Gait & Posture 74 (2019) 194–199

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Full length article

Impact of diabetic neuropathy severity on foot clearance complexity and variability during walking

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ARTICLE INFO

Keywords:
Foot clearance
Gait
Diabetic polyneuropathies
Falling
Kinematics
Complexity

ABSTRACT

Background: The control of foot trajectory during swing phase is important to achieve safe clearance with the ground. Complexity of a physiological control system arises from the interaction of structural units and regulatory feedback loops that operate to enable the organism to adapt to a non-static environment. Diabetic polyneuropathy (DPN) impairs peripheral feedback inputs and alters ankle control during gait, which might affect toe clearance (ToC) parameters and its complexity, predisposing DPN-subjects to tripping and falling.
Research question: How do different DPN-severity degrees change ToC trajectory and minimum ToC, and its complexity during gait of diabetic subjects?
Methods: 15 healthy controls and 69 diabetic subjects were assessed and classified into DPN-severity degrees by an expert fuzzy model: absent (n = 26), mild (n = 21) and severe (n = 22). Three-dimensional kinematics was measured during comfortable walking. ToC was the minimum vertical distance between the marker placed at the first metatarsal head and the ground during swing. Mean ToC, ToC standard deviation (SD) between trials, and sample entropy (SaEn) and standard deviation (SD) of ToC trajectory were calculated from the ToC temporal series. ANOVA and ANCOVA (with the walking speed as the covariate) and Bonferroni pairwise post-hoc tests ($P < 0.05$) were used to compare groups.
Results: Mean ToC and ToC SD did not show differences between groups (ANCOVA F = 0.436; df = 3; $P = 0.705$; F = 1.719; df = 3; P = 0.170, respectively). ToC trajectory SD also did not show differences between groups (ANCOVA F = 3.98; df = 3; $P = 0.755$). Severe-DPN subjects showed higher ToC_Traj_SaEn than controls (ANCOVA F = 2.60; df = 3; $P = 0.05$).
Significance: Severe-DPN subjects showed a more complex pattern of overall foot-ankle trajectory in swing phase in comparison to controls, although did not present lower minimum ToC values. The higher complexity of ToC might lead to an increase in the motor system output (more strategies, increase in variability), resulting in a more unstable system and selected motor strategies.

1. Introduction

One of the major motor functions during gait is the control of the foot trajectory to achieve safe clearance with the ground [1]. Foot clearance during the swing phase is directly related to the risk of tripping and falling [2]. Falls are a major concern due to their relationship to short- and long-term health problems and impact on quality of life [3]. For safe ground clearance, a proper control of the foot trajectory must be accomplished by the central nervous system that integrates the peripheral feedback with efferent commands, in addition to vestibular and visual inputs, to generate the correct patterns of force moment at each joint [1]. Diabetic peripheral polyneuropathy (DPN), a common complication of diabetes mellitus (DM) [4], is well known for impairing peripheral feedback inputs due to a loss of large myelinated fibers and other proprioceptive afferent fibers, causing disturbances in joint position sense and altering tactile, pressure, and vibratory sensitivity [5]. As a consequence, DPN impairs harmonious joint kinematic trajectories during gait [6], which in turn impacts foot clearance in the swing phase, increasing the risk of stumbling and falling in this population [3].

Minimum foot clearance, defined as the vertical distance between the ground and the foot at forward mid-swing, is generally affected by swing limb joint angles, step length, and walking velocity [7]. These parameters are commonly described as altered in the DPN-population

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https://doi.org/10.1016/j.gaitpost.2019.09.014
Received 22 August 2018; Received in revised form 4 September 2019; Accepted 13 September 2019

Table 1
Mean (standard deviation) anthropometric variables and clinical data for the experimental groups: control, absent DPN (AbN), mild DPN (MiN) and severe DPN (SeN).

