



The Peripheral Neuropathy Prevalence and Characteristics Are Comparable in People with Obesity and Long-Duration Type 1 Diabetes

J. Z. M. Lim · J. Burgess · C. G. Ooi · G. Ponirakis · R. A. Malik ·
J. P. H. Wilding · Uazman Alam

Received: May 4, 2022 / Accepted: May 26, 2022 / Published online: July 22, 2022
© The Author(s) 2022

ABSTRACT

Introduction: Peripheral neuropathy is reported in obesity even in the absence of hyperglycaemia.

Objective: To compare the prevalence and characterise the phenotype of peripheral neuropathy in people living with obesity (OB) and long-duration type 1 diabetes (T1D).

J. P. H. Wilding and Uazman Alam are joint senior authors.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12325-022-02208-z>.

J. Z. M. Lim · J. Burgess · J. P. H. Wilding ·
U. Alam (✉)

Department of Cardiovascular and Metabolic
Medicine, Institute of Life Course and Medical
Sciences, University of Liverpool, Liverpool, UK
e-mail: uazman.alam@liverpool.ac.uk

J. Z. M. Lim · C. G. Ooi · J. P. H. Wilding ·
U. Alam

Division of Diabetes and Endocrinology, Aintree
University Hospital, Liverpool University Hospitals
NHS Foundation Trust, Liverpool, UK

G. Ponirakis · R. A. Malik
Division of Medicine, Qatar Foundation, Weill
Cornell Medicine-Qatar, Doha, Qatar

U. Alam
Department of Diabetes, Endocrinology and
Gastroenterology, Faculty of Biology, Medicine and
Health, University of Manchester, Manchester, UK

Patients and Methods: We performed a prospective cross-sectional study of 130 participants including healthy volunteers (HV) ($n = 28$), people with T1D ($n = 51$), and OB (BMI 30–50 kg/m²) ($n = 51$). Participants underwent assessment of neuropathic symptoms (Neuropathy Symptom Profile, NSP), neurological deficits (Neuropathy Disability Score, NDS), vibration perception threshold (VPT) and evaluation of sural nerve conduction velocity and amplitude.

Results: Peripheral neuropathy was present in 43.1% of people with T1D (age 49.9 ± 12.9 years; duration of diabetes 23.4 ± 13.5 years) and 33.3% of OB (age 48.2 ± 10.8 years). VPT for high risk of neuropathic foot ulceration ($VPT \geq 25$ V) was present in 31.4% of T1D and 19.6% of OB. Participants living with OB were heavier (BMI 42.9 ± 3.5 kg/m²) and had greater centripetal adiposity with an increased body fat percentage (FM%) ($P < 0.001$) and waist circumference (WC) ($P < 0.001$) compared to T1D. The OB group had a higher NDS ($P < 0.001$), VAS for pain ($P < 0.001$), NSP ($P < 0.001$), VPT ($P < 0.001$) and reduced sural nerve conduction velocity ($P < 0.001$) and amplitude ($P < 0.001$) compared to HV, but these parameters were comparable in T1D. VPT was positively associated with increased WC ($P = 0.011$), FM% ($P = 0.001$) and HbA1c ($P < 0.001$) after adjusting for age ($R^2 = 0.547$). Subgroup analysis of respiratory quotient (RQ) measured in the OB group did not correlate with VPT ($P = 0.788$),

nerve conduction velocity ($P = 0.743$) or amplitude ($P = 0.677$).

Conclusion: The characteristics of peripheral neuropathy were comparable between normoglycaemic people living with obesity and people with long-duration T1D, suggesting that metabolic factors linked to obesity play a pivotal role in the development of peripheral neuropathy. Further studies are needed to investigate the mechanistic link between visceral adiposity and neuropathy.

Keywords: Diabetes; Diabetic neuropathies; Indirect calorimetry; Obesity; Peripheral neuropathy

Key Summary Points

Why carry out this study?

Prevalence of neuropathy in people living with obesity even with normoglycaemia is well recognized. This study aimed to evaluate the differences in neuropathy phenotype between primarily hyperglycaemia-driven versus obesity-driven cardiometabolic factors in the development of axonal peripheral neuropathy.

What was learned from the study?

The prevalence and phenotype of peripheral neuropathy are comparable between normoglycaemic people with obesity and long-duration type 1 diabetes, suggesting that obesity-related risk factors and hyperglycaemia may contribute equally to the development of neuropathy.

Higher centripetal adiposity, BMI, total body fat and triglycerides in people with obesity are independent risk factors for elevated vibration perception threshold and peripheral neuropathy.

Metabolic markers of impaired fat oxidation are not associated with peripheral neuropathy in obesity.

INTRODUCTION

The global prevalence of obesity has more than doubled since the 1980s, affecting an estimated 604 million adults and 108 million children [1]. Within the UK, 27% of adults are obese (body mass index (BMI) ≥ 30 kg/m²) [2], and 3–4% are severely obese (BMI ≥ 40 kg/m²) [3]. Furthermore, the prevalence of obesity is projected to rise substantially by 2030 in the USA, such that 48.9% of adults will be obese and 24.2% will be severely obese [4].

