Gait & Posture 58 (2017) 72–77

Contents lists available at ScienceDirect

Gait & Posture

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

Full length article

Gait alterations in the UAE population with and without diabetic complications using both traditional and entropy measures

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ARTICLE INFO

Keyword:
Type 2 diabetes
Diabetic foot
Plantar pressure
Human gait
Non-linear dynamics
Gait entropy
Diabetic peripheral neuropathy

ABSTRACT

Diabetic foot, one of the most common and debilitating manifestations of type 2 diabetes mellitus (T2DM), is the leading cause of worldwide non-traumatic lower extremity amputations. Diabetics who are at risk of ulceration are currently mainly identified by a thorough clinical examination of the feet, which typically does not show clear symptoms during the early stages of disease progression. In this study, we used a non-linear dynamics tool, gait entropy (GaitEN), in addition to traditional linear gait analysis methods, to investigate gait alterations amongst diabetic patients with combinations of three types of T2DM related complications: retinopathy, diabetic peripheral neuropathy (DPN) and nephropathy. Peak plantar pressure (PPP) was not significantly different in the group with DPN as compared to the control group (diabetics with no complications, CONT) in the forefoot region (DPN: mean ± SD: 396 ± 69.4 kPa, CONT: 409 ± 68.9 kPa), although it was significantly lower in the heel region (DPN: mean ± SD: 285 ± 43.1.4 kPa, CONT: 295 ± 61.8 kPa). On the other hand, gait entropy was significantly lower for the DPN compared to CONT group (DPN: 0.95 ± 0.34, CONT: 1.03 ± 0.28, $p < 0.05$). The significant low entropy was maintained when neuropathy was combined with either retinopathy or nephropathy. For the group with all three complications (ALL-C), the entropy was higher than CONT (ALL-C: 1.07 ± 0.26). This may indicate an intrinsic sensorimotor feedback mechanism for the DPN patients to regulate their gait. However, this feedback gets weaker as patients develop multiple complications. Further analysis with longer walking time and different speeds is needed to verify the entropy results.

1. Introduction

Diabetic foot, one of the most common and debilitating manifestations of type 2 diabetes mellitus (T2DM), is the leading cause of worldwide non-traumatic lower extremity amputations ensuing major medical, social and economic costs [1]. Statistics show that every 20 s a limb is lost as a result of T2DM and that more than 60% of all amputations occur in T2DM patients [1]. In the US alone, diabetes contributes to approximately 80% of the 120,000 nontraumatic amputations performed yearly and more than $130 billion are spent in direct and indirect costs. Statistics from the Health Authority Abu Dhabi (HAAD) show that one in five diabetics in the UAE, who develop foot ulcers, eventually needs limb amputations and that diabetic foot ulcers continue to be a major cause of morbidity leading to an amputation rate of 19% annually [2].

While ischemia, neuropathy and infection, are often present together as an etiological triad that typically leads to diabetic foot complications, biomechanical alterations associated with gait in T2DM neuropathy patients are believed to also play an integral role, although the mechanisms are not yet well understood [3].

Diabetic peripheral neuropathy (DPN), is characterized by damage to the peripheral nervous system resulting in reduced peripheral sensibility, and hence compromising the proprioceptive control feedback of human locomotion [4]. DPN affects sensory, motor and autonomic nerves and leads to progressive impairment of both the somatosensory and motor control systems, therefore decreasing the amount and quality

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http://dx.doi.org/10.1016/j.gaitpost.2017.07.109
Received 23 May 2016; Received in revised form 12 July 2017; Accepted 20 July 2017
0966-6362/ © 2017 Published by Elsevier B.V.

of sensory information that are critical for the complexity of gait generation and control [4].

Gait in patients with diabetes has recently emerged as a research area of great interest with over 900 publications in 2015 mostly emphasizing falls and foot ulceration [5]. Based on the literature, impaired gait in diabetics is multifaceted and typically attributed to a complex interplay of sensory impairment (impaired vibration and protective sensation), decreased lower-extremity strength, mobility, force-producing capacity, as well as central nervous system dysfunction [6]. Gait alterations in diabetic patients have been reported in terms of lower limb kinematics, kinetics, ground reaction forces, plantar pressure distribution, and EMG alterations [6–8]. Various studies have also explored the impact of DPN on postural stability as evaluated by measures of the center of pressure [9]. Monitoring of spatiotemporal parameters, intra-limb moments distribution and lower limb kinematics in T2DM patients revealed continuous alterations that may start before the development of DPN [10,11].

