Original Article

Force Variability in the Short- and Long-Term Type 2 Diabetes Mellitus

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Abstract

Background: Force variability is related to many kinesiological and neuromuscular properties of the body. This study was conducted to evaluate the effect of type 2 diabetes mellitus (T2DM) and sex on the several fractal and entropy indices of force changing during the repetitive isokinetic exercise of knee flexion-extension. **Methods:** Fifty individuals were allowed to participate in the study, and they consist of 18 patients with short-term T2DM, 12 patients with long-term T2DM, and 20 gender/body mass index/ankle imposed to brachial pressure index and physical activity index-matched healthy control (HC) individuals. Torque of knee flexion-extension was recorded for each cycle of 40 isokinetic repetitions at a velocity of 150°/s. The slope across the peak of torques and nonlinear fractal and entropy features in the time series was calculated. Two-way univariate analysis of variance was used to analyze the effect of the groups and gender on the variables. **Results:** The slope of flexor peak torques was significantly less in the long-term T2DM than the other groups. However, the fractal features such as SD1 and 2 of Poincare plot and fractal dimension katz were significantly decreased in the T2DM groups than the HC and in the women than men. Alpha detrended fluctuation analysis and empirical hurts exponent increased in women of short-term T2DM than men. **Conclusion:** The force variability decreased in the T2DM as compared to HC and in women as compared to men. However, the randomness of force was significantly increased in women of short-term T2DM.

Keywords: *Force variability, isokinetics, nonlinearity, type 2 diabetes mellitus*

Introduction

The muscle activity has a nonlinear pattern along the range of motion.[1] There are several hypotheses on the reason of variability in the motor system. A prominent theory is the Generalized Motor Program Theory that suggested the error in the prediction of the motor program causes variation in a movement pattern. Another prominent theory is the uncontrolled manifold. Motor variability has been associated with motor redundancy. Motor redundancy is the result of the existence of multiple solutions to a given motor problem. The third theory is the dynamical systems theory which proposes that biological systems are self-organized according to environmental, biomechanical, and morphological constraints to find the most stable solution for producing a given movement. Based on these theories, the motor control limits the variability to generate more efficient execution of a given movement pattern and show a highly stable behavior.[2] Out of the optimal variability, less variability occurs more in several pathologies such as Parkinson disease. A decrease in the optimal performance of motor control to produce controlled motions and forces promotes rigidity. The principle of optimality in movement variability relates in an inverted U-shape between the chaotic temporal variations in the steady state and the concept of predictability in a healthy biological system. Decrease in variability renders the system more predictable and rigid of motor behavior[3] or more randomness and noisy as compared to the healthy state.[4] Several nonlinear methods have analyzed the variability in the motor system. Most of them evaluate the kinematics of gait.[2,5]

During the repetitive isokinetic exercise, the output work by limb decline and the fatigue can be created.[6] Whenever the isokinetic exercise is limited in the determined range and velocity, the amount of produced force is always in the chaotic and nonrepetitive pattern[1] and fatigue influences the variability of muscle activity.[7] In the case of motor system control, the force produced

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with muscles and the pattern is too nonlinear and this is affected by condition[8] and disease.[2,9]

Type 2 diabetes mellitus (T2DM) impairs the insulin sensitivity, metabolic flexibility, and muscular and neuromuscular function. The muscle weakness and loss of its quality, especially in the lower limbs, are observed in the T2DM. Strength reduction has been associated with increased neuropathy and glycated hemoglobin (HbA1c) and a longer duration of diabetes.[10-17] The endurance response of diabetic muscles is different from the healthy ones. Hatef *et al*.[15,18] showed that the weakness increased with more years of diabetes; however, the short-time endurance of long-term T2DM is better than the short-term T2DM even health control. The study of muscular changes in the T2DM provide useful information about the identification of muscle function and role of insulin in the muscle activity and finally design of exercise program for control of diabetes.[19]

There is no study on the variability of force change during repetitive isokinetic exercise in the fatigue protocol in the T2DM. The aim of this study was to assess the effect of T2DM and sex on the many fractal and entropy indices of force changing during the repetitive isokinetic exercise of knee flexion-extension.

