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Dynamic postural stability in patients with diabetic peripheral neuropathy and relationship to presence of autonomic neuropathy

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Abstract

Diabetic neuropathy is a common complication that can negatively influence balance and is a major cause of falls. We evaluated the association between postural sway and diabetic autonomic neuropathy (DAN) among patients with diabetic peripheral neuropathy (DPN). Patients with DPN documented by typical symptoms with abnormal results of nerve conduction study were included and postural stability was assessed using dynamic posturography. Composite autonomic scoring scale (CASS) score was calculated by evaluating sudomotor, cardiovagal, and adrenergic functions. CASS score ≥2 indicated DAN and the severity of DAN was indicated by the CASS scores divided into three subscales of 10-point total CASS: none or mild autonomic failure (0-3), moderate failure (4-6), and severe failure (7-10). A total of 34 patients comprised the DAN group (n=19) and non-DAN group (n=15). Patients with DAN had higher prevalence of diabetic retinopathy(p=0.011), higher urine albumin-creatinine ratio (p = 0.009), and lower HbA1c levels (p<0.001) than those with non-DAN. With regard to dynamic postural instability, the presence (p=0.025) as well as the severity of DAN (p<0.05) was associated with postural instability in the eyes-opencondition. Interestingly, the poorer dynamic postural instability in moderate/severe DAN compared to mild DAN was observed only in medio-lateral direction and this association remained significant after adjusting for age, sex, and glycemic control state (HbA1c). In patients with DAN accompanied by DPN, the dynamic postural instability was affected by visual feedback and medio-lateral directional instability was closely associated with the severity of DAN.

Keywords: Autonomic neuropathy; diabetic neuropathy; postural instability

INTRODUCTION

Complex interactions between visual, vestibular, and somatosensory information and the cerebellar system are required to maintain a balanced upright position as the position of the body changes.[1] Patients with diabetic peripheral neuropathy (DPN) are more prone to have disturbed somatosensory perception and decreased proprioceptive functions.[2-4] These are associated with impaired balance, altered gait patterns, and increased risk of falling.[5] Falls are the common cause of morbidity and mortality in patients with diabetes. They usually present gait abnormalities including slower walk velocity, greater step variability, and higher plantar pressure than healthy controls, which can heighten the risk of falls.[6,7] Diminished sensory feedback that can be exacerbated by visual defects results in increased gait instability[8], and a degree of postural instability is more prominent in patients with DPN when visual feedback is occluded (eye-close state) than eye-open state.[9]

To detect early disequilibrium and to evaluate postural instability in patients with DPN, a dynamic posturography is widely used and

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quantifies dynamic balance performance and evaluates the ability to maintain equilibrium while standing on a movable support surface with varying degrees of instability. The negative correlations between heart rate variability and the degree of postural swayin patients with type 2 diabetes mellitus (T2DM)[10], and the observation that the risk of falling may be greater in patients with diabetes regardless of DPN, compared to healthy subjects[11] indicate involvement of other factors such as autonomic neuropathies besides DPN in the postural instability.[12]

The aim of this study was to compare the degree of postural sway in static/dynamic situations according to presence of DAN and to evaluate the association between the severity of autonomic neuropathy and postural instabilityin patients with DPN.