While there is abundant literature on gait alterations associated with T2DM, there continues to be several unresolved paradigms and unanswered questions. In particular, quantifying the role and degree of dynamic gait changes associated with various types of neuropathy complications remains unclear [12]. For example, most studies investigating diabetic gait have focused on DPN, despite evidence of disturbed gait occurring with other diabetic complications, such as nephropathy, cardiac autonomic neuropathy, vasculopathy, and retinopathy [6,8,13]. Furthermore, although certain parameters such as Peak plantar pressure (PPP) and peak pressure gradient (PPG) have been shown in literature to be associated with the development of diabetic foot ulcers, their contribution to the pathogenesis of these ulcers is still not well defined [14]. From a clinical perspective, routine clinical assessment of diabetic patients at risk of foot ulcerations, with or without neuropathy complications, is currently based on visual clinical examination and does not rely on any quantifiable and/or reproducible biomechanical-based parameters, despite the established strong associations between such parameters and the formation of ulcers.

Human gait is complex in nature, where gait attributes are typically characterized by nonlinearity, non-stationarity, asymmetry, and multiscale variability [15]. Various nonlinear dynamic techniques have been recently proposed to study the complex and irregular dynamics of gait that cannot be captured with conventional linear signal processing methods.

In the field of nonlinear dynamics, entropy is a measure that quantifies the irregularity of a system. The more predictable a signal is, the lower its entropy value. Normal biological signals exhibit high entropy values, reflecting the complexity and unpredictability of their associated systems, which is indicative of their integrity. On the other hand, signals associated with aging as well as various pathological systems tend to show reduced irregularity or less complex and more predictable system behavior, an indication of less adaptive and hence potentially pathological systems. Sample entropy (SamEn) has been previously applied to study variability in different biological and physiological signals including gait [15]. Recently, Karmakar et al. have used SamEn to study the relationship between minimum toe clearance and fall risk [16]. Their results demonstrated that SamEn is significantly different between healthy elderly and elderly with a history of trip-related falls, although no significant differences were detected among healthy subjects in different age groups. Mei et al. used SamEn to investigate the center of pressure (COP) irregularity between the normal foot and 3 types of feet with anatomical abnormalities. They concluded that SamEn could serve as a dependable measure for the evaluation of foot types and/or the selection of appropriate footwear [17].

The purpose of this study was to use conventional gait measures (gait speed, step length and width, PPP magnitude and location), as well a nonlinear dynamic measure using SamEn (hereafter, Gait entropy: GaitEn) to study gait alterations associated with different types of diabetic complications, including DPN, nephropathy, and retinopathy. To the best knowledge of the authors, this is the first study that uses entropy to quantify neuropathy-induced gait dysfunction and includes assessment of entropy associated with additional diabetes associated comorbidities.

2. Materials and methods

2.1. Subjects

As part of a randomized study, subjects were recruited from endocrinology and cardiology clinics at local hospitals in Abu Dhabi, UAE. Inclusion criteria comprised consenting UAE born Nationals above 18 years old, diabetic patients with and without complications, with walking ability, no history of ulcers, no current ulcers, and no history of orthopedic problems, lower limb surgery, or cardiovascular disease. The patients' feet were examined for skin lesions, bone deformations, ulcerations, and any signs of infection. 211 (136 females and 75 males) unrelated diabetic patients participated in the study. Each volunteer received a briefing session and signed an informed consent form that was approved by the Institutional Ethics Committee (REC-04062014 R292). The age mean ± standard deviation (SD) of the patients was 56.0 ± 10.6. Clinical assessment for each participant was completed at the clinic. T2DM and complication(s) diagnosis were confirmed by a qualified physician, based on the criteria outlined by the World Health Organization (WHO) consultation group report [18]. A patient was diagnosed with DPN if they presented with (1) foot ulcers, (2) loss of sensation/numbness/burning/tingling in the feet, (3) loss of toe, foot or leg due to diabetes, (4) pain in calf muscles while walking, or (5) peripheral vascular disease in legs [19]. The presence of nephropathy was determined by urine albumin level higher than 20 μg/min for microalbuminuria and higher than 200 μg/min for macroalbuminuria or if the Estimated Glomerular Filtration Rate (eGFR) was less than 60 ml/min/1.73 m^2. Retinopathy was defined as either white or red lesions or both present in the retina according to WHO criteria [20].

