INTRODUCTION: Human gait is a complex movement dependent on multilevel neural control, which allows a consistent, regular and complex periodic pattern, properties that characterize it as a nonlinear system. Sensory and motor deficits, with diminished proprioceptive responses, may reduce the adaptive capacity of the system, as demonstrated in Parkinson’s, Alzheimer’s and Huntington’s diseases. However, little is known about the effect of peripheral diabetic neuropathy on these responses. Objectives: To analyze the influence of peripheral diabetic neuropathy on entropy in different gait environments. Methods: Ten elderly patients, with and without a diagnosis of peripheral diabetic neuropathy, walked on a treadmill (initial speed of 3 km/h, with 0.5 km/h increments every 5 minutes up to the speed of 5 km/h) to record center of mass acceleration in the vertical, mediolateral and anteroposterior components throughout the test. The sample entropy of the three vectors was calculated for each test speed. Results: The vertical component did not show any statistically significant differences. The mediolateral component showed statistically significant difference for the factors group, speed, and interaction between factors (group and speed). The anteroposterior component showed statistically significant differences for the group factor, but not for speed and interaction between factors (group and speed). Effect sizes classified as large were found in all the comparisons. Conclusions: Peripheral diabetic neuropathy produced changes in the ability to adapt to changes in the environment during gait, probably due to changes in the complexity of the multilevel neural control system, which depends on motor and sensory feedback, known to be affected by peripheral diabetic neuropathy. Level of Evidence II; Diagnostic studies - Investigating a diagnostic test.

Keywords: Diabetes mellitus; Aging; Gait.

RESUMO

Introdução: A marcha humana é um movimento complexo dependente de controle neural multinível, que permite um padrão periódico uniforme, regular e complexo, que a caracterizam como um sistema não linear. O déficit sensitivo e motor com diminuição das respostas proprioceptivas pode diminuir a capacidade de adaptação do sistema, como já demonstrado nas doenças de Parkinson, Alzheimer e Huntington. Contudo, pouco se conhece sobre o efeito da neuropatia diabética periférica nessas respostas. Objetivos: Analisar a influência da neuropatia diabética periférica na entropia em diferentes ambientes de marcha. Métodos: Dez idosos, sem e com diagnóstico de neuropatia diabética periférica, caminham em esteira rolante (velocidade inicial 3 km/h e incremento de 0,5 km/h a cada 5 minutos até a velocidade 5 km/h) para o registro da aceleração do centro de massa nos componentes vertical, médiolateral, e anteroposterior ao longo de todo teste. A entropia amostral dos três vetores foi calculada para cada velocidade de teste. Resultados: O componente vertical não apresentou nenhuma diferença com significância estatística. O componente médiolateral mostrou diferenças com significância estatística para os fatores grupo, velocidade e interação entre os fatores (grupo e velocidade). O componente anteroposterior apresentou diferenças com significância estatística para o fator grupo, mas não para o fator velocidade e interação entre os fatores (grupo e velocidade). Em todas as comparações, foram encontrados tamanhos de efeito classificados como grandes. Conclusões: A neuropatia diabética periférica produziu alterações na capacidade de adaptação sobre as variações do ambiente durante a marcha, provavelmente, em decorrência de alterações na complexidade do sistema de controle neural multinível, que depende da retroalimentação sensitiva e motora, sabidamente afetadas pela neuropatia diabética periférica. Nível de Evidência II; Estudos diagnósticos – Investigação de um exame para diagnóstico.

Descritores: Diabetes mellitus; Envelhecimento; Marcha.
INTRODUCTION

Human locomotion can be defined as the action whereby the body moves in space, and is achieved through postural control, and dynamic motor control to adapt the projection of the center of mass (CoM) within the base of support, and the execution of fine, coordinated movements.1

It can be held that at the level of the central nervous system, a basic locomotor pattern is generated and executed under the control of the descending pathways.2 This locomotor pattern is fed back and adapted to environmental changes through information from the visual, vestibular and proprioceptive systems. Considering that the proprioceptive system, which promotes feedback about the state of the effector system and the environment, is composed of muscle, joint and skin receptors, it can be pointed out how gait requires complex and dynamic sensorimotor interactions.

