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Use of graded Semmes Weinstein monofilament testing for ascertaining peripheral neuropathy in people with and without diabetes

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ABSTRACT

Aims: To assess peripheral neuropathy (PN) using graded Semmes Weinstein monofilaments (SWMs) and determine factors associated with PN among adult volunteers with and without diabetes.

Methods: Adult volunteers were assessed for distal sensory PN using three graded SWMs. Four PN levels were defined: 0 (no PN; felt all three filaments), 1 (subclinical PN; insensate to 1-g filament), 2 (insensate to 10-g), or 3 (insensate to 75-g). Levels 2–3 were considered clinical PN. Associations with PN were determined using ordinal logistic regression.

Results: In 1564 subjects (median age 41.9 years, 50.1% women), PN was subclinical or worse in 68.9% and clinical in 11.2%. Age-sex-race-adjusted prevalence of clinical PN was greater in people with diabetes (15.3%) than without (6.1%; $P < 0.001$). Associated factors included older age, male sex, greater BMI, greater heart rate, lower mean arterial pressure, and family history of diabetes or cardiovascular diseases. Higher PN levels associated with worse albuminuria and retinopathy. Only older age and male sex associated with PN both in people with and without diabetes.

Conclusions: PN is common in our sample, notably in those without diabetes, although diabetes greatly increases its risk. Using graded SWMs may have a prognostic value as it permits the identification of subclinical PN.

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1. Introduction

Peripheral neuropathy (PN) is defined by a range of signs and symptoms of peripheral nerve dysfunction, and is caused by genetic disorders, infections, and several systemic diseases including diabetes [1,2]. Chronic PN could result in adverse outcomes, e.g. ulceration and amputations, with attendant poor quality of life. A commonly used method for the detecting PN in clinical settings is the relatively inexpensive, easy-to-use, and non-invasive Semmes Weinstein monofilament (SWM) test [3,4]. This test determines impaired or loss of protective sensation (sensory neuropathy) using the buckling

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force of monofilament gauges. Among people with diabetes in the United Kingdom, using three SWM grades (1-, 10-, and 75-g) was more sensitive (100%) in identifying those at risk of foot ulcers than an electronic tuning fork (79%) [5]. Although the 10-g monofilament gauge is widely recommended in practice [6], other buckling forces, e.g. 1- and 75-g gauges, may be used to ascertain PN severity.

PN is a diabetes complication but it also occurs in those without diabetes. Given that the pathophysiological pathway of PN extends beyond poor glycemic control, data on diabetic PN may not reflect pathophysiologic processes in those without diabetes. Factors associated with PN have been described in people with diabetes, including age, overweight/obesity, hypertension, nephropathy and retinopathy [7–10]. It is, however, unclear if these associations are present in people without diabetes.

We explored the use of graded SWMs for ascertaining the presence and severity of PN among adult volunteers in Phoenix, USA, with diabetes compared to those without diabetes; and compared the factors associated with PN severity in these two groups.

2. Subjects, materials and methods

This is a cross-sectional analysis of baseline data from an ongoing longitudinal study of diabetes and its complications. Subjects were enrolled between November 2011 and May 2016. Approval was obtained from the Institutional Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Phoenix Area Indian Health Service (IHS). Subjects provided informed consent.

2.1. Study subjects

Subjects were a convenience sample of non-pregnant volunteers aged ≥18 years residing in the metropolitan Phoenix and nearby Indian reservation areas of Arizona. Recruitment was through fliers (see Supplementary methods for the information provided on the flier), word-of-mouth, and telephone calls or walk-in visits by interested persons to the outpatient research clinic of the NIDDK. Since the research clinic is located on the campus of Phoenix Indian Medical Center, most volunteers were American Indians.

2.2. Interview, anthropometry and blood pressure measurement

Questionnaires were used to obtain data on sociodemographics, personal and family medical history, smoking or drinking habits. Family medical history included whether a first-degree relative had been diagnosed with a heart attack before the age of 60 years, or diagnosed/treated for diabetes, hypertension, stroke, or kidney failure at any age. Subjects also provided data on the use of medicines, including medicines known to cause PN, e.g. cancer therapy, antibiotics, vitamin B6, etc. [14]. Persons reporting equal heritage from more than one race were classified as having "mixed" race/ethnicity. Subjects also had standardized assessments of blood pressure (BP), heart rate and anthropometry. Hypertension was defined as having a systolic BP ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg or use of antihypertensive medicine, while the mean arterial pressure (MAP) was calculated as (2 * diastolic BP + systolic BP)/3.