The patients in this study were categorized into 8 different groups: 1) ALL-C group, which includes all patients with retinopathy, nephropathy and DPN; 2) RNp, which includes patients with retinopathy and nephropathy; 3) NNp, including all patients with DPN and nephropathy; 4) RN, including all patients with retinopathy and DPN; 5) DPN, including all patients with DPN; 6) R, including all patients with retinopathy; 7) Np, including all patients with nephropathy; and 8) a control group (CONT), which includes all patients with none of the three complications. The demographic data for these groups is presented in Table 1.

2.2. Data collection and processing

The patients walked with their normal speed on an instrumented gait assessment system, (Walkway, Tekscan Inc., MA) during two trials. Each trial included a minimum of 3 steps per foot. The Walkway system captured the spatial distribution of the plantar pressure per step at a rate of 30 frames per second and computed the main spatiotemporal parameters of gait, including step and gait time, distance, velocity, and cadence. An in-house Matlab code was created to extract the magnitude and the normalized (x,y) position of the PPP in the heel and forefoot regions per step as depicted in Fig. 1. Position normalization was performed for all the data in order to account for inter-subject variations in foot length. The mean of these features along with the steps were compared between the CONT group and each of the neuropathy complications groups. The other spatiotemporal features selected for analysis were: gait velocity, step length, and step width based on literature.

2.3. GaitEn computation

The mean plantar pressure as a function of the gait cycle was

Table 1
Demographic Data for the Patient Groups.

Clinical Variables	CONT (58)	ALL-C (15)	RNp (18)	NNp (7)	RN (33)	DPN (17)	R (54)	Np (9)
Age	53 ± 11	61 ± 14*	60 ± 7.5†	56 ± 13	58 ± 7.2*	52 ± 11	57 ± 9.7*	55 ± 13
DM years	8.8 ± 6.6	17 ± 6.9†	17 ± 9.8†	17 ± 5.7†	15 ± 7.7†	14 ± 8.1†	12 ± 6.7*	12 ± 8.9
BMI	32 ± 6.7	31 ± 5	34 ± 7.2	32 ± 5.2	33 ± 5.8	32 ± 6.2	33 ± 6.9	30 ± 6.3
Weight (kg)	82 ± 18	78 ± 17	87 ± 20	86 ± 21	82 ± 18	86 ± 20	82 ± 17	81 ± 22
Height (m)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
hba1c (%)	7.7 ± 1.9	7.7 ± 1.6	7.5 ± 1.0	7.1 ± 1.5	8.1 ± 1.9	8.2 ± 1.7	7.7 ± 1.5	6 ± 1.9

Clinical Variable abbreviations: 1) DM years: years of Diabetes Mellitus, 2) BMI: Body Mass Index, 3) HbA1c: Glycated Hemoglobin Level. Patient group abbreviations: 1) CONT: control group, 2) ALL-C: patients with retinopathy, neuropathy, and nephropathy. 3) RNp: patients with retinopathy and nephropathy, 4) NNp: patients with neuropathy and nephropathy, 5) RN: patients with retinopathy and neuropathy, 6) DPN: patients with neuropathy, 7) R: patients with retinopathy, 8) Np: patients with nephropathy. Values are presented in mean ± SD. Numbers in brackets represent number of patients in each group. †,*: significantly different from CONT ($p < 0.01$, $p < 0.05$ respectively).

