The relationship of one-leg standing time with peripheral nerve function and clinical neuropathy in patients with type 2 diabetes

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Received: 23 July 2017 / Accepted: 18 March 2018 / Published online: 24 March 2018
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Abstract

Objective This study aimed at exploring physical fitness including postural stability in relation to peripheral nerve function and clinical neuropathy in patients with type 2 diabetes across a wide range of ages.

Methods We analyzed data collected from 139 patients with type 2 diabetes aged between 19 and 81 years, which included the peripheral nerve conduction parameters and coefficient of variation for normal R–R intervals (CVRR) at rest and during deep breathing. The results of neurological examinations to diagnose probable and confirmed diabetic neuropathies based on the minimal criteria proposed by the Toronto diabetic neuropathy expert group and a battery of physical fitness tests including one-leg standing time with eyes open were also assessed. Multiple linear and logistic regressions were used to estimate the relationships of the physical fitness measures with the parameters of peripheral and cardiac autonomic nerve functions and clinical neuropathies, respectively. Receiver operating characteristic curves were generated to depict the relation between sensitivity and specificity of one-leg standing time for probable and confirmed neuropathies.

Results After adjustment for age and other potential confounders, one-leg standing time correlated with peripheral and cardiac autonomic nerve functions as well as with probable and confirmed neuropathies. The one-leg standing time of 23 s was found to be 66 and 63% sensitive and 81 and 77% specific for diagnosing probable and confirmed neuropathies, respectively.

Conclusions Short one-leg standing time was associated with peripheral and cardiac autonomic nerve dysfunction and clinical neuropathy in patients with type 2 diabetes, independent of age.

Keywords Physical fitness · Postural stability · Nerve conduction · Heart rate variability · Diabetic neuropathy

Introduction

Diabetic neuropathy is the most common and earliest complication of diabetes [1]. Recent studies have reported that even individuals with prediabetes have increased prevalence of distal sensory or sensorimotor neuropathy [2–5]. However, the mechanism underlying the early development of peripheral nerve dysfunction associated with glucose intolerance is not yet fully elucidated. In addition, an insufficient frequency of professional foot examinations has been shown

among those with prediabetes and diabetes in primary care practice, resulting in a high prevalence of undiagnosed and untreated clinical neuropathy in these populations [2].

Some evidence suggests that exercise may prevent and improve peripheral nerve dysfunction in patients with diabetes [6–8]. Low physical fitness is often observed early in the course of type 2 diabetes or even in prediabetes [9–11]. Although low physical fitness or disability has been considered to occur as a consequence of advanced diabetic neuropathy in older patients with diabetes [12, 13], few data are available on the relationship between low physical fitness and peripheral nerve dysfunction, along with potential confounders for diabetic neuropathy, in young or middle-aged patients with type 2 diabetes. In particular, no studies have examined whether low physical fitness correlates with cardiac autonomic nerve dysfunction in these patients. In this study, therefore, we hypothesized that certain objective measures of physical fitness would correlate with peripheral and cardiac autonomic nerve function as well as with clinical

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neuropathy, after adjustment for potential confounders for diabetic neuropathy, in patients with type 2 diabetes across a wide range of ages.

Materials and methods

Study sample

We analyzed data including neurological and physical fitness parameters as described below collected from 222 patients with type 2 diabetes aged between 19 and 86 years who were admitted to our hospital between February 2012 and May 2017 because of inadequate glycemic control, diabetes education, or both. Patients were excluded if they had abnormal cardiovascular response to exercise as determined by a double Master two-step test performed within 1 month prior to admission or exercise prescription, had a history of coronary heart disease, cerebrovascular disease, peripheral artery disease, or psychiatric disorder, had peripheral neuropathy attributable to a cause other than diabetes, or were taking drugs for diabetic neuropathy. One hundred and thirty-nine patients aged between 19 and 81 years were identified as eligible and analyzed in this study. Laboratory data including levels of plasma glucose, hemoglobin A1c, serum creatinine, lipids and C-peptide obtained from their fasting blood samples on the second day after admission, as well as levels of urinary excretion of albumin, creatinine and C-peptide over 24 h measured within 3 days after admission were retrieved.

Body composition and physical fitness

Body composition including fat mass and skeletal muscle mass was assessed by using a multifrequency bioelectrical impedance analyzer (InBody 720, Biospace, Tokyo, Japan). Our previous study has shown the beneficial effects of exercise training in reducing the treatment burden of patients with diabetes [14]. To prescribe exercise safely and effectively, we have evaluated the patients routinely by using a battery of physical fitness tests as follows. Maximal isometric muscle strength for knee extension was determined using a hydromusculator GT-160 (OG Giken, Okayama, Japan). Strength was expressed as an absolute value and relative to body weight. Strength was also normalized to leg muscle mass in kilograms to give a measure of leg muscle quality [15]. Leg muscle mass was determined by using the aforementioned impedance analyzer. One-leg standing time with eyes open was recorded, up to a maximum of 60 s, to assess functional balance. Muscle strength, muscle quality and one-leg standing time were measured for both legs, and the average of the two legs was used for statistical analysis. Whole-body reaction time was measured using a TKK-1264b (Takei Scientific Instruments, Niigata, Japan) to assess agility

performance. Five trials were performed, and the shortest reaction time from light stimulus to complete lift of both feet from the floor was used for statistical analysis. Maximal oxygen uptake was estimated to assess cardiopulmonary fitness. Maximal oxygen uptake was estimated using a computerized metabolic monitor (Aeromonitor AE-300S, Minato Medical Science, Osaka, Japan) during graded exercise on a bicycle ergometer (Well Bike BE-360, Fukuda Denshi, Tokyo, Japan) at an intensity up to 80% of age-predicted maximal heart rate (220 beats per minute—age).

Peripheral and cardiac autonomic nerve function

Peripheral sensory nerve function was assessed for the sural nerve and peripheral motor nerve function was assessed for the tibial nerve. Nerve conduction studies were performed using an electromyography system with surface electrodes for stimulation and recording (Viking Quest, CareFusion Japan, Tokyo, Japan). Cardiac autonomic nerve function was evaluated using the coefficient of variation of R–R interval (CVRR) measured on electrocardiogram (Cardio Star FCP-7541, Fukuda Denshi, Tokyo, Japan) at rest and during deep breathing (6 breaths per min).