2.3. Biochemical measurements

Blood samples were collected after an overnight fast for measuring fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c}), fasting insulin; total serum cholesterol (TC), HDL-cholesterol, triglycerides; and serum creatinine. An oral glucose tolerance test was performed after a 75-g oral glucose load to determine the two-hour plasma glucose (2-h PG), while untimed urine samples were collected for measuring albumin and creatinine. Diabetes was diagnosed if FPG was ≥126 mg/dL, 2-h PG was ≥200 mg/dL, HbA_{1c} was ≥6.5%, or if the participant was using diabetes medicines. In those without diabetes, impaired glucose regulation (IGR or prediabetes) was diagnosed if FPG = 100–125 mg/dL, 2-h PG = 140–199 mg/dL or HbA_{1c} = 5.7–6.4%. Dyslipidemia was defined as HDL-cholesterol <35 mg/dL and/or triglyceride ≥250 mg/dL. Albuminuria was defined by an albumin-creatinine ratio ≥30 mg/g. These conditions were defined using standard criteria [6]. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine (measured by an isotope dilution mass spectrometry standardized enzymatic method) using the CKD-EPI formula [12].

2.4. PN screening

Using the SWMs, trained clinicians examined the feet of subjects for distal sensory PN. The test involved applying three graded monofilaments (1-, 10- and 75-g gauges starting with the smallest gauge) perpendicularly to the skin until the filament buckled. Subjects were asked to provide feedback when there was a sensation. We tested three sites on the plantar surface of each foot, including the pulp of the big toe, the first metatarsal head, and the heel (total of six sites per subject). Filaments were applied only to sites with no callus, ulcers, edema, or amputation. Consequently, fewer testing sites were examined in 14 subjects due to amputations (n = 9) and ulcer, edema or callus (n = 5).

For each site, subjects were required to feel the touch of a monofilament gauge at four of five applications to be considered sensate to that gauge. The smallest gauge eliciting a response or lack of response to any gauge size (insensate) was ascertained. Subjects were assigned scores per site based on the response to the gauges and the average score was used to establish 4 levels of PN. These include 0 (no PN; being sensate to all three gauges; score = 0), 1 (subclinical PN; insensate to 1-g gauge; 0 < score ≤ 1), 2 (insensate to 10-g; 1 < score ≤ 2), or 3 (insensate to 75-g filament; score >2). Levels 2–3 were considered clinical PN.

PN was also assessed using a self-administered Michigan Neuropathy Screening Instrument (MNSI) questionnaire [13,14]. Subjects were assigned numerical scores based on abnormal responses to each of the 15 items in the questionnaire. A 'Yes' response to items 1–6, 8–12, 14–15 was each counted as 1 score and a 'No' response a 0 score. The reverse was the case for items 7 and 13. Given the inconsistences in the cut-offs for PN diagnosis using the MNSI [14], in the present study, PN was conservatively defined as a cumulative abnormal response score ≥7 and stringently defined as a cumulative abnormal response score ≥4. Because administration of the MNSI questionnaire did not commence in the study until August 2013, data on MNSI were available for a subset of the study sample (n = 674).

2.5. Other physical examinations

Subjects with known diabetes underwent remote diagnosis of retinopathy and macular edema by validated telemedicine using the Joslin Vision Network (JVN) protocol [15,16]. Retinal images were securely transmitted to a central reading center by a certified optometrist tele-retinal reader (DC) with supervision by an ophthalmologist (MBH). Grading was performed at the Phoenix IHS-JVN Teleophthalmology Program Reading Center with stereoscopic viewing using high-resolution displays that were color-calibrated and γ-corrected biannually [15]. To guarantee standardized reading quality across time and graders, the IHS-JVN undertook routine review of 10% of all readings by an expert adjudicator.

Retinopathy was graded, based on the International Clinical Diabetic Retinopathy Disease Severity Scale [17], and a numerical score from this scale was assigned for each eye based on the disease severity; ranging from 0 (no apparent retinopathy) to 7 (proliferative retinopathy; Supplementary Table 1). In the present study, retinopathy was analyzed as either a continuous measure (average numerical score for both eyes) or a categorical measure (defined as present if the score in either eye was >1 or there was a history of laser treatment or vitreous hemorrhage).

2.6. Statistical analysis

Characteristics of subjects were summarized using descriptive statistics and compared using the Wilcoxon rank-sum test, chi-square or Fisher's exact tests. Kappa statistics were used to ascertain the within-subject agreement of measures of symmetrical sensory PN for both feet. Age-sex-race-standardized prevalence of PN was estimated using binomial logistic regression models.

SWM scores were skewed with a substantial proportion of zeros, reflecting no PN. Therefore, ordinal multilevel logistic regression models were used to determine factors associated with PN, assuming that coefficients are similar across all four PN levels.[18] Three separate age-sex-race-adjusted models were constructed including those: (a) comprising data from all subjects; (b) restricted to subjects without diabetes; and (c) restricted to those with diabetes. Backward stepwise multivariable regression models were used to determine factors associated with PN. Variables were included in a multivariable model if there was low correlation (Pearson's correlation coefficient, $r < 0.5$) or multicollinearity (variance inflation factor < 5), with other candidate variables. Potential interactions between logical combination of variables were investigated using product terms.

We also compared PN screening using the SWM test with the MNSI questionnaire; correlated SWM scores with MNSI scores; and restricted regression models to subjects with no amputations, callus, or edema in the lower extremities, to subjects not taking medicines known to cause PN, and to subjects with eGFR < 90 mL/min/1.73 m^2. All analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Socio-demographic characteristics of subjects

We examined 1,572 subjects, with 4 (0.3%) having no data on PN. Therefore, 1,568 subjects were included in the present analyses (median age 41.9 years, 50.1% women, 58.2% American Indians; Table 1).