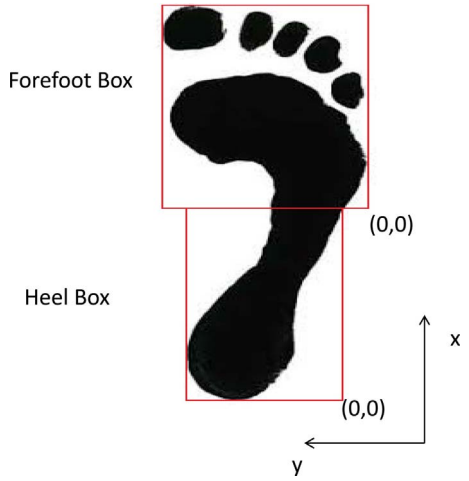


Fig. 1. Forefoot and heel boxes of the foot. In each box, the PPP magnitude and normalized x and y positions from the origin of the box are determined.

computed by the software. The pressure waveform during the stance phase of the gait cycle was truncated and concatenated to form a continuous wave for each of the right and left foot (Figs. 2 and 3). GaitEn of the difference between the right and left waveforms was then calculated (r = 0.25*SD and m = 2). Only waveforms with N > 100 were used, where N is the number of points in the waveform.

2.4. Statistical analysis

The Lilliefors test of normality was performed on all features to assess normal distribution. A Kruskal-Wallis nonparametric test of variance was also performed to test for the significance of the demographic data between the CONT group and each of the other 7 groups. We used a parametric analysis of covariance (ANCOVA) to correct for the age and years of diabetes and test feature significance between the CONT group and each of the other groups with complications. A non-parametric ANCOVA (Quade test) was used when the assumptions for the parametric ANCOVA were violated [21]. Spearman's correlation tests were performed between the PPP magnitude and location, GaitEn, as well as the remaining spatiotemporal features, including gait velocity, step length and width.

3. Results

The subject group consisted of 153 T2DM patients who were diagnosed with retinopathy, DPN, nephropathy, or combinations of these three complications (ALL-C), and 58 T2DM patients with no complications (CONT). Table 1 summarizes the clinical variables measured in the different patient groups in this study. Significant differences in the demographic variables (using the Kruskal-Wallis test) were observed in both age and DM years. Age was significantly lower in the CONT group as compared to ALL-C, RNp, RN, and R groups. DM years was significantly lower in the CONT group as compared to all groups except for Np. None of the other demographic data differed significantly as compared to the CONT group.

To correct for any confounding, we applied ANCOVA and included Age and DM years as covariates in the model. The results are shown for PPP, spatiotemporal parameters and GaitEn (Table 2). The PPP in the heel region was significantly higher in the CONT group as compared to ALL-C, RN, R, and DPN groups, but significantly lower than RNp. The PPP in the forefoot region was significantly higher in the CONT group as compared to all groups except for DPN and Np. The PPP normalized x position in the heel region was significantly higher in the CONT group as compared to ALL-C, RNp, RN, NNp and R, but significantly lower than DPN.

The gait velocity was significantly higher in the CONT group as compared to all groups except for Np. The step length was significantly longer for the CONT group as compared to all groups except for NNp and Np. No significant differences were found between the CONT group

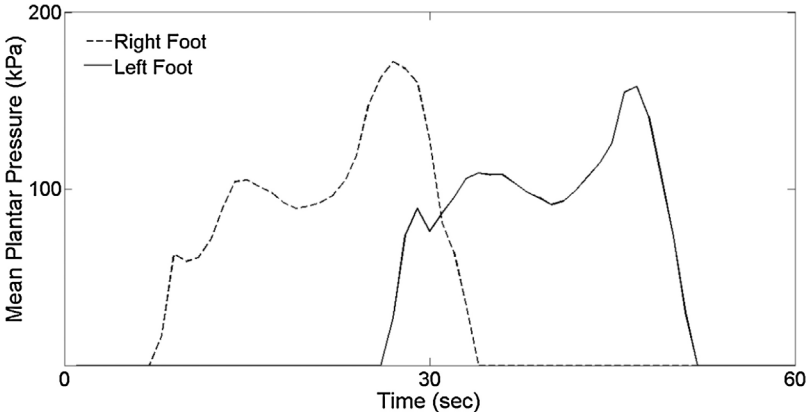


Fig. 2. Mean Plantar Pressure for the right and left foot during stance phase.