	Control (n = 15)	AbN (n = 26)	MiN (n = 21)	SeN (n = 22)	*P*
Age (years)	56.6 (7.5)[#]	57.7 (5.6)	58.3 (5.9)	59.9 (4.2)	0395[1]
Sex (% male)	56.3	47.8	33.3	35	0.219[2]
Body mass index (kg/m^2)	29.2 (4.1)	27.3 (2.3)	27.3 (7.7)	30.4 (4.5)	0.138[1]
Diabetes duration (years)	—	11.3 (9.0)	9.9 (7.6)	15.1 (12.5)	0.237[1]
HbA1C (%)	—	8.4 (1.8)	9.1 (1.8)	9.5 (1.9)	0.137[1]
Neuropathy degree score	1.2 (0.4)	1.3 (0.6)	2.7 (0.9)	7.6 (1.8)[#]	< 0.001[1]
Gait speed (m/s)	1.17 (0.12) [‡]	1.15 (0.13)	1.10 (0.14) [‡]	1.04 (0.15) [‡]	0.012[1]
Stride length (m)	1.29 (0.07) [‡, §]	1.16 (0.13) [§]	1.19 (0.13)	1.14 (0.13) [‡]	0.005[1]

[1] ANOVA test.
[2] Chi-square test.
[#] group statistically different from all others.
[‡] group statistically different between each other – Bonferroni pairwise comparisons.
[§] group statistically different between each other – Bonferroni pairwise comparisons.

[8]. In addition, alterations in ankle control during gait have already been described in DPN-subjects, who showed a less extended ankle and smaller ankle extensor moment at push-off [9]. The effects of these neuromotor and biomechanical alterations on foot trajectory control in DPN-subjects are unknown.

Young, healthy subjects exhibit two different strategies to successfully lower tripping risk: (i) increasing the minimum foot clearance height and (ii) diminishing the variability of minimum foot clearance [10]. Both strategies depend on the integrity of the motor control systems, which are impaired in the DPN-population. Particularly, variability is an important aspect of motor control during locomotion because it is directly related to the capacity to adapt to different environmental demands, such as surface irregularities and avoiding obstacles. Thus, an optimal variability would guarantee safe ground clearance. The amount of variability refers to the magnitude of fluctuations in the biological system's response and can be assessed by linear measures of error/variance. The structure of this variability refers to the variation of the biological system's output over time, which is independent of the signal magnitude and reflects the system's dynamics [11]. This structural variability can be measured by non-linear methods that measure the complexity of a physiological system output, such as sample entropy (SaEn). The complexity of a physiological control system arises from an interaction of structural units and regulatory feedback loops that operate to enable the organism to adapt to a non-static environment, such as when people walk. DPN-subjects might fall more [3] due to a lower minimum foot clearance and/or lower complexity of the minimum foot clearance. Although there have been studies on toe-obstacle clearance and tripping risk factors in DM subjects [12], there are no previous investigations on the minimum foot clearance and complexity thereof in DPN-subjects. The assessment of this parameter and its complexity can bring new insights to the understanding of how DPN affects motor control and provide explanations for why those subjects present an increased risk of falling.

The symptoms of DPN are monophasic or fluctuating over time [13], subclinical in the initial stages and worsening over the years, and show a continuous progression that is non-linear [14]. Because DPN-severity could also increase understanding of the expected biomechanical alterations throughout the disease, in this study we investigated how the altered foot kinematics due to different DPN-severity degrees change the resulting foot clearance values and variability during gait. Considering the evidence that a decrease in the complexity of the physiological system output could be expected with aging and the presence of a disease [15], we hypothesized that in the presence of DPN, mainly more severe cases, a lower minimum foot clearance value and an increase in its variability would be expected, together with an increase in the amount of variability and a decrease in the complexity of foot clearance trajectory.

2. Methods

2.1. Participants

A total of 84 subjects under 65 years of age were recruited for the study. Fifteen healthy adults participated as a control group, and 69 DM patients were divided into three groups with different DPN-severity stages: absence of neuropathy (AbN; n = 26), mild-DPN (MiN; n = 21), and severe-DPN (SeN; n = 22).

Exclusion criteria included vestibulopathy; severe visual deficits; limb amputations; Charcot arthropathy; plantar ulceration at the time of evaluation; neurological or orthopedic impairments due to stroke, Parkinson's disease, or cerebral palsy; poliomyelitis; rheumatoid arthritis; severe nephropathy causing edema [16]. This study was approved by the local ethics committee (522/11). All participants provided written informed consent prior to participation.