Diagnosis of clinical diabetic neuropathy

The diagnosis of clinical diabetic neuropathy was based on the minimal criteria proposed by the Toronto diabetic neuropathy expert group [16]. Clinical records including positive neuropathic sensory symptoms such as prickling tingling, burning or aching pain in both toes, feet or legs, ankle reflexes and distal touch perception were retrieved. Ankle reflexes were deemed abnormal if they were unequivocally decreased or absent despite reinforcement. Symmetric reduction of distal touch perception was determined by 10 g monofilament applied to the plantar surface of the great toes and feet. Probable diabetic neuropathy was diagnosed in the presence of a combination of neuropathic symptoms and signs which include any two or more of the following: neuropathic symptoms, reduced touch perception, or abnormal ankle reflexes. Confirmed diabetic neuropathy was diagnosed in the presence of an abnormality of the nerve conduction parameters and a neuropathic symptom or symptoms or a sign or signs as mentioned above.

We used the normal reference values of nerve conduction tests based on a previous study of healthy subjects without neuropathy and the abnormal values defined as < -2 standard deviations of normal mean values as follows: tibial motor nerve conduction velocity, < 39.2 m/s; tibial compound muscle action potential amplitude, < 1.55 mV; sural sensory nerve conduction velocity, < 40.0 m/s; sural sensory nerve action potential amplitude, < 1.60 μ V [17].

Vascular parameters

Bilateral brachial blood pressure, brachial-ankle pulse wave velocity, and ankle brachial index in a supine position were measured using a Form PWV/ABI (BP-203RPE, Omron Colin, Tokyo, Japan) and the values for the 2 sides were averaged for use in statistical analysis. Carotid plaque score was obtained by ultrasonographic examination (Aplio, Toshiba, Tokyo, Japan) according to a previously described method [18].

Data analysis

All statistical analyses were conducted with IBM SPSS software (version 25.0). Data are presented as mean $\pm$ SD for variables with a parametric distribution and median (interquartile range) for variables with a non-parametric distribution. The normality of data distribution was assessed by the Shapiro–Wilk test. Continuous variables were compared between males and females using the parametric Student's *t* test or the non-parametric Mann–Whitney *U* test as applicable. Categorical variables were compared between males and females using the Pearson χ^2 test. Simple linear regression analysis was conducted to assess the linear relationships of clinical data and measures of physical fitness (absolute muscle strength, relative muscle strength, leg muscle quality, one-leg standing time, whole-body reaction time, maximal oxygen uptake) with parameters of peripheral nerve function (sural sensory nerve conduction velocity (SNCV), sural sensory nerve action potential amplitude (SNAP), tibial motor nerve conduction velocity (MNCV), tibial compound muscle action potential amplitude (CMAP)) and cardiac autonomic nerve function (CVRr at rest, CVRR during deep breathing). A forced-entry multiple linear regression model was used to estimate the associations between the physical fitness measures and the parameters of peripheral and cardiac autonomic nerve function as mentioned above. In this model, the independent variables included age, duration of diabetes, height, body mass index, weight loss rate (maximal body weight minus body weight at entry divided by maximal body weight), carotid plaque score, HbA1c level and insulin use. These variables, except for HbA1c level, were selected from all potential confounders comprising gender, smoking history, alcohol use, systolic blood pressure and levels of fasting plasma glucose, serum C-peptide, total cholesterol, triglycerides and high-density lipoprotein cholesterol as well as physical fitness measures by a stepwise procedure. On the other hand, HbA1c was selected as an independent variable in light of its generally accepted association with diabetic complications. In a multiple logistic regression model, we calculated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of probable and confirmed neuropathies in relation to physical fitness measures. Receiver operating

characteristic (ROC) curves were generated to depict the relation between sensitivity and specificity of one-leg standing time for diagnosing probable and confirmed neuropathies. *P* values < 0.05 were considered significant.

Results

The clinical characteristics of the 139 (100 male; 39 female) patients are shown in Table 1. For all patients, the mean (SD) age was 51 (14) years, and the median (interquartile range) duration of diabetes and A1c level were 7 (2–14) years and 90 (74–104) mmol/mol, respectively. Female patients included more never smokers, were of shorter stature and had greater fat mass, less skeletal muscle mass, lower diastolic pressure, lower ankle brachial index, lower A1 and lower serum creatinine than male patients. Other clinical variables did not differ between male and female patients. On the neurological examination, 33 (23.7%) patients had sensory symptoms, 75 (54.0%) had abnormal ankle reflexes and 38 (27.3%) had reduced touch perceptions. This study included 38 (27.3%) and 32 (23.0%) patients who had been diagnosed as having probable and confirmed neuropathies, respectively. The prevalence of these neuropathic symptoms, signs or clinical neuropathies did not differ between male and female patients (Table 1).

Physical fitness

Female patients had worse performance with respect to knee extension strength and whole-body reaction time than male patients, while other measures of physical fitness did not differ between male and female patients (Table 2).

Peripheral and cardiac autonomic nerve function

Peripheral nerve function was generally preserved. Female patients had higher CMAP and faster SNCV than male patients (Table 3).

Relation between physical fitness and peripheral and cardiac autonomic nerve function

Simple linear regression analyses showed that leg muscle quality and one-leg standing time significantly correlated with all of the peripheral nerve function parameters, while knee extension strength (in kilograms and as a percentage of body weight) and whole-body reaction time correlated with part of them (Table 4). Only maximal oxygen uptake showed no correlation with these parameters. On the other hand, all of the physical fitness measures correlated with CVRR at rest and during deep breathing (Table 4). Among the clinical variables, age and retinopathy significantly correlated with