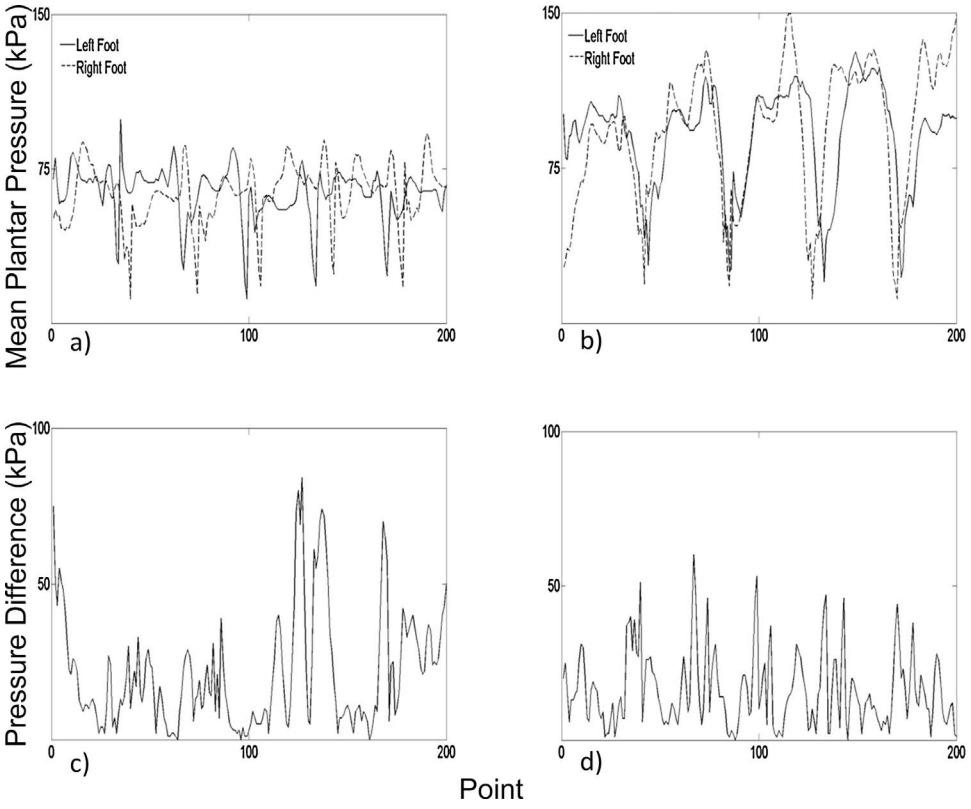


Fig. 3. Examples of the concatenated mean plantar pressure in the right and left foot for a a) CONT subject and b) a subject from the DPN group and the pressure difference between right and left feet for the same subjects c), d).

and any of the other groups in step width. GaitEn was significantly higher in the CONT group as compared to all groups except for ALL-C and Np.

The correlation analysis showed significant correlation between the PPP in the forefoot region (PPP_Ffoot) and both the gait velocity and step length for the CONT group ($p < 0.01$, $p < 0.05$ respectively), but no significant correlation was found in all the groups with complications. Furthermore, no significant correlation was found between the PPP normalized position or GaitEn and the spatiotemporal parameters for any of the patient groups.

4. Discussion

Diabetic foot remains one of the most serious complications of T2DM. The vicious cycle of gait alterations increasing the risk of foot ulcers, which when combined with pathological biomechanical and tissue changes, instigates further gait dysfunction is well known [4]. On the other hand, routine clinical assessment of diabetic patients at risk of foot ulcerations, with or without neuropathy complications, continues to be based on visual clinical inspection despite the numerous studies that have shown potential useful biomechanically-based parameters that may enhance the diagnostic process.

Moreover, while it is well established in literature that DPN impairs the somatosensory and motor control systems, which in turn affects gait generation and control [6], much less information is known regarding the effect of other diabetic complications and/or a combination of complications on gait. This study examined the effect of a number of diabetic complications and their combinations on gait parameters towards the identification of biomechanical markers that could predict the risk of gait anomalies before the onset of clinically detectable neuropathy and diabetic comorbidities (particularly during early asymptomatic or mild symptomatic stages). Both conventional gait measures (gait speed, step length and width, PPP magnitude and location), as well as a non-linear dynamic measure (GaitEn) were used to study gait alterations due to different types of diabetic complications, including DPN, nephropathy, and retinopathy.

Table 2
PPP Magnitude, Normalized Position in the Heel and Forefoot Regions, GaitEn, and Spatiotemporal Features for the Patient Groups.

