Journal of Diabetes and Its Complications 36 (2022) 108134

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

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

The association between physical activity time and neuropathy in longstanding type 1 diabetes: A cross-sectional analysis of the Canadian study of longevity in type 1 diabetes

Evan J.H. Lewis [a,*], Leif E. Lovblom [a], Sebastien Lanctot [a], Daniel Scarr [a], Nancy Cardinez [a], Genevieve Boulet [b], Alanna Weisman [a,b], Julie A. Lovshin [b,c], Yuliya Lytvyn [c], Hillary A. Keenan [d], Michael H. Brent [e], Narinder Paul [f], David Z.I. Cherney [c], Vera Bril [g], Bruce A. Perkins [a,b]

[a] Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
[b] Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto. Toronto, Ontario, Canada
[c] Division of Nephrology, Department of Medicine, University of Toronto. Toronto, Ontario, Canada
[d] Research Division, Joslin Diabetes Center. Boston, MA, USA.
[e] Department of Ophthalmology and Vision Sciences, Department of Medicine, University of Toronto. Toronto, Ontario, Canada
[f] Joint Department of Medical Imaging, Division of Cardiothoracic Radiology, University Health Network, Toronto, Ontario, Canada.
[g] The Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Krembil Neuroscience Centre, Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada.

ARTICLE INFO

Keywords:
Physical activity
Exercise
Type 1 diabetes
Neuropathy
Complications

ABSTRACT

Aim: Physical activity (PA) is recommended to improve glycemic control in T1D; however, the effect of PA on distal symmetric polyneuropathy (DSPN) and cardiac autonomic function in longstanding T1D is unknown.
Methods: Data from 75 participants were collected as part of the Canadian Study of Longevity in T1D. Participants completed a physical exam, medical history, extensive complications phenotyping and reported their daily PA from the preceding 12-months. Pearson and Spearman correlations were used to assess PA time and complications variables. Linear regression was used to test associations between PA time, neurological and electrophysiological measures. Univariable regression was used to indicate the change in the given independent variables associated with a 30-min increase in PA per week.
Results: Participants were 66 ± 8 years old with diabetes duration of 54 [52,58] years, HbA_{1c} was 7.3 ± 0.8, 65 (89%) had DSPN. Weekly PA time was 156 ± 132 min, and 35(47%) reported ≧150 min/week. Participants with DSPN reported lower PA time compared to individuals without DSPN (141 ± 124 min/week vs. 258 ± 129 min/week; $p = 0.015$). PA time was associated with better cooling detection threshold ($r = 0.24$; $p = 0.043$), peroneal and sural amplitude ($r = 0.36$; $p = 0.0017$, $r_s = 0.26$; $p = 0.024$) and conduction velocity ($r_s = 0.28$; $p = 0.015$, $r = 0.23$; $p = 0.050$). Linear regression adjusting for age and HbA1c, showed that for each 30-min of PA there was a 0.09mv higher peroneal amplitude ($p = 0.032$) and 0.048 ms lower peroneal F-wave latency ($p = 0.022$).
Conclusion: In longstanding T1D, PA time is associated with superior large nerve fibre function in the lower limbs and some better measures of small nerve fibre function.

1. Introduction

Diabetes is associated with increased risk of complications from chronic exposure to hyperglycaemia. Diabetic distal symmetric polyneuropathy (DSPN) is the most prevalent diabetes complication that affects 50% of people with diabetes[1]. While DSPN affects sensory and motor nerves, cardiac autonomic neuropathy (CAN) affects the autonomic nervous system that regulates cardiovascular function and these frequently coexist. CAN is present in up to 30% of people with diabetes[2]. The development and progression of DSPN and CAN directly affects

* Corresponding author at: Lunenfeld-Tanenbaum Research Institute, Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, L5209-60 Murray Street Box 16, Toronto, Ontario M5T3L9, Canada.
E-mail address: evan470@icloud.com (E.J.H. Lewis).

https://doi.org/10.1016/j.jdiacomp.2022.108134
Received 16 July 2021; Received in revised form 18 August 2021; Accepted 25 September 2021
Available online 31 January 2022

quality of life and increases morbidity[3] and mortality[4].

For individuals with diabetes, current clinical practice guidelines recommended at least 150 min/week of physical activity[5]. In addition to supporting healthy blood glucose control that reduces the risk of developing DSPN and CAN, physical activity can support peripheral nerve health by numerous mechanisms including increasing nerve blood flow[6], inducing axonal sprouting[7], increasing the concentration of neurotransmitters[8] and Na/K ATPase[9] that can result in improved nerve conduction velocity[10]. There is consistent evidence demonstrating a causal relationship between physical activity and benefits for DSPN and CAN in participants with type 2 diabetes (T2D). Recent systematic reviews in this population have shown that physical activity improves blood glucose control, DSPN and CAN[11,12]. This includes improvements in small nerve fibre morphology measured by intra-epidermal nerve fibre density (IENFD)[11] and physical outcomes including ambulation measured by the 10-metre walk test and six-minute walk test[13]. A recent systematic review of exercise interventions for CAN in T2D showed a benefit for heart rate variability (HRV), baroreflex sensitivity (BRS) and heart rate recovery (HRR)[12].