Materials and Methods

Subjects

The study was a case control. A total of 30 T2DM patients under medication were recruited. The inclusion criteria were age between 25 and 70 years, no intermittent claudication, no foot ulcers, no uncontrolled cardiovascular disturbance diagnosed by a specialist, no acute knee arthritis, and ABI between 0.9 and 1.5. Patients were classified based on the duration of diagnosed diabetes into two groups, 18 patients with <10 years of disease were introduced as the short-term T2DM group and 12 patients with equal or more than 10 years of the disease were introduced as the long-term T2DM group. The HC group comprised 20 individuals that matched regarding sex, body mass index (BMI), ABI, and physical activity index (PAI) with the two T2DM groups. The HC group had the HbA1c <6%. Written informed consent was obtained from all participants, and the protocol was approved by the Medical Ethics Committee of the Tarbiat Modares University.

Procedure

HbA1c and fasting blood sugar (FBS) by the blood sample and ABI by Doppler ultrasound in the supine position from the dominant leg were measured in all participants. The method of measurement of the ABI and PAI score was earlier explained.[17]

Isokinetic protocol

Repetitive concentric of knee extension/flexion was performed with an isokinetic dynamometer (HUMAC NORM, USA) for the dominant leg which was determined by the leg preferred for kicking a ball. The instruction and procedure of the study were explained in the previous articles.[17] For familiarity, participants did five trials of submaximal isokinetic of knee extension and flexion between 0° and 75° range in the knee flexion. After 2 min of rest, they were instructed to push and pull "as hard and fast as possible" through the full available ROM at all 40 repetitions without holding their breath and resting. Their heart rate was controlled during the protocol with a finger heartbeat controller device attached to the middle finger of the opposite hand.

Data analysis

The isokinetic instrument was used to record the amount of torque in each sample rate of 100 point/s for 40 repetitions of knee flexion and extension [Figure 1]. The amount of peak torque (Newton meter) per repetition was calculated using the software of isokinetic instrument. The peak torque of 40 repetitions was normalized to maximal peak torque and the slope of the best fit line across these 40 points was measured.[20] The slope was calculated for knee extension and flexion separately. The nonlinear features were extracted from torque in the time series. First, the phase space for torque data in the time series (X) was calculated [Figure 2]. Then, SD1 and SD2 of Poincare plot, fractal dimension (FD) KATZ, correlation dimension, sample entropy, approximate entropy, alpha 4000 detrended fluctuation analysis (DFA), and empirical Hurst exponent were calculated.

Poincaré plot

Poincaré plot is a return map which represents qualitative visualization of the biomedical signal. SD1 and SD2 represent the visual inspection of time series dispersion. SD1 is related to quick changes in data and SD2 is related to long-term changes in data. SD1 and SD2 are minor and major medial axes of fitted ellipse that actually come from the correlation [Figure 3]. More SD represents less self-similarity in the data set.[21-23] SD1 and SD2 are defined in Eqs. 1 and 2:

$$SD1 = \frac{\sqrt{2}}{2} SD(X_n - X_{n+1}) \quad (1)$$

$$SD1 = \sqrt{2SD(X_n)^2} - \frac{1}{2} SD(X_n - X_{n+1})^2 \quad (2)$$

Where SD is a standard deviation of the time series.

Katz's fractal dimension

The FD measures the rate of addition of structural details with increased magnification, scale or resolution, and quantifier of complexity. Katz's FD of the waveform shows the time series signal defined as in Eq. 3:

