficult to maintain postural control, with the resulting falls and associated injuries (Cimbiz & Cakir, 2005).

Postural instability in patients with diabetic polyneuropathy is related to psychological distress due to restrictions on everyday life activities, as they lose their independence (Yardley, 2006). Changes that occur in diabetic polyneuropathy at the level of sensory receptors, decreased motor response, and postural instability, will decrease the ability to perform daily living activities, leading to depression (Pomeroy, 1999). The analysis of pain revealed that the higher the pain intensity, the greater the presence of depressive symptoms. These data agreed with what was reported by other authors that refer to pain as the most distressing symptom of diabetic peripheral neuropathy and the main reason to seek medical care. The experience of pain is a complex process that involves not only sensory but also cognitive and emotional mechanisms that can lead to depression (Tesfaye & Selvarajah, 2012).

Peripheral diabetic neuropathy is a source of serious physical dysfunction, emotional suffering, and loss of quality of life (Galer et al. 2000). This clinical situation, sometimes accompanied by disabling pain, promotes a negative change In sleep, the ability to work effectively (functionality), humor, recreational activities, mobility and overall quality of life, damaging the competence perceptions on important family roles (Quattrini & Tesfay, 2003). Some patients may feel a constant state of fatigue due to sleep deprivation; others are unable to keep a job and when the situation is serious, a marked reduction in physical threshold may occur, which interferes with daily activities and can lead to depression (Quattrini & Tesfay, 2003). Recent research, with 1120 patients with PND shows a high level of anxiety, depression, and sleep disturbance. Thus, experts and clinics, and are suggested to focus on reducing these psychiatric symptoms (Davoudi et al., 2021).

CONCLUSIONS

The main object of the present study was to assess the severity of neuropathy in four domains: pain, loss of sensitivity, postural instability, and depression, in a Portuguese sample of diabetic patients, what we think is a new approach for the characterization of diabetic peripheral neuropathy. From our results, we can conclude that most diabetic patients presented loss of sensitivity, moderate pain, high to moderate risk of falls, and some symptomatology of depression.

It was also an objective of the present work the comparison of neuropathic characteristics between sexes and associated to age. This comparison revealed that females presented more pain, more instability, and more depressive symptomatology. The results obtained pointed out an association between age and postural instability, loss of functionality, and depression. We also found an association between age and the severity of diabetic neuropathy, assessed by the presence of neuropathic signs and symptoms and

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intensity of pain.

Finally, we also investigated the possible association between neuropathic characteristics with postural instability, functionality, and depression. From our results, we can conclude that there is an association between neuropathic signs and instability, functionality, and depression. We also found an association between the intensity of pain and depression.

The diabetic foot is one of the complications of diabetes with a greater impact, given both the morbidity it causes, and the socioeconomic impact it generates (Associação Protectora dos Diabéticos de Portugal, 2010). In conclusion, we can say that the results of the present study, although they must be confirmed in a large sample, are important in a context of a follow-up of diabetic patients by a multidisciplinary team, including a podiatrist as they can contribute to the prevention and early identification of risk factors and possible future complications.

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