Obesity is associated with systemic inflammation and endothelial dysfunction which can lead to peripheral neuropathy in both type 2 diabetes (T2D) [5], and type 1 diabetes (T1D) [6]. The EURODIAB study demonstrated that BMI, hypertension and dyslipidaemia had comparable risk to HbA1c for incident neuropathy in people with T1D [7]. The Anglo-Danish-Dutch study of Intensive Treatment of Diabetes in Primary Care (ADDITION) confirmed that abdominal obesity independently predicted peripheral neuropathy in newly diagnosed patients with T2D [8]. Furthermore, obesity has been associated with peripheral neuropathy independent of hyperglycaemia and hypertriglyceridemia [9]. The Rotterdam study reported that abdominal obesity, metabolic syndrome and dyslipidaemia were strongly associated with peripheral neuropathy in the absence of diabetes [10]. In addition, symptomatic peripheral neuropathy is more common in metabolic syndrome, independent of glycaemic status [11]. Indeed, the Monica/Kora Augsburg study demonstrated that neuropathic pain was independently associated with body weight and waist circumference in subjects with impaired glucose tolerance (IGT) [12].

The pathognomonic manifestations of insulin resistance, which include a decrease in metabolic flexibility and impaired ability to switch between fat and carbohydrate metabolism, are putative factors linking obesity and peripheral neuropathy [13]. Insulin resistance is associated with low-grade inflammation which contributes to endothelial dysfunction and microvascular complications [13]. Our study compared the prevalence and characteristics of

peripheral neuropathy in people with obesity to people with long-duration T1D. We have evaluated the putative link between respiratory quotient (as a marker of substrate oxidation at rest) and peripheral neuropathy in people with obesity.

METHODS

Selection of Patients

We performed a prospective cross-sectional study from January 2019 to March 2021 in (1) healthy volunteers (HV), (2) people with T1D and (3) people with obesity (OB) (BMI 30–50 kg/m²) without diabetes were recruited from Liverpool University Hospitals NHS Foundation Trust clinics. The exclusion criteria for participants in the OB group were (1) previous bariatric surgery, (2) thyroid disorders, (3) concurrent use of weight loss medication, including orlistat, phentermine, sibutramine, naltrexone/bupropion, glucagon-like peptide 1 (GLP-1) receptor agonist within 3 months prior to screening and (4) a formal diagnosis of peripheral neuropathy of any origin. The exclusion criteria for T1D group were (1) people with class 2 or 3 obesity (BMI \geq 30 kg/m²), (2) excessive alcohol intake, (3) neuropathy of non-diabetes origin. HVs were excluded if they were taking medications for hypertension or hyperlipidaemia. The sample size was not calculated formally as we were recruiting unselected patients for feasibility. We intended to base the sample size calculation upon the vibration perception threshold measurements and these data for future studies. The study received relevant research ethics approval by the University of Liverpool Clinical Trials Unit and the Northwest Research Ethics Committee (18/NW/0532). This study received the health regulatory approval and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). All subjects provided informed consent to participate in the study.

Clinical Assessments

Eligible subjects underwent weight, waist circumference (WC), BMI, total body fat percentage (FM%), and blood pressure measurements. Body composition was determined using the two-electrode leg-to-leg bio-impedance analyser machine (Tanita TBF-300MA, Tanita Corporation, Tokyo, Japan). Normoglycaemia (HbA1c < 39 mmol/mol), prediabetes (HbA1c 39–47 mmol/mol), and diabetes mellitus (HbA1c \geq 48 mmol/mol) were classified according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [14].

Neurological Assessment

Neurologic deficits according to the Neuropathy Disability Score (NDS), with a score of 0–2 (out of 10) graded as no neuropathy, 3–4 mild neuropathy, 5–8 moderate neuropathy, 9–10 severe neuropathy, and the neuropathy symptom profile (NSP) (out of 38) was assessed. All subjects scored the average intensity of their neuropathic pain over the previous 2 weeks on a continuous visual analogue scale (VAS), where “0” and “10” indicated “no pain” and “worst possible pain”, respectively.

Peripheral neuropathy was defined according to the Toronto consensus [15] i.e. the presence of an abnormality of nerve conduction and a symptom or symptoms and/or a sign or signs of neuropathy. Vibration perception threshold (VPT) was measured from an average of three values on the large toe using a neurothesiometer (Horwell, Scientific Laboratory Supplies, Wilford, Nottingham, UK). Participants with impaired VPT were defined by VPT of 15–24 V, whilst participants with \geq 25 V were deemed at high risk for neuropathic foot ulcer.

Sural nerve conduction velocity (SNCV) and sural nerve action potential (SNAP) were measured using the point-of-care device NC-Stat[®] DPNCheck[™] system (Neurometrix, Waltham, USA). The NC-Stat DPNCheck has good reliability and reproducibility and correlates well with SNCV ($R = 0.81$) and moderately with SNAP ($R = 0.62$) derived from nerve conduction

studies (NCS) as a reference method [16]. The point-of-care conduction device results were evaluated against the reference values provided for the device (abnormal result defined by amplitude $\leq 4 \mu\text{V}$ or conduction velocity $\leq 44 \text{ m/s}$). The device cannot detect SNAP signals of $< 2.1 \mu\text{V}$ and automatically calibrates these values as zero [16]; therefore, all zero results were recorded as $2.0 \mu\text{V}$. For instances when operators were unable to attain or detect SNCV or SNAP signals, the results were recorded as clinical neuropathy. Operators were trained to reduce errors by using a fixed conduction distance and filter settings and maximizing amplitude to improve the signal to noise ratio [16].