$$(R/S)_m = \frac{1}{d} \sum_{n=1}^{d} A_n \quad (3)$$

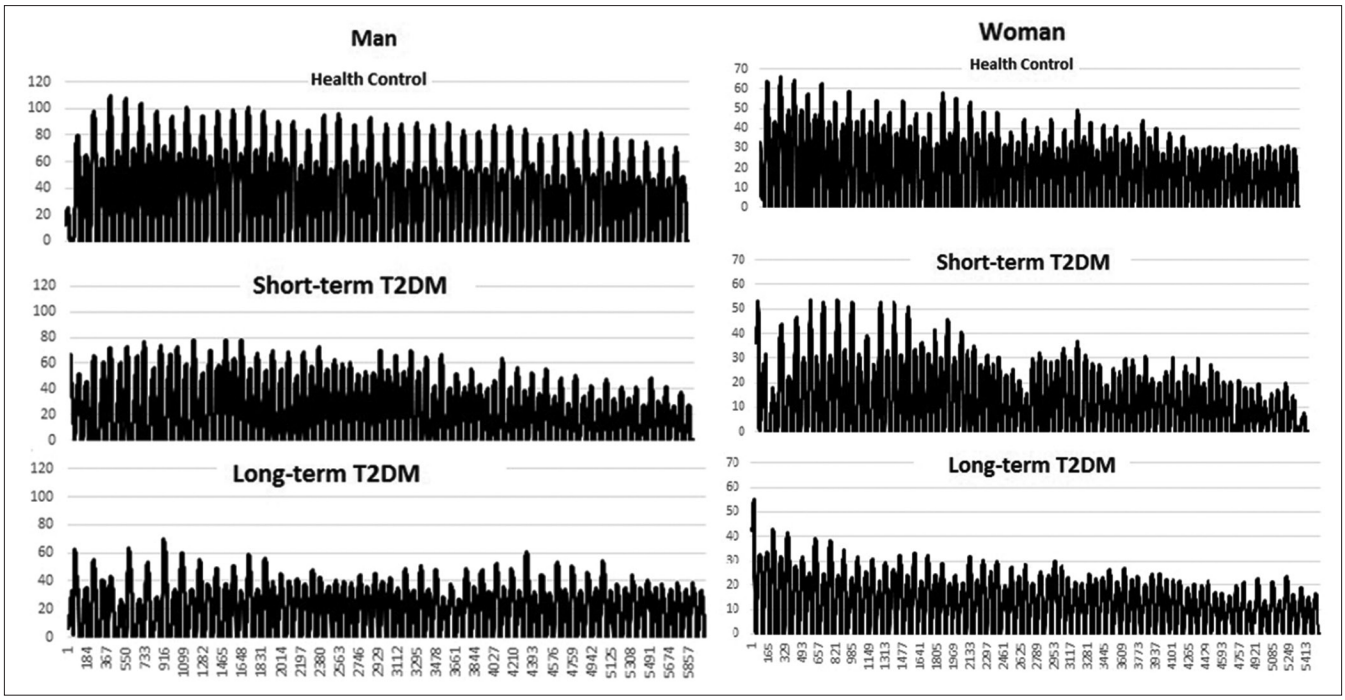

Figure 1: The recording torques of 40 isokinetic knee extension-flexion in the two genders and three groups (healthy control, short-term type 2 diabetes mellitus, long-term type 2 diabetes mellitus)

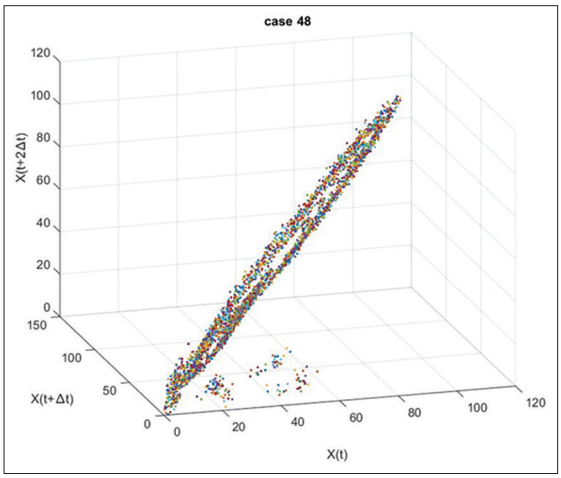

Figure 2: Phase space diagram in three dimensions of the time series signal X of case 48. Δt is the step time

Where L is the total length of the time series, d is the distance from the first point and the point, which is the largest distance from the first point in the time series. A is the average step or average distance between successive points, and $n = L/a$, n is the number of steps in the waveform.[24]

Detrended fluctuation analysis

DFA is a method used to quantify correlation in time series and is defined as in Eqs. 4 and 5:

$$y(k) = \sum_{i=1}^{k} (X[i] - X_{avg}) \quad (4)$$

Where the X(i) is the ith data of time series and X_{avg} is the average data and it is calculated as:

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}(y[k] - y_n[k])^2} \quad (5)$$

Where N is the total length of the time series. Then, α is calculated using the line relating log $F(n)$ to log n. For clinical application, α indicates over two different time. One short α1 and one long α2, as shown in Figure 4.[25] In this paper, α1 is considered for the analysis and 40 windows in DFA method.

