Gait & Posture 32 (2010) 317–320

Contents lists available at ScienceDirect

Gait & Posture

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

Identification of peripheral neuropathy in type-2 diabetic subjects by static posturography and linear discriminant analysis

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ARTICLE INFO

Article history:
Received 14 July 2009
Received in revised form 6 May 2010
Accepted 28 May 2010

Keywords:
Diabetic neuropathy
Static posturography
Statistical classification

ABSTRACT

Background: An early diagnosis of peripheral neuropathy in diabetic patients is useful in order to slow down the progress of this complication. Nerve conduction tests are the gold standard for this diagnosis but they are challenging for the patients. This study examines whether it is possible to assess the presence of diabetic neuropathy at an early stage by static posturography tests.
Methods: Static posturography tests were performed on 37 type-2 diabetic subjects (25 neuropathic patients and 12 non-neuropathic control subjects). Each subject was tested twice under two visual conditions: open and closed eyes. Both "global" (classic) and "structural" (model-based) posturographic parameters (PP) were derived from centre-of-pressure trajectories. A total of 65 PP were computed but only five were selected, normalized and fed to a linear classifier based on linear discriminant analysis.
Results: This method correctly classified 86.5% of the patients. Five subjects were misclassified and only 2 false negatives out of 25 neuropathic subjects were erroneously diagnosed as control subjects.
Conclusions: This paper shows that "global" and "structural" parameters derived by static posturography tests, and classic linear statistical approaches, can be used for the diagnosis of neuropathy provided PP are properly chosen and normalized.

1. Introduction

Neuropathy affects up to 50% of diabetic patients showing different clinical features [1]. The most prevalent type of diabetic neuropathy (DN) is distal symmetric, primarily sensory, peripheral polyneuropathy. Nerve conduction studies are the gold standard for diagnosing peripheral neuropathy [2] but these tests can be challenging for both the patient and the testing physician. An early diagnosis in asymptomatic patients is useful in order to make the patients aware of their condition and to activate educational programs oriented to encourage some changes in lifestyle (i.e. avoiding dangerous situations, using additional care in walking, etc.). Moreover, effective treatments are available to prevent further complications. These observations suggest the need of new, easy and reliable tools for the diagnosis of DN.

The loss of sensory perception secondary to diabetic distal symmetrical sensory neuropathy has a markedly detrimental effect on postural stability during stance and gait [3–5] that might contribute to increased fall risk [6,7]. Evaluation of postural steadiness is usually based on the interpretation of centre-of-pressure (COP) measures using a dynamometric platform [8] but only a few studies have addressed the problem of postural instability during quiet standing in DN patients [4–6,9,10]. High correlations have been found in previous works between the severity of neuropathy and the COP measures [6,9,10], but no automatic classification tool based on COP measures has been developed in order to distinguish DN patients from diabetic non-neuropathic subjects. The COP measures that usually have been considered are those obtained by classic, conventional analysis of COP trajectory aimed at describing its geometric and spectral characteristics, such as its length, the area it covers, and the frequency content of its power spectrum (see [8] for a review).

Besides these "global" measures, more "structural" parameterizations can be applied to posturographic data. These latter are related to models aimed at identifying sub-units in the COP trajectory and at relating them to the underlying motor control processes. For instance, they refer to the sway density function [11] or describe COP trajectory as the realization of a stochastic process [12] or by means of the chaos theory [13]; briefly, they take into account the dynamics governing the time evolution of the COP signal. Many parameters have been validated in literature for the dynamics of sway by means of non-linear techniques but are not yet widely used [14–17].

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doi:10.1016/j.gaitpost.2010.05.017

A crucial aspect in the analysis of static posturography results is the large variability in the parameter values. In order to reduce such variability it is important to properly design the experimental protocol and evaluate the reliability of PP and to introduce data normalization procedures [18]. This study examines whether it is possible to assess the presence of diabetic neuropathy at an early stage by static posturography by means of simple linear classifier software tools based on the classic linear discriminant analysis method.