Fat Oxidation Assessment

Respiratory quotient (RQ) serves as an index of substrate metabolised by active tissue and is represented by the ratio of volume of oxygen inspired (VO_2) to the volume of carbon dioxide exhaled (VCO_2) during a (fasted) resting metabolic state. The novel open-circuit portable indirect calorimeter ECALTM (Metabolic Health Solutions, Australia) (ISO 13485) utilised a proprietary mouthpiece (single use) and a nose clip. VO_2 is measured using a galvanic fuel cell oxygen analyser. VCO_2 is measured using a patented ultra-low power VCO_2 analyser which uses light-emitting diode and detector technology in a novel non-dispersive near-infrared absorption sensor. Calibrations were performed using 5% carbon dioxide. A successful test was defined as a steady state achieved with a minimum of five consecutive minutes with less than 10% coefficient of variation in FEO_2 and FECO_2 .

Statistical Analysis

Descriptive statistics were presented as mean \pm standard deviation or value with percentage. Means were compared between the three groups (HVs, OB and T1D) using the analysis of covariance (ANCOVA) adjusted for age with Bonferroni adjustment or Kruskal–Wallis with post hoc test. Univariate

and multivariate linear regression was used to model VPT as a function of the metabolic syndrome components (WC, HDL, triglycerides, systolic blood pressure), after adjusting for age. Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographics

One hundred and thirty participants (HV, $n = 28$; T1D, $n = 51$; OB, $n = 51$) matched for age were studied; however, the proportion of female participants in the OB group (75%) was greater than the T1D group (47%) ($P = 0.005$). The demographics, anthropometric measures, clinical and metabolic phenotyping are summarised in Table 1. The mean duration of T1D was 23.4 ± 13.5 years. As expected, participants with obesity (OB) had a greater BMI ($P < 0.001$), body fat percentage ($P < 0.001$), WC ($P < 0.001$), total cholesterol ($P < 0.001$), LDL-cholesterol ($P < 0.001$) and triglycerides ($P < 0.001$) compared to participants with T1D. According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) definition of metabolic syndrome, 58% of participants fulfilled the criteria for metabolic syndrome in the OB group.

Neuropathy Assessment

Peripheral neuropathy measures are summarised in Table 2. Peripheral neuropathy was present in 43.1% of participants with T1D and 33.3% of participants living with OB according to the Toronto consensus criteria for peripheral neuropathy. Impaired VPT (15–24 V) and advanced VPT deemed at high risk of neuropathic ulcer ($\geq 25 \text{ V}$) were present in 19.6% and 31.4% in T1D and 23.5% and 19.6% of participants living with OB. There were no differences in VAS for pain, NSP, NDS, VPT, SNCV and SNAP between T1D and OB groups. However, both T1D and OB groups demonstrated greater VAS for pain, NDS, NSP, VPT, SNCV and SNAP

Table 1 Demographics, clinical and metabolic characteristics in HVs and participants with T1D and OB

	HV (<i>n</i> = 28)	T1D (<i>n</i> = 51)	OB (<i>n</i> = 51)	<i>P</i> value		
				HV vs T1D	HV vs OB	OB vs T1D
Age (years)	43.0 ± 6.9	49.9 ± 12.9	48.2 ± 10.8	0.067	0.146	0.960
Duration of T1D (years)	–	23.4 ± 13.5	–	–	–	–
Female, <i>n</i> (%)	18 (64)	24 (47)	38 (75)	0.383	0.133	0.005
Weight (kg)	67.6 ± 10.1	80.6 ± 20.9	116.2 ± 12.9	0.002	< 0.001	< 0.001
BMI (kg/m ²)	23.3 ± 2.6	28.0 ± 5.1	42.9 ± 4.0	< 0.001	< 0.001	< 0.001
WC (cm)	89.1 ± 11.6	95.1 ± 19.1	125.5 ± 14.9	0.924	< 0.001	< 0.001
FM% (%)	24.6 ± 2.9	26.5 ± 3.4	52.4 ± 2.7	0.457	< 0.001	< 0.001
HbA1c (%)	5.5 ± 0.2	8.7 ± 1.3	5.6 ± 0.3	< 0.001	0.430	< 0.001
HbA1c (mmol/mol)	37.0 ± 2.2	76.2 ± 14.1	37.8 ± 2.7	< 0.001	0.441	< 0.001
TChol (mmol/l)	4.1 ± 0.2	4.4 ± 1.1	5.0 ± 0.8	0.869	< 0.001	< 0.001
HDL (mmol/l)	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	0.712	0.712	0.712
LDL (mmol/l)	2.0 ± 0.3	2.1 ± 0.9	2.9 ± 0.9	0.917	< 0.001	< 0.001
TRIG (mmol/l)	1.2 ± 0.2	1.4 ± 0.9	2.2 ± 0.7	0.906	< 0.001	< 0.001
eGFR (ml/min/1.73 m ²)	82 ± 9	79 ± 18	80 ± 11	0.863	0.895	0.883

Data presented as mean ± SD with significant differences measured by ANCOVA adjusted for age with Bonferroni adjustment or Kruskal–Wallis test with post hoc test

NS non-significant, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *FM%* body fat percentage, *HbA1c* glycated haemoglobin, *HDL* HDL-cholesterol, *LDL* LDL-cholesterol, *HV* healthy volunteers, *OB* obesity, *T1D* type 1 diabetes, *TChol* total cholesterol, *TRIG* triglycerides, *WC* waist circumference

compared to HV ($P < 0.001$). There was an association between VPT and VAS pain ($R^2 = 0.330$) (Fig. S1 in the supplementary material).