Table 1 Clinical characteristics of patients

	All	Male	Female	<i>P</i> value Male versus female
<i>N</i>	139	100	39	
Age (years)	51 ± 14	50 ± 14	53 ± 15	0.278
Diabetes duration (years)	7 (2–14)	7 (1–12)	9 (4–18)	0.530
Smoking history, <i>n</i> (%)				0.024
Current	60 (43.2)	48 (48.0)	12 (30.8)	
Former	32 (23.0)	25 (25.0)	7 (17.9)	
Never	47 (33.8)	27 (27.0)	20 (51.3)	
Alcohol use, <i>n</i> (%)				0.059
Current	50 (36.0)	42 (42.0)	8 (20.5)	
Former	15 (10.8)	10 (10.0)	5 (12.8)	
Never	74 (53.2)	48 (48.0)	26 (66.7)	
Height (cm)	166.1 ± 10.8	170.7 ± 8.3	154.3 ± 6.5	< 0.001
Body mass index (kg/m ²)	24.7 (21.8–28.7)	25.1 (22.4–28.8)	23.3 (20.8–28.5)	0.276
Fat mass (%)	29.0 ± 9.5	26.7 ± 8.0	34.9 ± 10.6	< 0.001
Skeletal muscle mass (%)	38.7 ± 5.5	40.3 ± 4.6	34.5 ± 5.4	< 0.001
Weight loss rate (%)	13.0 (8.0–21.8)	13.2 (8.1–21.6)	12.5 (5.9–22.8)	0.558
Systolic BP (mmHg)	126 (116–136)	127 (116–138)	122 (109–134)	0.247
Diastolic BP (mmHg)	78 (71–84)	79 (72–85)	74 (68–82)	0.042
Brachial-ankle PWV (cm/s)	1355 (1217–1625)	1366 (1214–1624)	1343 (1230–1658)	0.822
Ankle brachial index	1.13 ± 0.08	1.14 ± 0.08	1.10 ± 0.07	0.008
Carotid plaque score	3.0 (1.1–6.3)	3.3 (1.2–6.7)	2.2 (1.1–5.8)	0.223
Fasting PG (mmol/l)	8.9 (7.2–12.1)	8.9 (7.2–12.5)	8.7 (7.2–10.1)	0.570
A1c [mmol/mol (%)]	90 (74–104) [10.6 (9.0–11.8)]	92 (78–106) [10.8 (9.4–12.0)]	86 (68–101) [10.1 (8.4–11.5)]	0.030
Serum creatinine (μmol/l)	63 (53–74)	69 (59–79)	52 (46–61)	< 0.001
Total cholesterol (mmol/l)	4.6 (3.9–5.2)	4.5 (3.9–5.1)	4.9 (4.0–5.3)	0.249
Triglycerides (mmol/l)	1.7 (1.2–2.3)	1.7 (1.2–2.4)	1.7 (1.2–2.2)	0.540
HDL-cholesterol (mmol/l)	1.1 (0.9–1.3)	1.1 (0.9–1.2)	1.1 (1.0–1.4)	0.157
Fasting serum C-peptide (nmol/l)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.782
UCPE (nmol/day)	17 (10–28)	19 (11–31)	16 (7–26)	0.176
UACR (mg/mmol)	1.4 (0.7–4.4)	1.5 (0.6–4.5)	1.2 (0.7–3.2)	0.724
Neuropathy, <i>n</i> (%)				
Sensory symptoms	33 (23.7)	27 (27.0)	6 (15.4)	0.148
Abnormal ankle reflex	75 (54.0)	53 (53.0)	22 (56.4)	0.717
Reduced touch perception	38 (27.3)	30 (30.0)	8 (20.5)	0.260
Probable neuropathy	38 (27.3)	31 (31.0)	7 (17.9)	0.121
Confirmed neuropathy	32 (23.0)	26 (26.0)	6 (15.4)	0.182
Retinopathy, <i>n</i> (%)	35 (25.2)	25 (25.0)	10 (25.6)	0.938
Insulin use, <i>n</i> (%)	37 (26.6)	30 (30.0)	7 (17.9)	0.149

Data are given as number (%), mean ± SD and median (interquartile range) for variables with a skewed distribution, or number (percent)

Weight loss rate = (maximal body weight (kg) – body weight at entry (kg)) × 100/maximal body weight (kg)

BP blood pressure, HDL high-density lipoprotein, PG plasma glucose, PWV pulse wave velocity, UACR urine albumin to creatinine ratio; UCPE, urine C-peptide excretion

all of the peripheral and cardiac autonomic nerve function parameters (Table 4).

In a forced-entry multiple linear regression model, one-leg standing time significantly correlated with CMAP,

SNAP and CVRR during deep breathing (Table 5). Among the clinical variables, age, diabetes duration and weight loss rate showed significant correlations with CVRR at

Table 2 Physical fitness of patients

	All	Male	Female	<i>P</i> value Male versus female
Knee extension strength (kg)	49.3 ± 18.6	54.9 ± 17.3	35.0 ± 13.7	< 0.001
Knee extension strength (% body weight)	65.0 (54.0–82.5)	70.0 (58.5–87.4)	55.0 (48.5–63.5)	< 0.001
Leg muscle quality	6.0 (5.1–7.2)	6.4 (5.2–7.4)	5.7 (5.1–6.9)	0.219
One-leg standing time with eyes open (s)	48 (17–60)	49 (18–60)	48 (13–60)	0.485
Whole-body reaction time (s)	0.369 (0.338–0.422)	0.359 (0.334–0.406)	0.393 (0.363–0.488)	0.001
Maximal oxygen uptake (ml/kg/min)	19.3 (16.1–22.4)	19.9 (16.3–22.9)	18.6 (14.9–22.2)	0.082

Data are mean ± SD or median (interquartile range) for variables with a skewed distribution or percent. Leg muscle quality is knee extension strength per unit of leg muscle mass

Table 3 Peripheral and cardiac autonomic nerve function of patients

	All	Male	Female	<i>P</i> value Male versus female
Tibial MNCV (m/s)	41.8 (39.3–45.1)	41.0 (38.9–45.0)	42.9 (40.4–45.3)	0.129
Tibial CMAP (mV)	11.9 ± 5.0	11.3 ± 4.6	13.4 ± 5.5	0.025
Sural SNCV (m/s)	48.4 ± 5.2	47.8 ± 5.3	49.9 ± 4.8	0.029
Sural SNAP (µV)	8.0 (4.3–13.3)	7.6 (4.2–12.5)	10.4 (4.7–14.7)	0.148
CVRR at rest (%)	2.1 (1.5–2.7)	2.2 (1.6–2.8)	1.8 (1.4–2.6)	0.081
CVRR during deep breathing (%)	5.1 (3.3–7.6)	5.3 (3.7–8.1)	4.4 (2.8–6.9)	0.070

Data are mean ± SD or median (interquartile range) for variables with a skewed distribution

CMAP compound muscle action potential amplitude, CVRR coefficient of variation of R–R interval, MNCV motor nerve conduction velocity, SNAP sensory nerve action potential amplitude, SNCV sensory nerve conduction velocity

rest, with CVRR at rest and during deep breathing and with SNCV, respectively (Table 5).