All participants were assessed by a trained physical therapist, who evaluated (i) vibratory perception with a 128 Hz tuning fork, (ii) tactile sensitivity with a 10 g Semmes-Weinstein monofilament, and (iii) neuropathy symptoms (Michigan Neuropathy Screening Instrument) in both feet, as described in previous studies [17]. Participants underwent these three clinical assessments to classify them into different DPN-severity stages, with these variables used as linguistic inputs into a fuzzy model [18]. The model performs a combinatory analysis of the input variables using an *if-then* rule base, linking them with the fuzzy output sets (Mamdani inference process). Those output sets are transformed into a numerical value by the center of area defuzzification method, resulting in a DPN-degree score (0–10 points). This model has shown high sensitivity and specificity in discriminating patients with and without DPN (ROC = 0.91) [18]. The DPN degree score (x) was sorted in: (i) $x \leq 2.0$ means AbN, (ii) $2.0 < \times < 4.5$ means MiN, and (iii) $x \geq 4.5$ means SeN. Patients with a history of ulceration were automatically classified as SeN [18]. The participants' anthropometric and clinical data are shown in Table 1.

2.2. Data acquisition

Kinematic data from one leg that was randomly selected were acquired using six infrared cameras at 100 Hz (OptiTrack/Natural Point, V100 model, 45° viewing angle, 4.5 mm focal length, accuracy < 1 mm, Corvallis, USA). Retro-reflective markers with a 20 mm diameter were placed on anatomical reference points based on a standard Cleveland Clinic marker set to acquire kinematic data. An extra marker was placed on the first metatarsal head lateral aspect to assess toe clearance. A relaxed standing calibration trial was recorded. Participants were asked to walk barefoot at a comfortable walking pace in a 10-m walkway. Ten trials were recorded after a habituation period in the laboratory environment. One swing phase (i.e., toe off to heel strike) per trial was

considered for data analysis. Toe off was identified at the local maximum of the horizontal component of acceleration of the toe marker. Heel strike was identified at the time when the vertical component of acceleration of the lateral malleoli marker changes from negative to positive. Surface electromyography and ground reaction forces were also acquired but not analyzed in the current study.

2.3. Data analysis

The markers were used to create an anatomical reference frame and model of the foot segment using standard procedures within the Visual3D software suite (CMotion, Inc., MD, USA). Raw data of the markers were low-pass filtered with a 4th order zero-lag Butterworth Filter using a cut-off frequency of 10 Hz. A custom-written Matlab function was used to calculate all ToC values (MathWorks, Natick, MA, USA). Foot clearance was defined based on the temporal series of the marker on the first metatarsal head, which we named the toe clearance (ToC) trajectory. Data was not normalized in time. The minimum vertical distance between this marker and the ground during swing was defined as the minimum ToC value. Mean (Min_ToC_Mean) and standard deviation (Min_ToC_SD) of the minimum Toc values between 10 trials for each subject were computed.

The ToC trajectory (temporal series) of the swing phase of ten steps (ten trials) per subject were combined for the analysis of the amount and structure of ToC variability (Fig. 1). The amount of variability of the ToC trajectory was inferred by the SD of the combined temporal series (ToC_Traj_SD) and the structure of the variability of the ToC trajectory was inferred by SaEn (ToC_Traj_SaEn). SaEn measures variations in the system output along time, which is independent of the signal magnitude. Therefore, it measures the way that the system output changes over time, and thus the structure of the variability of a given biological sign or of the system dynamics [11]. SaEn determines if there are any repeated patterns of various lengths within a time series by assessing the probability that equal sequences of an m length will remain similar along time within a similarity criterion r. The lower the SaEn value is, the higher the similarity in the temporal series, and, therefore, the less complex the temporal series is [11]. For SaEn calculations, the embedding dimension m was set to 2 and the tolerance distance r was set to 0.2xSD.

2.4. Statistical analysis

Analysis of variance (ANOVA) followed by Bonferroni pairwise tests were performed to compare ToC variables between groups ($P < 0.05$). The DPN groups (mild and severe) walked significantly slower than the control group (Table 1), so it was decided to also test for statistical differences in the ToC variables using an analysis of covariance (ANCOVA) with walking speed as the covariate.