In contrast, there has been limited investigation into the effects of physical activity on DSPN and CAN in T1D. The Diabetes Complications and Control Trial was the first lifestyle intervention study to show that intensive blood glucose management in conjunction with diet and exercise counseling reduced the incidence of DSPN and CAN in individuals with T1D[14]. More recently, two recent meta-analyses show consistent benefits of physical activity for individuals with T1D including improved HbA1c, lower daily insulin dose, increased aerobic capacity and cardiovascular health[15,16]; however, the included studies did not consistently report changes in DSPN or CAN. While recent observational studies provide mechanistic insights into the effects of DSPN on neuromuscular function in T1D[17,18] more data on the relationship between physical activity and DSPN and CAN in T1D are needed.

Though T1D is generally seen as a risk factor for DSPN and CAN, it is presently not known if physical activity time is associated with DSPN or CAN in those who have essentially experienced a lifetime of exposure to T1D. We aimed to determine the association between physical activity, DSPN and CAN as an exploratory analysis in the Canadian Study of Longevity in Type 1 Diabetes.

2. Subjects, materials and methods

2.1. Study design

The present study is an analysis of Phase 2 of the Canadian Study of Longevity in Type 1 Diabetes (JDRF operating grant 17–2013-312). The first phase of the Canadian Study of Longevity in Type 1 Diabetes was a cross-sectional study of over 300 adults living with T1D for ≥50 years. The primary objective of Phase 1 of the study was to establish a baseline national registry to determine factors associated with the development of complications of longstanding disease duration[19–21], and in Phase 2 to deeply phenotype for complications a subset of these individuals [22–26].

2.2. Study population

Between February 2015 and September 2016, 75 participants with ≥50 years of T1D participated in Phase 2 of the study. Participant search criteria for Phase 2 included those living in the Greater Toronto Area (i.e. proximity to the University Health Network and Mount Sinai Hospital in Toronto, Ontario, Canada where the study was conducted), or a willingness to travel for two study days and ≥ 50 years of T1D duration. Exclusion criteria included 1) any current eye infection, corneal damage, severe movement disorder, or proparacaine allergy to preclude safe corneal confocal microscopy examination and 2) blood pressure > 140/90 mmHg to preclude angiotensin II infusion procedures, HbA1c or severe complications were not an exclusion criterion for this study. All participants provided written informed consent, and the study and its procedures were approved by the institutional ethics board at the University Health Network and Mount Sinai Hospital in Toronto, ON, Canada. REB file number 13–0056-E.

2.3. Data collection

Participants first completed a medical history and physical exam before completing objective neurological testing including nerve conduction study, assessment of the peroneal and sural nerves using the Counterpoint device (Alpine Biomed Corporation; Fountain Valley, United States) according to the standards of the American Association for Neuromuscular and Electrodiagnostic Medicine[27]. Vibration perception threshold testing (Neurothesiometer; Bailey Instruments Limited, UK) was performed using method of limits algorithms[28], such that higher levels were associated with worse large nerve function. Cooling-detection thresholds testing (Medoc TSA-II NeuroSensory Analyzer; Ramat-Yishai, Israel) was performed using method of limits algorithms[28], such that lower levels were associated with worse small nerve fibre function. Next, participants had bilateral examinations of the nerve plexus adjacent to the Bowman's layer of the cornea using the Rostock Cornea Module of the Heidelberg Tomograph III using a 300 lens (Heidelberg Engineering, Smithfield RI, USA) to determine corneal nerve fibre length (CNFL) according to our validated procedure[29,30]. Then blood samples were collected for biochemical analysis of standard clinical parameters including: HbA_{1c}, lipid profile, calcium, parathyroid hormone (PTH), phosphate, alkaline phosphatase, electrolytes, serum creatinine, estimated glomerular filtration rate (eGFR), spot albumin/creatinine ratio (ACR), thyroid stimulating hormone (TSH) and estradiol using standard University Health Network procedures analyzed on Abbott Architect Chemistry Analyzer (Abbott, Illinois USA).