We evaluated correlation between VPT as the primary dependent variable with anthropometric, metabolic and body composition measurements in the whole cohort (OB, HV, and T1D) using Pearson's correlation analysis (Table 3). VPT correlated with NSP ($\rho = 0.841$, $P < 0.001$), VAS ($\rho = 0.761$, $P < 0.001$) and WC ($\rho = 0.420$, $P < 0.001$). VPT also correlated with age ($\rho = 0.269$, $P = 0.002$), BMI ($\rho = 0.348$, $P < 0.001$), body fat percentage (FM%) ($\rho = 0.280$, $P = 0.001$), HbA1c ($\rho = 0.400$, $P < 0.001$), total cholesterol ($\rho = 0.227$, $P = 0.010$), triglycerides ($\rho = 0.299$, $P = 0.001$), systolic BP ($\rho = 0.379$, $P < 0.001$), and diastolic

BP ($\rho = 0.350$, $P < 0.001$) (Table 3). Subgroup analysis was performed in the OB group to evaluate the association between VPT and that of metabolic biomarkers obtained from indirect calorimetry (REE and RQ). REE and RQ data were obtained and performed in the OB group only (Table 3).

Stepwise multivariate linear regression modelling was performed with VPT as the dependent variable from the entire cohort (HV, T1D and OB) (Table 4). In model 1, BMI ($\beta = 0.333$; $P < 0.001$) and age ($\beta = 0.249$; $P = 0.002$) correlated with VPT as the primary dependent variable. In model 2, VPT correlated with age ($\beta = 0.257$; $P < 0.001$) and WC ($\beta = 0.433$; $P < 0.001$), but not BMI ($P = 0.214$) and FM% ($P = 0.119$). In model 3, VPT correlated with age ($\beta = 0.149$; $P = 0.037$), WC

Table 2 Peripheral neuropathy measurements in HVs and participants with T1D and OB

	HV (<i>n</i> = 28)	T1D (<i>n</i> = 51)	OB (<i>n</i> = 51)	<i>P</i> value		
				HV vs T1D	HV vs OB	OB vs T1D
VAS Pain	0.3 ± 0.6	3.3 ± 3.5	3.0 ± 1.5	< 0.001	< 0.001	0.50
(–/10)	0 (0–0.5)	3 (0–7)	3 (2–4)			
Median (IQR)						
NDS (–/10)	0 ± 0	3.3 ± 3.8	2.4 ± 2.9	< 0.001	< 0.001	0.52
Median (IQR)	0 (0–0)	2 (0–8)	1 (0–6)			
NSP (–/34)	0.1 ± 0.5	9.3 ± 8.6	9.1 ± 7.7	< 0.001	< 0.001	0.28
Median (IQR)	0 (0–2)	6 (2–18)	6 (2–16)			
VPT (V)	8.9 ± 2.0	18.9 ± 10.2	17.5 ± 5.8	< 0.001	< 0.001	0.33
SNCV (m/s)	50.5 ± 3.4	41.2 ± 7.7	42.2 ± 6.1	< 0.001	< 0.001	0.75
SNAP (µV)	15.7 ± 2.2	7.3 ± 3.4	7.5 ± 2.9	< 0.001	< 0.001	0.94
Impaired VPT (15–24 V) (%)	0	19.6	23.5	–	–	–
Advanced VPT (≥ 25 V) (%)	0	31.4	19.6	–	–	–
Toronto criteria (%)	0	43.1	33.3	–	–	–

Data presented as mean ± SD

HV healthy volunteers, NCS nerve conduction study, NDS neuropathy disability score, NSP neuropathy symptom profile, OB obesity, SNAP sural nerve action potential, SNCV sural nerve conduction velocity, T1D type 1 diabetes, Toronto consensus criteria for peripheral neuropathy, VAS pain visual analogue score for pain, VPT vibration perception threshold

($\beta = 0.382$; $P = 0.018$), FM% ($\beta = 0.783$; $P < 0.001$) and HbA1c ($\beta = 1.051$; $P < 0.001$) but there was no significant correlation with BMI, total cholesterol, triglycerides, systolic and diastolic blood pressure.

