RESEARCH REPORT

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Protection from neuropathy in extreme duration type 1 diabetes

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Abstract

A proportion of individuals with type 1 diabetes mellitus for more than 50 years (medallists) may be protected from developing nephropathy, retinopathy and neuropathy. Detailed neuropathy phenotyping was undertaken in a cohort of 33 medallists aged 63.7 ± 1.4 years with diabetes for 58.5 ± 0.8 years and HbA1c of 65.9 ± 2.1 mmol/mmol. Medallists had a significantly higher HbA1c ($P < .001$), lower estimated glomerular filtration rate (eGFR) ($P = .005$) and higher albumin creatinine excretion ratio (ACR) ($P = .01$), but a lower total cholesterol ($P < .001$), triacylglycerols ($P = .001$), low density lipoprotein-cholesterol ($P < .001$) and higher high density lipoprotein-cholesterol ($P = .03$), compared to controls. Twenty-four percent of participants were identified as "escapers" without confirmed diabetic neuropathy. They had a lower neuropathy symptom profile ($P = .002$), vibration perception threshold ($P = .02$), warm threshold ($P = .05$), higher peroneal amplitude ($P = .005$), nerve conduction velocity ($P = .03$), heart rate variability ($P = .001$), corneal nerve fibre density ($P = 0.001$), branch density ($P < .001$) and length ($P = .001$), compared to medallists with diabetic neuropathy. Escapers had a shorter duration of diabetes ($P = .006$), lower alcohol consumption ($P = .04$), lower total cholesterol ($P = .04$) and LDL ($P = .02$), higher eGFR ($P = .001$) and lower ACR ($P < .001$). Patients with extreme duration diabetes without diabetic neuropathy have a comparable HbA1c, blood pressure and body mass index, but a more favourable lipid profile and consume less alcohol compared to those with diabetic neuropathy.

KEYWORDS

corneal confocal microscopy, extreme duration diabetes, neuropathy, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is associated with varying degrees of diabetic retinopathy, nephropathy and neuropathy, despite optimal glycaemic control.[1] Diabetes UK award the Alan Nabarro and RD Lawrence medals to individuals with more than 50 and 60 years of T1DM, respectively, and they are referred to as "medallists." These individuals with extreme duration T1DM are a unique

cohort to identify factors that may afford protection from long-term complications.[2]

Most studies on in medallists have lacked detailed phenotyping, relying on case notes and clinical history and moreover have focused on nephropathy and retinopathy.[3,4] The Golden Years Study showed a relative protection from diabetic nephropathy in association with an elevated HDL-cholesterol (HDL-C).[5] Similarly, using patient and physician records, the Joslin medallist study reported proliferative diabetic retinopathy and neuropathy in approximately 50% of their patients[6] and attributed protection from complications to residual insulin production, a higher HDL-C and lower triglycerides.[7] In a recent study of 325 medallists from Canada, a lower burden of microvascular complications, derived from case records, was associated with current physical activity and higher HDL-C.[8] The same group have shown that large rather than small fibre neuropathy is associated with coronary artery calcification in medallists.[9] We have previously demonstrated minimal evidence of diastolic dysfunction and cardiac fibrosis and a higher HDL-C in a cohort of medallists.[10] More recently we have demonstrated no structural or functional abnormality on cardiac MRI in medallists.[11]

We have had the unique opportunity to undertake comprehensive phenotyping of neuropathy in a cohort of medallists and identified factors that may protect them from diabetic neuropathy.

2 | METHODS

2.1 | Selection of patients

Thirty-three individuals with T1DM for >50 years and 19 age-matched controls were recruited from Central Manchester and Manchester Children's University Hospital. Exclusion criteria were any history of neuropathy due to a non-diabetic cause and any history of corneal trauma or surgery, or systemic or ocular disease that may affect the cornea. The Central Manchester Research and Ethics Committee approved this study and written informed consent was obtained from all subjects participating in the study. This research adhered to the tenets of the declaration of Helsinki.