3.2. Prevalence of PN

There was a good agreement of SWM scores for sites on both feet (Kappa 0.72; 95% CI 0.69–0.75). A total of 487 subjects (31.1%) felt all three filaments (Level 0, no PN), 905 (57.7%) were insensate to 1-g filament (Level 1, subclinical PN), 152 (9.7%) were insensate to 10-g filament (Level 2; clinical PN), and 24 (1.5%) were insensate to 75-g filament (Level 3; clinical PN). Given the small number of subjects at Level 3, Levels 2 and 3 were combined in descriptive analyses. Overall, clinical PN was present in 11.2% (95% CI 9.7–12.9), and it was more prevalent in men than women (Table 1; Fig. 1). Age-sex-adjusted prevalence of clinical PN was greatest in American Indians (11.6%) and lowest in African Americans (4.8%); and was greater in those with a personal history of diabetes, hypertension, and CVD, or complications (albuminuria and retinopathy), or with a family history of these abnormalities/-complications (Table 1). Both alcohol use and tobacco smoking were not significantly associated with the prevalence of clinical PN.

Age-sex-race-adjusted prevalence of clinical PN was particularly elevated in those with diabetes (15.3%) when compared to those without diabetes (6.1%; $P < 0.001$). This pattern was more evident with increasing age and duration of diabetes (Fig. 1). Results were similar in an analysis excluding 177 subjects with eGFR < 90 mL/min/1.73 m^2, with a greater prevalence observed in subjects with diabetes (15.0%) than without diabetes (5.8%; $P < 0.001$). Among subjects with no diabetes, there was no difference in the adjusted prevalence of clinical PN in those with normal glucose regulation (NGR; 6.5%) compared to those with IGR (6.0%; $P = 0.700$). Similarly, there was no difference in the adjusted prevalence of subclinical or worse PN between subjects with NGR (67.2%) and those with IGR (70.6%, $P = 0.251$; see Fig. 1C for unadjusted prevalence estimates).

3.3. PN level ascertained using the graded SWMs by MNSI score, pain-related symptoms, and levels of nephropathy and retinopathy

Among 674 subjects who were screened for PN using both the SWM test and the MNSI questionnaire, clinical PN was detected in 65 subjects (9.6%) using the SWM test, 67 (9.9%) using the cut point ≥7 MNSI score, and 198 (29.4%) using

Table 1 – Characteristics of subjects and prevalence of PN.

	Total	PN Prevalence*			
	n (%)	n	Unadjusted	Adjusted†	
			% (95% CI)	%	P-value
Age (years)					
<30	354 (22.6)	12	3.4 (1.5, 5.3)	3.1	<0.001
30–39	357 (22.8)	19	5.3 (3.0, 7.7)	4.8	
40–49	402 (25.6)	48	11.9 (8.8, 15.1)	11.4	
≥50	455 (29.0)	97	21.3 (17.6, 25.1)	20.9	
Sex					
Male	783 (49.9)	104	13.3 (10.9, 15.7)	10.6	0.011
Female	785 (50.1)	72	9.2 (7.2, 11.2)	7.3	
Race/ethnicity					
American Indian	913 (58.2)	113	12.4 (10.2, 14.5)	11.0	0.008
Non-Hispanic white	169 (10.8)	25	16.0 (10.5, 21.5)	8.8	
African American	135 (8.6)	13	9.6 (4.7, 14.6)	4.8	
Hispanic	119 (7.6)	10	8.4 (4.1, 14.9)	6.1	
Other and Mixed	232 (14.8)	12	5.3 (2.4, 8.2)	5.1	
Body mass index (kg/m^2)					
<25	288 (18.4)	38	13.2 (9.3, 17.1)	10.8	0.067
25–29	433 (27.7)	57	13.2 (10.0, 16.4)	8.7	
30–34	361 (23.1)	26	7.2 (4.5, 9.9)	5.5	
≥35	480 (30.7)	51	10.6 (7.9, 13.4)	9.1	
Current daily smoking (cigarettes)‡					
No	718 (62.5)	85	11.8 (9.6, 14.4)	7.9	0.398
1–5	245 (21.3)	28	11.4 (7.7, 16.1)	10.6	
6–14	118 (10.3)	18	15.3 (9.3, 23.0)	11.9	
≥14	68 (5.9)	9	13.2 (6.2, 23.6)	8.5	
Current daily alcohol intake (kcal)					
0	372 (32.1)	60	16.1 (12.5, 20.3)	11.1	0.197
1–100	477 (41.2)	53	11.1 (8.3, 13.9)	8.7	
101–200	123 (10.6)	9	7.3 (2.7, 11.9)	5.3	
200	186 (16.1)	20	10.8 (6.3, 15.2)	8.8	
Diabetes§					
No	1127 (71.9)	8	7.4 (5.8, 8.9)	6.1	<0.001
Yes	441 (28.1)	93	21.1 (17.3, 24.9)	15.3	
Diabetes duration (years)‖					
<10	149 (47.6)	18	12.1 (6.9–17.3)	11.1	<0.001
10–19	107 (34.2)	29	27.1 (18.7, 35.5)	24.7	
≥20	57 (18.2)	24	42.1 (29.3, 54.9)	35.9	
Family history of diabetes					
No	672 (42.9)	56	8.3 (6.2, 10.4)	6.8	0.027
Yes	896 (57.1)	120	13.4 (11.1, 15.6)	9.9	
Hypertension¶					
No	1392 (88.8)	298	8.6 (7.0, 10.2)	7.0	<0.001
Yes	176 (11.2)	73	19.7 (15.6, 23.7)	13.5	
Albuminuria#					
Normoalbuminuria	1299 (83.2)	115	8.9 (7.3, 10.4)	7.0	<0.001
Microalbuminuria or worse	263 (16.8)	58	22.1 (17.0, 27.1)	16.3	
Family history of dialysis					
No	1299 (82.8)	133	10.2 (8.6, 11.9)	8.0	0.083
Yes	269 (17.2)	43	16.0 (11.6, 20.4)	11.0	
Retinopathy**					
No	220 (66.3)	29	13.2 (8.7, 17.7)	10.4	<0.001
Yes	112 (33.7)	44	39.3 (30.2, 48.3)	32.9	