3. Results

Fig. 2 shows the results of ToC variables for the studied groups. For ANOVAs, Min_ToC_Mean did not show significant differences across groups ($F = 0.281$; $df = 3$; $P = 0.839$). Min_ToC_SD also showed no

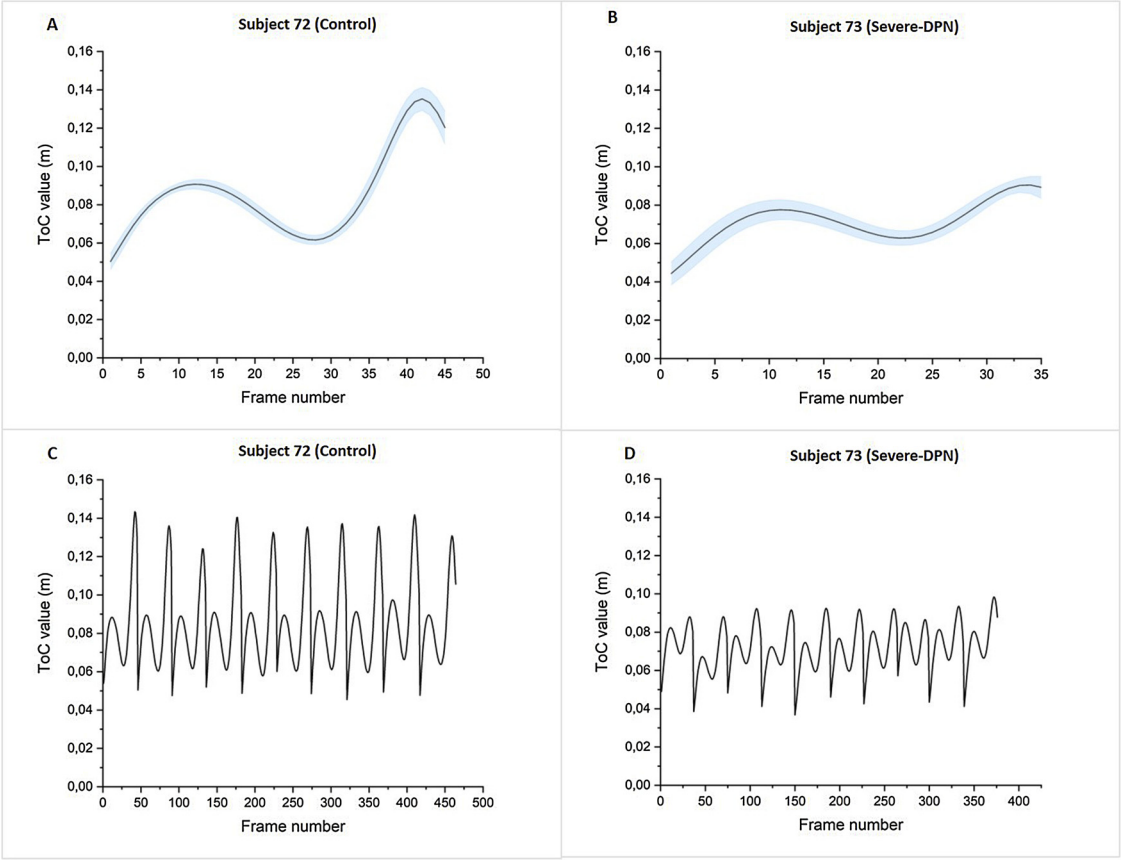

Fig. 1. Time series of the analysed trajectory of the marker on the first metatarsal head throughout the swing phase of 10 steps. The graphs above (A and B) represent the mean and standard deviation (shadowed region) of ten trials of a control (left side, minimum ToC value = 0.061 m, minimum ToC value variability (SD) = 0.002 m) and a DPN-subject (right side, minimum ToC value = 0.063 m, minimum ToC value variability (SD) = 0.004 m). The graphs in the bottom (C and D) represent the reconstructed time series containing the analysed swing phases used to compute the variability and complexity of the ToC trajectory of both a control (left side, ToC trajectory amount of variability = 0.023 m and ToC trajectory sample entropy = 0.349) and a DPN-subject (right side, ToC trajectory amount of variability = 0.012 m and ToC trajectory sample entropy = 0.508).