2.2 | Clinical metabolic and neuropathy assessment

Study participants underwent assessment of body mass index (BMI), blood pressure, HbA1c, lipid profile (total cholesterol, low density lipoprotein [LDL-C], HDL-C and triglycerides), albumin creatinine excretion ratio (ACR) and estimated glomerular filtration rate (eGFR). Symptoms of DPN were assessed using the Neuropathy Symptom Profile (NSP) and neurological deficits were evaluated using the modified neuropathy disability score (NDS). Vibration perception threshold (VPT) was tested using a Neurothesiometer (Horwell, Scientific Laboratory Supplies, Wilfrod, Nottingham, UK). Cold (CT) and warm (WT) thresholds were assessed on the foot using the TSA-II NeuroSensory Analyser (Medoc Ltd., Ramat-Yishai, Israel). Sural sensory nerve amplitude (SSNamp),

sural sensory nerve conduction velocity (SSNCV), sural sensory nerve latency (SSNL), peroneal motor nerve amplitude (PMNamp), peroneal motor nerve latency (PMNL) and peroneal motor nerve conduction velocity (PMNCV) were assessed by a consultant neurophysiologist using a Dantec "Keypoint" system (Dantec Dynamics Ltd, Bristol, UK). Heart rate variability (HRV) was assessed with an ANX 3.0 autonomic nervous system monitoring device (ANSAR Medical Technologies Inc., Philadelphia, PA, USA). Patients underwent examination with the CCM (Heidelberg Retinal Tomograph III Rostock Cornea Module, Heidelberg Engineering GmbH, Heidelberg, Germany) according to our established protocol.[12] Six non-overlapping images/patient (three per eye) from the centre of the cornea were selected and quantified in a masked fashion. Three corneal nerve parameters were quantified: Corneal nerve fibre density (CNFD)-the total number of major nerves/mm^2 of corneal tissue, Corneal nerve branch density (CNBD)-the number of branches emanating from the major nerve trunks/mm^2 and Corneal nerve fibre length (CNFL)-the total length of all nerve fibres and branches (mm/mm^2) within the area of corneal tissue. Analysis of corneal nerve morphology was performed using the software (CCMetrics).[13] Participants were divided according to the Toronto criteria, which relies on the presence of an abnormality of nerve conduction and a symptom or symptoms or a sign or signs of neuropathy into medallist with and without confirmed diabetic neuropathy.[14]

2.3 | Statistical analyses

Analyses were carried out on SPSS for Mac (Version 19.0, IBM Corporation, New York, USA). All data are expressed as mean ± SD. The data was tested for normality by using the Shapiro Wilk Normality test and by visualising the histogram and normal Q-Q plot. To assess within and between group differences we used one-way analysis of variance (non-parametric-Kruskal–Wallis). A significant P value was considered to be <.05 (post hoc-Tukey). Sample size was calculated from previous published data.

3 | RESULTS

3.1 | Baseline demographic data

3.1.1 | Medallists

Medallist's had a significantly lower total cholesterol ($P < .001$), LDL-C ($P < .001$) and triglycerides ($P = .001$) with a higher HDL-C ($P = .03$) and HbA1c ($P < .001$), compared to controls. 47% of medallist had a previous history of retinopathy and a significantly lower eGFR ($P = .005$) and higher ACR ($P = .01$) compared to controls (Table 1). NSP, NDS, VPT, sural and peroneal nerve latencies were significantly higher and sural and peroneal nerve amplitude and conduction velocity were lower ($P < .001$ for all). CT ($P < .001$) and WT ($P = .002$) were higher and DB-HRV ($P = .006$), CNFD ($P < .001$), CNBD ($P < .001$) and CNFL ($P < .001$) were significantly lower in the medallist group compared to controls (Table 2).

TABLE 1 Clinical demographic and metabolic parameters in controls, medallists without neuropathy and medallists with neuropathy

	Control (n = 19)	Medallists without neuropathy (n = 8)	Medallists with neuropathy (n = 25)
Age (years)	61.7 ± 1.2	58.7 ± 2.8	65.2 ± 1.7
Gender (F/M)	7/12		
Smoking (cigarette/day)	0.4 ± 0.4	0 ± 0	1.5 ± 1.0
Alcohol consumption (units/week)	5.7 ± 2.0	0.8 ± 0.5	4.9 ± 1.6§
Duration of diabetes (years)	N/A	54.8 ± 0.8	59.9 ± 0.9§
Patients on statin, n (%)	N/A	7 (88%)	22 (88%)
Patients on antihypertensive, n (%)	N/A	7 (88%)	22 (88%)
Blood pressure sys/dia (mm Hg)	137 ± 3.5/71.2 ± 2.6	144.5 ± 7.2/72.9 ± 2.9	148.4 ± 3.8/70.5 ± 2.0
Height (cm)	170.1 ± 2.5	167.7 ± 3.2	170.0 ± 1.7
BMI (kg/m^2)	26.8 ± 0.7	29.2 ± 1.9	27.1 ± 0.8
HbA1c DCCT (%)	32.2 ± 2.5	61.8 ± 2.5	65.9 ± 2.4
IFCC (mmol/mol)	5.1 ± 0.4**	7.8 ± 0.4	8.2 ± 0.2
Total cholesterol (mmol/L)	5.4 ± 0.2**	3.9 ± 0.3	4.5 ± 0.2§
HDL-C (mmol/L)	1.6 ± 0.07*	1.7 ± 0.2	1.8 ± 0.1
Triacylglycerol (mmol/L)	1.8 ± 0.1**	1.1 ± 0.2	1.2 ± 0.2
LDL-C (mmol/L)	3.0 ± 0.2**	1.6 ± 0.2	2.1 ± 0.2§
ACR (mg/mmol)	0.3 ± 0.01*	0.2 ± 0.02	11.3 ± 3.6$^+$
eGFR (mL/min/L)	80.4 ± 1.8*	82.7 ± 2.7	55.4 ± 4.8$^+$