METHODS

Study design and patients

The cross-sectional, non-interventional study included 34 T2DM patients with neuropathic symptoms and DPN. They were recruited from Gyeongsang National University Hospital between April 2012 and March 2013. Eligibility requirements included subjects with T2DM, age 18-69 years, and documented DPN by nerve conduction study (NCS). Exclusion criteria were paresis, peripheral artery disease, diabetic foot ulcer or infection, alcoholic neuropathy, malignancy associated neuropathy, pan-hypopituitarism, severe renal or liver disease, or any musculoskeletal disorders. The patients were divided into two groups based on the presence of DAN determined by the Composite Autonomic Scoring Scale (CASS). The scale has a total of 10 points and DAN was defined as minimum score of one in at least two of the three CASS sudomotor, cardiovagal, and adrenergic domains, or a minimum score of two in one domain.[13] The DAN and non-DAN group comprised 19 and 15 patients, respectively. Diabetic retinopathy was evaluated through fundus photography by an experienced ophthalmologist. Patients with proliferative retinopathy who had received laser photocoagulation therapy were definedto have diabetic proliferative retinopathy (DPR). Diabetic nephropathy was defined if spot urine albumin to creatinine ratio (uACR) was more than 300 μg/mg or renal function was decreased (estimated GFR less than 60ml/min/1.73m^2, using the 2009 CKD-EPI creatinine equation). All subjects provided signed informed consent to participate. The study was conducted according to the principles expressed in the Declaration of Helsinki and Ethnics and approval was obtained from the Gyeongsang National University Institutional Review Board Ethnic committee with informed consents (No. 2012-04-007).

Assessment of diabetic neuropathy

DPN was defined according to presence of symmetrical sensory symptoms in the foot (tingling, aching, numbness, and burning sensation) with a distribution of graded stocking pattern, abnormal results of 10-g monofilament test (inability to detect more than one site out of eight sites), abnormal 128-Hz tuning fork vibration test (presence of difference in vibration perception time between patient and physician), and two or more nerves displaying an abnormality in the NCS (velocity, amplitude and latency of sensory and motor nerve). NCS was performed using the Keypoint device (Natus Medical Incorporated, Middleton, WI, USA). The presence and severity of DAN were evaluated using CASS, which assesses the severity and distribution of postganglionic sudomotor, adrenergic, and cardiovagal functions.[14] Sympathetic postganglionic cholinergic function was evaluated using the quantitative sweat axon reflex test (QSWEAT; WR Medical Electronics Co., Stillwater, OK, USA). Adrenergic and cardiovagal functions were assessed using heart rate response to the head-up tilt test, Valsalva maneuver, and heart rate response to deep breathing. The severity of DAN was indicated by the CASS scores divided into three subscales of 10-point total CASS: none or mild autonomic failure (0-3), moderate failure (4-6), and severe failure (7-10).[14]

Balance assessment

Postural sway was assessed by dynamic posturography using the BSS (Biodex Stability System).[15] BSS uses a circular platform that is free to move simultaneously in the antero-posterior (AP) and medio-lateral (ML) directions. The stability of the platform can be changed to evaluate the position at which patients can maintain a moving point in the center or near the center of displayed circles, with a difficulty level of 8 (easiest level, with the most resistance to the unstable platform), in which eight springs located underneath the outer edge of the platform provide the resistance to movement. The patients were instructed to look straight ahead with their head erect and to maintain their balance. Six successive trials were conducted, with three trials done with eyes open (EO) and three trials done with eyes closed (EC) under each condition (static and dynamic posturography). Data were gathered for three successive trials lasting 30 seconds with a rest period of two minutes between trials. The results were averaged under each condition. The BSS device was interfaced with dedicated Biodex Version 3.1 software (Biodex Medical Systems) that is used for calculation of overall stability index (OSI) from the degrees of tilt about the AP and ML axes, and separately calculated ML stability index (MLI) and AP stability index (API), in which a higher score in the indexes indicated poor balance.[16]

Data analyses

Normally distributed data are expressed as mean ± standard deviation (SD), whereas unevenly distributed data are presented as median (interquartile range: 25th to 75th percentile) for continuous variables. Categorical variables are expressed as number and proportion (%). To assess the significance of the differences between groups, the Student's t-test or the nonparametric Mann-Whitney U-test was used to compare the means of continuous variables. The categorical variables of the two groups were compared using the Chi-square test. Spearman' correlation coefficient was used to evaluate the strength of the association between postural instability and CASS score.