Table 1 – (continued)

	Total	PN Prevalence*			
	n (%)	n	Unadjusted	Adjusted†	
			% (95% CI)	%	P-value
History of cardiovascular disease††					
Personal					
No	1462 (94.7)	150	10.3 (8.7, 11.8)	8.2	0.026
Yes	81 (5.3)	21	25.9 (16.4–35.5)	14.5	
Family					
No	1110 (70.8)	106	9.5 (7.8–11.4)	7.8	<0.079
Yes	458 (29.2)	70	15.3 (12.0–18.6)	10.3	
Use drugs associated with PN‡‡					
No	1469 (93.7)	155	10.6 (9.0–12.1)	8.4	0.258
Yes	99 (6.3)	21	21.2 (13.2–29.3)	11.2	

* Defined based on an average SWM score >1.
† Adjusted for age, sex and/or race.
‡ Data available for 1158 subjects.
§ FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL, HbA_{1c} ≥ 6.5% or using diabetes medicine.
|| Data on time of diabetes diagnosis not available for 101 subjects with diabetes.
¶ Systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg or using antihypertensive medicine.
# Albumin-creatinine ratio ≥30 mg/g.
** JVN > 1 or history of laser eye treatment or vitreous hemorrhage in subjects with known diabetes.
†† Includes heart attack, heart surgery/procedure, or stroke.
‡‡ Include cancer therapy, antibiotics, vitamin B6, etc. [11].

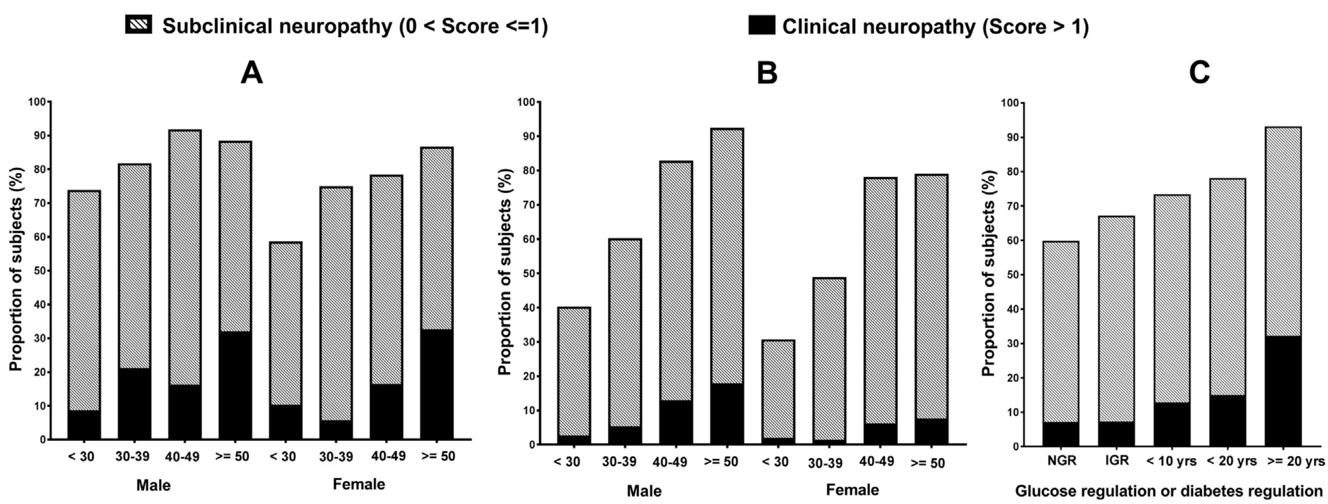

Fig. 1 – Prevalence of peripheral neuropathy by (a) age and sex in subjects with diabetes, (b) age and sex in subjects without diabetes, and (c) glucose regulation or diabetes duration (unadjusted for age, sex, and race/ethnicity). NGR, normal glucose regulation; IGR, impaired glucose regulation.