Note: *$P < .05$, **$P < .001$ control vs medallist; $^§P < .05$, $^+ P < .001$ medallists without neuropathy vs medallists with neuropathy.
Abbreviations: ACR, albumin creatinine excretion ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

TABLE 2 Neuropathy assessments in controls and medallists with and without neuropathy

	Control (n = 19)	Medallists without neuropathy (n = 8)	Medallists with neuropathy (n = 25)
NSP	0.3 ± 0.1**	1.3 ± 0.5⌘	6.9 ± 1.2$^∧$
NDS (0–10)	1.2 ± 0.3**	5.4 ± 0.9 ^{λ}	5.4 ± 0.6
VPT (volts)	9.7 ± 1.6**	16.1 ± 2.8	29.5 ± 2.6§
Sural latency (ms)	2.9 ± 0.1**	3.7 ± 0.3 ^{β}	4.2 ± 0.2§
Sural amplitude (μv)	13.5 ± 1.8**	4.0 ± 0.9^β	2.7 ± 0.6
Sural velocity (m/s)	48.9 ± 1.3**	37.9 ± 2.9^β	34.0 ± 1.3
Peroneal latency (ms)	4.3 ± 0.1**	4.8 ± 0.3	6.2 ± 0.3$^∧$
Peroneal amplitude (mV)	4.9 ± 0.3**	2.5 ± 0.6^β	0.9 ± 0.2$^∧$
Peroneal velocity (m/s)	45.7 ± 0.7**	40.2 ± 1.7^β	31.9 ± 2.1§
Cold threshold (°C)	27.6 ± 0.5**	24.4 ± 1.5⌘	20.7 ± 1.7
Warm threshold (°C)	38.0 ± 0.7*	39.4 ± 1.2	42.9 ± 0.9§
CNFD (no./mm^2)	37.4 ± 1.6**	23.7 ± 2.1 ^{λ}	15.7 ± 2.3§
CNBD (no./mm^2)	82.9 ± 7.9**	62.1 ± 11.6	35.1 ± 6.9§
CNFL (mm/mm^2)	25.6 ± 1.0**	20.2 ± 1.4§	12.1 ± 1.4§
DB-HRV (beats/min)	20.9 ± 3.0*	17.5 ± 3.6	9.4 ± 0.9$^+$

Note: *$P < .05$, **$P < .001$ Control vs medallist; ⌘$P < .05$, $^βP < .005$, $^λP < .0001$ Control vs medallists without neuropathy; $^§P < .05$, $^∧P < .005$, $^+P = .001$ medallists without neuropathy vs medallists with neuropathy.
Abbreviations: CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; HRV, heart rate variability; NDS, neuropathy disability score; NSP, neuropathy symptom profile; VPT, vibration perception threshold.

3.1.2 | Medallists without neuropathy (escapers)