RESULTS

Characteristics of subjects and parameters of postural sway

A total of 34 patients with DPN were included (23 men, 11 women) and the mean HbA1c level was 11.0%. The mean age and the median disease duration was 48 years and 12.5 years respectively. Ten patients (27.0%) had DM retinopathy and 19 patients (55.9%) had DAN (CASS score ≥2) in which 7 patients (36.8%) had moderate to severe DAN (Table 1). Compared to eyes-open condition with static platform (median 0.8 with interquartile range [IQR] 0.5-1.2), the postural instability increased significantly as eyes were closed (median 1.9 with IQR of 1.5-2.5 in static-EC condition) or as the dynamic platform was applied (median 1.3 with IQR of 1.0-1.8 in dynamic-EO condition) and it maximized in condition of eyes-closed state with dynamic posture (median 4.1 with IQR of 3.2-5.3) (all $p<0.0001$; Figure 1). The DAN group had lower HbA1c levels (mean 10.2% vs. 13.5%; $p<0.001$), higher median uACR levels (median 60.6 mg/g vs. 6.3mg/g; $p=0.009$), and higher prevalence of DR (9% vs. 0%; $p=0.011$) compared to non-DAN group (Table 2). With regard to stability index, the postural sway between DAN and non-DAN group was significantly different only in OSI during testing with the dynamic platform and eyes-open (median 1.50 vs. 1.20; $p=0.025$, Table 2). Meanwhile, the postural sway in DEC condition was not different between two groups.

Association between degree of autonomic dysfunction and parameters of postural sway

The degree of postural sway was positively correlated with the severity of autonomic dysfunction (CASS scores) in all directions during the dynamic EO condition ($p<0.005$, Table 3). Especially, a higher dynamic postural stability index in patients with moderate to severe DAN (n=7) compared within those with mild DAN (n=27; Fig. 2) was observed in OSI (median 1.8 with IQR of 1.3-2.2 vs. median 1.2 with IQR of 0.8-1.5, $p=0.017$) and MLI (median 1.3 with IQR of 0.9-1.4 vs. median 0.8 with IQR of 0.5-0.9, $p = 0.005$), respectively. In addition, moderate to severe DAN is independently associated with higher postural instability (MLI) in condition of DEO compared with mild DAN even after adjusting for age, sex, and HbA1c levels (Odds ratio 19.57 with 95% confidence interval of 1.24-30.79; $p = 0.034$, Table 4).

DISCUSSION

We attempted to quantitatively evaluate the postural sway in patients with DPN according to presence of DAN under static and dynamic conditions with eyes open or occlusion. Compared to stable posture with normal vision, the overall postural instability was increased as vision was impeded or as dynamic posture was applied. In the dynamic eyes-open condition, the presence and severity of DAN were positively correlated with the degree of postural sway in all directions. Especially, higher dynamic postural instability in ML direction was observed in patients with moderate/severe DAN compared to those with mild DAN. However, there were no significant differences in parameters of postural sway according to the presence orseverity of DAN in the static position or eye closure situation.

An increased postural sway was observed when patients with DPN adopted the eye-closed dynamic

Table 1: Baseline characteristics and biochemical parameters of patients with type 2 diabetes

		Mean ± SD (median [IQR])
Age (years)		48.7 ± 11.5
Male/Female		23/11
Body mass index (kg/m^2)		25.9 ± 9.0
Duration of diabetes (years)		12.5 (5.2-18.5)
HbA1c (%)		11.6 ± 2.9
Glycated albumin (%)		34.2 ± 13.2
C-peptide (ng/mL)		2.1 (1.3-2.7)
Creatinine (mg/dL)		0.84 ± 0.26
UACR (mg/g)		12.6 (3.8-97.3)
Cholesterol (mg/dL)		191 ± 52
Triglyceride (mg/dL)		144 (101-286)
LDL-C (mg/dL)		115 ± 44
HDL-C (mg/dL)		45 ± 17
Insulin treatment (n, %)		9 (26.5)
DM retinopathy (n,%)		9 (26.5)
DM nephropathy (n,%)		0 (0)
Autonomic neuropathy (n,%)		19 (55.9)
CASS		2 (1-3)
Sudomotor subscore		1 (0-2)
Cardiovagal subscore		1 (0-1)
Adrenergic subscore		0 (0-1.25)
S-EO	OSI	0.50 (0.50-1.35)
	API	0.55 (0.40-0.83)
	MLI	0.30 (0.20-0.70)
S-EC	OSI	1.95 (1.48-2.60)
	API	1.45 (1.08-2.28)
	MLI	0.85 (0.40-1.28)
D-EO	OSI	1.30 (1.00-1.73)
	API	0.80 (0.68-1.03)
	MLI	0.90 (0.58-1.13)
D-EC	OSI	4.10 (3.13-5.28)
	API	3.05 (2.00-3.55)
	MLI	2.60 (1.70-3.35)