Obese With and Without Peripheral Neuropathy

Of the 51 participants with OB, 33.3% ($n = 17$) fulfilled the criteria for peripheral neuropathy according to the Toronto consensus criteria on peripheral neuropathy [15]. Within the OB group, the prevalence of impaired VPT (15–24 V) was 23.5% ($n = 12$) and prevalence of advanced VPT deemed at high risk of neuropathic ulcer (VPT ≥ 25 V) was 19.6% ($n = 10$). The peripheral neuropathy subgroup within OB had a greater NSP ($P < 0.001$), VAS for pain ($P < 0.001$) and VPT ($P < 0.001$) with lower

SNCV ($P < 0.001$) and SNAP ($P = 0.003$). WC ($P = 0.028$) and FM% ($P < 0.001$) were significantly higher in obese participants with peripheral neuropathy compared to those without peripheral neuropathy.

In the OB group, measured substrate oxidation, represented by the RQ (mean RQ = 1.016; 95% CI 0.9888–1.044) during the rested and overnight fasted metabolic state, was not associated with VPT ($P = 0.934$), sural nerve conduction velocity (SNCV) ($P = 0.743$) or sural nerve amplitude (SNAP) ($P = 0.677$).

DISCUSSION

This cross-sectional study demonstrated a comparable prevalence of peripheral neuropathy in normoglycaemic people with obesity compared to people with long-duration T1D. This advocates that peripheral neuropathy is a

Table 3 Pearson's correlation of variables against vibration perception threshold

	VPT	
	ρ	<i>P</i>
Age	0.269	0.002
Female	0.110	0.214
BMI	0.348	< 0.001
WC	0.420	< 0.001
FM%	0.280	0.001
TRIG	0.299	0.001
LDL	0.168	0.071
HDL	0.045	0.633
TChol	0.227	0.010
HbA1c	0.400	< 0.001
SBP	0.379	< 0.001
DBP	0.350	< 0.001
NSP	0.841	< 0.001
VAS	0.761	< 0.001
REE [§]	0.042	0.768
RQ [§]	0.012	0.934

BMI body mass index, *DBP* diastolic blood pressure, *FM%* body fat percentage, *HDL* HDL-cholesterol, *HbA1c* glycosylated haemoglobin, *LDL* LDL-cholesterol, *NSP* neuropathy symptom profile, *SBP* systolic blood pressure, *TChol* total cholesterol, *TRIG* triglycerides, *VAS* visual analogue scale for pain, *VPT* vibration perception threshold, *WC* waist circumference

[§]Consists of subgroup analysis between VPT against REE and RQ data set within the OB group only

result of a culmination of complex interaction of several aetiologically linked pathophysiological processes. Furthermore, our report demonstrates that there is a positive association between obesity and greater centripetal adiposity, approximated by increased waist circumference and increased body fat percentage, with increased and/or impaired VPT. The link between obesity and peripheral neuropathy have been attributed to metabolically driven

cardiovascular risk factors such as hypertension, hyperlipidaemia and inflammation [7, 17] leading to degenerative processes within the small nerve fibres. However, these mechanisms are not fully elucidated. Obesity and hypertriglyceridemia predict the development of diabetic neuropathy in T2D, independent of glycaemic control [18]. In a recent cross-sectional study of 47 participants with severe obesity and 30 age-matched controls, participants with severe obesity had a higher NSP, abnormal thermal thresholds and lower sural and peroneal nerve amplitudes compared to controls, and those with obesity and small nerve fibre damage had higher triglycerides and prevalence of metabolic syndrome (58% vs 23%; $P = 0.02$) [19]. Interestingly, we did not demonstrate an association between neuropathy and triglycerides, likely because of the good control of lipids in the OB cohort as they were under the care of a tertiary weight management clinic. Experimental studies have demonstrated that neurones send vasoactive signals to increase vascular permeability and attract adaptive immunogenic cells in high fat diet-fed rodents with obesity, dyslipidaemia and neuropathy [20, 21]. Although initially a protective mechanism, persistent dysfunction secondary to obesity-mediated inflammation results in structural neuronal damage. Further, inflammatory mediators (tumour necrosis alpha and interleukin-1B) and macrophages promote a long-term microvascular inflammatory response and impairment of insulin signalling in the peripheral nervous system [22]. Peripheral neuropathy has been associated with increased abdominal and visceral obesity [23]. In addition, obstructive sleep apnoea (OSA) which is prevalent in severe obesity and even in T1D is an independent risk factor for axonal dysfunction of peripheral sensory nerves [24]. Unfortunately, OSA data was not available within this cohort and this risk factor could not be further investigated in the current study.

Autonomic dysfunction may be involved in the development of obesity and visceral/central obesity with increased peripheral insulin resistance [25, 26]. Xu et al. showed that BMI was an independent risk factor for abnormal plantar pressures and increased VPT [27]. In patients

Table 4 Multivariate linear regression model using VPT as the dependent variable

Model	Variable	β coefficients	95% CI	P	R ²
1	BMI	0.333	0.170; 0.480	< 0.001	0.170
	Age	0.249	0.074; 0.336	0.002	
2	BMI	0.208	− 0.184; 0.457	0.214	0.253
	Age	0.257	0.091; 0.342	0.001	
	WC	0.433	0.098; 0.313	0.001	
	FM%	0.250	0.056; 0.377	0.119	
3	BMI	0.063	− 0.290; 0.423	0.711	0.538
	Age	0.149	0.007; 0.259	0.037	
	WC	0.382	0.041; 0.213	0.018	
	FM%	0.783	0.248; 0.884	< 0.001	
	TChol	0.078	− 2.512; 1.004	0.396	
	TRIG	0.043	− 1.357; 2.098	0.671	
	HbA1c	1.051	0.323; 0.595	< 0.001	
	SBP	0.043	− 0.042; 0.171	0.232	
	DBP	− 0.045	− 0.216; 0.131	0.627	