Based on Toronto criteria, confirmed diabetic neuropathy was not present in 8/33 (24%) medallists. They had a significantly lower NSP ($P = .002$) and VPT ($P = .05$), higher sural latency ($P = .05$), peroneal latency ($P = .005$), amplitude ($P = .005$) and conduction velocity ($P = .03$), lower warm perception threshold ($P = .05$) and higher DB-HRV ($P = .001$), CNFD ($P = .022$), CNBD ($P = .016$) and CNFL
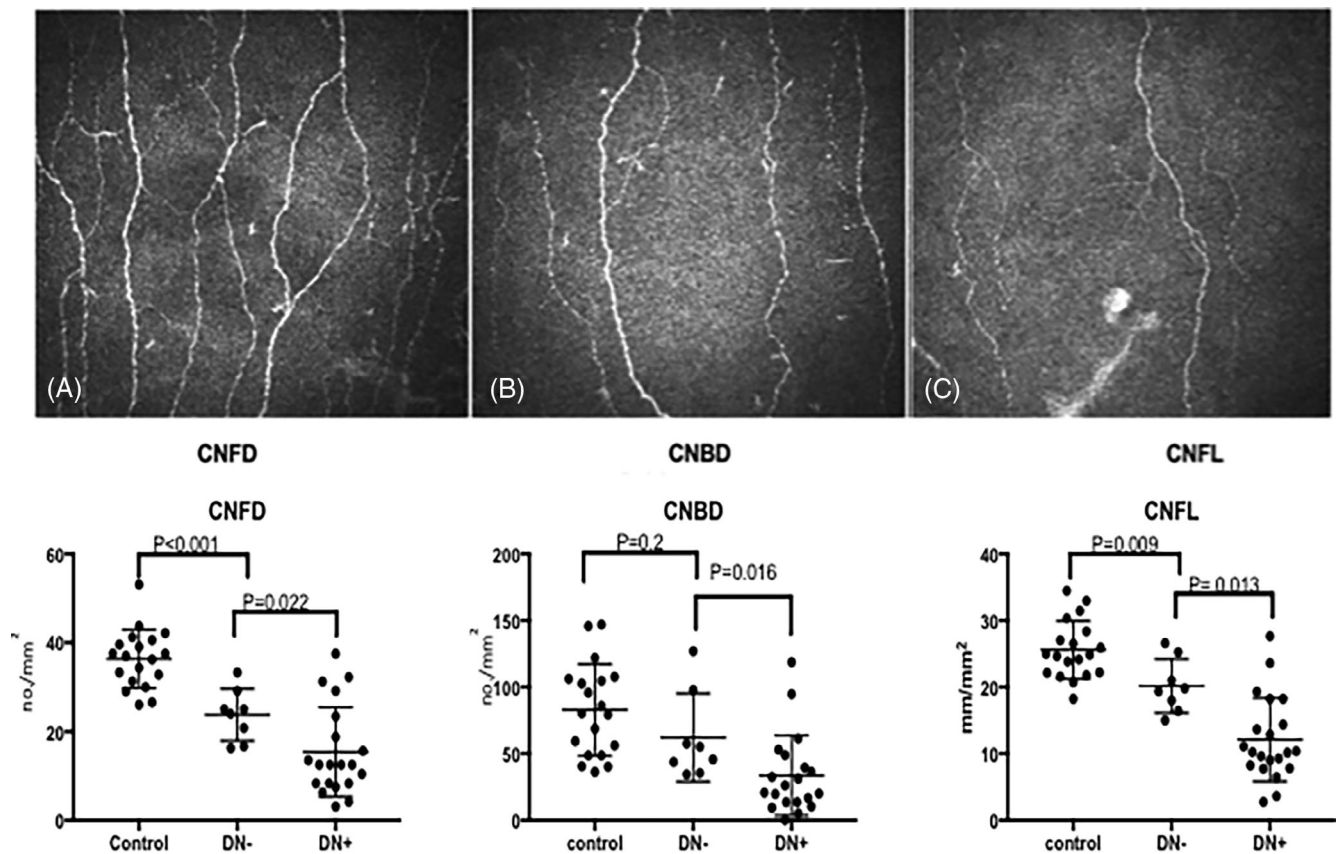
FIGURE 1 Corneal confocal images of a control participant, A; medallist without neuropathy, B; medallist with neuropathy, C. Corneal confocal parameters, D-F, in control participants, medallists without (DN−) and with neuropathy (DN+)

(P = .013) (Figure 1) compared to medallists with neuropathy. There was no difference in smoking status, blood pressure, BMI or HbA1c, but they had a significantly shorter duration of diabetes (P < .001), lower alcohol intake (P < .001), lower total cholesterol (P < .05), LDL-C (P < .05) and ACR (P < .001) and a higher eGFR (P < .001). An equally high proportion (88%) of medallists with and without neuropathy were being treated with a statin or ACE inhibitor.

4 | DISCUSSION

This is the first detailed phenotyping study of neuropathy which has identified that 24% of medallists did not have confirmed diabetic peripheral neuropathy according to the Toronto criteria. This was associated with a shorter duration of diabetes, less alcohol intake, lower total cholesterol, LDL-C and ACR and higher eGFR.