Feature	CONT (58)	ALL-C (15)	RNp (18)	NNp (7)	RN (33)	DPN (17)	R (54)	Np (9)
PPP Heel (kPa)	295 ± 61.8	274 ± 41.9†	298 ± 75.3*	297 ± 53.5	286 ± 68.3†	285 ± 43.1*	281 ± 52.6*	288 ± 76.3
PPP Ffoot (kPa)	409 ± 68.9	370 ± 66.7†	375 ± 76.7†	347 ± 47.9†	370 ± 93.4†	396 ± 69.4	390 ± 75.5*	372 ± 112
PPx Heel	0.36 ± 0.1	0.36 ± 0.07*	0.33 ± 0.07†	0.35 ± 0.13*	0.33 ± 0.08†	0.37 ± 0.1*	0.35 ± 0.08*	0.32 ± 0.1
PPy Heel	0.71 ± 0.1	0.77 ± 0.07	0.76 ± 0.07	0.75 ± 0.12	0.76 ± 0.08	0.73 ± 0.1	0.75 ± 0.08	0.72 ± 0.12
PPx Ffoot	0.59 ± 0.13	0.57 ± 0.14*	0.60 ± 0.13	0.57 ± 0.13	0.61 ± 0.11	0.62 ± 0.12	0.6 ± 0.13	0.55 ± 0.14
PPy Ffoot	0.63 ± 0.12	0.63 ± 0.16	0.63 ± 0.12	0.66 ± 0.15	0.63 ± 1.0	0.63 ± 0.1	0.63 ± 0.13	0.55 ± 0.14
GaitEn	1.03 ± 0.28	1.07 ± 0.26	0.9 ± 0.23†	0.9 ± 0.36*	0.89 ± 0.21†	0.95 ± 0.34*	0.90 ± 0.20†	0.92 ± 0.18
Gait velocity (cm/s)	64 ± 13	58.5 ± 18.5†	56.5 ± 11.4†	51.9 ± 18.5†	62.5 ± 13.7†	57 ± 13†	61 ± 14†	64 ± 24
Step length (cm)	44 ± 6.2	39.6 ± 9.8†	39.1 ± 6.7†	52.5 ± 19.4	42.5 ± 7.3*	42 ± 5.6*	42 ± 6.1*	43 ± 11
Step width (cm)	8.6 ± 3.4	9.1 ± 2.8	9.3 ± 2.9	11.2 ± 3.3	9.5 ± 2.9	8.3 ± 2.6	9.6 ± 2.9	10 ± 3.2

Feature abbreviations: 1) PPx Heel: normalized PPP x position in the heel region, 2)PPy Heel: normalized PPP y position in the heel region, 3) PPx Ffoot: normalized PPP x position in the forefoot region, 4) PPy Ffoot: normalized PPP y position in the forefoot region. 5) GaitEn: Gait entropy. Values are presented in mean ± SD. Numbers in brackets represent number of patients in each group. †,*: significantly different from CONT ($p < 0.01$, $p < 0.05$ respectively).

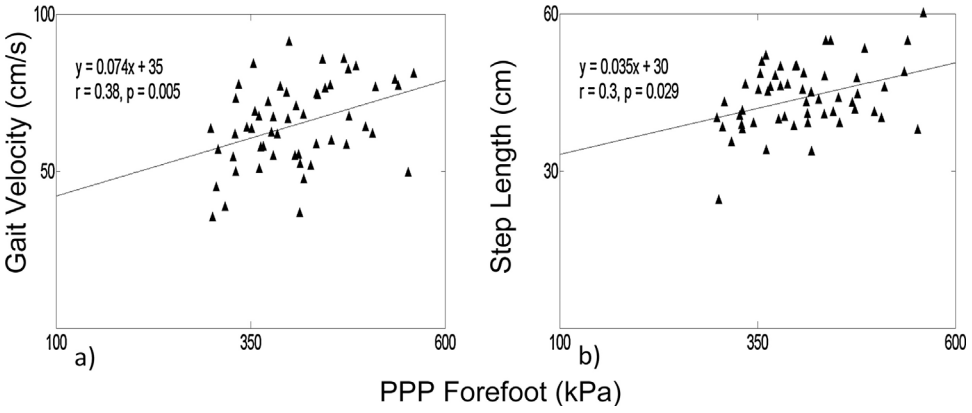


Fig. 4. correlation between PPP Forefoot and gait velocity (a) and step length (b) for CONT group.