2.3.1. Assessment and definition of diabetes complications

Diabetic neuropathy was defined according to Toronto consensus criteria of abnormal nerve conduction study in two nerves, plus the presence of neuropathic signs and/or symptoms (27). Neuropathic pain was determined using the Michigan Neuropathy Screening Instrument Questionnaire (the questions concerning allodynia, pain, tingling, and burning in the extremities), or from self-reported use of medications for neuropathic pain. Diabetic nephropathy was defined based on the presence of albuminuria according to an albumin-to-creatinine ratio (ACR) >2 mg/mmol as well as stage 3 chronic kidney disease (CKD3) by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) Study Equation. Presence of diabetic retinopathy, and its classification as proliferative (PDR) or non-proliferative (NPDR), was diagnosed based on wide-field retinal scanning (Optos Tx200, Optos, Dunfermile Scotland UK) and interpretation by a retinal specialist (M.H.B.). Cardiovascular disease (CVD) was defined based on the presence of history of myocardial infarction or coronary artery disease (CAD).

2.3.2. Physical activity status

Participants completed the Lifetime Physical Activity Questionnaire[31] specific to the previous 12-months during their clinic visit. Participation in leisure and household activities were reported as minutes per week and averaged over the 12-month period.

2.4. Statistical analysis

Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC). The Student's *t*-test, the Wilcoxon rank sum test, ANOVA or the χ2-test were used to compare clinical and complications variables between participants that reported less than and greater than 150 min/week of physical activity (PA). We investigated the effect of sex, pain and DSPN status on PA using ANOVA (with PA as the dependent variable). The association between PA time and each individual complication variable was assessed using Pearson and

Spearman correlations. We then explored these correlations using multivariable linear regression with PA time as a continuous independent variable and neurological and electrophysiological measures as dependent variables in separate models. These models were adjusted for age and HbA1c, and the resulting regression parameters indicate the adjusted change in neurological and electrophysiological measurements associated with a 30-min increase in PA per week. We also explored the effects of sex and interactions between sex and PA in these models. An α-level of 0.05 was used for tests of statistical significance.

3. Results

The characteristics of the participants are shown in Table 1. Forty-one (55%) participants were female, mean ± SD age was 66 ± 8 years, median duration of T1D was 54 [52,58] years, BMI was 26.6 ± 3.8 kg/m^2 and mean HbA_{1c} was 7.3 ± 0.8%. DSPN was present in 65 (89%), CKD3 was present in 8(11%) and CVD was present in 15(20%) participants (Table 2).

Participants reported 156 ± 132 min/week of PA (Fig. 1A**).** Thirty-five (47%) of participants reported meeting current clinical practice guideline recommendations of ≥150 min/week and 28(37%) reported ≥210 min/week. Males and females reported similar PA time respectively (126 [45–210] min/week vs. 150 [60–225] min/week, $p = 0.63$]), as did participants that were using pain medication and those who did not (116 ± 110 min/week vs. 169 ± 137 min/week; $p = 0.13$). Linear regression of clinical characteristics showed that PA time was not associated with BMI ($p = 0.22$), $HbA1_c$ ($p = 0.95$) or DSPN pain ($p = 0.56$).

Participants with DSPN reported less PA time compared to individuals without DSPN (141 ± 124 min/week vs. 258 ± 129 min/week; $p = 0.015$). Participants that reported PA time of >150 min/week had 12% lower incidence of DSPN compared to those who reported <150 min/week (37 (95%) vs. 28 (83%); p = 0.015). We further investigated the effect of DSPN on PA by grouping participants into three categories, no DSPN, DSPN with no pain and DSPN with pain. PA time was progressively lower with increasing DSPN status (p for trend = 0.015) (Fig. 1B).

Correlation analysis showed that higher PA time was associated with better cooling detection threshold ($r = 0.24$; $p = 0.043$). Small nerve fibre morphology as measured by CNFL was not correlated with PA time ($r = 0.23$; $p = 0.055$). Greater PA time was associated with better peroneal and sural amplitude ($r = 0.36$; $p = 0.0017$, $r_s = 0.26$; $p = 0.024$) and better conduction velocity ($r_s = 0.28$; $p = 0.015$, $r = 0.23$; $p = 0.050$). Greater PA time was associated with better peroneal F-wave latency ($r_s = -0.34$; $p = 0.0031$). Better vibration perception threshold at the toe was associated with higher PA ($r = -0.31$; $p = 0.025$), whereas there was no association at the finger.

In multivariable regression for NCS as dependent variables, adjusting for age and A1c, we observed that for each 30 min of PA there was improved nerve function measured by 0.09 mv higher peroneal amplitude ($p = 0.032$) and 0.048 ms lower peroneal F-wave latency ($p = 0.022$). No other significant associations were found in the models and we did not find an interaction with sex.

The effect of PA time on blood pressure and CAN are shown in Table 3**.** Correlation analysis showed no association between PA time and heart rate variability ($r = -0.062$; $p = 0.60$) heart rate variability triangulation index ($r = 0.045$; $p = 0.70$) or low frequency power ($r = -0.10$; $p = 0.41$). In multivariable regression for blood pressure and CAN as dependent variables, adjusting for age and A1c, there were no significant associations in the models, and we did not find an interaction with sex.