Human gait is a complex movement dependent on multilevel neural control, which allows a consistent, regular and periodic pattern of kinetic, kinematic, and muscle activity variables.3,4

It is important to note that the complexity of the systems that interact to produce this movement, characterize gait as a non-constant regular and periodic consistent pattern phenomenon.4 Thus it is a non-linear system, since given the high sensitivity to initial changes in the system, and the impossibility of knowing such conditions, it is highly unpredictable in terms of response over time series.5

With this in mind, diseases characterized by sensory and motor deficits of any kind, with diminished proprioceptive responses, may reduce the system’s ability to adapt to environmental changes in routine tasks, such as walking. This condition has already been demonstrated in degenerative diseases such as Parkinson’s and Alzheimer’s.6

In this condition, type 2 Diabetes (T2D), a disease characterized by elevated blood glucose due to a change in the secretion or action of the hormone insulin, must be taken into account, since the main complications include peripheral diabetic neuropathy (PDN), which is characterized by sensory and motor deficit besides gradual loss of sensitivity, entailing diminished proprioceptive responses.7

In such a scenario, PDN could result in impaired sensory feedback from the visual, vestibular and proprioceptive systems, and consequently bring about a decrease in the system’s ability to adapt to changes in the environment.

Although the indicators of fluctuation in the gait parameters of young adults, the elderly and people with neurodegenerative diseases are already known,4 these indicators achieve their purpose through classical paradigms based on linear measures (absolute variability; amplitude and standard deviation or relative variability; coefficient of variation)8 that fail to fulfill fundamental aspects of human movement, such as degrees of freedom, reconciliation of consistency, skilled movement variability and motor equivalence.9

In view of this condition, knowledge about the possible influence of PDN on the impairment of sensory feedback and the system’s adaptability to environmental changes in daily tasks such as gait, is still based on hypothetical situations, besides using linear measurements.

Therefore, the objective of this study was to analyze the influence of PDN on the system’s ability to adapt to changes in the environment during gait, using nonlinear measurement.

MATERIALS AND METHODS

This is a cross-sectional study approved by the institutional review board of Universidade São Judas Tadeu under CAAE (Ethics Evaluation Submission Certificate) no. 68816517.3.0000.0089. All the participants signed the informed consent form (ICF).

We assessed ten elderly subjects with T2D subdivided into two groups, as follows: T2D without a diagnosis of PDN (without PDN: n = 5; age: 69 ± 4 years; height: 1.6 ± 0.1 m; body mass: 78.1 ± 8.4 kg; BMI = 29.6 ± 3.2 kg/m²), and T2D with a diagnosis of PDN (with PDN; n = 5; age: 72 ± 4 years; height: 1.8 ± 0.1 m; body mass: 88.0 ± 19.9 kg; BMI = 28.4 ± 6.1 kg/m²).

The inclusion criteria were: male subjects with T2D for more than 5 years, aged between 60 to 79 years, functional independence, absence of disease or functional impairment of the auditory, vestibular, proprioceptive, neurological and mental systems, and not having undergone any kind of orthopedic surgery. All conditions were identified by medical assessment. Exclusion criteria were discomfort or inability to walk on a treadmill for 30 minutes.

Assessments

The subjects were initially presented with a questionnaire containing demographic data, then underwent the following anthropometric assessments: body mass and height, followed by calculation of Body Mass Index (BMI).9

To identify PDN, changes in sensitivity to mechanical stimulus were assessed using esthesiometry. Test specimen contact in different thermal conditions was used for thermal stimulus and tuning fork contact, as recommended by the literature, for vibratory stimulus.10

The volunteers then underwent the gait test on a computerized treadmill, model KT 10200 (Inbramed®, Porto Alegre, Rio Grande do Sul, Brazil), in order to quantify the parameters related to the CoM acceleration time series. An initial speed of 3.0 km/h was adopted, with increments of 0.5 km/h in the treadmill speed every 5 minutes, until the

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Descriptores: Diabetes mellitus; Envejecimiento; Marcha.
volunteer could no longer keep up the gait but had to start running, or was required to submit a self-report of inability to continue the test.

The CoM acceleration time series was quantified by means of an isostructural (ISO) sensor, positioned over the sacrum and fixed by an elastic bandage wrapped around the circumference of the subject’s hip. We used an isostructural (ISO) sensor composed of a programmable Arduino® GENIUS 101® board with a dual-core Intel® Curie™ module, 384 KB flash memory, an accelerometer and 6-axis gyroscope.

The CoM acceleration time series were acquired in the vertical (aceLV), mediolateral (aceML) and anteroposterior (aceAP) components, at a sampling frequency of 294 Hz.

The programming for operation of the ISO was written in algorithm (sketch) via Integrated Development Environment (IDE) version 1.8.1 for MacBook®, language software based on C/C++, and developed specifically by Arduino.