R/S analysis for empirical hurst exponent

To investigate the long-term memory in a time series signal, hurst exponent by R/S analysis method was used:[26] the signal $(X_k)_{k\in\overline{1,N}}$ is divided into d sub-series. Per sub-series $n = 1,\ldots, d$. Then Z_{in} is defined as in Eq. 6 to:[12]

$$Z_{in} = X_{in} - E_n, \; i = 1,..., m \quad (6)$$

Where E_n is the average of sub-series. Then, Y_{in} is defined as:

$$Y_{in} = \sum_{j=1}^{i} Z_{jn}, \; i = 1, ..., m \quad (7)$$

the range of Y_{in} is calculated as:

$$R_n = \max Y_{jn_{j=\overline{1,m}}} - \min Y_{jn_{j=\overline{1,m}}} \quad (8)$$

Rescaling it to:

$$E(R/S)_n = \begin{cases} \frac{n-\frac{1}{2}}{n} \frac{\Gamma\frac{n-1}{2}}{\sqrt{\pi\Gamma(\frac{n}{2})}} \sum_{i=1}^{n-1} \sqrt{\frac{n-i}{i}}, \; n \le 340 \\ \frac{n-\frac{1}{2}}{n} \frac{1}{\sqrt{n\pi/2}} \sum_{i=1}^{n-1} \sqrt{\frac{n-i}{i}}, \; n > 340 \end{cases} \quad (9)$$

Then, the average of rescaled range for subseries is calculated as:

$$(R/S)_m = \frac{1}{d}\sum_{n=1}^{d} A_n \quad (10)$$

with (R/S) scales by power-law as time increases, Hurst is calculated as:

$$(R/S)_t = c.t^H \quad (11)$$

Approximate or empirical (R/S) analysis is considered for some reasons like white noise:[27]

$$E(R/S)_n = \begin{cases} \frac{n-\frac{1}{2}}{n}\frac{\Gamma\frac{n-1}{2}}{\sqrt{\pi}\Gamma(\frac{n}{2})}\sum_{i=1}^{n-1}\sqrt{\frac{n-i}{i}}, n \le 340 \\ \frac{n-\frac{1}{2}}{n}\frac{1}{\sqrt{n\pi/2}}\sum_{i=1}^{n-1}\sqrt{\frac{n-i}{i}}, n > 340 \end{cases} \quad (12)$$

r is the Euler gamma function. The empirical H was calculated as 0.5 in addition to the slope of $(R/S)_n$ –$E(R/S)_n$ Figure 5 shows the empirical hurst exponent with R/S analysis for case 1.

Correlation dimension

If R is considered as a distance between data X = x_1,…, x_k, k∈N. Then CR is defined as in Eq. 13:

$$C(R) = \frac{1}{N(N-1)}\sum_{i=1}^{N}\sum_{j=1,j\neq i}^{N}\theta(R-|X_i - X_j|) \quad (13)$$

N is the data series and Θ is a Heaviside function. If a distance from x_j to x_i is R, the amount of x_j is 1; else one is to be zero. The curve of log *C* (*R*) in relation to log R is drawn. Then, the line is fitted to the data. The slope of this line is the correlation dimension [Figure 6].[28]

Sample entropy

Sample entropy is used to investigate the irregularity of the system.[28,29] At first, the present new form from time series $X = X_1,...,X_k, k \in N$ with embedding dimension m (calculated in this paper with False Nearest Neighbor method[30]) as: $Z^m = (Z_1^m, Z_2^m,..., Z_{N-m+1}^m)$, such that Z_i^m is equal to $(X_1, X_{i+1},..., X_{i+m-1}), i = 1,2,..., N-m+1$. Then, it is defined as: $B^m(r)$ which 5s the probability of Z_i^m similar

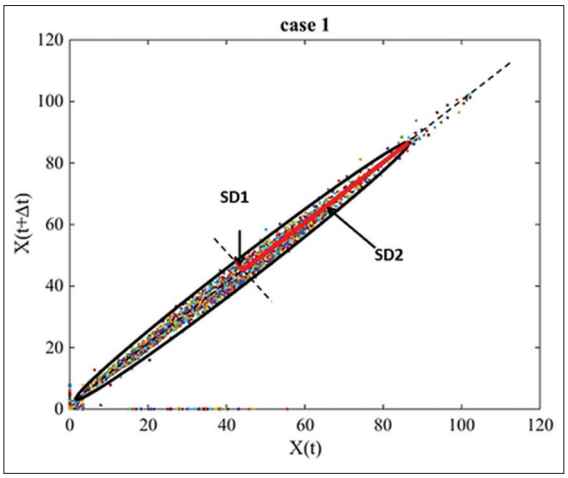

Figure 3: Poincare plot of case 1. SD1 and SD2 are minor and major of medial axes of fitted ellipse. Δt is the step time. SD1 = 2.8, SD2 = 31