Table 1
Characteristics of participants with longstanding type 1 diabetes and stratified by physical activity time.

Clinical characteristics	T1D $n = 75$	Activity ≦150 min/wk. $n = 40$	Activity ≧150 min/wk. $n = 35$	*P*-value
Exercise time (min/week)	156 ± 132	57 ± 53	268 ± 102	<0.001
Female sex, n (%)	41 (55%)	24 (60%)	17 (47%)	0.32
Age (years)	66 ± 8	67 ± 8	64 ± 8	0.042
Diabetes duration (years)	54 [52,58]	55 ± 6	54 ± 5	0.26
Daily Insulin Dose (units)	35.6 ± 13.2	37.3 ± 15.3	33.7 ± 10.3	0.20
Pain Medication (%)	19 (25%)	11 (27%)	8 (23%)	0.64
Current smoking, n (%)	3 (4%)	1 (3%)	2 (6%)	0.46
Current alcohol consumption, n (%)	59 (80%)	31 (79%)	28 (80%)	0.96
BMI (kg/m^2)	26.6 ± 3.8	27.1 ± 4.1	26.0 ± 3.4	0.20
Biochemical characteristics				
HbA_{1c} (%)	7.3 ± 0.8	7.4 ± 0.7	7.3 ± 0.9	0.63
HbA_{1c} (mmol/mol)	56 ± 8	57 ± 8	56 ± 10	0.63
Fasted Plasma Glucose (mmol/L)	8.54 ± 3.6	9.34 ± 3.52	7.63 ± 3.59	0.041
Total Cholesterol (mmol/L)	3.8 ± 0.77	3.87 ± 0.82	3.87 ± 0.72	0.98
HDL (mmol/L)	1.6 ± 0.45	1.68 ± 0.47	1.62 ± 0.42	0.59
LDL (mmol/L)	1.9 ± 0.54	1.83 ± 0.53	1.89 ± 0.56	0.60
Triglycerides (mmol/L)	0.78 ± 0.39	0.79 ± 0.39	0.78 ± 0.41	0.89
$eGFR_{MDRD}$ (ml/min/1.73m^2)	72 ± 17	68 ± 16	77 ± 17	0.015
Phosphate (mmol/L)	1.0 ± 0.20	1.0 ± 0.20	1.0 ± 0.20	0.48
PTH (pmol/L)	4.8 [3.4,7.0]	4.6 [3.0,6.9]	5.0 [3.7,7.6]	0.19
Serum Creatinine (umol/L)	84 ± 22	80 ± 15	88 ± 27	0.10
Albumin: Creatinine (mg/mmol))	6.6 ± 13.4	4.7 ± 12.1	7.1 ± 14.6	0.44
Sodium (mmol/L)	137 ± 4	138 ± 3	136 ± 4	0.052
Potassium (mmol/L)	3.9 ± 0.34	3.9 ± 0.32	4.0 ± 0.35	0.75
Chloride (mmol/L)	103 ± 4	103 ± 4	103 ± 4	0.40
Estradiol (pmol/L)	41 [37,64]	51 ± 20	66 ± 60	0.28
TSH (mIU/L)	2.1 ± 1.4	2.1 ± 1.3	2.1 ± 1.5	0.97
Presence of complications				
Number of severe hypoglycemic events in the past year	0.09 ± 0.33	0.11 ± 0.39	0.06 ± 0.24	0.54
Neuropathy	65 (89%)	37 (95%)	28 (83%)	
None	8 (11%)	2 (5%)	6 (18%)	0.015
DSPN no pain	47 (63%)	26 (67%)	21 (62%)	
DSPN with pain	18 (24%)	11 (28%)	7 (21%)	
Retinopathy				
None	12 (16%)	6 (15%)	6 (17%)	0.96
NPDR	24 (32%)	13 (32%)	11 (31%)	
PDR	39 (52%)	21 (52%)	18 (51%)	
Nephropathy	25 (33%)	15 (37%)	10 (29%)	0.41
Cardiovascular disease	15 (20%)	8 (20%)	7 (20%)	0.97

Data are mean ± SD, median [IQR], or n (%). Student's t-test, the Wilcoxon rank sum test or the χ^2-test were used to compare were used to compare clinical and complications variables between participants where appropriate.
T1D: type 1 diabetes mellitus, BMI: body mass index, ALP, PTH eGFR: estimated glomerular filtration rate; NPDR: non-proliferative diabetic retinopathy, PDR: proliferative, PTH: parathyroid hormoneTSH: thyroid stimulating hormone.