the cut point ≥4 MNSI score. The distribution of the MNSI scores based on PN level is shown in Fig. 2A. Overall, there was a significant positive correlation between the SWM and MNSI scores (r = 0.46, P < 0.001). Moreover, pain-related symptoms assessed using the MNSI were more common in subjects with greater level of PN (Supplementary Table 2). Greater PN level also increased with higher levels of albuminuria (Fig. 2B) and retinopathy (Fig. 2C). Similar findings were observed when analyses were restricted to subjects without clinical PN (Supplementary Fig. 1).

3.4. *Other factors associated with PN severity*

In age-sex-race adjusted analyses restricted to subjects without diabetes, PN was associated with non-biochemical variables such as older age (odds ratio; OR 1.48 per 5 years, 95% CI 1.40–1.57), male sex (OR 1.77, CI 1.38–2.26), not having some college or higher education (OR 0.73, CI 0.53–0.99), greater BMI (OR 1.22 per 5 kg/m^2, CI 1.12–1.33), and having a family history of diabetes (OR 1.52, CI 1.18–1.95) or CVD (OR 1.45, CI 1.09–1.95; Table 2). Among subjects with diabetes, only older age (OR

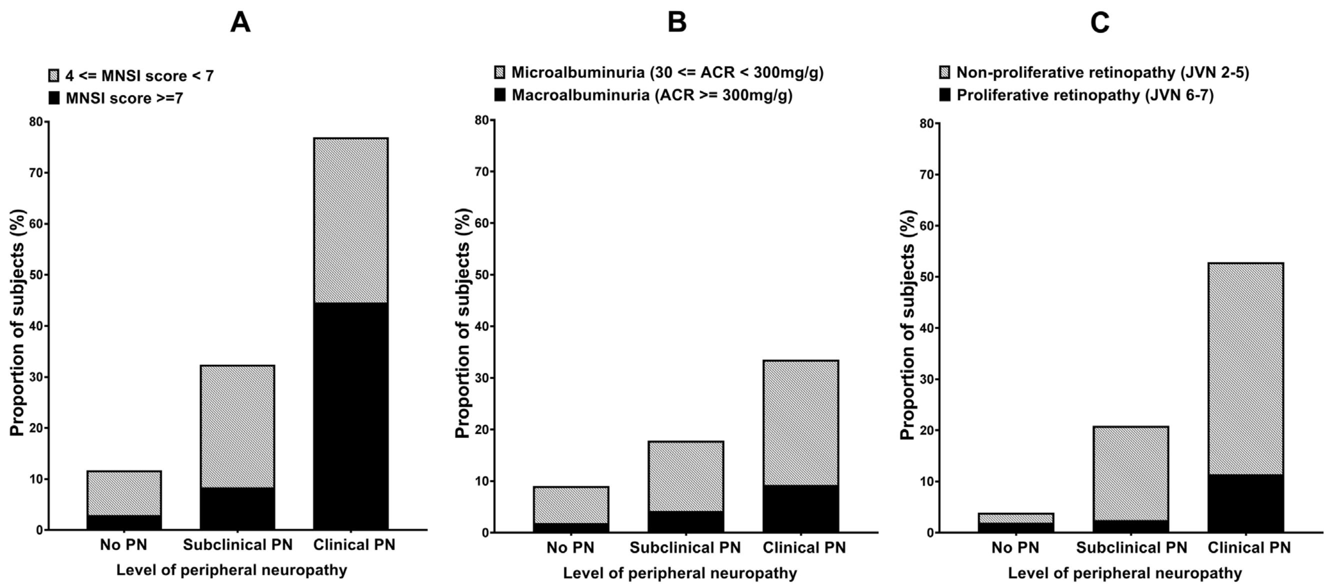

Fig. 2 – Peripheral neuropathy levels ascertained using grades of the Semmes Weinstein monofilaments by (a) MNSI score, (b) level of nephropathy (albuminuria), and (c) level of retinopathy. MNSI, Michigan Neuropathy Screening Instrument; PN, peripheral neuropathy; ACR, albumin-creatinine ratio; JVN, Joslin Vision Network.

1.28 per 5 years, CI 1.17–1.39) and increasingly severe retinal scores (OR 1.56 per 1 worse retinal score, CI 1.36–1.79) were associated with PN (Table 2). No association was observed between biochemical measures and PN in subjects without diabetes (Table 3). In contrast, among subjects with diabetes, PN was associated with greater HbA_{1c} (OR 1.26 per 1%, CI 1.16–1.37), FPG (OR 1.04 per 10 mg/dL, CI 1.02–1.07) or heart rate (OR 1.26 per 10 bpm, CI 1.07–1.48), and longer duration of diabetes (OR 1.46 per 5 years, CI 1.27–1.68). Overall, the association between greater BMI and PN was significantly stronger in subjects without diabetes than with diabetes (P-value for interaction = 0.012), while PN was more related to greater heart rate in those with than without diabetes (P-value for interaction = 0.025).