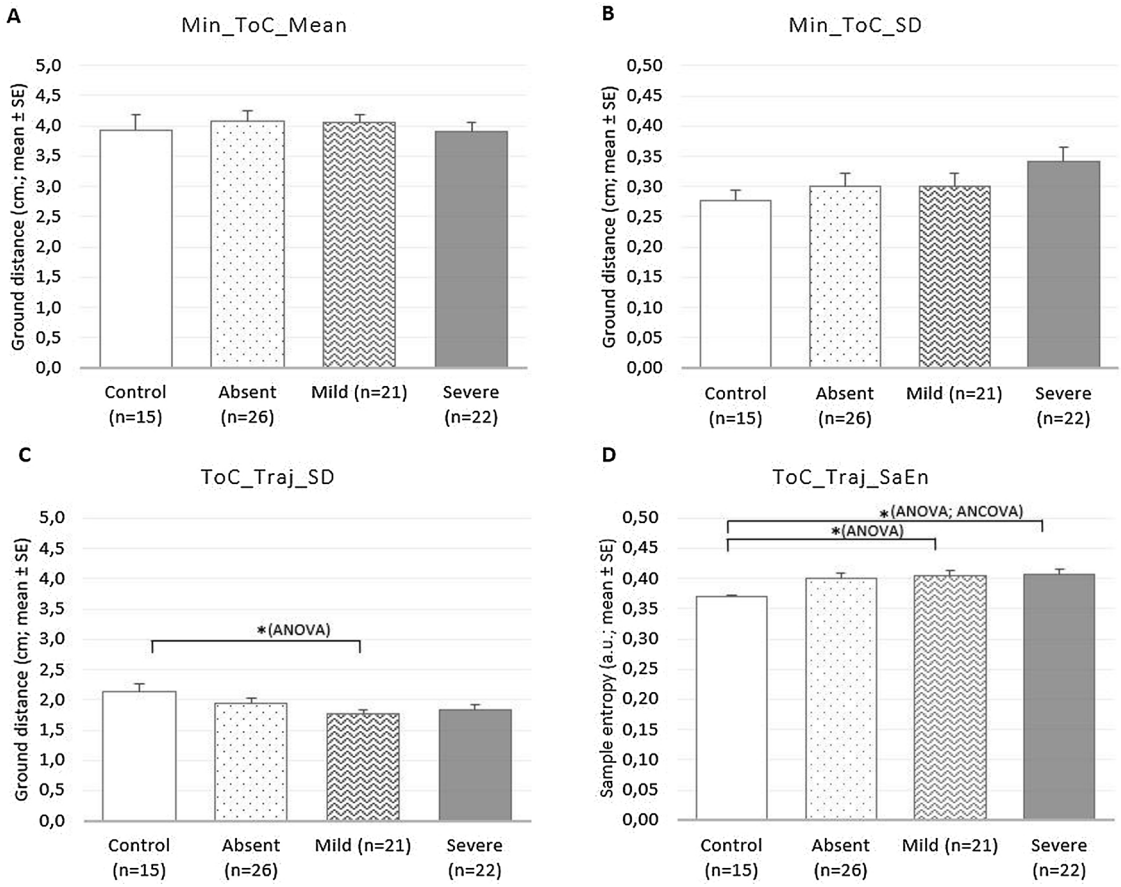

Fig. 2. Minimum toe clearance mean values (Min_ToC_Mean) (A, in the top left, mean ± SE), minimum toe clearance values variability between trials (Min_ToC_SD) (B, in the top right, mean ± SE), toe clearance trajectory amount of variability (ToC_Traj_SD) (C, in the bottom left, mean ± SE), and toe clearance trajectory sample entropy (ToC_Traj_SaEn) (D in the bottom right, mean ± SE) for the studied groups. *Shows the significant differences between groups, pointed out by the horizontal black lines for ANOVAs and ANCOVAs (Bonferroni pairwise comparisons, $P < 0.05$).

significant differences across groups ($F = 1.287$; $df = 3$; $P = 0.839$). MiN subjects showed a significantly lower ToC trajectory amount of variability (ToC_Traj_SD – $F = 2.85$; $df = 3$; $P = 0.043$) when compared to controls. DPN-subjects (MiN and SeN) showed significantly higher ToC_Traj_SaEn when compared to controls ($F = 3.24$; $df = 3$; $P = 0.026$). When walking speed was taken into account by ANCOVAs, Min_ToC_Mean and Min_ToC_SD did not show significant differences across groups ($F = 0.468$; $df = 3$; $P = 0.705$; and $F = 1.719$; $df = 3$; $P = 0.170$, respectively). The differences for Min_ToC_SD across groups were not present anymore ($F = 3.98$; $df = 3$; $P = 0.755$), and severe-DPN subjects showed higher ToC_Traj_SaEn than controls ($F = 2.60$; $df = 3$; $P = 0.05$).