4. Discussion

In this analysis of the Canadian Study of Longevity in Type 1 Diabetes, PA time was associated with a 12% lower incidence of DSPN, preserved large nerve fibre function in the lower limb and inconsistent association for different small nerve fibre measures. We could not determine an association between PA and measures of CAN, which suggests PA might not be cardioprotective in longstanding T1D. We

Table 2
Neurological characteristics of participants with longstanding type 1 diabetes and stratified by physical activity time.

Clinical Characteristics	Activity ≦ 150 min/wk. $n = 40$	Activity ≧ 150 min/wk. $n = 35$	P-value
Toronto Clinical Neuropathy Score	7 ± 4	6 ± 3	0.13
Small Fibre Measures			
Corneal nerve fibre length (mm/mm^2)	8.0 ± 4.8	8.6 ± 3.9	0.54
Cooling detection threshold (°C)	20.4 ± 6.9	21.9 ± 6.7	0.37
Large Fibre Measures			
Vibration Perception Threshold – Hand (V)	6.3 ± 1.8	6.1 ± 2.1	0.69
Vibration Perception Threshold – Toe (V)	25.2 ± 9.4	21.24 ± 11.1	0.17
Peroneal Nerve Amplitude (mV)	1.5 ± 1.3	2.17 ± 1.6	0.53
Peroneal Nerve Conduction Velocity (m/s)	34.5 ± 8.2	37.66 ± 7.3	0.093
Peroneal Nerve F-wave Latency (ms)	63.9 ± 7.4	61.79 ± 8.0	0.23
Sural Nerve Amplitude (mV)	2.6 ± 3.0	3.36 ± 2.8	0.26
Sural Nerve Conduction Velocity (m/s)	35.4 ± 5.9	37.70 ± 6.4	0.11

Data are mean ± SD or median [IQR]. Student's t-test, the Wilcoxon rank sum test or the χ^2-test were used to compare were used to compare clinical and complications variables between participants where appropriate.

showed no difference in PA time based on sex or use of pain medication; however, PA time was lower with the presence of DSPN and further with painful DSPN. An analysis of PA and the relationship to DSPN status and CAN has not been previously reported in longstanding T1D and the present study provides novel findings on the potential role of lifestyle in the prevention and management of diabetes complications.

Although the data collected in this study reflects participants' previous 12-months of PA, it is likely that it is somewhat reflective of lifetime PA habits established by these participants over the preceding 50 years of T1D management[31]. It is encouraging that almost half of the cohort reported PA levels that meet or exceed current clinical practice guideline recommendations[5], which is notably higher than the 20% of participants from a recent prospective study in T2D[32]. This might be related to differences in lifestyle education delivery between T1D and T2D, interaction with diabetes educators[33,34], or with the association of PA and the likelihood of longstanding T1D survival.

Measurement of glucose metabolisms showed a mixed affect from PA time. Participants that reported >150 min/wk. of PA had lower fasting blood glucose levels compared to those reporting <150 min/week, which suggests improved glucose handling with higher PA. In contrast, there was no association between PA time and $HbA1_c$ in our study population. Recent meta-analyses of PA interventions in T1D showed that PA lowered $HbA1_{ca}$[15,16]; however, in our population with >50 years of T1D it is possible that a an established pharmacotherapy regime could allow for similar HbA1c between participants that report higher PA levels compared to those who report lower levels. PA intervention studies are often subject to selection bias of participants with limited prior exercise experience[35]. In contrast, previous PA intervention studies in individuals with DSPN from metabolic syndrome or T2D demonstrated that structured PA promotes the reinnervation intraepidermal nerve fibres collected from the thigh without changes in metabolic control or body mass[36,37]. This suggests PA provides regional or limb specific neuroprotection through mechanisms other than improved glucose metabolism. It is likely that PA affects multiple mechanisms in concert, including increased nerve blood flow and release of nitric

Table 3
Cardiovascular and heart rate variability characteristics of participants with longstanding type 1 diabetes and stratified by physical activity time.

Clinical characteristics	Activity ≦ 150 min/wk $n = 40$	Activity ≧ 150 min/wk $n = 35$	P-value
Pulse (beat/min)	70 ± 11	70 ± 11	0.96
Systolic blood pressure (mmHg)	132 ± 15	133 ± 16	0.91
Diastolic blood pressure	69 ± 10	71 ± 8	0.30
SD-NN (ms)	45 ± 42	33 ± 21	0.13
RMSSD (ms)	33 ± 29	24 ± 28	0.18
Triangulation Index	6.6 ± 4.0	5.5 ± 2.6	0.43
LF Power (ms^2)	468 ± 857	209 ± 484	0.11
HF Power (ms^2)	381 ± 865	172 ± 517	0.21
LF:HF Ratio (%)	2.20 ± 2.0	2.8 ± 2.3	0.27

Data are mean ± SD or median [IQR]. Student's t-test, the Wilcoxon rank sum test or the χ^2-test were used to compare were used to compare clinical and complications variables between participants where appropriate.SD: standard deviation, NN: interbeat interval, RMSSD: root mean square of RR interval, LF: Low frequency, HF: high frequency.