Stepwise multivariable analyses comprising data from all subjects (Supplementary Table 3) revealed associations of PN with older age, male sex, greater BMI, lower MAP, and the presence of diabetes, albuminuria, a family history of diabetes or a family history of CVDs. There was no significant association between race/ethnicity and PN severity in the stepwise models. When analyses were stratified by diabetes, only older age and male sex were associated with PN in both models. Other factors associated with PN in subjects without diabetes included greater BMI, lower educational attainment, lower fasting insulin, lower triglycerides, or having a family history of diabetes or a personal history of CVDs. By contrast, in those with diabetes, other factors associated with PN included greater HbA_{1c}, greater heart rate, or longer diabetes duration. Results were similar in analyses restricted to 1392 subjects without clinical PN to determine factors associated with subclinical PN (Supplementary Table 3); in analyses excluding 14 subjects (48% with clinical PN, 82% with diabetes) having amputations, callus, or edema in the lower extremities; and in analyses excluding 99 subjects (21% with clinical PN, 74% with diabetes) taking medicines known to cause PN.

4. Discussion

PN is common in this sample of US adults and varies by sociodemographic characteristics and the presence/absence of diabetes, hypertension, kidney dialysis, CVD, albuminuria, or retinopathy. PN was notably common in subjects without diabetes, but diabetes greatly increased its risk. However, only older age and male sex were commonly associated with PN in people with diabetes compared to those without diabetes. Importantly, using graded filaments allowed us to ascertain PN severity, particularly subclinical PN, which was frequently observed in our subjects.

To our knowledge, the most recent data from a wider US population, including people without diabetes, were obtained in elderly Oklahoma residents between 1999 and 2000.[19] In this population, the prevalence of PN, screened using a combination of the 5-g SWM and the vibration perception tests, was 31%. However, reliable comparison of our findings with those from this prior study [21], or other large studies [20,21], is difficult because of differences in the target population and method of PN diagnosis. Our estimates are perhaps most comparable to those of a Canadian First Nations population, screened for PN using the 10-g SWM [22]. The difference in prevalence estimates reported in this Canadian study (7%) and our American Indian sample (12.4%) may be because our population was more often ≥50 years (23% vs. 18%) and has higher diabetes prevalence (34% vs. 29%).

PN is a complication of diabetes, but it also occurs in individuals without diabetes. Our findings on the greater prevalence of PN in people with diabetes than those without diabetes agrees with those of others [22–28]. However, most

Table 2 – Age-sex-race-adjusted ordinal logistic regression analyses of the association of non-biochemical measures with peripheral neuropathy in all subjects and stratified by diabetes.

	All subjects (n = 1568)		Subjects without diabetes (n = 1127)		Subjects with diabetes (n = 441)		
	OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value	P_{int}
Age (per 5 years)	1.43 (1.36, 1.50)	<0.001	1.48 (1.40, 1.57)	<0.001	1.28 (1.17, 1.39)	<0.001	0.063
Male	1.55 (1.26, 1.90)	<0.001	1.77 (1.38, 2.26)	<0.001	1.40 (0.95, 2.04)	0.088	0.454
Race/ethnicity							
American Indian (referent)	1.00		1.00		1.00		0.888
Non-Hispanic white	0.94 (0.66, 1.33)	0.720	1.10 (0.74, 1.64)	0.637	1.60 (0.67, 3.83)	0.291	
African American	0.60 (0.41, 0.88)	0.009	0.69 (0.44, 1.07)	0.100	0.74 (0.33, 1.63)	0.448	
Hispanic	0.67 (0.45, 1.00)	0.050	0.67 (0.43, 1.07)	0.093	1.00 (0.44, 2.30)	0.999	
Other or Mixed	0.69 (0.51, 0.93)	0.014	0.74 (0.52, 1.06)	0.101	0.67 (0.38, 1.18)	0.164	
Education							
No high school certificate (referent)	1.00		1.00		1.00		0.872
Have high school certificate	0.72 (0.56, 0.92)	0.010	0.75 (0.55, 1.02)	0.071	0.78 (0.49, 1.23)	0.282	
Some college/higher education	0.71 (0.55, 0.91)	0.007	0.73 (0.53, 0.99)	0.042	0.89 (0.49, 1.40)	0.617	
Body mass index (per 5 kg/m^2)	1.19 (1.11, 1.27)	<0.001	1.22 (1.12, 1.33)	<0.001	0.98 (0.87, 1.17)	0.805	0.012
Current daily smoking†							
No (referent)	1.00		1.00		1.00		0.288
1–5 cigarettes	1.03 (0.76, 1.39)	0.854	1.21 (0.85, 1.72)	0.280	0.83 (0.44, 1.55)	0.548	
6–14 cigarettes	1.48 (0.98, 2.22)	0.063	1.51 (0.93, 2.47)	0.099	1.85 (0.85, 4.03)	0.121	
>14 cigarettes	1.12 (0.66, 1.88)	0.683	1.18 (0.67, 2.11)	0.566	4.47 (1.04, 19.30)‡	0.045	
Current daily alcohol intake (per 100 Kcal)†	1.05 (0.60, 1.83)	0.870	1.18 (0.63, 2.19)	0.606	1.16 (0.27, 4.91)	0.842	0.943
Joslin Vision Network (per 1 severity grade)§	1.57 (1.36, 1.80)	<0.001	NA	NA	1.56 (1.36, 1.79)	<0.001	NA
Self-reported family history of comorbidities							
Diabetes	1.72 (1.39, 2.12)	<0.001	1.52 (1.18, 1.95)	0.001	1.47 (0.93, 2.32)	0.100	0.881
Hypertension	1.28 (1.04, 1.58)	0.020	1.20 (0.93, 1.54)	0.155	1.25 (0.83, 1.88)	0.282	0.856
Kidney dialysis	1.55 (1.18, 2.03)	0.002	1.32 (0.92, 1.90)	0.134	1.46 (0.96, 2.24)	0.078	0.595
Cardiovascular disease‖	1.49 (1.19, 1.88)	<0.001	1.45 (1.09, 1.95)	0.012	1.41 (0.95, 2.08)	0.086	0.934
Self-reported personal history of comorbidities							
Cardiovascular disease‖	1.53 (0.96, 2.42)	0.073	1.88 (0.94, 3.76)	0.074	1.09 (0.58, 2.05)	0.798	0.179
Use medicines associated with PN¶	1.37 (0.90, 2.11)	0.144	0.82 (0.36, 1.91)	0.651	1.15 (0.69, 1.93)	0.583	0.714