Moreover, aiming to minimize potential influences of the treadmill familiarization process, subjects initially underwent a 10-minute walking session at 3.0 km/h using the same test treadmill and equipment, before the measurement acquisition procedures.

Once determined, aceLV, aceML and aceAP were exported to the Matrix Laboratory® (MATLAB®) environment [MathWorks Inc., Natick, USA, version R20016a for Mac@], where we then estimated the statistical parameter of nonlinear dynamical system sample entropy (SampEn) for aceLV, aceML and aceAP (SampEn_acelV, SampEn_acelML and SampEn_acelAP, respectively) at each speed (5-minute stage) of the treadmill test (SampEn_acelV_3.0, SampEn_acelV_3.5, SampEn_acelV_4.0), assuming that these were complexity indicators. The parameters embedding dimension=2 and tolerance employed=0.2 were used in all the analyses.

Statistical analysis

Normality and homoscedasticity were checked using the Shapiro-Wilk and Levene test. We applied the repeated measures ANOVA (analysis of variance) test (General Linear Model [GLM]) to analyze the entropy values (SampEn) for aceLV, aceML and aceAP (SampEn_acelV, SampEn_acelML and SampEn_acelAP, respectively) at each speed (5-minute stage) of the treadmill test (SampEn_acelV_3.0, SampEn_acelV_3.5, SampEn_acelV_4.0), assuming that these were complexity indicators. The parameters embedding dimension=2 and tolerance employed=0.2 were used in all the analyses.

RESULTS

The descriptive values of the parameters obtained are presented in Table 1.

In the acceleration time series analysis in the vertical component, we found evidence of differences without statistical significance for the factors group [F (1.4) = 2.566, p = 0.184, η² = 0.391, power = 0.236], speed [F (4.16) = 1.107, p = 0.387, η² = 0.217, power = 0.27], and interaction between group*speed factors [F (3.47,16) = 1.2, p = 0.352, η² = 0.231, power = 0.222]. However, large effect sizes were found in all the comparisons.

For the mediolateral component, significant differences were found for the factors group [F (1.4) = 10.692, p = 0.031, η² = 0.728, power = 0.690], speed [F (4.16) = 3.433, p = 0.036, η² = 0.455, power = 0.716], and interaction between group*speed factors [F (4.16) = 3.726, p = 0.025, η² = 0.482, power = 0.494], as well as large effect sizes.

For the anteroposterior component, significant differences were found for the group factor [F (1.4) = 9.66, p = 0.036, η² = 0.70, power = 0.646], but without statistical differences for speed [F (4.16) = 2.967, p = 0.052, η² = 0.426, power = 0.657] and interaction between group*speed factors [F (4.16) = 1.446, p = 0.295, η² = 0.266, power = 0.155], with large effect sizes. There were differences in entropy between the groups with (0.284) and without (0.478, p = 0.031) PDN, and between the speeds 3.5 km/h (SampEn_acelML_3.5 = 0.439) and 5 km/h (SampEn_acelML_5.0 = 0.308, p = 0.036) (Figure 1).

Regarding interaction between the group*speed factors, differences were found in the group with PDN at speeds of 4 km/h (SampEn_acelML_4.0 = 0.203), 4.5 km/h (SampEn_acelML_4.5 = 0.157), and 5 km/h (SampEn_acelML_5.0 = 0.160) compared to the group without PDN (4 km/h (SampEn_acelML_4.0 = 0.275, p = 0.013), 4.5 km/h (SampEn_acelML_4.5 = 0.281, p = 0.004) and 5 km/h (SampEn_acelML_5.0 = 0.268, p=0.018)) (Figure 2).

In the anteroposterior component, significant differences were found in the group factor [F (1.4) = 9.606, p = 0.036, η² = 0.706, power = 0.646], but not for the speed factor [F (4.16) = 2.967, p<0.052, η² = 0.426, power = 0.657] and interaction between the group*speed factors [F (2,105,16) = 1.071, p<0.389, η² = 0.211, power = 0.182]. The observed effect sizes were classified as large. There were differences in entropy between the groups with (0.259) and without (0.308, p = 0.036) PDN (Figure 1).

Table 1. Mean and standard deviation of the nonlinear dynamical system sample entropy (SampEn) of the groups with and without peripheral diabetic neuropathy with speed increments.