BMI body mass index, CI confidence interval, DBP diastolic blood pressure, FM% body fat percentage, HbA1c glycated haemoglobin, HDL HDL-cholesterol, LDL LDL-cholesterol, TCHOL total cholesterol, TRIG triglycerides, RQ respiratory quotient, REE resting energy expenditure, SBP systolic blood pressure, VPT vibration perception threshold, WC waist circumference

with T2D, Gao et al. [28] reported that those with the highest fat mass index had the highest risk of neuropathy (HR 1.93, 95% CI 1.74–2.15). In a cross-sectional study, Callaghan et al. [29] observed that the prevalence of peripheral neuropathy was 12.1% in obese participants with normoglycaemia and 40.8% in obese participants with diabetes.

Our findings concur with previous studies [29–31] demonstrating that obesity is associated with peripheral neuropathy. Indeed, Herman et al. [30] reported that people with severe obesity had a predominant small fibre neuropathy. In the National Health and Nutrition Examination Survey of adults over 40 years of age, whilst 9% had peripheral neuropathy the obese group had at twofold greater risk (OR 2.20, 95% CI 1.43–3.39) of neuropathy compared to non-obese individuals [32].

Participants with obesity and reduced insulin sensitivity show reduced tibial and peroneal nerve compound and sensory amplitudes [31]. Roustit et al. [33] demonstrated that a higher WC and obesity were independently associated with VPT. Spallone et al. prospectively assessed 135 patients with diabetes and showed that BMI was an independent risk factor for DPN [34]. The KORA/Augsburg study followed 513 subjects over 6.5 years and showed that being overweight (OR 3.06, 95% CI 1.57–5.97) and obese (OR 3.47, 95% CI 1.72–7.00) increased the risk of developing peripheral neuropathy [35].

Emerging research suggests that the development and progression of neuropathy is associated with an impaired metabolic switch from glucose to fatty acid or lipid oxidation [36] with an association between cholesterol oxidation and glycated LDL and the pathogenesis of

neuropathy [37]. Reduced peripheral insulin sensitivity also leads to increased fatty acid flux into Schwann cells and subsequent peripheral neuropathy [38, 39]. Obesity is associated with the loss of peripheral sensory neurons and pathology to intra-epidermal nerve fibres [40, 41]. Local fat metabolism in the peripheral nerve is of importance in maintaining an intact and functional peripheral nerve. Previous data has demonstrated that several genes are only maximally expressed in the mature nerve, after the completion of myelination, and are also linked to the metabolism of storage lipids [42]. Within obesity and T2D, there is intracellular accumulation of metabolites with enhanced fatty acid uptake and blunted fatty acid oxidation and lack of insulin-mediated inhibition of lipolysis [43]. This leads to excess circulatory ‘spill’ with uptake by non-adipose tissue like the liver, muscle, heart and pancreas leading to ectopic fat deposition and dyslipidemia. Consequent to the dyslipidemia state, free fatty acid-induced lipotoxicity alters lipid-induced intracellular signaling and drives neurological dysfunction and neurodegeneration [44]. Whilst this study has shown impaired fat oxidation and ‘overreliance’ on glucose oxidation in obesity, fat oxidation per se was not associated with peripheral neuropathy measures. However, cross-sectional measures of fat oxidation which are fluid may not correlate with more ‘fixed’ quantitative measures of peripheral neuropathy.

In a large retrospective cohort study of 88,981 patients with T2D, bariatric surgery was associated with significantly lower rates of microvascular and macrovascular complications, compared to a non-surgically treated group over 9 years [45], and this has been corroborated by other studies [46]. Bariatric surgery in people with obesity with and without T2D is associated with improved biomarkers of neuropathy, specifically evidence of small nerve fibre regeneration over 12 months [40, 41] evaluated with corneal confocal microscopy. The prevalence of peripheral neuropathy measured with the Michigan Neuropathy Screening Instrument (MNSI) was found to be reduced (pre-bariatric surgery 20.4% to post-bariatric surgery 10.5%) approximately 10 years after

Roux-en-Y gastric bypass and sleeve gastrectomy [47]. Several randomized controlled studies (DiRECT, DROPLET and PREVIEW) have demonstrated the efficacy of low-calorie diets (LCDs; 800–850 kcal/day) in severe obesity [48–50]; and recently, a dietary weight loss study of 800 kcal/day (for 12 weeks) followed by 1200–1500 kcal/day resulted in an improvement in metabolic parameters, whilst intra-epidermal nerve fibre density (IENFD) remained stable after 2 years [51].

We acknowledge that causality between obesity and neuropathy cannot be inferred from a cross-sectional study. We have also not undertaken small fibre phenotyping which may be more relevant to obesity-related neuropathy. A larger sample size may also have allowed adjustment of confounding factors for neuropathy in relation to RQ or index of fat oxidation, and RQ subanalysis may be limited because of the severe obesity present in the participant population.