OR; odds ratio; *Pint*, p-value for interaction with diabetes; NA, not included in the model.

* Four peripheral neuropathy levels were defined. Regression analysis based on the assumption of equal coefficients across peripheral neuropathy levels with separate models conducted for all subjects, those without diabetes, and those with diabetes.

† Data available for 1149 subjects (827 without diabetes and 322 with diabetes).

‡ Estimates may be biased by small cell sizes.

§ Score was obtained using the JVN nonmydriatic imaging.

‖ Includes heart attack, heart surgery/procedure, or stroke.

¶ Include cancer therapy, antibiotics, vitamin B6, etc. [11].

Table 3 – Age-race-adjusted ordinal logistic regression analyses of the association of biochemical measures with peripheral neuropathy in all subjects and stratified by diabetes.

	All subjects (n = 1568)		Subjects without diabetes (n = 1127)		Subjects with diabetes (n = 441)		
	OR (95% CI)*	P-value	OR (95% CI)*	P-value	OR (95% CI)*	P-value	P_{int}
Diabetes-related measures							
Glycated hemoglobin (per 1%)	1.31 (1.23, 1.39)	<0.001	1.19 (0.80, 1.57)	0.516	1.26 (1.16, 1.37)	<0.001	NA
Fasting plasma glucose (per 10 mg/dL)	1.07 (1.05, 1.09)	<0.001	0.96 (0.84, 1.10)	0.549	1.04 (1.02, 1.07)	<0.001	NA
Fasting insulin (per 10 mIU/L)	1.04 (1.01, 1.06)	0.003	0.97 (0.90, 1.05)	0.446	1.02 (1.00, 1.05)	0.076	0.152
2-h plasma glucose (mg/dL)†	1.02 (0.99, 1.05)	0.300	1.03 (0.98, 1.07)	0.237	0.96 (0.89, 1.04)	0.280	0.164
Duration of diabetes (per 5 years)‡	–	–	NA	NA	1.46 (1.27, 1.68)	<0.001	NA
Hypertension-related measures							
Systolic blood pressure (per 10 mmHg)	1.03 (0.97, 1.11)	0.329	1.04 (0.95, 1.13)	0.444	0.95 (0.85, 1.05)	0.310	0.096
Diastolic blood pressure (per 10 mmHg)	1.06 (0.96, 1.17)	0.284	1.07 (0.95, 1.21)	0.264	0.84 (0.69, 1.02)	0.084	0.029
Heart rate (per 10 bpm)	1.17 (1.07, 1.28)	<0.001	1.05 (0.94, 1.18)	0.376	1.26 (1.07, 1.48)	0.005	0.025
Mean arterial pressure (per 10 mmHg)	1.05 (0.96, 1.16)	0.264	1.06 (0.95, 1.19)	0.296	0.88 (0.74, 1.04)	0.127	0.032
Dyslipidemia-related measures							
Total cholesterol (per 10 mg/dL)	1.00 (0.97, 1.03)	0.837	0.99 (0.96, 1.02)	0.549	1.00 (0.96, 1.05)	0.961	0.869
HDL-cholesterol (per 10 mg/dL)	0.94 (0.89, 1.00)	0.033	0.98 (0.91, 1.05)	0.513	0.98 (0.86, 1.12)	0.768	0.726
Triglycerides (per 10 mg/dL)	1.08 (0.98, 1.20)	0.142	0.90 (0.77, 1.05)	0.164	1.05 (0.91, 1.22)	0.478	0.108
Kidney function measures							
eGFR (per 10 mL/min/1.73 m^2)	0.77 (0.73, 0.81)	<0.001	1.04 (0.94, 1.15)	0.436	0.93 (0.84, 1.02)	0.128	0.928

OR; odds ratio; P*int*, p-value for interaction with diabetes; NA, not included in the model; eGFR; estimated glomerular filtration rate; HDL, high-density lipoprotein.