4. Discussion

The aim of this study was to evaluate how foot kinematics during gait are altered due to DPN and across its severity levels, as specified in changes in the foot clearance values and in the amount and structure of variability of foot clearance trajectory. The minimum ToC and the variability thereof between walking trials were not different across groups. However, the variability magnitude of ToC trajectory was lower in the MiN group compared to controls, and the structure of ToC trajectory variability (complexity) was increased in both mild and severe subjects when compared to controls. The differences found for mild-DPN subjects can be explained by taking into account the walking speeds of the participants, which were reduced in both mild and severe-DPN groups. The ToC trajectory complexity is increased in severe-DPN subjects regardless the effect of the reduced walking speed, showing a clear effect of the disease. The results are contrary to the initial hypothesis of the study, since it was expected that the more severe subjects would present a lower minimum foot clearance, with an increased variability of minimum ToC values and ToC trajectory and a decreased complexity. In the following paragraphs, the reasons for this contradiction are discussed.

Foot trajectory control during gait is highly important for safe foot ground clearance [1] and therefore avoiding tripping. DPN-subjects did not show differences in minimum ToC values (mean or SD across strides) in comparison to healthy controls, but MiN presented a lower variability of ToC trajectory. This finding is a result of the lower walking speed showed by mild-DPN subjects, reflecting a more conservative and therefore less destabilizing gait pattern probably to compensate for the loss of sensory information available due to sensitive and proprioceptive losses resulting from DPN. The same trend found in MiN was also clear for SeN subjects, as they presented a lower ToC_Traj_SD compared to controls, but this was not significant. The absence of a statistically significant difference could be due to an 'apparent recovery' of motor control strategies in the severe cases, where they might have more adaptations and learning process to overcome the disease challenges that resulted in variability magnitudes closer to the controls, even though their gait velocity is reduced as a long-term consequence of DPN [19]. However, the fact that the complexity did not present this same "apparent recovery" shows that the motor control of the more severe subjects is still altered.

Mettelinge et al. [20] showed that non-DPN diabetic elderly adults present a more conservative gait with reduced speed and shorter strides when compared to controls, although these patients increase the gait

variability, represented by the stride length coefficient of variation. Paul et al. [21] also found a more conservative gait pattern in DPN-subjects when compared to non-DPN subjects: slower velocity, shorter steps, lower cadence, and longer double support time. On the other hand, variability during gait, and specifically the variability of foot trajectory, is directly related to stability during gait, since the maintenance of balance during dynamic activities relies on suitable foot placement to correct the base of support relative to the center of mass [22]. If variability is too high, it can be harder to correct errors, especially in a biological system where the inputs are diminished due to the damage caused in the afferent pathways, as with DPN-subjects. Therefore, the lower walking speed causes a less variable pattern of foot placement might help DPN-subjects to compensate for sensorial losses and avoid tripping. Additionally, this attempt to adopt a safer gait pattern that leads to a lower variability may indicate that the system is responding in a more stereotypical way, apparently less capable of adapting to perturbations [17] and still predisposing subjects to tripping. These alterations are probably consequences of both DPN and the lower walking speed observed in these subjects. It is important to note that the reduction in gait velocity is one of the most typical and more frequently described biomechanical alterations in diabetes and DPN [19], thus one should take into account that the observed alterations in the variability pattern and in the speed will be coexistent in DPN-subjects during daily living activities.

The complexity of a biological system reflects its ability to adapt and function in a constantly changing environment, and this complexity arises from the interaction of structural units and regulatory feedback loops. Consequently, structural or functional alterations resulting from DPN would reduce the adaptive capacity of the sensory motor system [23]. The higher SaEn values of ToC trajectory in severe-DPN subjects showed a higher complexity of their systems. The loss of tactile and vibratory inputs to the motor system due to DPN likely cause an imbalance in the system. If the input is diminished, as in DPN, the number of responses that the system will output can be increased trying to target the goal of the task, reflecting the higher SaEn values.

Vaillancourt and Newell [24] postulated that the complexity of a biological system can either increase or decrease in the presence of a disease or aging depending on the intrinsic dynamic properties of the system and motor task demands. This statement is based on the knowledge that most definitions of complexity are driven by the operational consideration that this complexity relies on the number of system elements and their functional interactions. Therefore, it would depend on the number of structural components of the system and the existing coupling between them. Aging and disease can cause the loss of structural components of the system and/or change the coupling between the components. Additionally, increases in the number of structural components of the system and, consequently, increments in the coupling functions between these components might occur, increasing complexity. If we consider that DPN-subjects are using more attentional resources (cognitive inputs) to compensate for the reduced distal afferent information for controlling foot clearance during gait, then more structural elements and coupling functions would be employed to task execution. With this point of view, the observed higher complexity of severe-DPN subjects could also be expected and might represent an adaptive strategy during gait that, while solving mechanical demands, is not necessarily efficient. This motor strategy might also be a function of erratic levels of jerk at the joints, or increased joint stiffness, as observed in DPN [19] respectively.