CONCLUSION

The prevalence and characteristics of peripheral neuropathy were comparable between normoglycaemic people with obesity and long-duration T1D, suggesting that metabolic factors linked to obesity play a significant role in development of peripheral neuropathy. Further studies are needed to investigate the role of visceral adiposity in peripheral neuropathy.

ACKNOWLEDGEMENTS

Funding. This work was supported and funded by a grant received from the Association of Physicians of Great Britain and Ireland (Young Investigator Award 2018) to UA and the University of Liverpool (UoL001379), UK. The Open Access fee was funded by the University of Liverpool.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this

article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Author Contributions. The study investigators JZML, JPHW and UA were responsible for creating the research question, design of the study, obtaining ethical approval, the acquisition of funding and subsequent data and oversight of the study. JB, GP, CGO and RAM were responsible for creating the research question, design of the study and acquisition of data and oversight of the study. JZML was responsible for collating the data and performing the appropriate statistical analyses. All authors contributed towards drafting of the manuscript.

List of Investigators. The principal investigators in the study include CGO, JPHW, GP, RAM and UA. The sub-principal investigators in the study include JZML and JB.

Disclosures. Jonathan Zhang Ming Lim, Jamie Burgess, Cheong Guan Ooi, Georgios Ponirakis, Rayaz A. Malik, John P.H. Wilding and Uazman Alam all have nothing to disclose. The funding source and funding bodies did not have any input into the design of the study, the collection or analysis of data, the preparation of this manuscript or the decision to submit this manuscript for publication.

Competing Interests. JZML, JB, CGO, GP, RAM, JPHW and UA have no relevant conflict of interests to declare.

Compliance with Ethics Guidelines. This study received approval by the University of Liverpool Clinical Trials Unit and the Northwest Research Ethics Committee (18/NW/0532). This study received the health regulatory approval and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). All subjects provided informed consent to participate in the study.

Data Availability. The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract.* 2017;128:40–50.
2. World Health Organisation. WHO Global Health Observatory Data Repository 2020. <https://apps.who.int/gho/data/view.main>. Accessed 1 Feb 2022.
3. Health and Social Care Information Centre. Statistics on obesity, physical activity and diet, England. NHS Digital. 2019. <https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2019/part-3-adult-obesity>. Accessed 1 Feb 2022.
4. Ward ZJ, Bleich SN, Cradock AL, et al. Projected US state-level prevalence of adult obesity and severe obesity. *N Engl J Med.* 2019;381(25):2440–50.
5. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers.* 2019;5(1):42.
6. Pop-Busui R, Herman WH, Feldman EL, et al. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. *Curr Diab Rep.* 2010;10(4):276–82.

7. Tesfaye S, Selvarajah D. The Eurodiab study: what has this taught us about diabetic peripheral neuropathy? *Curr Diab Rep*. 2009;9(6):432–4.
8. Andersen ST, Witte DR, Dalsgaard EM, et al. Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. *Diabetes Care*. 2018;41(5):1068–75.
9. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg surveys S2 and S3. *Diabetes Care*. 2008;31(3):464–9.
10. Hanewinkel R, Drenthen J, Ligthart S, et al. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: a prospective population-based cohort study. *J Neurol Neurosurg Psychiatry*. 2016;87(12):1336–42.
11. Callaghan BC, Xia R, Banerjee M, et al. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. *Diabetes Care*. 2016;39(5):801–7.
12. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg surveys S2 and S3. *Diabetes Care*. 2008;31(3):464–9.
13. Viader A, Sasaki Y, Kim S, et al. Aberrant Schwann cell lipid metabolism linked to mitochondrial deficits leads to axon degeneration and neuropathy. *Neuron*. 2013;77(5):886–98.
14. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28(12):1039–57.
15. Dyck PJ, Albers JW, Andersen H, et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab Res Rev*. 2011;27(7):620–8.
16. Lee JA, Halpern EM, Lovblom LE, Yeung E, Bril V, Perkins BA. Reliability and validity of a point-of-care sural nerve conduction device for identification of diabetic neuropathy. *PLoS ONE*. 2014;9(1):e86515.
17. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. *N Engl J Med*. 2005;352(4):341–50.
18. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. *J Diabetes Complications*. 2013;27(5):436–42.
19. Azmi S, Ferdousi M, Liu Y, et al. The role of abnormalities of lipoproteins and HDL functionality in small fibre dysfunction in people with severe obesity. *Sci Rep*. 2021;11(1):12573.
20. Buckman LB, Hasty AH, Flaherty DK, et al. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system. *Brain Behav Immun*. 2014;35:33–42.
21. Guillemot-Legris O, Masquelier J, Everard A, Cani PD, Alhouayek M, Muccioli GG. High-fat diet feeding differentially affects the development of inflammation in the central nervous system. *J Neuroinflammation*. 2016;13(1):206.
22. O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. *Lancet Neurol*. 2017;16(6):465–77.
23. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy. *Diabetes Care*. 2008;31(3):464.
24. Dzierwas R, Schilling M, Engel P, et al. Treatment for obstructive sleep apnoea: effect on peripheral nerve function. *J Neurol Neurosurg Psychiatry*. 2007;78(3):295–7.
25. Fidan-Yaylali G, Yaylali YT, Erdogan Ç, et al. The association between central adiposity and autonomic dysfunction in obesity. *Med Princ Pract*. 2016;25(5):442–8.
26. Guarino D, Nannipieri M, Iervasi G, Taddei S, Bruno RM. The role of the autonomic nervous system in the pathophysiology of obesity. *Front Physiol*. 2017;8:665.
27. Xu L, Zeng H, Zhao J, et al. Index of plantar pressure alters with prolonged diabetes duration. *Diabetes Ther*. 2019;10(6):2139–52.
28. Gao S, Zhang H, Long C, Xing Z. Association between obesity and microvascular diseases in patients with type 2 diabetes mellitus. *Front Endocrinol (Lausanne)*. 2021;12(1307).
29. Callaghan BC, Reynolds E, Banerjee M, Chant E, Villegas-Umana E, Feldman EL. Central obesity is associated with neuropathy in the severely obese. *Mayo Clin Proc*. 2020;95(7):1342–53.
30. Herman RM, Brower JB, Stoddard DG, et al. Prevalence of somatic small fiber neuropathy in obesity. *Int J Obes (Lond)*. 2007;31(2):226–35.