SD, standard deviation; IQR, interquartile range; HbA1c, glycated hemoglobin, UACR, urine albumin creatinine ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; CASS, composite autonomic scoring scale; S, static; EO, eyes-open; EC, eyes-closed; D, dynamic; OSI, overall stability index; API, anteroposterior index; MLI, mediolateral index

posture, compared with those adopting an eyes open-static posture. Balance control mechanisms are based on a feedback system generated from different combinations of muscle action, information detected by visual, somatosensory, and vestibular peripheral receptors. Given that delayed reaction and recovery times from sudden postural changes on irregular surfaces increase the risk for falls[15] and DPN is associated with decreased proprioception and increased reflex reaction time[17,18], postural sway during the dynamic condition may increase the challenge in maintaining balance stability in patients with DPN. In addition, vestibulo-ocular information alters the style of postural control in patients with DPN[4] and visual impairments and/or changes in postural coordination may also increase postural sway in the eyes-closed condition.[19]

Significant differences in postural sway between the DAN and non-DAN groups were observed only in the dynamic eyes-open condition. Postural control under the static condition indicates postural steadiness, whereas the dynamic postural response indicates postural stability.[20] Meanwhile, the reaction and recovery times from sudden postural changes are delayed in patients

Table 2: Demographic data between DAN and non-DAN patients

		DAN (n = 19)	Non-DAN (n = 15)	*p*-value
Age (years)		51.1 ± 10.6	45.8 ± 12.3	0.191
Male (n, %)		13 (68.4)	10 (66.7)	0.914
Body mass index (kg/m^2)		24.8 (20.0-27.5)	25.7 (22.6-29.0)	0.391
Duration of diabetes (years)		15 (10-25)	10 (5-16)	0.077
History of smoking (n, %)		7 (46.7)	8 (42.1)	0.790
HbA1c (%)		10.2 ± 1.9	13.5 ± 2.9	**<0.001**
Glycated albumin (%)		27.5 ± 8.9	42.1 ± 13.4	**0.001**
C-peptide (ng/mL)		2.1 (1.1-3.5)	2.1 (1.3-2.4)	0.483
Creatinine (mg/dL)		0.85 ± 0.32	0.83 ± 0.16	0.836
UACR (mg/g)		60.6 (7.3-183.4)	6.3 (1.7-15.5)	**0.009**
Total cholesterol (mg/dL)		179 ± 47	205 ± 56	0.173
Triglyceride (mg/dL)		142 (111-454)	145 (80-240)	0.242
LDL-C (mg/dL)		108 ± 40	123 ± 49	0.346
HDL-C (mg/dL)		41 ± 18	50 ± 16	0.109
Insulin treatment (n,%)		7 (36.8)	2 (13.3)	0.123
Retinopathy (n,%)		9 (47.4)	0 (0)	**0.002**
CASS		3 (2-6)	1 (0-1)	**<0.001**
	sudomotor subscore	1 (0-3)	0 (0-1)	**0.004**
	cardiovagal subscore	1 (0-2)	0 (0-1)	**0.006**
	adrenergic subscore	1 (0-3)	0 (0)	**0.003**
S-EO	OSI	0.80 (0.50-1.50)	0.80 (0.50-1.00)	0.706
	API	0.60 (0.40-1.00)	0.50 (0.40-0.70)	0.336
	MLI	0.30 (0.20-0.70)	0.40 (0.20-0.60)	0.973
S-EC	OSI	2.00 (1.60-2.70)	1.70 (1.40-2.60)	0.391
	API	1.70 (1.20-2.50)	1.20 (0.90-2.20)	0.120
	MLI	0.70 (0.40-1.20)	0.90 (0.40-1.50)	0.584
D-EO	OSI	1.50 (1.20-1.90)	1.20 (0.70-1.40)	**0.025**
	API	0.90 (0.80-1.20)	0.80 (0.50-1.00)	0.083
	MLI	0.90 (0.60-1.20)	0.70 (0.50-0.90)	0.167
D-EC	OSI	4.10 (3.20-4.60)	4.60 (2.80-6.30)	0.430
	API	3.00 (2.00-3.30)	3.20 (1.70-4.10)	0.493
	MLI	2.50 (1.70-3.10)	2.90 (1.80-3.60)	0.256