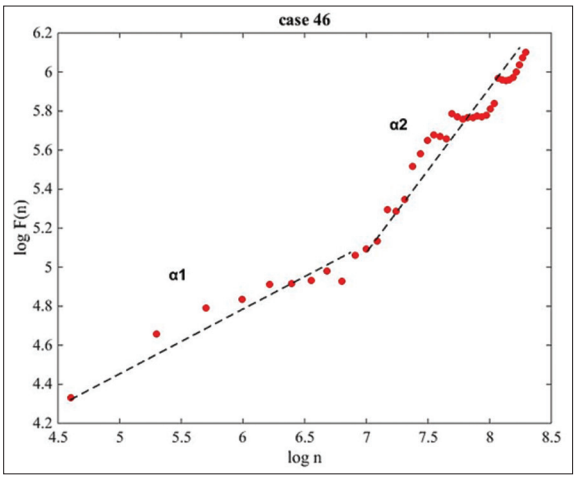

Figure 4: Plot of log F *(n)* versus log *n*. For time series signal of case 46. In this case α1 = 0.51

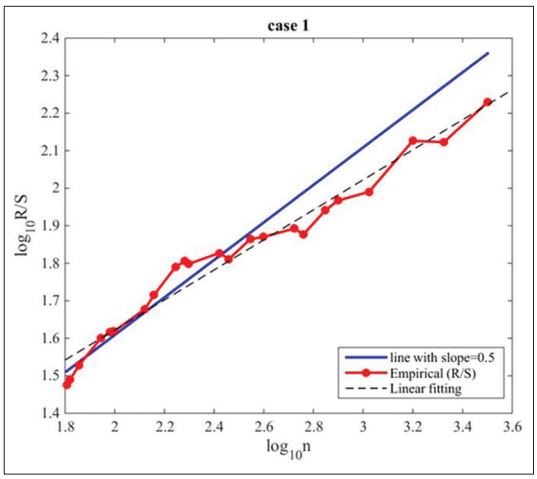

Figure 5: Is shown the empirical hurst exponent with R/S analysis for case 1. The slope of linear fitting for Empirical (R/S) shows empirical *H* = 0.4003

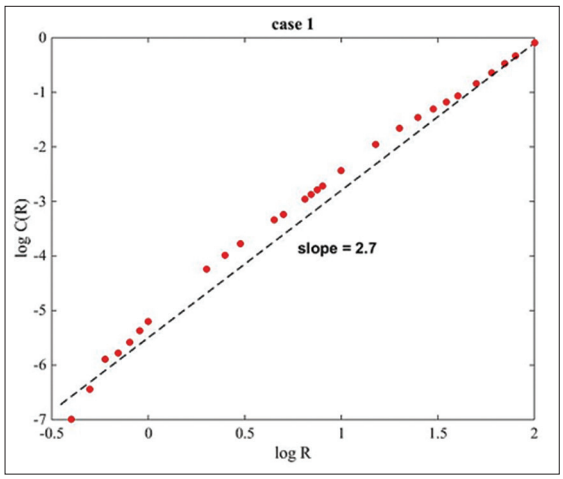

Figure 6: Plot log *C (R)* versus log *R*. The slope in the scaling region is correlation dimension of case 1. DC = 2.7

to Z_j^m in similarity tolerance r (r is tolerance for accepting matches):

$$\text{Similarity tolerance} = r \times (\text{standard deviation of set}) \quad (14)$$

To arriving at $B^m(r)$, follow these step:

Step 1:

$$d(Z_i^m, Z_j^m) = \max(|X_{i+k-1} - X_{j+k-1}|), k = 1, 2, ..., m \quad (15)$$

Step 2:

$$H(d[Z_i^m, Z_j^m]) = \begin{cases} 1 : d(Z_i^m, Z_j^m) \le r \\ 0 : d(Z_i^m, Z_j^m) > r \end{cases} \quad (16)$$