Relation between physical fitness and probable and confirmed neuropathies

The unadjusted and age- and gender-adjusted logistic regression models (Table 6: Crude model and Model 1, respectively) indicated that leg muscle quality and one-leg standing time were associated with both probable and confirmed neuropathies. However, after additional adjustment for duration of diabetes, only one-leg standing time significantly correlated with both probable and confirmed neuropathies (the adjusted ORs (95% CIs) of probable and confirmed neuropathies were 0.925 (0.892–0.960) and 0.952 (0.924–0.981), respectively, per 1-s increment in one-leg standing time) (Table 6: Model 2).

Figure 1 shows the ROC curves for the accuracy of one-leg standing time with the true-positive rate (sensitivity) as a function of the false-positive rate (1 – specificity) for diagnosing probable and confirmed neuropathies. The area under the curve was larger for probable neuropathy (0.812)

than for confirmed neuropathy (0.754). The one-leg standing time of 23 s had the highest diagnostic performance with a sensitivity of 66% and a specificity of 81% for probable neuropathy and a sensitivity of 63% and a specificity of 77% for confirmed neuropathy.

Discussion

The current study is the first to demonstrate that certain objective measures of physical fitness correlate with peripheral and cardiac autonomic nerve function in patients with type 2 diabetes across a wide range of ages. In simple linear regression analyses, leg muscle quality and one-leg standing time correlated with all of the parameters of the peripheral and cardiac autonomic nerve function, while the other measures of physical fitness correlated with part of these. After adjustment for age and other potential confounders selected by a stepwise procedure, one-leg standing time still showed significant associations with CMAP, SNAP and CVRR during deep breathing. Thus, the relationship between one-leg

Table 4 Simple regression analyses of peripheral and cardiac autonomic nerve function in relation to patients' characteristics and physical fitness measures

	Coefficient (95% CIs)		P value	
	Tibial MNCV (m/s)	Tibial CMAP (mV)	Sural SNCV (m/s)	Sural SNAP (μ V)
Male gender	-0.915 (-2.681 to -0.852) 0.308	-2.096 (-3.928 to -0.263) 0.025	-2.178 (-4.134 to -0.222) 0.029	-2.069 (-4.789 to 0.651) 0.135
Age (years)	-0.064 (-0.119 to -0.008) 0.025	-0.093 (-0.150 to -0.036) 0.002	-0.090 (-0.152 to -0.028) 0.005	-0.190 (-0.271 to -0.110) < 0.001
Diabetes duration (years)	-0.099 (-0.212 to 0.014) 0.085	-0.159 (-0.275 to -0.043) 0.008	-0.085 (-0.215 to 0.045) 0.195	-0.311 (-0.482 to -0.140) < 0.001
Smoking history	-0.110 (-1.025 to 0.805) 0.813	-0.653 (-1.608 to 0.302) 0.179	-0.352 (-1.386 to 0.682) 0.502	-0.424 (-0.835 to 0.987) 0.553
Alcohol use	0.433 (-0.426 to 1.291) 0.321	0.068 (-0.883 to 0.970) 0.148	-0.236 (-1.218 to 0.746) 0.635	-0.877 (-2.196 to 0.112) 0.191
Height (cm)	-0.052 (-0.126 to 0.022) 0.164	-0.050 (-0.127 to 0.028) 0.209	-0.020 (-0.106 to 0.065) 0.638	-0.073 (-0.187 to 0.041) 0.207
Body mass index (kg/m ²)	0.180 (0.031 to 0.328) 0.018	0.180 (0.030 to 0.330) 0.019	0.294 (0.135 to 0.453) < 0.001	0.087 (-0.137 to 0.312) 0.442
Fat mass (%)	0.109 (0.026 to 0.192) 0.010	0.140 (0.055 to 0.226) 0.001	0.205 (0.114 to 0.295) < 0.001	0.129 (0.001 to 0.258) 0.048
Skeletal muscle mass (%)	-0.152 (-0.296 to -0.008) 0.039	-0.190 (-0.340 to -0.040) 0.014	-0.317 (-0.476 to -0.159) < 0.001	-0.197 (-0.420 to 0.025) 0.082
Weight loss rate (%)	-0.168 (-0.252 to -0.084) < 0.001	-0.121 (-0.212 to -0.030) 0.010	-0.243 (-0.336 to -0.150) < 0.001	-0.153 (-0.288 to -0.018) 0.026
Systolic BP (mmHg)	-0.040 (-0.084 to 0.003) 0.070	-0.031 (-0.076 to 0.014) 0.173	-0.030 (-0.078 to 0.018) 0.217	-0.052 (-0.118 to 0.014) 0.124
Diastolic BP (mmHg)	-0.051 (-0.119 to 0.016) 0.136	-0.036 (-0.107 to 0.036) 0.329	-0.057 (-0.134 to 0.020) 0.144	-0.010 (-0.019 to 0.000) 0.040
Brachial-ankle PWV (cm/s)	0.002 (-0.004 to 0.001) 0.171	-0.002 (-0.005 to 0.000) 0.052	-0.002 (-0.005 to 0.000) 0.072	-0.004 (-0.007 to 0.000) 0.042
Ankle brachial index	-7.651 (-17.517 to 2.214) 0.127	-12.756 (-22.963 to -2.550) 0.015	-7.287 (-18.237 to 3.662) 0.190	-12.804 (-27.979 to 2.371) 0.098
				0.794
				0.066 (0.018 to 0.114) 0.007
				0.032 (0.000 to 0.063) 0.485
				-0.003 (-0.022 to 0.016) 0.738
				0.020 (-0.013 to 0.052) 0.017
				-0.034 (-0.093 to 0.026) 0.263
				-0.049 (-0.077 to -0.020) 0.001
				-0.060 (-0.107 to -0.013) 0.013
				-0.004 (-0.005 to -0.002) < 0.001
				1.091 (-5.621 to 7.804) 0.748

Table 4 (continued)