2. Patients and methods

2.1. Subjects and measurement protocol

Thirty-seven patients affected by type-2 diabetes mellitus were tested: 12 diabetic non-neuropathic subjects (control subjects = CNTR) and 25 neuropathic subjects (DN). Among DN patients, eight were asymptomatic (AN) and 17 were symptomatic (SN). The absence or presence of neuropathy was assessed by determining motor and sensory nerve conduction velocity as described in [19]. Neuropathic subjects were classified as symptomatic on the basis of the Diabetic Neuropathy Symptom score, which was considered positive with a score of 1 or higher [20].

The study was approved by the Ethic Committee of INRCA Hospital (process 124/2006) and all subjects gave their informed consent before the test. Their clinical data are shown in Table 1. Exclusion criteria were: neuropathy other than that of diabetic origin or neurological diseases; peripheral arterial disease; any medication potentially affecting peripheral nerve function.

The measurement protocol consisted in standing barefoot on a dynamometric platform (Kistler 9281 type). To minimize subject's discomfort during the whole experimental session, the width of the base of support was kept approximately equal to the pelvic width. In order to reduce variability in COP measures, while maintaining the whole duration of the experimental session within reasonable time limits, each test was performed twice with eyes open (EO) and twice with eyes closed (EC); each pair of PP obtained in the same visual condition was then averaged. Feet were positioned in the same manner in all the trials. During EO condition the subjects had to look at a visual target placed 3 m in front, at the height of the subject's eyes. Anthropometric data were recorded, with particular attention to height (164 ± 10 cm), body mass (77 ± 13 kg), base-of-support area (359 ± 58 cm^2), maximum-foot-width (10 ± 1 cm) and feet-opening angle ($7^\circ \pm 4^\circ$) [18].

For each trial, force-plate data were acquired for 60 s at a sampling frequency of 100 Hz. The anterior–posterior (AP) and medial–lateral (ML) COP co-ordinates were filtered with a cut-off frequency of 5 Hz by a 4-th order low-pass Butterworth filter. COP filtered data were processed according to classic and model-based approaches; 65 PP were obtained from COP tracings as described in [8,11–13].

2.2. Data pre-processing and classification

In order to identify the presence of diabetic neuropathy among the whole population of diabetic subjects we chose a classic and well-assessed classification method: linear discriminant analysis (LDA) [21]. The use of LDA, however, carries several restrictive assumptions on the PP, which must be linearly independent, should present low values of correlation, and must have distributions verifying conditions of homoschedasticity (i.e. equality of variances among groups) and normality.

Only PP showing at least a fair-to-good level of reliability (Intraclass Correlation Coefficient higher than 0.6 [22,23]) were considered. Each PP was submitted to a normalization procedure in order to eliminate its dependence from anthropometric factors. The detrending normalization described in [24] was performed only for parameters that showed significant correlation ($r > 0.3$ and $p < 0.01$) with at least one biomechanical factor. In the case of linear correlation between a parameter (y) and only one anthropometric factor (x) of the type $y = a_0 + a_1 x$, the normalized parameter value for each ith subject is computed as: $y_{iNORM} = y_i - a_0 - a_1 x + \bar{y}$ where y_i is the parameter value for the ith subject, y_{iNORM} is the normalized value for the ith subject and $\bar{y}$ is the parameter mean value for the whole population. In the case of significant correlation with more than one biomechanical factor, multiple regression was performed.

To test normality of PP the "Kolgomorov–Smirnov" and "Shapiro–Wilks" tests were used; homoschedasticity was evaluated by Levene's statistics test.

As a result of LDA, a set of linear discriminant functions was obtained and only those functions with a statistically significant discriminant power and characterized by the minimum number of independent variables were selected. Wilks' lambda statistics was used to test the efficacy of the discriminant functions in producing significant differences among the target groups [21]. The resulting discriminant function was aimed at distinguishing in an optimal way all DN patients (i.e. AN and SN considered in a unique class) from non-neuropathic ones (CNTR).

Due to the limited number of subjects, model validation was carried out using the leave-one-out cross-validation technique: the data of a single subject from the original data set were used as validation data, and the data of the remaining subjects were used as training data. This procedure was repeated so that the data of each subject in the data set were used once as validation data. Data analysis was carried out separately for EO and EC conditions. The SPSS statistical software package (version 16.0) was used.

Table 1
Clinical data of the analyzed subjects.