Step 3:

$$B_i^m I = \frac{1}{N-m-1} \sum_{j=1}^{N-m} H(d[Z_i^m, Z_j^m]), i \neq j \quad (17)$$

Step 4:

$$B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r) \quad (18)$$

In addition, if Z_i^{m+1} and Z_j^{m+1} follow the steps above and obviously $j = 1, 2, N - m$ and $i \neq j$, finally we have:

$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \quad (19)$$

At least, the sample entropy is:

$$\text{SampEn} = -\log \frac{A^m(r)}{B^m(r)} \quad (20)$$

Statistical analysis

Chi-squared was used to compare the distribution of sex and PAI and analysis of variance (ANOVA) was used to compare the age, weight, length, BMI, ABI, HbA1c, FBS and blood glucose test between the three groups. To assess the effect of the group (HC, short- and long-term T2DM) and sex in the slopes and nonlinear features, two-way ANOVA, and Tukey *post hoc* tests were used. $P < 0.05$ was considered as statistically significant.

Results

A total of 18 short-term T2DM patients, 12 long-term T2DM patients, and 20 sex-matched HC individuals were included in the study. Demographic and blood chemical analyses are shown in Table 1. T2DM patients with good-to-moderate blood glucose control were included in the study. Sex, BMI, PAI, and ABI were matched in the three groups. The long-term T2DM group was 10 years older than HC group ($P = 0.02$). HbA1c, FBS, and glucose tests of the two T2DM groups were not significantly different.

Two-way univariate ANOVA showed that the slope of knee flexion was significantly less in the long-term T2DM than other groups. This difference was observed in both sexes ($P = 0.001$) [Figure 7]. No significant difference was observed in the slope of extensor torque between groups and sex.

The result of two-way univariate ANOVA analysis in the fractal features showed that the patients had less

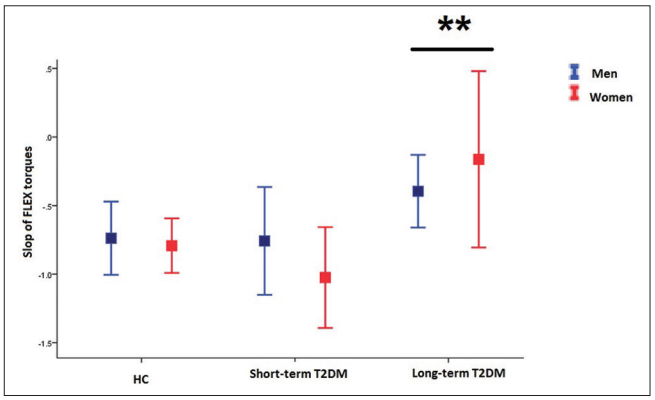

Figure 7: The error bar plot shows the slope of flexor torques during repetitive isokinetic exercise of long-term type 2 diabetes mellitus significantly less than two other groups (healthy control and short-term type 2 diabetes mellitus). **$P = 0.001$

Table 1: Demographic and blood characters of three groups and *P* value Source: Hatef B *et al.*[18]

	HC (n=19)	Short-term T2DM (n=18)	Long-term T2DM (n=12)	P
Number of cases (women/men)	20 (10/10)	18 (9/9)	12 (6/6)	1[#]
Age (years)	49.55±10	52.11±9.2	59.17±7.1	0.02*
Weight (kg)	73.68±7.7	77.61±12.5	77.72±12.4	0.47
Height (cm)	167.89±9.2	164.33±8.3	166.09±11	0.51
BMI	26.25±3	28.71±4.1	28.54±3.6	0.09
Duration of diabetes (years)		4.8±2	15.5±7	
Medication (insulin + drugs/drugs) (number of cases)		1/17	3/9	
PAI (sedentary/poor/fair) (%)	63.2/26.3/10.5	66.7/27.8/5.6	45.5/54.5/0	0.83
ABI	1.17±0.08	1.22±0.09	1.14±0.14	0.43
HbA1c (%)	4.7±0.8	7.02±1.5	7.3±1.4	0.000[†]
FBS (mmol/l)	91±12.6	141.65±36.9	160.91±31.4	0.000[†]
Blood sugar (mmol/l)	114.05±17.7	167.39±44.23	205.20±84.24	0.000[†]