	Coefficient (95% CIs) <i>P</i> value		Tibial MNCV (m/s)	Tibial CMAP (mV)	Sural SNCV (m/s)	Sural SNAP (μV)	CVRR at rest (%)	CVRR during deep breath- ing (%)
Carotid plaque score	– 0.367 (– 0.550 to – 0.184) < 0.001	– 0.375 (– 0.567 to – 0.182) < 0.001	– 0.417 (– 0.619 to – 0.214) < 0.001	– 0.569 (– 0.851 to – 0.287) < 0.001	– 0.039 (– 0.080 to 0.002) 0.061	– 0.167 (– 0.292 to – 0.042) 0.009		
Fasting PG (mmol/l)	– 0.229 (– 0.491 to 0.033) 0.087	– 0.211 (– 0.483 to 0.062) 0.128	– 0.368 (– 0.652 to – 0.083) 0.012	– 0.056 (– 0.458 to 0.347) 0.786	– 0.010 (– 0.065 to 0.045) 0.714	0.107 (– 0.067 to 0.280) 0.225		
A1c [mmol/mol (%)]	– 0.043 (– 0.076 to – 0.009) 0.013	– 0.021 (– 0.057 to 0.015) 0.244	– 0.042 (– 0.079 to – 0.005) 0.027	– 0.006 (– 0.059 to 0.047) 0.818	0.005 (– 0.002 to 0.012) 0.173	0.013 (– 0.010 to 0.035) 0.267		
Serum creatinine (μmol/l)	– 0.003 (– 0.044 to 0.039) 0.905	– 0.026 (– 0.070 to 0.017) 0.233	0.006 (– 0.043 to 0.055) 0.810	– 0.023 (– 0.087 to 0.041) 0.484	– 0.004 (– 0.013 to 0.005) 0.370	– 0.004 (– 0.033 to 0.025) 0.804		
Total cholesterol (mmol/l)	0.233 (– 0.477 to 0.944) 0.517	0.233 (– 0.522 to 0.969) 0.554	– 0.176 (– 0.959 to 0.607) 0.658	0.941 (– 0.148 to 2.029) 0.090	0.084 (– 0.068 to 0.236) 0.277	0.264 (– 0.205 to 0.733) 0.267		
Triglycerides (mmol/l)	0.185 (– 0.325 to 0.694) 0.475	0.131 (– 0.405 to 0.666) 0.631	– 0.190 (– 0.749 to 0.369) 0.503	0.230 (– 0.559 to 1.020) 0.565	0.128 (0.021 to 0.235) 0.019	0.198 (– 0.139 to 0.536) 0.247		
HDL-cholesterol (mmol/l)	– 1.093 (– 3.412 to 1.226) 0.353	– 1.597 (– 4.024 to 0.829) 0.195	– 0.906 (– 3.542 to 1.729) 0.497	– 1.065 (– 4.659 to 2.530) 0.559	– 0.543 (– 1.040 to – 0.045) 0.033	– 0.856 (– 2.396 to 0.685) 0.274		
Fasting serum C-peptide (nmol/l)	2.995 (0.578 to 5.411) 0.016	2.929 (0.382 to 5.477) 0.025	3.251 (0.547 to 5.955) 0.019	2.085 (– 1.725 to 5.895) 0.281	0.173 (– 0.364 to 0.711) 0.524	0.088 (– 1.579 to 1.755) 0.917		
UCPE (nmol/day)	0.017 (– 0.030 to 0.064) 0.477	0.035 (– 0.014 to 0.084) 0.160	0.013 (– 0.039 to 0.065) 0.618	0.001 (– 0.073 to 0.075) 0.978	0.008 (– 0.002 to 0.018) 0.107	0.015 (– 0.016 to 0.047) 0.335		
UA/ACR (mg/mmol)	– 0.197 (– 0.295 to – 0.099) < 0.001	– 0.140 (– 0.241 to – 0.039) 0.007	– 0.143 (– 0.251 to – 0.035) 0.010	– 0.112 (– 0.269 to 0.046) 0.163	– 0.017 (– 0.039 to 0.005) 0.138	– 0.036 (– 0.105 to 0.033) 0.304		
Retinopathy	– 3.512 (– 5.248 to – 1.777) < 0.001	– 3.333 (– 5.181 to – 1.484) 0.001	– 4.328 (– 6.428 to – 2.228) < 0.001	– 6.717 (– 9.319 to – 4.114) < 0.001	– 0.639 (– 1.027 to – 0.251) 0.001	– 2.388 (– 3.561 to – 1.214) < 0.001		
Insulin use	0.577 (– 1.223 to 2.377) 0.527	0.342 (– 1.555 to 2.238) 0.722	1.703 (– 0.338 to 3.743) 0.101	1.015 (– 1.767 to 3.798) 0.472	0.450 (0.063 to 0.838) 0.023	1.149 (– 0.043 to 2.342) 0.059		

Table 4 (continued)

Coefficient (95% CIs) <i>P</i> value						
	Tibial MNCV (m/s)	Tibial CMAP (mV)	Sural SNCV (m/s)	Sural SNAP (μV)	CVRR at rest (%)	CVRR during deep breathing (%)
Knee extension strength (kg)	0.052 (0.009 to 0.094) 0.017	0.032 (− 0.013 to 0.077) 0.160	0.057 (0.010 to 0.104) 0.017	0.075 (0.010 to 0.141) 0.024	0.022 (0.013 to 0.030) < 0.001	0.068 (0.042 to 0.094) < 0.001
Knee extension strength (%BW)	0.053 (0.013 to 0.093) 0.010	0.020 (− 0.023 to 0.064) 0.355	0.028 (− 0.019 to 0.075) 0.236	0.105 (0.044 to 0.166) 0.001	0.017 (0.009 to 0.026) < 0.001	0.068 (0.043 to 0.093) < 0.001
Leg muscle quality (kg/kg)	0.995 (0.525 to 1.466) < 0.001	0.733 (0.221 to 1.245) 0.005	0.912 (0.367 to 1.457) 0.001	1.826 (1.116 to 2.536) < 0.001	0.203 (0.101 to 0.306) < 0.001	0.735 (0.423 to 1.046) < 0.001
One-leg standing time with eyes open (s)	0.082 (0.047 to 0.116) < 0.001	0.100 (0.065 to 0.135) < 0.001	0.071 (0.031 to 0.111) 0.001	0.154 (0.103 to 0.205) < 0.001	0.021 (0.013 to 0.028) < 0.001	0.080 (0.059 to 0.101) < 0.001
Whole-body reaction time (s)	− 3.695 (− 11.085 to 3.696) 0.325	− 4.162 (− 11.873 to 3.549) 0.288	− 3.365 (− 11.849 to 5.118) 0.434	− 12.388 (− 23.687 to − 1.088) 0.032	− 2.110 (− 3.693 to − 0.527) 0.009	− 8.512 (− 13.290 to − 3.735) 0.001
Maximal oxygen uptake (ml/kg/min)	0.136 (− 0.019 to 0.291) 0.084	0.116 (− 0.048 to 0.280) 0.164	− 0.001 (− 0.184 to 0.182) 0.993	0.161 (− 0.080 to 0.401) 0.189	0.042 (0.009 to 0.076) 0.014	0.172 (0.071 to 0.273) 0.001