DAN, diabetic autonomic neuropathy; HbA1c, glycated hemoglobin, UACR, urine albumin creatinine ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CASS, composite autonomic scoring scale; S, static; EO, eyes-open; EC, eyes-closed; D, dynamic; OSI, overall stability index; API, anteroposterior index; MLI, mediolateral index

with DPN[21], and a shift from physiological ankle control to hip postural control due to sensory impairment with DPN was associated with postural instability.[22] However, because most of the enrolled patients in the present study had no or mild autonomic dysfunction and autonomic neuropathy has been known to be an integral part of most cases of peripheral neuropathy[23], an additional effect of DAN on general postural instability in patients with pre-existing DPN was not predominant in the current study design. Further studies with patients who have moderate to severe DAN might clarify the difference in postural instability.

The presence of DAN as well as the severity of DAN was associated with increased postural instability under the condition of dynamic body position with intact visual feedback (dynamic eyes-open condition), but not with eyes-closed condition. Multisensory interactions among vestibular, visual, and somatosensory signals were required to maintain body position[24] and among them, vision is important to facilitate proprioceptive feedback, providing the brain with continually updated information regarding the position and movement in relation to environment.[25] Meanwhile, previous studies in T2DM patients demonstrated that diabetic

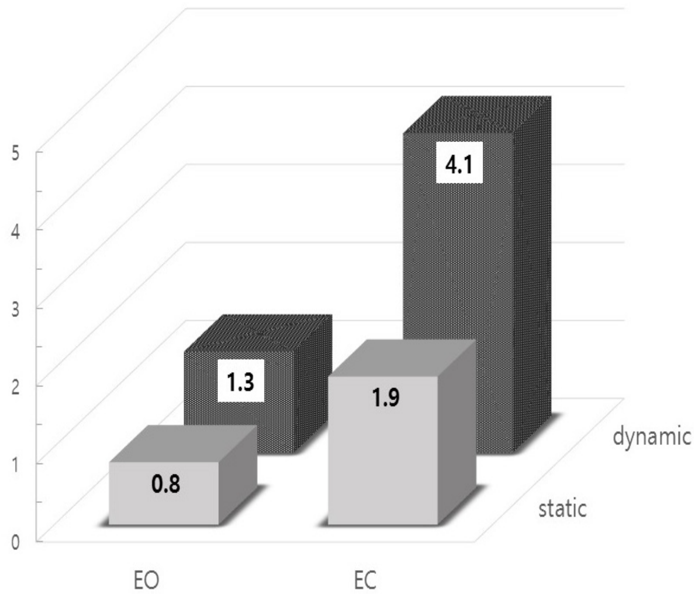

Figure 1. Postural sway (overall stability index) according to platform and vision state.
EO, eyes-open; EC, eyes-closed; variables represent a median value of OSI.

retinopathy is closely related to severity of cardiac autonomic neuropathy (CAN)[26] and may be a strong predictor for CAN.[27,28] These results suggest that impaired visual feedback might be an important contributing factor associated with postural instability, and that the contribution of autonomic function to balance control in individuals with DPN can be affected by visual feedback in the situation of dynamic challenging conditions that required more multisensory interaction. Further studies considering multifactorial interaction including visual feedback and autonomic neuropathy might be necessary to evaluate and manage the postural instability in patients with T2DM with DPN.