Data are mean±SD[#]. **Post hoc* between health and long-term T2DM groups, [†]*Post hoc* between healthy and long-term T2DM and short-term T2DM groups. FBS – Fasting blood sugar; BMI – Body mass index; API – Physical activity index; ABI – Ankle-brachial index; HbA1c – Glycated hemoglobin; SD – Standard deviation; T2DM – Type 2 diabetes mellitus; HC – Healthy control

complexity than HC individuals and women had less complexity than men. SD1 and SD2 from Eqs. 1 and 2 of Poincare plot (effect of group: $P < 0.00001$, effect of sex: $P < 0.000001$) and FD katz from Eq. 3 (effect of groups: $P < 0.005$, effect of sex: $P < 0.00000$) of both sexes of the patients were significantly decreased as compared to HC group, and their amount in the long-term was significantly less than short-term T2DM. These features were significantly less in women than men. The amount of correlation dimension of the short-term T2DM was significantly less than the HC group (Tukey HSD pairwise comparison between HC and short-term T2DM: $P < 0.02$) [Figure 8].

The interaction effect between group and sex was seen in the alpha 4000 DFA and empirical Hurst exponent that get from R/S analysis ($P < 0.03$). Pairwise comparison of both groups and sex showed that the women were significantly more than the men in the short-term T2DM group [Figure 9]. The sample entropy from Eq. 20 did not show any significant difference between the groups; however, the women had more sample entropy than men ($P < 0.05$) [Figure 9].

Discussion

The aim of this study was to assess the variability of force during repetitive isokinetic flexion-extension of knee in both healthy and T2DM individuals. The results showed that diabetes decreased the complexity and increased the randomness in the variability of force produced by knee muscles especially in the women. The main findings were lower fractal complexity (katz, correlation dimension and SDs of Poincare plot) of diabetic groups as compared to HC group in both sexes. The katz FD and SD1 and 2 of Poincare plot of women were also significantly lower than men. The sample entropy, alpha of DFA, and empirical hurst exponent were higher in the women than men in the patients groups, and it was only significant in the short-term T2DM group.

The force variability in motion is defined based on the sarcomere length nonuniformity theory that explained the force variability depending on the joint angle, type of muscular contraction, and muscle orientation related to joint. In addition, the recruitment threshold and synchrony of motor units and firing rate of motor unit also change the force variability.[1] In the current study, whenever the muscles and type of motion used are the same, then the differences seen between groups might be due to the effect of T2DM on muscle morphology and function. On the other hand, the differences between genders could be as a result of different muscle properties. Previous studies have shown that the peak isometric and isotonic torques of knee flexion and extension, and the root mean square of knee flexors and extensors of T2DM patients are less than the HC group and women are less than the men.[31] Due to insulin resistance impairment, the muscle density reduces and muscle fibers transform to fast fibers type in T2DM gradually. Concurrently, the oxidative and glycolytic enzymes of all types of muscle fibers and the density of GLUT4 in the type 2 muscle fibers were increased.[32-34] Mitochondrial function was studied in the progressive aerobic exercise in patients who had T2DM for 6 years or more than 12 years. The short-term diabetes group had longer phosphocreatine recovery halftime than the BMI-matched healthy group. Intramyocellular lipid concentration content was only increased in the long-term diabetes group.[35,36] Then, the rapid fuel of diabetic muscles was raised gradually.