Bold values indicate statistical significance ($P < 0.05$)

Weight loss rate = (maximal body weight (kg) − body weight at entry (kg)) $\times$ 100/maximal body weight (kg)

CI confidence interval, BP blood pressure, CMAP compound muscle action potential amplitude, CVRR coefficient of variation of R–R interval, HDL high-density lipoprotein, MNCV motor nerve conduction velocity, SNAP sensory nerve action potential amplitude, SNCV sensory nerve conduction velocity, PG plasma glucose, PWV pulse wave velocity, UACR urine albumin to creatinine ratio, UCPE urine C-peptide excretion

Table 5 Forced-entry multiple regression analyses of peripheral and cardiac autonomic nerve function in relation to the selected potential confounders

Coefficient (95% CIs) <i>P</i> value							
	Tibial MNCV (m/s)	Tibial CMAP (mV)	Sural SNCV (m/s)	Sural SNAP (μV)	CVRR at rest (%)	CVRR during deep breathing (%)	
Age (years)	0.17 (− 0.070 to 0.103)	0.010 (− 0.082 to 0.102)	− 0.008 (− 0.108 to 0.093)	− 0.089 (− 0.215 to 0.036)	− 0.032 (− 0.050 to − 0.014)	− 0.025 (− 0.080 to 0.029)	
Diabetes duration (years)	0.703	0.830	0.877	0.160	0.001	0.355	
	0.006 (− 0.129 to 0.141)	− 0.059 (− 0.203 to 0.086)	0.036 (− 0.122 to 0.193)	− 0.195 (− 0.392 to 0.001)	− 0.033 (− 0.061 to − 0.005)	− 0.090 (− 0.175 to − 0.004)	
Height (cm)	0.931	0.421	0.654	0.052	0.022	0.039	
Height (cm)	− 0.142 (− 0.363 to 0.080)	− 0.096 (− 0.333 to 0.141)	− 0.063 (− 0.322 to 0.195)	− 0.095 (− 0.417 to 0.227)	− 0.040 (− 0.085 to 0.006)	− 0.062 (− 0.202 to 0.077)	
	0.207	0.421	0.626	0.560	0.089	0.377	
Body mass index (kg/m ²)	0.183 (− 0.265 to 0.632)	− 0.081 (− 0.561 to 0.399)	0.046 (− 0.478 to 0.569)	− 0.429 (− 1.083 to 0.224)	− 0.057 (− 0.150 to 0.036)	− 0.233 (− 0.516 to 0.051)	
	0.419	0.738	0.862	0.195	0.225	0.106	
Weight loss rate (%)	− 0.096 (− 0.212 to 0.020)	− 0.020 (− 0.144 to 0.104)	− 0.145 (− 0.280 to − 0.010)	− 0.053 (− 0.222 to 0.155)	0.005 (− 0.019 to 0.029)	0.006 (− 0.067 to 0.079)	
	0.102	0.752	0.036	0.530	0.689	0.877	
Carotid plaque score	− 0.202 (− 0.434 to 0.030)	− 0.193 (− 0.441 to 0.056)	− 0.237 (− 0.508 to 0.033)	− 0.275 (− 0.613 to 0.063)	0.014 (− 0.034 to 0.062)	− 0.059 (− 0.206 to 0.088)	
	0.087	0.127	0.085	0.110	0.554	0.426	
A1c [mmol/mol (%)]	− 0.025 (− 0.063 to 0.013)	− 0.008 (− 0.048 to 0.032)	− 0.018 (− 0.062 to 0.026)	− 0.001 (− 0.056 to 0.054)	− 0.002 (− 0.010 to 0.005)	− 0.001 (− 0.025 to 0.022)	
	0.191	0.695	0.427	0.965	0.536	0.907	
Insulin use	0.207 (− 1.745 to 2.158)	0.837 (− 1.252 to 2.925)	1.370 (− 0.906 to 3.646)	1.402 (− 1.439 to 4.243)	0.390 (− 0.013 to 0.793)	0.916 (− 0.317 to 2.149)	
	0.834	0.428	0.235	0.330	0.058	0.143	
Knee extension strength (kg)	0.007 (− 0.248 to 0.263)	0.043 (− 0.231 to 0.317)	0.016 (− 0.282 to 0.314)	− 0.016 (− 0.388 to 0.356)	0.045 (− 0.008 to 0.098)	0.111 (− 0.051 to 0.272)	
	0.955	0.756	0.914	0.933	0.093	0.176	
Knee extension strength (%BW)	0.058 (− 0.132 to 0.248)	− 0.140 (− 0.343 to 0.063)	− 0.067 (− 0.288 to 0.155)	− 0.148 (− 0.424 to 0.128)	− 0.004 (− 0.044 to 0.035)	− 0.035 (− 0.155 to 0.085)	
	0.546	0.173	0.551	0.289	0.826	0.565	
Leg muscle quality (kg/kg)	− 0.218 (− 2.239 to 1.802)	1.190 (− 0.973 to 3.353)	0.953 (− 1.404 to 3.310)	2.697 (− 0.245 to 5.639)	− 0.246 (− 0.663 to 0.172)	− 0.178 (− 1.455 to 1.099)	
	0.831	0.277	0.423	0.072	0.245	0.782	
One-leg standing time with eyes open (s)	0.052 (− 0.001 to 0.104)	0.091 (0.035 to 0.147)	0.043 (− 0.018 to 0.104)	0.083 (0.007 to 0.159)	0.004 (− 0.007 to 0.015)	0.042 (0.009 to 0.075)	
	0.053	0.002	0.163	0.033	0.470	0.014	
Whole-body reaction time (s)	0.016 (− 8.574 to 8.606)	− 0.810 (− 10.005 to 8.384)	− 0.856 (− 9.163 to 10.875)	− 3.354 (− 15.862 to 9.153)	− 0.012 (− 1.787 to 1.763)	− 1.826 (− 7.254 to 3.601)	
	0.997	0.861	0.865	0.596	0.989	0.505	
Maximal oxygen uptake (ml/kg/min)	0.084 (− 0.109 to 0.276)	0.033 (− 0.174 to 0.239)	0.012 (− 0.213 to 0.237)	− 0.162 (− 0.442 to 0.119)	− 0.007 (− 0.047 to 0.033)	− 0.006 (− 0.128 to 0.116)	
	0.391	0.754	0.914	0.256	0.736	0.918	