The literature shows studies in which the use of more cognitive resources during the execution of a motor task led to increases in the complexity of the studied output. Donker et al. [25] showed higher SaEn and lower SD of the center of pressure in static posture in healthy young subjects performing a cognitive dual-task, but only when the eyes were closed—a condition where the sensorial input was diminished, and, therefore, the cognitive resources were required to compensate for this afferent reduction. Thus, it appears that the results observed in severe-DPN subjects in our study during walking – higher SaEn – may correspond to the use of more cognitive resources to control the foot-ankle complex trajectories, since this joint complex is more affected by DPN, although the trajectory of the whole lower limb might be affected as well.

Contrary to our expectations, DPN-subjects did not present a lower minimum ToC. Apparently, they cope with their sensorial and musculoskeletal deficits, such as reduced dorsiflexion range of motion [26] and reduced dorsiflexor force [27] and activation [18] which may lead to a lower toe clearance. Likely, they are compensating for this behavior with an increased participation of upper adjacent joints for safe foot clearance in swing phase [28]. However, severe-DPN subjects present a higher ToC trajectory complexity associated to a non-altered minimum ToC, showing that the disease affects the choice and implementation of adaptability strategies due to different mechanical demands. This higher complexity is likely due to a combination of reduced afferent information (tactile and vibratory sensations) and more cognitive inputs to deal with the mechanical challenges of the swing phase. At the same time, MiN subjects would respond in a more stereotyped way, since they showed a lower variability of ToC compared to controls as a result of their lower walking speeds. The fact that the subjects with severe-DPN did not show the same response as mild-DPN individuals, even though they also showed lower walking speeds, is probably due to a myriad of alterations that occur with the progression of the disease. Not only the sensitivity is gradually lost, with the progressive lack of tactile and vibratory sensitivity, and proprioception, affecting the inputs of the neuromuscular system, as the output of the system is affected. The motor dysfunction in DPN is a consequence of both motor neuron impairments [29], and alterations in the properties of the skeletal muscles. Additionally, the loss of motor axons and motor units cause collateral reinnervation and axonal sprouting [30], phenomes that are not able to keep pace with the rate of axonal loss, but also interfere with the output of the system, such as strength losses at the ankle joint [27] which in turn affects foot clearance. The augmented complexity in severe-DPN shows that the system is altered, even though the SeN group was not different from controls in the ToC trajectory variability. Complex measures as SaEn show hidden patterns that reflect the system dynamics that we do not see in linear measures.

This study has some limitations. We are aware that the chosen position for the marker on the metatarsal head lateral aspect in our study is not one of the common options used as representative of the toe clearance. Ever since, we used the same procedure across the subjects for comparison purposes, and, thus, we can rely on the between groups results. It is also important to acknowledge that the analysis of minimum of toe clearance results in this study are limited to the vertical trajectory of the marker on the first metatarsal head. When the ankle presents inversion or dorsiflexion, the marker on the toe will not represent the closest part of the foot to the ground. Further studies investigating the foot motion in all three planes of movements may be required. A further limitation of the study is that only one leg per subject was assessed.

In conclusion, severe-DPN subjects showed a more complex pattern of overall foot-ankle trajectory in swing phase in comparison to controls, although did not present lower minimum foot clearance values. The higher complexity of ToC might lead to an increase in the motor system output (more strategies), resulting in a more unstable system, which in turn might make DPN-subjects more prone to tripping and falling. The higher complexity of ToC also shows that severe-DPN subjects may rely more on cognitive resources while controlling the lower limb trajectory, especially the foot-ankle complex, during the swing phase of gait, making this task less automatic. Thus, rehabilitation approaches should take into account that the control of the foot-ankle trajectory is likely more complex and dependent on cognitive resources in severe-DPN subjects.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

This study was supported by São Paulo Research Foundation (FAPESP, 2017/15449-4&2016/17077-4) and by the Brazilian National Council for Scientific and Technological Development (CNPq, 304124/2018-4).

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