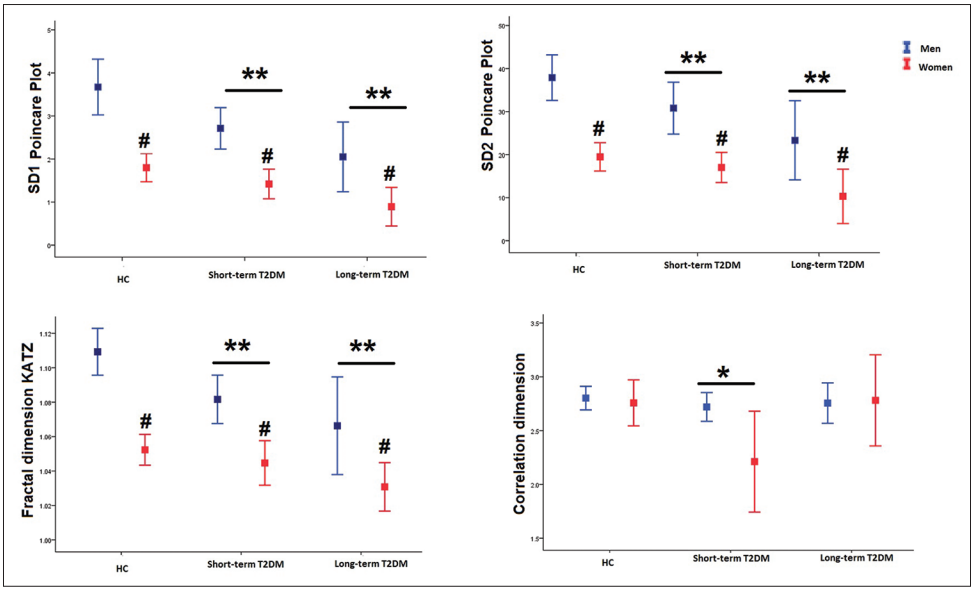

Figure 8: The sample entropy as an index of irregularity of signal showed that this feature did not significantly different between healthy control and patients groups. But this was significantly higher in the women than men. **$P < 0.002$: comparison between healthy control and other group; #$P < 0.0000$: comparison between genders; *$P < 0.02$: Comparison between healthy control and short-term type 2 diabetes mellitus

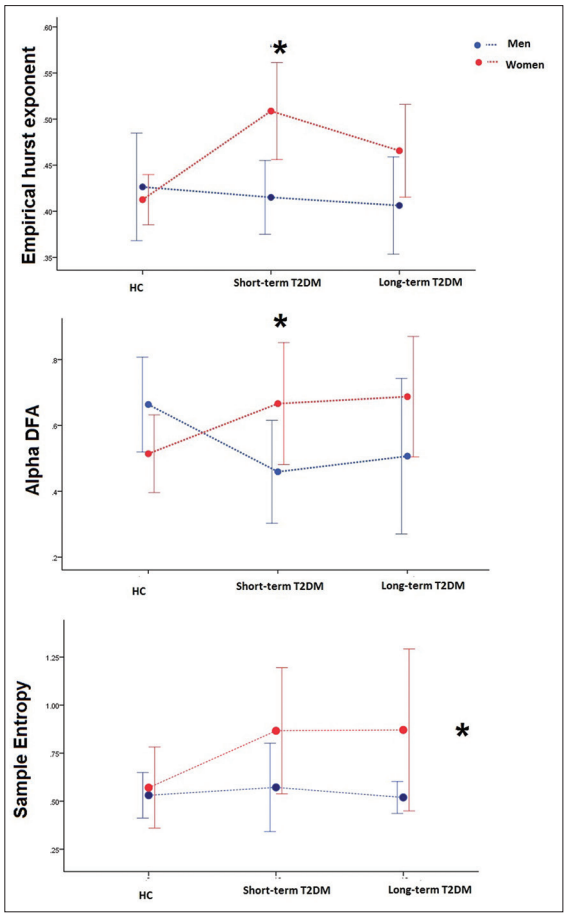

Figure 9: The line plots show mean and 95% confidence interval of empirical hurts exponent, alpha 4000 detrended fluctuation analysis and sample entropy in the three groups and two genders. *$P < 0.05$

Several studies supported this changes and showed that the long-term T2DM is more resistant to fatigue as compared to short-term T2DM.[11,19] The added result of the study showed that the nonlinear features of torque fluctuation during short-term fatigable exercise are not in agreement with the result of the slope of peak torques, especially in the knee flexion but showed a pattern-like strength indices as presented earlier.[31] The FD katz and SD1 and SD2 of Poincare plot of the 40 repetitions of isokinetic exercise of knee flexion-extension were decreased in the patients as compared to HC and in the women as compared to men. Then, it can be concluded that the nonlinearity of muscle activity is related to factors effect of strength such as speed of contraction, muscle length and composition, cross-section area, sex, and age.[37,38] The decrease of muscle cross section and type I muscle fiber proportion and increase in intramuscular lipid are seen in the diabetic muscle. The cross-section area of the muscle and the proportion of type I muscle fiber and its area and totally the muscle strength are less in the T2DM as compared to HC[10] and in the women as compared to men.[38,39] The limitation of the study comprised nonseparation of flexor and extensor torques to calculate the nonlinear features. This study suggested that the different range of motion or speed should be compared and the muscle biopsy should be used to evaluate the role of the proportion of the type of muscle fiber to produce force variability.

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None.

Conflicts of interest

There are no conflicts of interest.

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