<table>
<thead>
<tr>
<th>Group</th>
<th>Speed</th>
<th>SampEn_acelV</th>
<th>SampEn_acelML</th>
<th>SampEn_acelAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>With PDN</td>
<td>3.0 km/h</td>
<td>0.205</td>
<td>0.118</td>
<td>0.407</td>
</tr>
<tr>
<td></td>
<td>3.5 km/h</td>
<td>0.214</td>
<td>0.114</td>
<td>0.344</td>
</tr>
<tr>
<td></td>
<td>4.0 km/h</td>
<td>0.203</td>
<td>0.121</td>
<td>0.261</td>
</tr>
<tr>
<td></td>
<td>4.5 km/h</td>
<td>0.157</td>
<td>0.080</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>5.0 km/h</td>
<td>0.160</td>
<td>0.069</td>
<td>0.200</td>
</tr>
<tr>
<td>Without PDN</td>
<td>3.0 km/h</td>
<td>0.256</td>
<td>0.034</td>
<td>0.472</td>
</tr>
<tr>
<td></td>
<td>3.5 km/h</td>
<td>0.283</td>
<td>0.067</td>
<td>0.464</td>
</tr>
<tr>
<td></td>
<td>4.0 km/h</td>
<td>0.275</td>
<td>0.037</td>
<td>0.505</td>
</tr>
<tr>
<td></td>
<td>4.5 km/h</td>
<td>0.281</td>
<td>0.052</td>
<td>0.533</td>
</tr>
<tr>
<td></td>
<td>5.0 km/h</td>
<td>0.268</td>
<td>0.033</td>
<td>0.415</td>
</tr>
</tbody>
</table>

Key: nonlinear dynamical system sample entropy (SampEn), CoM: acceleration in the vertical (aceLV), mediolateral (aceML) and anteroposterior (aceAP) components; sd: standard deviation; PDN: peripheral diabetic neuropathy.

Figure 1. Graphical representation of sample entropy (SampEn) values, considering the speed factor of the center of mass acceleration time series in the vertical (aceLV), mediolateral (aceML) and anteroposterior (aceAP) components, and the group factor of the same time series.
Therefore, an ideal CoM displacement must be produced in terms of a conversion of gravitational potential energy into kinetic energy. 

... depression and positive acceleration in the second half of the support phase are characterized by conversion of kinetic energy into gravitational potential, whereas depression and positive acceleration in the first half of the gait cycle is characterized by conversion of kinetic energy into gravitational potential and restitution of elastic energy during gait, requiring a greater contribution from the contractile components of the plantar region, thereby increasing muscle work and CoW.

... changes in gait are also associated with other diabetic complications such as impaired visual acuity and balance, which compromise space-time organization, positioning and control of lower limb movement. This would have an impact on postural stability and be a possible source of explanation for the greater disturbance in the fluctuation of CoM displacement and CoW in a subject with PDN.

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**DISCUSSION**

The findings of the study show that elderly people with PDN had decreased entropy values in the mediolateral vector concomitantly with an increase in gait speed. Accordingly, it can be said that PDN influenced entropy from CoM displacement in the mediolateral and anteroposterior vectors, but not in the vertical vector, which is consistent with the literature where changes related to PDN lead to functional adaptations of gait, such as lower self-selected and maximum speed, shorter strides, and higher cadence. Considering that PDN is characterized by sensory and motor deficit, a decrease in the system’s ability to adapt to changes in the environment in routine tasks has been pinpointed as a possible explanation for changes in gait.

Given that SampEn is conceptually indicative of complexity, informing the adaptability of a system to changes in the environment, a system with restricted adaptability to changes in the environment generally has a regular behavior with low entropy value. This phenomenon is the opposite of that found in a system without adaptation restrictions.

In the gait cycle, CoM displacement can be represented as an inverted pendulum with a sine wave. Thus, the highest entropy values found in subjects with PDN reflect a greater variability in CoM displacement, thus signaling an irregular system.

The statistically higher values of entropy reflect greater disturbance in CoM displacement in diabetics with PDN in the anteroposterior and mediolateral vectors, but not in the vertical vector. These differences merit attention, because both the increase in CoM displacement and the decrease/absence of CoM displacement increase the metabolic cost of walking (CoW).

... changes in gait are also associated with other diabetic complications such as impaired visual acuity and balance, which compromise space-time organization, positioning and control of lower limb movement. This would have an impact on postural stability and be a possible source of explanation for the greater disturbance in the fluctuation of CoM displacement and CoW in a subject with PDN.

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**CONCLUSIONS**

Peripheral diabetic neuropathy produced changes in the sensorimotor adaptability to respond to changes in the environment experienced during gait.

We could consider the possibility of this response being representative of changes in the complexity of the multilevel neural control system, which is dependent on sensory and motor feedback, affected by peripheral diabetic neuropathy.

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