* Four peripheral neuropathy levels were defined. Regression analysis based on the assumption of equal coefficients across peripheral neuropathy levels with separate models conducted for all subjects, those without diabetes, and those with diabetes.

† Subjects without diabetes only (n = 1127).

‡ Subjects with diabetes only (n = 441).

of these prior studies are limited by small sample size or lack of glucose tolerance testing. The lack of difference in the prevalence of PN between subjects with NGR and those with IGR agrees with findings of some previous studies [22–25] and disagrees with those of others [26–28]. Discrepancies in findings may be due to variation in methods of PN ascertainment.

We found no significant association between PN level and race/ethnicity. The relationship between higher PN level and older age in our population may be explained by the progressive neurologic, metabolic/vascular disorders associated with ageing [29]. This explanation is consistent with the greater PN prevalence in subjects with, than in those without, a personal or family history of diabetes, hypertension, kidney dialysis, or CVD, or a longer history of diabetes.

Associations of PN with older age, having diabetes or nephropathy, greater BMI or HbA_{1C}, and lower MAP, have been similarly reported by others [19,22]. As these metabolic/vascular conditions are potentially modifiable, identifying and effectively managing people with poor metabolic profile could help delay PN. Moreover, the observed association between PN and having a family history of diabetes, hypertension, kidney dialysis, or CVD suggests that identifying and screening for genetic markers of these disorders, especially in high-risk populations, could trigger an early intervention. The identified association between male sex and PN is inconsistent with the literature [19,22]. In people with diabetes, we found that PN is strongly associated with glucose regulation and duration of diabetes, and with albuminuria and retinopathy. This is consistent with the notion that PN is itself a microvascular complication of diabetes.

A major finding of our study is that PN is also common in people without diabetes, and that pathways driving the development of PN may be somewhat different in people with diabetes compared to those without diabetes. Indeed, in our study population, only age and sex were significantly associated with PN in both groups. Moreover, our hypothesis was supported by the fact that BMI, lower educational attainment, and having a history of CVD or a family history of diabetes were associated with PN in people without diabetes only, and that greater heart rate (a sign of autonomic dysfunction) was associated with PN only in those with diabetes. Evidence exists on mechanisms driving the presence and progression of diabetic PN, but such evidence is limited in people without diabetes.

In primary care settings, use of SWM is almost exclusively limited to the 10-g gauge [6,30]. Our findings demonstrate the potential additional prognostic value of using three grades (1-, 10-, and 75-g) of the SWM for ascertaining the presence and severity of PN in clinical settings. This is important given that identifying a subclinical PN (being insensate to 1-g filament) may indicate the presence, albeit generally less severe form, of glucose intolerance and other microvascular conditions, i.e. nephropathy and retinopathy. Therefore, using grades of the SWM adds precision to PN screening, allowing early identification of PN at a preclinical stage, and possibly leading to prevention or delayed progression of neuropathy or microvascular disease.

This study has some limitations. Our sample is not representative of the US population. PN screening was largely based on a single test rather than the recommended multiple tests. Also, we did not screen for other common signs/symptoms of PN such as motor or autonomic nerve damage. Although we avoided areas with gross callus formation, we tested the plantar aspect of the foot where modest skin thickening could reduce sensation and limit the sensitivity of our examination. Also, our findings were not adjusted for the presence of other conditions that could cause PN, e.g. autoimmune diseases, anemia, chronic hepatitis, etc. Although our findings should be interpreted in the context of these limitations, their wider application is enhanced by the fact that the SWM test is widely recommended for detecting PN in clinical settings [3,6,31].

Major strengths of our study include the use of objective tests for diabetes. Further, our relatively large sample size helped improve the robustness of our estimates and allowed analysis of population sub-groups.

Our study provides data on PN among adult volunteers in the US, including comparing the prevalence and associated factors of PN in people with diabetes to those without diabetes. We also demonstrated the potential prognostic value of using graded SWM rather than the standard use of a single grade for PN screening in clinical settings. The present findings may be helpful to clinicians and health policy makers, especially for identifying groups that are more likely to benefit from an early intervention to prevent or delay PN.

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Declaration of interest

The authors declared that there is no conflict of interest.

Contributors

RLH and WCK conceptualized and designed the study. RLH, KGK, MS, RGN, DC, and MBH collected the data. MTO analyzed the data, did literature review, and prepared the first draft of the manuscript. All authors interpreted the data, revised the manuscript for intellectual content, and approved the final draft of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.029.

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