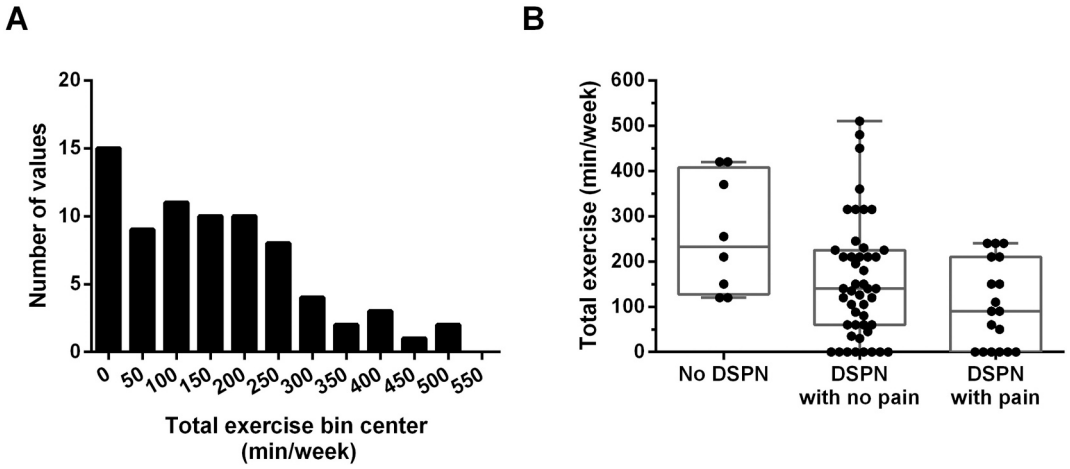

Fig. 1. The distribution of physical activity time and by diabetic distal symmetric polyneuropathy status.
Panel A: The distribution of participants' physical activity (PA) time in minutes per week.
Panel B: Participants were grouped by diabetic distal symmetric polyneuropathy (DSPN) status: no DSPN, DSPN, painful DSPN. PA time was inversely proportional to DSPN status (p for trend = 0.015). PA time for participants with painful DSPN was lower compared to those without DSPN ($p = 0.011$). The no DSPN and DSPN groups were not different ($p = 0.084$), as was DSPN and painful DSPN ($p = 0.26$).

oxide[38], the release of neurotrophic factors including nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) [7,39] and increased antioxidant status[40]. This theory is supported by our small and large nerve fibre data as we show PA was associated with better large nerve fibre function measured by VPT in the lower limb compared to the upper limb and small fibre function better cooling detection in the lower limb compared to no effect on corneal nerve fibre length; however, further research is required to better elucidate these mechanisms and determine if the neuroprotective effects of PA are limited to the nerves in the active limbs or if the effects extend throughout the body.

It is important to note the limitations of the current study. We used a cross-sectional study design, which allow an association rather than a causality assessment and our measure of PA was obtained from self-reported questionnaire as an exploratory measure. The present findings could be affected by reverse causality, whereby individuals with DSPN have lower PA time as their symptoms are limiting; however, we have attempted to account for this by comparing pain medication use and differentiating DSPN with and without pain. Measurement of HbA_{1c} would allow us to assess the glucose control over the last three months but not long-term control. While seen as an advantage of this particular analysis, our study is subject to a selection bias as we are only examining participants with $\geq$50 years T1D. As such, a higher proportion of the population have DSPN and therefore the results presented here might not be applicable to the broader population.

5. Conclusion

In conclusion, this analysis provides insights into the association of PA on DSPN and CAN in individuals with longstanding T1D. In this population, higher PA time was associated with preserved large nerve fibre function and some benefit to small fibre function, but this was not observed with CAN. These findings support future investigation of PA interventions to attenuate the onset or progression of DSPN in T1D.

Declaration of competing interest

EJHL reports grants from CIHR and is part owner of Nutarniq Corp., which researches and develops targeted nutritional therapies for chronic diseases and disease complications. L.E.L. received support from a CIHR Canada Graduate Scholarship Doctoral Award. J.A.L. has received consulting fees, speaking honoraria, or both from Novo Nordisk, Eli Lilly & Co., Merck Sharp & Dohme, Prometic, Intarcia Therapeutics, Inc., and AstraZeneca and has received grant support from Sanofi and Merck. D.Z.I.C. has received consulting fees or speaking honorarium or both from Janssen, Boehringer Ingelheim-Eli, Lilly, AstraZeneca, Merck, and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli, Lilly, AstraZeneca and Merck. B.A.P. has received speaker honoraria from Abbott, Medtronic, Insulet, and Novo-Nordisk; research support to his research institute from Boehringer Ingleheim and the Bank of Montreal (BMO), and has served as a consultant to Boehringer Ingelheim, Abbott, and Novo-Nordisk. J.A.L. has received either consulting fees or speaking honorarium or both from Novo Nordisk.