	CNTR	DN	
		AN	SN
Number of subjects	12	8	17
Age (years)	70 ± 5	68 ± 8	67 ± 10
Body mass index (kg/m^2)	28.7 ± 4.2	28.4 ± 3.4	28.9 ± 4.8
Gender (M/F)	8/7	5/5	14/11
Duration of diabetes (years)	8.1 ± 7.3	10.4 ± 9.1	13.2 ± 10.7
HbA1c (%)	7.3 ± 0.9	7.5 ± 0.8	7.6 ± 1.0

CNTR, diabetic non-neuropathic subjects; DN, diabetic neuropathic patients; AN, asymptomatic neuropathic subjects; SN, symptomatic neuropathic subjects; HbA1c, glycosylated hemoglobin.

3. Results

Thirteen PP satisfied the reliability test at least at a fair-to-good level: nine were "global" PP and four "structural" PP. In particular the nine "global" PP were: Mean-Distance-AP, Mean-Distance-ML, Mean-Velocity-AP, Mean-Velocity-ML, Sway-Area, Power-AP, Power-ML, Frequency-95%-AP, Frequency-95%-ML. The four "structural" PP were: Mean-Time (SDP-MT), Mean-Distance-of-Peaks (SDP-MD), Mean-Value-of-Peaks (SDP-MP) and the Dominant-Lyapunov-Exponent (DLE). The first three structural PP are related to the analysis of the Sway Density Plot (SDP) function [11], whilst the fourth refers to the non-linear analysis of the COP trajectory [13].

For both visual conditions the normalization procedure was performed on each parameter by means of different linear regression models. Boxplot analysis of normalized data revealed that only in EC condition could some variables have enough discriminant power, whereas in EO condition no variable showed a good predictive power. Consequently, further statistical analysis was carried out only on PP for EC condition.

Frequency-95%-AP, Frequency-95%-ML, DLE, and SDP-MT did not show good discriminant power and so these four PP were discarded from further analysis. The remaining nine variables satisfied the conditions of normality and homoschedasticity, turning out to be potentially good for LDA.

The most significant discriminant functions proved to be dependent on the following five PP: Mean-Distance-AP, Sway-Area, Power-AP, SDP-MD, and SDP-MP. All these PP, with the exception of the Sway-Area, required multiple regression for their normalization. While the Sway-Area was correlated only with the body mass index, all other PP were also correlated with the base of support.

Fig. 1 shows the boxplots for the five PP used for LDA. The analysis of variance shows a statistically significant difference among the three groups of patients ($p < 0.0001$) for all five PP used for LDA (Mean-Distance-AP: $F(2,34) = 12.6$; Sway-Area: $F(2,34) = 13.7$; Power-AP: $F(2,34) = 9.9$; SDP-MD: $F(2,34) = 16.5$; SDP-MP: $F(2,34) = 17.2$). The analysis of the Structure Matrix [21] showed that, of the five selected PP, the structural parameters SDP-MP and SDP-MD have higher correlations with the discriminant functions.

The LDA results aimed at distinguishing DN patients (i.e. AN and SN subjects taken together) from CNTR ones, are summarized in Table 2. Only 3 subjects out of 37 were misclassified in the training set, resulting in an overall success rate of 91.9% This percentage drops to 86.5% in the validation phase (i.e. for the leave-one-out cross-validated grouped cases). In this case five subjects were misclassified out of the whole population. In particular only 2 false