During the 1970s several reports identified the characteristics of the "long term survivor" of Type 1 diabetes and showed that they had a lower prevalence of smoking, better glycaemic control, more regular physical activity, frequent medical contact, lower insulin dose and a normal or below weight BMI.[15] Indeed, patients with more than 50 years of Type 1 diabetes and complications have been termed survivors, those with subclinical complications as delayers and those with no detectable complications as escapers.[2] Most previous cohort studies of medallists, have evaluated complications crudely using patient and physician records. Paz Guevara et al showed that in patients with more than 40 years of T1DM, retinopathy was present in 75%, nephropathy in 59% and neuropathy based on symptoms and neurological deficits in 50%.[16] Conversely, the Steno reported that 53% of their extreme duration patients had no major complications.[1] Oakley et al demonstrated that only 16.3% of patients with more than 40 years of T1DM had neuropathy.[17]

All previous studies in medallists have lacked detailed neuropathy phenotyping and therefore failed to accurately identify those individuals who were truly protected from neuropathy. The Golden Years Study, assessed ∼400 participants and showed that 35.7% of participants had an elevated urinary albumin creatinine ratio and 43% had previously undergone laser photocoagulation for diabetic retinopathy; however, neuropathy was not assessed.[5] Similarly, the Joslin Medallist study reported that 46.8% of medallists had no significant microvascular complications, but no objective assessment of neuropathy was undertaken.[7] In a follow up study of the Joslin cohort, 42.6% of medallists remained free from proliferative diabetic retinopathy, 86.9% from nephropathy and 39.4% from neuropathy, evaluated using the Michigan Screening Instrument.[6] Furthermore, in a recent study comparing two large cohorts of medallists from the US and Canada, neuropathy was identified using the questionnaire component of the MNSI in 42.5% and 44.9%, respectively.[18] In the present study based

on the Toronto criteria, 24% of medallists did not have confirmed diabetic peripheral neuropathy. However, even these "escapers" have mildly abnormal neurophysiology and corneal nerve fibre measures were significantly better in escapers without diabetic neuropathy compared to medallists with confirmed diabetic neuropathy. This is consistent with recent studies showing the excellent diagnostic utility of this technique in patients with diabetes[19] and medallists.[20,21]

Glucose mediated overproduction of superoxide by the mitochondrial electron transport chain[22] and shunting of various glycolytic intermediates to damaging pathways has been proposed as a major mechanism for diabetic neuropathy.[23] However, hypertension, lipids, and BMI have also been shown to be independent risk factors for the development of diabetic somatic[24] and autonomic[25] neuropathy and increased mortality[26] in patients with diabetes.[27] In the present study we show no difference in HbA1c, blood pressure or HDL between medallists with and without DPN. However, these were single measurements at the time of investigation and may not adequately reflect cumulative exposure to these risk factors. Indeed in a recent study, comparing a US and Canadian medallist cohort, despite a significant difference in HbA1c there was no difference in the prevalence of retinopathy or neuropathy.[18] We do however show that escapers have a shorter duration of diabetes and a lower total cholesterol, LDL-C and ACR with a higher eGFR. The EURODIAB study has previously shown that the duration of diabetes, cigarette smoking, BMI, blood pressure and triglycerides were associated with the development of neuropathy in a cohort of people with T1DM.[28] A higher HDL-C has been associated with protection from the development of retinopathy and nephropathy,[5] whilst higher triglycerides and insulin requirement[7] and lower residual insulin production[29] may lead to the development of microvascular complications amongst medallists.

We show that almost a quarter of patients with T1DM for over 50 years have escaped diabetic neuropathy and this is associated with lower alcohol intake and total and LDL cholesterol. More detailed genomic and mechanistic studies of larger cohorts of medallists may provide a more precise understanding of the factors that protect medallists and indeed patients from diabetic neuropathy.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Shazli Azmi researched data, performed analysis and wrote the manuscript, Maryam Ferdousi researched data performed analysis and reviewed the manuscript, Alise Kalteniece researched data, Ioannis N. Petropoulos researched data, Georgios Ponirakis researched data, Uazman Alam researched data, Omar Asghar researched data, Andrew Marshall researched data, Adhithya Sankar researched data, Andrew J. M. Boulton reviewed the manuscript, Handrean Soran reviewed the manuscript, Nathan Efron is joint principal investigator and reviewed the manuscript. Rayaz A. Malik designed the study, reviewed and revised the manuscript and is joint principal investigator of the study. Rayaz A. Malik is the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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