Interestingly, according to the severity of DAN, increased dynamic postural instabilities in overall as well as in ML directions were observed in

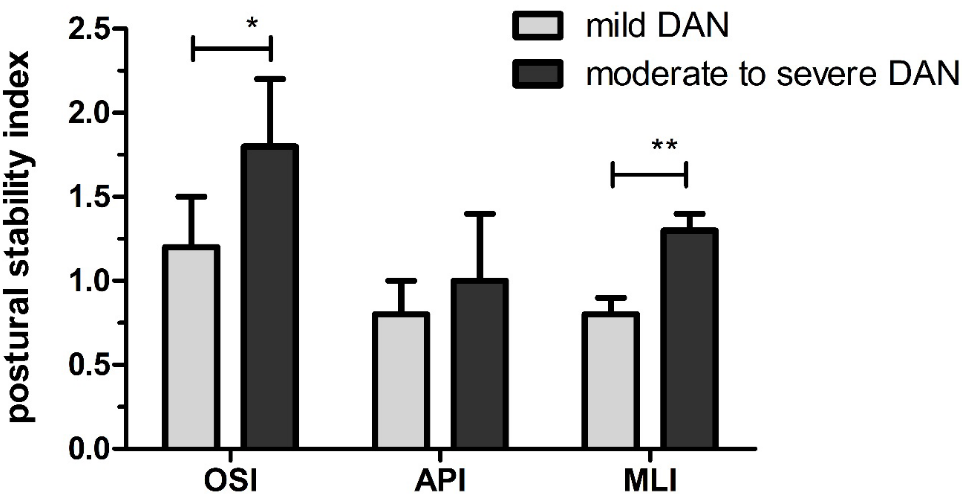

Figure 2. Comparison of dynamic postural stability index according to the severity of diabetic autonomic neuropathy in the overall, anteroposterior, and mediolateral directions.
OSI, overall stability index; API, anteroposterior index; MLI, mediolateral index; DAN, diabetic autonomic neuropathy; * $p<0.05$ ** $p<0.01$.

Table 3: Univariate Spearman correlation analysis between the severity of autonomic dysfunction and postural sway

	S-EO			S-EC			D-EO			D-EC		
	OSI	API	MLI	OSI	API	MLI	OSI	API	MLI	OSI	API	MLI
CASS score	0.099	0.189	0.037	0.217	0.321	0.019	**0.486****	**0.394***	**0.369***	-0.201	-0.192	-0.222
Sudomotor score	-0.140	-0.004	-0.186	0.178	0.297	-0.044	**0.419***	**0.348***	**0.402***	-0.122	-0.016	-0.258
Cardiovagal score	-0.037	0.017	-0.024	-0.076	-0.095	0.030	0.285	0.188	**0.381***	-0.044	-0.120	0.022
Adrenergic score	0.256	0.216	0.231	0.202	0.298	0.110	0.222	0.143	0.169	-0.171	-0.245	-0.070

CASS, composite autonomic scoring scale; S, static; EO, eyes-open; EC, eyes-closed; D, dynamic; OSI, overall stability index; API, anteroposterior index; MLI, mediolateral index; * p<0.05 ** p<0.01

patients who had moderate to severe autonomic dysfunction compared to those with mild DAN in the eyes-open condition. In addition, a dynamic postural instability in MLI is independently associated with the severity of DAN. A shift from physiological ankle control to hip postural control due to sensory impairment with DPN has been documented[29] and compensation with postural control at the hip level makes patients more dependent on information in the ML axis.[12] Previous studies also demonstrated postural instability in the ML direction in patients with DPN[9,11,30,31] which represents the distance between the center of pressure (COP) and association of increased risk of hip fracture due to left-to-right falling.[32] Meanwhile, in our study, dynamic postural instability in the ML direction increased in accordance with the severity of DAN even in patients with documented DPN. It suggests that not only the presence of DPN but also the severity of DAN might contribute to the dynamic postural stability in ML direction in patients with diabetes.