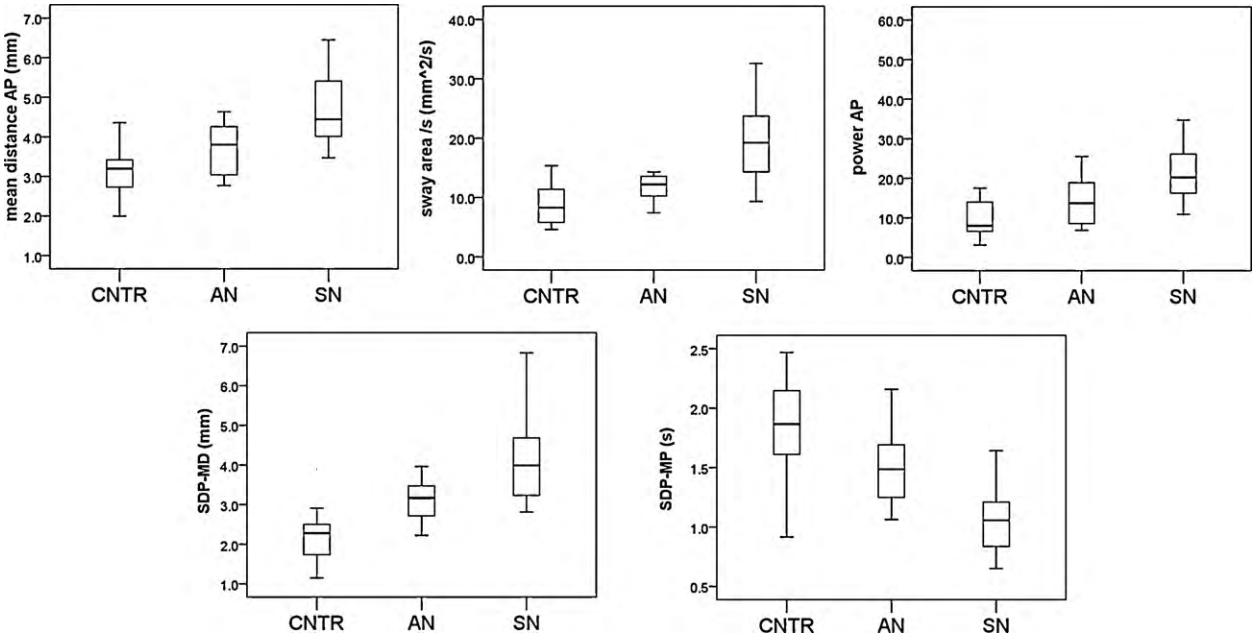

Fig. 1. Boxplot diagrams of the five posturographic parameters used for linear discriminant analysis. CNTR, diabetic non-neuropathic subjects; AN, asymptomatic neuropathic subjects; SN, symptomatic neuropathic subjects. Mean-Distance-AP, average AP distance from the mean COP; Sway-Area, area enclosed by the COP path per unit of time; Power-AP, integrated area of the power spectrum of the AP component of the COP trajectory [9]; SDP-MD, Mean-Distance-of-Peaks; SDP-MP, Mean-Value-of-Peak [11].

Table 2
Classification results for the two-class model. Leave-one-out cross-validation is done only for cases used in the linear discriminant analysis. In cross validation, each case is classified by the discriminant function obtained from all the other cases.

Real group	Predicted group membership		
	CNTR	DN (AN + SN)	Total
CNTR	10 (83.3%)	2(16.7%)	12 (100%)
DN (AN + SN)	1 (4.0%)	24 (96.0%)	25 (100%)
Predicted group membership for leave-one-out cross validation			
CNTR	9 (75.0%)	3 (25.0%)	12 (100%)
DN (AN + SN)	2 (8.0%)	23 (92.0%)	25 (100%)

CNTR, diabetic non-neuropathic subjects; DN, diabetic neuropathic patients; AN, asymptomatic neuropathic subjects; SN, symptomatic neuropathic subjects.

negatives out of 25 neuropathic subjects were erroneously diagnosed as control subjects.

4. Discussion

LDA is a simple, linear classification technique that was already successfully applied to COP data in [25] to identify subjects susceptible to motion sickness. With respect to more general classification methods, LDA requires data that have to satisfy a number of statistical assumptions. Among the whole set of PP taken into account, only five PP were identified which both satisfied the LDA assumptions and showed discriminant power able to identify the presence of diabetic neuropathy. The "global" parameters Mean-Distance-AP, Sway-Area, and Power-AP are classic PP connected with a geometric or spectral description of the COP trajectory [8]. The "structural" parameters Mean-Distance-of-Peaks, and Mean-Value of-Peaks showed the most predictive power among the five PP chosen for classification. Peaks of sway density function correspond to time instants in which COP is more stable. In particular SDP-MD is the distance between one peak and another and quantifies the amplitude of the COP postural shifts. SDP-MP represents the time spent by the COP around a point of stability and quantifies how stable the posturographic signal is between one shift and another.