Bold values indicate statistical significance ($P < 0.05$)

Weight loss rate = (maximal body weight (kg) − body weight at entry (kg)) × 100/maximal body weight (kg)

CI confidence interval, *CMAP* compound muscle action potential amplitude, *CVRR* coefficient of variation of R–R interval, *HDL* high-density lipoprotein, *MNCV* motor nerve conduction velocity, *SNAP* sensory nerve action potential amplitude, *SNCV* sensory nerve conduction velocity

Table 6 Adjusted ORs with CIs for associations of physical fitness parameters with probable and confirmed neuropathies

Crude model	Probable neuropathy		Confirmed neuropathy	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Knee extension strength (kg)	0.971 (0.950–0.994)	0.012	0.979 (0.957–1.002)	0.067
Knee extension strength (%BW)	0.975 (0.954–0.997)	0.026	0.982 (0.960–1.004)	0.109
Leg muscle quality (kg/kg)	0.605 (0.450–0.814)	0.001	0.704 (0.528–0.940)	0.017
One-leg standing time with eyes open (s)	0.942 (0.922–0.963)	< 0.001	0.957 (0.937–0.976)	< 0.001
Whole-body reaction time (s)	2.130 (0.080–56.671)	0.651	3.210 (0.114–90.738)	0.494
Maximal oxygen uptake (ml/kg/min)	0.879 (0.802–0.963)	0.006	0.932 (0.855–1.017)	0.113
Model 1	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Knee extension strength (kg)	0.961 (0.930–0.992)	0.014	0.970 (0.940–1.001)	0.060
Knee extension strength (%BW)	0.967 (0.942–0.993)	0.013	0.976 (0.951–1.002)	0.070
Leg muscle quality (kg/kg)	0.618 (0.449–0.853)	0.003	0.728 (0.535–0.990)	0.043
One-leg standing time with eyes open (s)	0.939 (0.915–0.964)	< 0.001	0.954 (0.931–0.978)	< 0.001
Whole-body reaction time (s)	1.120 (0.025–50.647)	0.953	2.772 (0.066–116.810)	0.593
Maximal oxygen uptake (ml/kg/min)	0.887 (0.805–0.977)	0.015	0.940 (0.859–1.029)	0.180
Model 2	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Knee extension strength (kg)	0.961 (0.923–1.000)	0.050	0.982 (0.948–1.017)	0.314
Knee extension strength (%BW)	0.953 (0.921–0.987)	0.007	0.971 (0.941–1.001)	0.058
Leg muscle quality (kg/kg)	0.491 (0.316–0.763)	0.002	0.714 (0.497–1.024)	0.067
One-leg standing time with eyes open (s)	0.925 (0.892–0.960)	< 0.001	0.952 (0.924–0.981)	0.001
Whole-body reaction time (s)	0.537 (0.009–32.263)	0.766	1.423 (0.024–85.212)	0.866
Maximal oxygen uptake (ml/kg/min)	0.820 (0.707–0.952)	0.009	0.887 (0.781–1.007)	0.063

Bold values indicate statistical significance ($P < 0.05$)

Model 1 is adjusted for age and gender. Model 2 is additionally adjusted for duration of diabetes

CI confidence interval, OR odds ratio

Fig. 1 ROC curves of one-leg standing time in relation to probable (a) and confirmed neuropathies (b). AUC area under the curve, CI confidence interval

standing time and peripheral nerve function may not be confined to older patients, but be present independent of age.

The prevalence of diabetic neuropathy varies as a consequence of variations in the population and location of the studies, the severity of diabetes and the diagnostic criteria for diabetic neuropathy itself. In this study, 27.3 and 23.0% of the patients had been diagnosed with probable

and confirmed neuropathies, respectively, based on the minimal criteria proposed by the Toronto diabetic neuropathy expert group [16], and the observed prevalence seemed to be consistent with that in the previous studies showing approximately 30% in hospital-based populations and 20% in community-based samples [19]. This study demonstrated that, among the physical fitness measures,

Fig. 2 The regulation of one-leg standing balance/postural stability by multiple physiological systems: the impacts of diabetes and its complication

only one-leg standing time was associated with both probable and confirmed neuropathies after adjustment for age, gender and duration of diabetes. The ROC curves evaluated the diagnostic performance of one-leg standing time for probable and confirmed neuropathies and showed that the cutoff value of 23 s had the highest diagnostic performance with a sensitivity of 66% and a specificity of 81% for probable neuropathy and a sensitivity of 63% and a specificity of 77% for confirmed neuropathy.

It has been reported that postural instability, as assessed using posturography, force platform or accelerometer, was associated with clinical neuropathies in patients with diabetes [20]. To make an early diagnosis of diabetic neuropathy, detailed assessments of the feet are required with the aid of a battery of objective testing such as quantitative sensory testing, nerve conduction measurement and autonomic function tests [21]. However, such assessments are often difficult to perform in routine clinical practice. In this regard, one-leg standing time is easily assessed in most circumstances without the need for specific skills and instruments and may possibly be used as a proxy measure to indicate the presence of peripheral and cardiac autonomic nerve dysfunction as well as of clinical neuropathies in patients with type 2 diabetes.