There are several limitations in the study. The number of enrolled patients was small because both NCS and CASS studies have to be performed simultaneously. Moreover, our study focused on patients with DPN and did not include a control group. Also, many patients had no to mild autonomic neuropathy, which precludes the evaluation of the full effects of DAN on postural sway. More elaborate studies are needed to evaluate the association between visual feedback and autonomic neuropathy and their effects on postural sway in patients with DPN.

In conclusion, this study of postural sway between patients with and without DAN reveal that the presence of DAN as well as the severity of autonomic dysfunction is associated with postural instability only when patients with DPN are in a dynamic eyes-open condition, which requires more complex information to maintain balance. Meanwhile, an independent association between the severity of DAN and dynamic postural instability was observed only in medio-lateral direction.

DISCLOSURES

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Table 4: Association between the severity of diabetic autonomic neuropathy and postural instability

		Adjusted OR (with 95% CI)*	*p*-value
SEO	OSI	1.64 (0.35-7.64)	0.528
	API	1.93 (0.25-15.04)	0.530
	MLI	2.14 (0.17-27.27)	0.558
SEC	OSI	2.10 (0.99-4.46)	0.054
	API	2.53 (0.93-6.89)	0.069
	MLI	2.59 (0.90-7.48)	0.079
DEO	OSI	3.07 (0.84-11.23)	0.091
	API	2.21 (0.74-6.60)	0.157
	MLI	19.57 (1.24-30.79)	**0.034**
DEC	OSI	1.04 (0.55-1.96)	0.908
	API	1.03 (0.43-2.46)	0.956
	MLI	1.09 (0.46-2.63)	0.842

*Multivariate logistic regression analysis adjusting for age, sex, and HbA1c
SEO, static eyes-open; OSI, overall stability index; API, antero-posterior index; MLI, medio-lateral index; SEC, static eyes-closed; DEO, dynamic eyes-open; DEC, dynamic eyes-closed; OR, odds ratio; CI, confidence interval