As shown in Fig. 1, this work confirms previous studies, reporting that DN subjects are less stable than non-neuropathic diabetic patients and normal subjects [3–5,9,10,26,27]. The classic parameters detect the qualitative observation that the size of the posturogram is bigger in neuropathic patients than in non-neuropathic ones, particularly in EC condition, when the subject cannot use the visual input and lacks an accurate proprioceptive feedback from the lower limbs. The non-discriminant power of PP in EO condition may be due to compensatory visual correction similar in the groups studied [9], or simply to the lack of a visually demanding task [28]. The classic parameters showed statistically significant differences only between SN patients and the control group, while the two structural parameters were able to detect statistically significant differences ($p < 0.001$) not only between the SN and CNTR groups but also between SN and AN patients ($p < 0.01$). In particular, SDP-MD increased in a statistically significant manner, while SDP-MP decreased in SN compared both with CNTR and with AN patients. This suggests that neuropathic symptomatic subjects are less stable than control subjects and patients affected by neuropathy in the asymptomatic stage, as they show more distant COP stability points and remain on a stability point for a shorter time. Literature has already shown that posturography can identify significant differences between controls and diabetic patients with and without neuropathy (see f.i. [4,6,9,10]), but no tool has been developed to diagnose neuropathy based only on the analysis of COP trajectories as done in the present work. A number of screening instruments and methods have been proposed as alternative diagnostic procedures to detect diabetic neuropathy at a preclinical stage in addition to nerve conduction velocity, but they are generally characterized by low sensitivity when compared with standard diagnostic tests [29]. Moreover, these methods give rise to qualitative rather than quantitative results and therefore cannot be used to follow-up neuropathic patients.

The results of the present study suggest that the multivariate statistical analysis of PP might be a valid screening instrument able

to discriminate the presence of peripheral neuropathy in diabetic patients even in the absence of symptoms. In fact, the two-class model gave rise to cross-validated results characterized by a high level of sensitivity (92%). It was able to recognize 23 neuropathic subjects out of a total of 25 DN subjects (AN and SN). Only two neuropathic subjects proved to be false negatives and in both cases they were asymptomatic patients. One fourth of the controls (3 out of a total of 12 subjects) were erroneously classified as neuropathic, giving rise to 75% specificity. Nonetheless, the percentage of patients correctly classified as non-neuropathic or neuropathic was satisfactorily high (86.5%) in the cross-validated group, suggesting that the present test might be used in clinical settings for the screening of diabetic neuropathy.

The satisfactory classification by LDA was made possible by the normalization of posturographic parameters. In fact, if non-normalized PP were used, posturography would continue to show statistically significant differences between diabetic patients with and without neuropathy, but the classification tool, based on LDA, is no more reliable. The present results have shown that "structural" parameters are the most predictive ones, suggesting that model-based approaches give a more meaningful description of posturographic properties in normal and pathological subjects, than those given by other approaches based on "global" parameterization.

In conclusion, although a specific treatment for nerve damage is currently not available, an early diagnosis of diabetic neuropathy is important as it indicates the need for improved glycemic control and careful foot care. The present results suggest that posturographic screening might detect neuropathy in asymptomatic subjects by means of LDA, which could be embedded in a friendly interface for its application in the clinic. Further studies are in progress in order to develop such an interface. Posturographic analysis, which can easily be performed in daily practice and is well-accepted by patients, might be proposed as a simple, non-intrusive and quantitative method for the early detection of diabetic neuropathy.

Acknowledgements

This work has been financed by MIUR 2006 funds "Ricerca Scientifica di Ateneo" project #2033.

Conflict of interest statement

Financial and/or personal relationship with other people or organizations that could inappropriately influence this work do not exist.

