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

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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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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