31. Miscio G, Guastamacchia G, Brunani A, Priano L, Baudo S, Mauro A. Obesity and peripheral neuropathy risk: a dangerous liaison. *J Peripher Nerv Syst.* 2005;10(4):354–8.
32. Ylitalo KR, Sowers M, Heeringa S. Peripheral vascular disease and peripheral neuropathy in individuals with cardiometabolic clustering and obesity. *Diabetes Care.* 2011;34(7):1642.
33. Roustit M, Loader J, Deusenbery C, Baltzis D, Veves A. Endothelial dysfunction as a link between cardiovascular risk factors and peripheral neuropathy in diabetes. *J Clin Endocrinol Metab.* 2016;101(9):3401–8.
34. Spallone V, Morganti R, D'Amato C, et al. Clinical correlates of painful diabetic neuropathy and relationship of neuropathic pain with sensorimotor and autonomic nerve function. *Eur J Pain.* 2011;15(2):153–60.
35. Schlesinger S, Herder C, Kannenberg JM, et al. General and abdominal obesity and incident distal sensorimotor polyneuropathy: insights into inflammatory biomarkers as potential mediators in the KORA F4/FF4 cohort. *Diabetes Care.* 2019;42(2):240.
36. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab.* 2017;25(2):262–84.
37. Bruce KD, Zsombok A, Eckel RH. Lipid processing in the brain: a key regulator of systemic metabolism. *Front Endocrinol.* 2017;8:60.
38. Coccurello R, Nazio F, Rossi C, et al. Effects of caloric restriction on neuropathic pain, peripheral nerve degeneration and inflammation in normometabolic and autophagy defective prediabetic *Ambra1* mice. *PLoS ONE.* 2018;13(12):e0208596.
39. Rumora AE, LoGrasso G, Hayes JM, et al. The divergent roles of dietary saturated and monounsaturated fatty acids on nerve function in murine models of obesity. *J Neurosci.* 2019;39(19):3770–81.
40. Iqbal Z, Kalteniece A, Ferdousi M, et al. Corneal keratocyte density and corneal nerves are reduced in patients with severe obesity and improve after bariatric surgery. *Investig Ophthalmol Vis Sci.* 2021;62(1):20.
41. Adam S, Azmi S, Ho JH, et al. Improvements in diabetic neuropathy and nephropathy after bariatric surgery: a prospective cohort study. *Obes Surg.* 2021;31(2):554–63.
42. Verheijen MH, Chrast R, Burrola P, Lemke G. Local regulation of fat metabolism in peripheral nerves. *Genes Dev.* 2003;17(19):2450–64.
43. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci.* 2012;15(8):1063–7.
44. Visser NA, Vrancken AF, van der Schouw YT, van den Berg LH, Notermans NC. Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. *Diabetes Care.* 2013;36(4):817–22.
45. Goldberg I, Nie L, Yang J, et al. Impact of bariatric surgery on the development of diabetic microvascular and macrovascular complications. *Surg Endosc.* 2021;35(7):3923–31.
46. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. *Ann Intern Med.* 2018;169(5):300–10.
47. Machado FD, Nienov OH, Schmid H. Prevalence of peripheral polyneuropathy before and after Roux-en-Y gastric bypass and sleeve gastrectomy. *Obes Surg.* 2021;31(10):4427–35.
48. Astbury NM, Aveyard P, Nickless A, et al. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. *BMJ.* 2018;362: k3760.
49. Fogelholm M, Larsen TM, Westerterp-Plantenga M, et al. PREVIEW: prevention of diabetes through lifestyle intervention and population studies in Europe and around the world. Design, methods, and baseline participant description of an adult cohort enrolled into a three-year randomised clinical trial. *Nutrients.* 2017;9(6):632.
50. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet.* 2018;391(10120):541–51.
51. Callaghan BC, Reynolds EL, Banerjee M, et al. Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology. *Obesity (Silver Spring).* 2021;29(12):2108–18.