References

[1] Gries FA, Cameron NE, Low PA, Ziegler D. Textbook of diabetic neuropathy. Stuttgart: Thieme; 2003.
[2] Oh SJ. Clinical electromyography: nerve conduction studies. Baltimore: University Park Press; 1984.
[3] 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 1992;9:469–74.
[4] Lafond D, Corriveau H, Prince F. Postural control mechanisms during quiet standing in patients with diabetic sensory neuropathy. Diabetes Care 2004; 27:173–8.
[5] Schilling RJ, Bollt EM, Fulk GD, Skufca JD, Al-Ajlouni AF, Robinson CJ. A quiet standing index for testing postural sway of healthy and diabetic adults across a range of ages. IEEE Trans Biomed Eng 2009;56:292–302.
[6] Simoneau GG, Ulbrecht JS, Derr JA, Becker MB, Cavanagh PR. Postural instability in patients with diabetic sensory neuropathy. Diabetes Care 1994;17: 1411–21.
[7] Richardson JK, Ching C, Hurvitz EA. The relationship between electromyographically documented peripheral neuropathy and falls. J Am Geriatr Soc 1992;40:1008–12.
[8] Prieto TE, Myklebust JB, Hoffmann RG, Lovett EG, Myklebust BM. Measures of postural steadiness: differences between healthy young and elderly adults. IEEE Trans Biomed Eng 1996;43:956–66.
[9] Uccioli L, Giacomini PG, Monticone G, Magrini A, Durola L, Bruno E, et al. Body sway in diabetic neuropathy. Diabetes Care 1995;18:339–44.
[10] Yamamoto R, Kinoshita T, Momoki T, Arai T, Okamura A, Hirao K, et al. Postural sway and diabetic peripheral neuropathy. Diabet Res Clin Pract 2001;52: 213–21.
[11] Baratto L, Morasso PG, Spada G. A new look at posturographic analysis in the clinical context: sway-density versus other parameterization techniques. Motor Control 2002;6:246–70.
[12] Collins JJ, De Luca CJ. Open loop and closed loop control of posture: a random walk analysis of center-of-pressure trajectories. Exp Brain Res 1993;95: 308–18.
[13] Ladislao L, Fioretti S. Nonlinear analysis of posturographic data. Med Bio Eng Comput 2007;45:679–88.
[14] Riley MA, Balasubramaniam R, Turvey MT. Recurrence quantification analysis of postural fluctuations. Gait Posture 1999;9:65–78.
[15] Duarte M, Zatsiorsky VM. On the fractal properties of natural human standing. Neurosci Lett 2000;283:173–6.
[16] Bonnet CT, Faugloire EM, Riley MA, Bardy BG, Stoffregen TA. Motion sickness preceded by unstable displacements of the center of pressure. Hum Movement Sci 2006;25:800–20.
[17] Stins JF, Michielsen ME, Roerdink M, Beek PJ. Sway regularity reflects attentional involvement in postural control: effects of expertise, vision and cognition. Gait Posture 2009;30:106–9.
[18] Chiari L, Rocchi L, Cappello A. Stabilometric parameters are affected by anthropometry and foot placement. Clin Biomech 2002;17:666–77.
[19] Ziegler D. Validation of a novel screening device (Neuroquick) for quantitative assessment of small nerve fiber dysfunction as an early feature of diabetic polyneuropathy. Diabetes Care 2005;28:1169–74.
[20] Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the diabetic neuropathy symptom score. Diabet Med 2002;19:962–5.
[21] Huberty CJ. Applied discriminant analysis. New York: Wiley; 1994.
[22] Fleiss JL. The design and analysis of clinical experiments. New York: Wiley & Sons; 1986.
[23] Fioretti S, Ladislao L. About reliability of posturographic parameters. IFMBE Proc Medicon Health Telematics 2004;6:70.
[24] O'Malley MJ. Normalization of temporal distance parameters in pediatric gait. J Biomech 1996;29:619–25.
[25] Smart LJ, Stoffregen TA, Bardy BG. Visually-induced motion sickness predicted by postural instability. Hum Factors 2002;44:451–65.
[26] Giacomini PG, Bruno E, Monticone G, Di Girolamo S, Magrini A, Parisi L, et al. Postural rearrangement in IDDM patients with peripheral neuropathy. Diabetes Care 1996;19:372–4.
[27] Reid VA, Adbulhadi H, Black KR, Kerrigan C, Cros D. Using posturography to detect unsteadiness in 13 patients with peripheral neuropathy: a pilot study. Neurol Clin Neurophysiol 2002;4:2–7.
[28] Prado JM, Stoffregen TA, Duarte M. Postural sway during dual tasks in young and elderly adults. Gerontology 2007;53:274–81.
[29] Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care 2001;4:250–6.