Acknowledgements

We greatly appreciate our distinguished study participants, who have inspired our team and spent considerable time participating in this study. We would like to thank our colleagues who contributed to data acquisition for the Longevity cohort: Vesta Lai, Leslie Cham, Josephine Tse, Mohammed A. Farooqi and Andrej Orszag. We acknowledge Diabetes Canada for their non-financial support with study advertisement.

Funding

This project was generously supported by JDRF Canada and its Canadian Clinical Trial Network (operating grant 17-2013-312), The Menkes Fund and BMO (Bank of Montreal) provided financial support for this study. EJHL is supported by a post-doctoral fellowship from the Canadian Institute for Health Research. LEL is supported by a doctoral research award from the Canadian Institute for Health Research.

CRediT authorship contribution statement

E.J.H.L, L.E.L and B.A.P developed the research question and with S. L. and D.S. completed the statistical analysis. E.J.H.L and L.E.L wrote the first draft of the manuscript. All other others contributed to data interpretation and manuscript preparation. B.A.P. and D.Z.I.C. created the hypothesis and objectives, designed the Canadian Study of Longevity in Diabetes. B.A.P. is the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Dyck J, Dyck P. *Diabetic neuropathy*. Philadelphia: W B Saunders; 1999.
2. Serhiyenko V, Serhiyenko A. Cardiac autonomic neuropathy: risk factors, diagnosis and treatment. *World Diabetes J*. 2018;9:1–14.
3. Vinik E, Hayes R, Oglesby A, et al. The development and validation of the Norfolk QOL-DN, a new measure of Patients' perception of the effects of diabetes and diabetic neuropathy. *Diabetes Technol Ther*. 2005;7:497–508.
4. Astrup A, Tarnow L, Rossing P, Hansen B, Hilsted J, Parving H. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care*. 2006;29:334–339.
5. Colberg S, Sigal R, Yardley J, Riddell M, Al E. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39:2065–2079.
6. Cobianchi S, Arbat-Plana A, Lopez-Alvarez V, Navaro X. Neuroprotective effects of exercise treatments after injury: the dual role of neurotrophic factors. *Curr Neuropharmacol*. 2017;15:495–518.
7. Funakoshi H, Belluardo N, Arenas E, et al. Muscle-derived neurotrophin-4 as an activity-dependent trophic signal for adult motor neurons. *Science*. 1995;268:1495–1499.
8. Gisiger V, Belisle M, Gardiner P. Acetylcholinesterase adaptation to voluntary wheel running is proportional to the volume of activity in fast, but not slow, rat hindlimb muscles. *Eur J Neurosci*. 1994;6:673–680.
9. Kjeldsen K, Richter EA, Galbo H, Lortie G, Clausen T. Training increases the concentration of [3H]ouabain-binding sites in rat skeletal muscle. *Biochim Biophys Acta*. 1986;11:708–712.
10. Balducci S, Iancobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. *J Diabetes Complications*. 2006;20:216–223.
11 Zilliox L, Russell J. Physical activity and dietary interventions in diabetic neuropathy: a systematic review. *Clin Auton Res*. 2019;29:443–455.
12. Bhati P, Shenoy S, Hussain M. Exercise training and cardiac autonomic function in type 2 diabetes mellitus: a systematic review. *Diabetes Metab Syndr*. 2018;12:69–78.
13. Melese H, Alamer A, Temesgen M, Kahsay G. Effectiveness of exercise therapy on gait function in diabetic peripheral neuropathy patients: a systematic review of randomized controlled trials. *Diabetes Metab Syndr Obes*. 2020;13:2753–2764.
14. Group DCaCTDR. Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of diabetes control and complications trial (DCCT). *Diabetes*. 1988;37:476–481.
15. Yardley J, Hay J, Abou-Setta A, Marks S, McGavock J. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2014;106:393–400.
16. Wu N, Bredin S, Dickinson K, et al. Cardiovascular health benefits of exercise training in persons living with type 1 diabetes: a systematic review and meta-analysis. *J Clin Med*. 2019;8:253.
17. Almeida S, Riddell M, Cafarelli E. Slower conduction velocity and motor unit discharge frequency are associated with muscle fatigue during isometric exercise in type 1 diabetes mellitus. *Muscle Nerve*. 2008;37:231–240.
18. Allen M, Choi I, Kimpinski K, Doherty T, Rice CL. Motor unit loss and weakness in association with diabetic neuropathy in humans. *Muscle Nerve*. 2013;48:298–300.
19. Lovshin J, Boulet G, Lytvyn Y, et al. Renin-angiotensin-aldosterone system activation in long-standing type 1 diabetes. *JCI Insight*. 2018;3, e96968.
20. Weisman A, Rovinski R, Farooqi M, et al. Commonly measured clinical variables are not associated with burden of complications in long-standing type 1 diabetes: results from the Canadian study of longevity in diabetes. *Diabetes Care*. 2016;39:e67–e68.
21. Weisman A, Lovblom L, Keenan H, et al. Diabetes care disparities in long-standing type 1 diabetes in Canada and the U.S.: a cross-sectional comparison. *Diabetes Care*. 2018;41:88–95.
22. Bjornstad P, Lovshin J, Lytvyn Y, et al. Adiposity impacts intrarenal hemodynamic function in adults with long-standing type 1 diabetes with and without diabetic nephropathy: results from the Canadian study of longevity in type 1 diabetes. *Diabetes Care*. 2018;41:831–839.
23. Bai J, Lovblom L, Cardinez M, et al. Neuropathy and presence of emotional distress and depression in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. *J Diabetes Complications*. 2017;31:1318–1324.