There are multiple physiological systems that regulate one-leg standing balance/postural stability, including proprioception, somatosensory input, motor output, visual function, vestibular function, cognitive function, musculoskeletal function and cardiovascular function (Fig. 2). Diabetes and its complications may affect all of these functions [22, 23]: (1) Diabetic peripheral sensorimotor neuropathy affects

somatosensory input that is touch and pressure sensation, proprioceptive feedback from the muscle and joint sensors, and muscle reaction time and strength, in the feet and legs. (2) The greatest impairment in postural stability observed in people with diabetic neuropathy and eyes closed suggests a reliance on vision to compensate for sensory deficits [24]. This reliance can be reduced in the presence of diabetic retinopathy, cataract or macular edema. (3) The prevalence of vestibular dysfunction is higher among people with diabetes. Diabetes exerts vestibulotoxic effects through ischemia of the vestibular structures induced by diabetic microangiopathy and altered metabolism of inner ear fluids induced by high glucose [23]. (4) Type 2 diabetes-related deficits of cognitive function such as learning and attention disrupt central processing to control posture and prevent falls [20]. (5) Type 2 diabetes-related impairments of glucose metabolism and insulin resistance affect mechanical and metabolic muscle function due to reduced skeletal muscle substrate utilization and mitochondrial response to insulin. Such impairments result in abnormal accumulation of free fatty acids and triglycerides in skeletal muscle cells, possibly leading to an increased risk for physical disability, frailty and falling associated with progressive declines in leg muscle mass and strength [25]. Of note, impaired musculoskeletal function due to an increase in adiposity may also increase the risk of postural instability [26]. Furthermore, accelerated loss of muscle mass and strength in the feet and legs has been observed in patients with diabetic neuropathy, being related to the slowing of movements and unstable gait, and more frequent falls [27]. (6) Orthostatic hypotension (OH) is

characterized by a sudden and sustained reduction in blood pressure upon standing secondary to underlying systemic diseases involving autonomic nerves such as diabetic autonomic neuropathy and believed to contribute to an increased fall risk. Although a recent meta-analysis failed to demonstrate an independent association between OH and falling [28], our results suggest a possible link between postural instability (one-leg standing time) and cardiac autonomic neuropathy (CVRR) in patients with type 2 diabetes and concur with a previous report by Yamamoto et al. [29]. Besides, stable upright posture can be maintained through information exchange between cardio-postural–musculoskeletal systems [30]. Under orthostatic stress, contraction of pelvic and leg skeletal muscles increases blood flow back to the heart and maintains cardiac output (skeletal muscle pump) [31]. Therefore, reduced muscle mass and strength in musculoskeletal disorders under orthostatic challenge could lead to a substantial drop in blood pressure (OH) and contribute to balance deficits, which is common among patients with neurodegenerative disorders such as diabetic neuropathy [32]. Collectively, diabetic peripheral sensorimotor and possibly autonomic neuropathies could be the major determinants of postural instability associated with diabetes.

It is well known that lifestyle intervention involving healthy diet and exercise can significantly reduce the incidence of diabetes and its complications including neuropathy. A previous study reported that lifestyle intervention with diet and exercise counselling in patients with neuropathy associated with prediabetes results in epidermal nerve fiber reinnervation and pain relief [33]. More recently, Singleton et al. [34] reported that exercise-induced improvement in metabolic syndrome features increased cutaneous regenerative capacity in patients with metabolic syndrome without symptoms or examination evidence of neuropathy. Based on a systematic review of the research on the effects of exercise programs on heart rate variability, baroreflex sensitivity or heart rate recovery in patients with type 2 diabetes, exercise training leads to improvements in cardiac autonomic function [35]. Taking all these into account, it is possible that exercise could induce metabolic improvements, slow or prevent the progression of peripheral and autonomic neuropathies, and improve physical fitness including gait and balance in patients with prediabetes and type 2 diabetes [36, 37]. Although there is a paucity of knowledge about the exercise-related mechanism(s) slowing or preventing the development of diabetic neuropathy, one possible explanation for the linkage of physical inactivity to diabetic neuropathy is insulin resistance, which is common in obesity, sedentary lifestyle and metabolic syndrome and may contribute to neuronal injuries via inducing oxidative stress due to mitochondrial dysfunction and enhanced proinflammatory states, and impaired insulin signaling affecting downstream phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase pathways in neurons [38].

There are limitations to our study. First, it was not possible to assess the causality of the relation between low physical fitness and peripheral nerve dysfunction or neuropathy due to the cross-sectional nature of the study. Second, the observed relations need to be interpreted with caution when extrapolating to patients under tight glycemic control, as our study population included many patients with poor glycemic control. Although we controlled for A1c levels, it is possible that certain relations may have occurred only in the presence of poor glycemic control. Third, we examined patients who had normal cardiovascular response to the double two-step Master exercise test and relatively preserved peripheral nerve function. Therefore, our findings may not be generalizable to patients with clinical cardiovascular diseases or those with more severe neuropathy. Fourth, we did not investigate potential confounders such as asymptomatic cerebrovascular lesions and daily physical activity, but these variables might affect the relations observed in our study. Fifth, this study included a relatively small number of female patients. However, there were no significant associations of gender with peripheral nerve function parameters in multiple linear regression analyses. In addition, our preliminary data that evaluated peripheral nerve functions in 299 patients (212 men; 87 women) with type 2 diabetes gave essentially the same results (data not shown).

Conclusions

In summary, short one-leg standing time with eyes open correlated with peripheral and cardiac autonomic nerve dysfunction in patients with type 2 diabetes across a wide range of ages. The one-leg standing time of 23 s was found to be 66 and 63% sensitive and 81 and 77% specific for diagnosing probable and confirmed neuropathies, respectively, in these patients.

Acknowledgements The authors gratefully acknowledge the contribution of Izumi Furukawa, Masanori Chiba and Yukinori Arakawa for data collection and analysis.

Author Contributions KS contributed to the study design, data collection, analysis, interpretation, writing and approving the manuscript. TH, AT and TY contributed to data collection and final approval of the manuscript. SS and TS contributed to reviewing the draft and final approval of the manuscript.

Compliance with ethical standards

Conflicts of interest The authors have nothing to declare.

Human rights statement and informed consent All analyses were conducted with the approval of the Ethical Committee of the Ohta Nishinouchi Hospital (approval no. N/A, approval date: 30 July 2014) and

in accordance with the Helsinki Declaration of 1964 and later versions. No informed consent was given because existing data were retrieved and analyzed anonymously.

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