Conflict of interest: None

REFERENCES

1. Nashner LM, McCollum G. The organization of human postural movements: A formal basis and experimental synthesis. *Behav Brain Sci* 1985; 8:135-50.
2. Holewski JJ, Stess RM, Graf PM, Grunfeld C. Aesthesiometry: quantification of cutaneous pressure sensation in diabetic peripheral neuropathy. *J Rehabil Res Dev* 1988; 25:1-10.
3. Lord SR, Caplan GA, Colagiuri R, Colagiuri S, Ward JA. Sensori-motor function in older persons with diabetes. *Diabet Med J Br Diabet Assoc* 1993; 10:614-8.
4. Horak FB, Hlavacka F. Somatosensory loss increases vestibulospinal sensitivity. *J Neurophysiol* 2001; 86:575-85.
5. Boucher P, Teasdale N, Courtemanche R, Bard C, Fleury M. Postural Stability in Diabetic Polyneuropathy. *Diabetes Care* 1995; 18:638-45.
6. Allet L, Armand S, Golay A, Monnin D, de Bie RA, de Bruin ED. Gait characteristics of diabetic patients: a systematic review. *Diabetes Metab Res Rev*2008; 24:173-91.
7. Cavanagh PR, Derr JA, Ulbrecht JS, Maser RE, Orchard TJ. Problems with gait and posture in neuropathic patients with insulin-dependent diabetes mellitus. *Diabet Med J Br Diabet Assoc*1992; 9:469-74
8. Menz HB, Lord SR, George RS, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy1. *Arch Phys Med Rehabil* 2004; 85:245-52.
9. Corriveau H, Prince F, Hébert R, et al. Evaluation of postural stability in elderly with diabetic neuropathy. *Diabetes Care* 2000; 23:1187-91.
10. Yamamoto R, Kinoshita T, Momoki T, et al. Postural sway and diabetic peripheral neuropathy. *Diabetes Res Clin Pract* 2001; 52:213-21.
11. Lim KB, Kim DJ, Noh JH, Yoo J, Moon JW. Comparison of balance ability between patients with type 2 diabetes and with and without peripheral neuropathy. *PMR* 2014; 6:209-14.
12. Bonnet C, Carello C, Turvey MT. Diabetes and postural stability: review and hypotheses. *J Mot Behav* 2009; 41:172-90.
13. Hinman MR. Factors affecting reliability of the biodex balance system: A summary of four studies. *J Sport Rehabil* 2000; 9:240-52.
14. Low PA, Benrud-Larson LM, Sletten DM, *et al*. Autonomic symptoms and diabetic neuropathy. *Diabetes Care* 2004; 27:2942-7.
15. Arnold BL, Schmitz RJ. Examination of balance measures produced by the biodex stability system. *J Athl Train* 1998; 33:323-7.
16. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc* 1993; 68:748-52.
17. Lord SR, Castell S. Physical activity program for older persons: effect on balance, strength, neuromuscular control, and reaction time. *Arch Phys Med Rehabil* 1994; 75:648-52.
18. Richerson SJ, Robinson CJ, Shum J. A comparative study of reaction times between type II diabetics and non-diabetics. *Biomed Eng OnLine* 2005; 4:12.
19. Uccioli L, Giacomini PG, Monticone G, *et al*.Body sway in diabetic neuropathy. *Diabetes Care* 1995; 18:339-44.
20. Bonnet CT, Ray C. Peripheral neuropathy may not be the only fundamental reason explaining increased sway in diabetic individuals. *Clin Biomech* 2011; 26:699-706.
21. Prieto TE, Myklebust JB, Myklebust BM. Characterization and modeling of postural steadiness in the elderly: a review.*IEEE Trans Rehabil Eng* 1993; 1:26-34.
22. Lee K, Lee S, Song C. Whole-body vibration training improves balance, muscle strength and glycosylated hemoglobin in elderly patients with diabetic neuropathy. *Tohoku J Exp Med*2013; 231:305-14.
23. Giacomini PG, Bruno E, Monticone G, *et al*. Postural

rearrangement in IDDM patients with peripheral neuropathy. *Diabetes Care* 1996; 19:372-4.
24. Dyck PJ, Kratz KM, Karnes JL, *et al*. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 1993; 43:817-24
25. Ferrè ER, Walther LE, Haggard P. Multisensory interactions between vestibular, visual and somatosensory signals. *PLoS ONE* 2015; 10.
26. Paulus W, Straube A, Krafczyk S, Brandt T. Differential effects of retinal target displacement, changing size and changing disparity in the control of anterior/posterior and lateral body sway. *Exp Brain Res* 1989; 78:243-52.
27. Bilal N, Erdogan M, Ozbek M, *et al*. Increasing severity of cardiac autonomic neuropathy is associated with increasing prevalence of nephropathy, retinopathy, and peripheral neuropathy in Turkish type 2 diabetics. *J Diabetes Complications* 2008; 22:181-5.
28. Schmid H, Schaan B, Cecconello F, Maestri T, Neumann C. Proliferative diabetic retinopathy is related to cardiovascular autonomic neuropathy in non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1995; 29:163-8.
29. Huang CC, Lee JJ, Lin TK, *et al*. Diabetic retinopathy is strongly predictive of cardiovascular autonomic neuropathy in type 2 diabetes. *J Diabetes Res* 2016:e6090749.
30. Cimbiz A, Cakir O. Evaluation of balance and physical fitness in diabetic neuropathic patients. *J Diabetes Complications* 2005; 19:160-4.
31. Ghanavati T, Shaterzadeh Yazdi MJ, Goharpey S, Arastoo AA. Functional balance in elderly with diabetic neuropathy. *Diabetes Res Clin Pract* 2012; 96:24-8.
32. Maki BE, Holliday PJ, Topper AK. A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. *J Gerontol*1994; 49:M72-84.