24. Scarr D, Lovblom L, Lovshin J, et al. Lower corneal nerve fibre length identifies diabetic neuropathy in older adults with diabetes: results from the Canadian study of longevity in type 1 diabetes. *Diabetologia*. 2017;60:2529–2531.
25. Boulet G, Halpern E, Lovblom L, et al. Prevalence of insulin pump therapy and its association with measures of glycemic control: results from the Canadian study of longevity in type 1 diabetes. *Diabetes Technol Ther*. 2016;18:298–307.
26. Bai J, Boulet G, Halpern E, et al. Cardiovascular disease guideline adherence and self-reported statin use in longstanding type 1 diabetes: results from the Canadian study of longevity in diabetes cohort. *Cardiovasc Diabetol*. 2016;25:14.
27. England J, Gronseth G, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the american Association of Electrodiagnostic Medicine, and the American Academy of physical medicine and rehabilitation. *Neurology*. 2005;64:199–207.
28. Yarnitsky D. Quantitative sensory testing. *Muscle Nerve*. 1997;20:198–204.
29. Ahmed A, Bril V, Orsazag A, et al. Detection of diabetic sensorimotor polyneuropathy by corneal confocal microscopy in type 1 diabetes: a concurrent validity study. *Diabetes Care*. 2012;35:821–828.
30. Wu T, Ahmed A, Bril V, et al. Variables associated with corneal confocal microscopy parameters in healthy volunteers: implications for diabetic neuropathy screening. *Diabetes Med*. 2012;29:297–303.
31. Chasan-Taber L, Erickson J, McBride J, Nasca P, Chasan-Taber S, Freedson P. Reproducibility of a self-administered lifetime physical activity questionnaire among female college alumnae. *Am J Epidemiol*. 2002;155:282–289.
32. Gregg E, Gerzoff R, C C. Relationship of walking to mortality among US adults with diabetes. *Archives of Internal Medicine*. 2003;163:1440–1447.
33. Ellis S, Speroff T, Dittus R, B. A, Pichert J, Elasy T. Diabetes patient education: a meta-analysis and meta-regression. *Patient Educ Couns*. 2004;52:97–105.
34. Trento M, Tomelini M, Basile M, et al. The locus of control in patients with type 1 and type 2 diabetes managed by individual and group care. *Diabet Med*. 2008;25:86–90.
35. de Souto BP, Ferrandez A, Saliba-Serre B. Are older adults who volunteer to participate in an exercise study fitter and healthier than nonvolunteers? The participation bias of the study population. *J Phys Act Health*. 2013;10:359–367.
36. Singleton J, Marcus R, Lessard M, Jackson J, Smith A. Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. *Ann Neurol*. 2015;77:146–153.
37. Singleton J, Marcus R, Jackson J, Lessard M, Graham TE, Smith A. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. *Ann Clin Transplant Neurol*. 2014;1:844–849.
38. Olver T, McDonald M, Grise K, et al. Exercise training enhances insulin-stimulated nerve arterial vasodilation in rats with insulin-treated experimental diabetes. *Am J Physiol Regul Integr Comp Physiol*. 2014;306:R941–R950.
39. Spartano N, Davis-Plourde K, Himali J, et al. Self-reported physical activity and relations to growth and neurotrophic factors in diabetes mellitus: the Framingham offspring study. *Journal of Diabetes Research*. 2018;9:2718465.
40. Iborra R, Ribeiro I, Neves M, et al. Aerobic exercise training improves the role of high-density lipoprotein antioxidant and reduces plasma lipid peroxidation in type 2 diabetes mellitus. *Scand J Med Sci Sports*. 2008;18:742–750.