Our results for the gait velocity and step length are consistent with previous research, where patients with DPN were shown to have slower gait velocity and shorter stride length as compared to T2DM control patients [13]. In agreement with other studies, we also observed that the gait alterations investigated here, as associated with diabetic complications other than DPN, seemed more linked to the type of complication and the sensitivity of the test rather than any sensory loss [22]. This confirms the theory that diabetic patients may develop gait dysfunction/alterations well before the loss of sensory information from the feet. The quantitative reduction in spatiotemporal gait parameters, therefore, reflects more conservative gait patterns as an adaptive compensatory mechanism for the pathology in the proprioceptive system. In other words, the alteration in gait is not only due to the reduced peripheral sensory information available to the local peripheral system and by extension to the central nervous system, but also because of the increased attentional demands necessary for controlling and regulating gait complexity [23].

Our results demonstrate that the PPP was significantly higher in the control group as compared to most of the groups in both the heel and forefoot regions (Table 2). This is in contradiction with some studies that reported DPN patients having no significant difference in PPP from DM patient with no DPN in the heel area and significantly higher PPP in the forefoot area [24,25]. This contradiction could be due to the higher gait velocity for the CONT group, which is known to influence the PPP [26]. The influence of gait speed on PPP for the CONT group is observed in the significant positive correlation between the gait speed and the PPP in the forefoot region ($p < 0.01$, Fig. 4(a)). In addition, sensor size and number associated with the walking platform can lead to different results in PPP between studies, as suggested previously [27]. Consistent with clinical signs of DPN, there is a significant reduction of the PPP in the heel due to the marked decrease in stride length observed in patients with DPN suggesting that measuring PPP in the heel may be a more useful risk indicator for future ulceration. Treatment such as callus removal also leads to lower PPP and this may have contributed to the lower PPP in the DPN group [27]. This study indeed confirms the challenges inherent to using peak plantar pressure variations for the assessment and prediction of diabetic foot ulceration. These results confirm the challenges inherent to using peak plantar pressure variations for the assessment and prediction of diabetic foot ulceration. Peak plantar pressure is obviously affected by the gait kinematics such as the speed. The variation in the PPP magnitude due to gait speed and several other factors renders it a nonoptimal indicator for DPN or foot ulceration [26]. Moreover, there is currently no standard or specific threshold of PPP that predicts the development of foot ulceration [28]. In fact, recent studies show that, as evidenced by the continuous high rate ulcer recurrence and amputation, PPP may not be an effective predictor of diabetic ulcer occurrences and/or recurrences [29]. Several studies found that foot ulcers do not necessarily occur at peak pressure sites but may occur at sites that experience normal pressure [12].

In our recent previous study we have shown that dynamic variation in PPP location using shape analysis can be used effectively to distinguish between DPN and diabetic patients with no complications [30]. In this study, we evaluated the mean PPP location, which provided additional information on changes in diabetic foot associated with DPN. Specifically, the significant difference in the location of the PPP in the heel region indicates a shift in the posterior direction of the PPP. This suggests an early heel strike, which is supported by the shorter step length found in the groups with diabetic complications. Classification of forefoot peak plantar pressure location and distribution has the potential to provide means for the quantification of the diabetic foot.

The high value of GaitEn in the CONT group as compared to other groups indicates more irregularity in the plantar pressure during the normal gait cycle. This is analogous to findings from different biological and physiological systems where healthy groups demonstrate more irregularity than groups with abnormalities [16]. Furthermore, since the GaitEn measure studied here showed no correlation with the other spatiotemporal features, as compared to the peak plantar pressure, which was highly correlated with gait speed, GaitEn may represent an intrinsic adaptation of the nervous system to control the gait due to the DM complications. Further work is needed to explore entropy measures and their value for quantifying diabetic gait towards the early prediction of ulcers.

Conflict of interest

The authors declare that there was no conflict of interest of any kind, including financial, associated with this manuscript.

Acknowledgments

We acknowledge the volunteers who made this study possible and contributions from nurses and students who helped acquire the gait data from the patients. This study was supported by research incentive funds from Khalifa University Internal Research Fund Level 2 granted to Dr. Habiba Al Safar.

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