Peripheral Neuropathy and Nerve Dysfunction in Individuals at High Risk for Type 2 Diabetes: The PROMISE Cohort

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OBJECTIVE

Emerging evidence suggests that peripheral neuropathy begins in the early stages of diabetes pathogenesis. Our objective was to describe the prevalence of peripheral neuropathy and nerve dysfunction according to glucose tolerance and metabolic syndrome status and examine how these conditions are associated with neurological changes in individuals at risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS

We studied 467 individuals in the longitudinal PROMISE (Prospective Metabolism and Islet Cell Evaluation) cohort. Peripheral neuropathy was defined by Michigan Neuropathy Screening Instrument (MNSI) scores (>2), and the severity of nerve dysfunction was measured objectively by vibration perception thresholds (VPTs) using a neurothesiometer. Metabolic syndrome was defined using the International Diabetes Federation/American Heart Association harmonized criteria.

RESULTS

The prevalence of peripheral neuropathy was 29%, 49%, and 50% for normal glycemia, prediabetes, and new-onset diabetes, respectively ($P < 0.001$ for trend). The mean VPT was 6.5 V for normal glycemia, 7.9 V for prediabetes, and 7.6 V for new-onset diabetes ($P = 0.024$ for trend). Prediabetes was associated with higher MNSI scores ($P = 0.01$) and VPTs ($P = 0.004$) versus normal glycemia, independent of known risk factors. Additionally, progression of glucose intolerance over 3 years predicted a higher risk of peripheral neuropathy ($P = 0.007$) and nerve dysfunction ($P = 0.002$). Metabolic syndrome was not independently associated with MNSI scores or VPTs.

CONCLUSIONS

In individuals with multiple risk factors for diabetes, prediabetes was associated with similar risks of peripheral neuropathy and severity of nerve dysfunction as new-onset diabetes. Prediabetes, but not metabolic syndrome, was independently associated with both the presence of peripheral neuropathy and the severity of nerve dysfunction.

Peripheral neuropathy is a serious complication of diabetes. It plays a major contributory role in the initiation of foot ulceration and the subsequent development of lower-extremity amputation, resulting in severe disability, reduced quality of life, and a significant economic burden to the health care system (1). Peripheral neuropathy is

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classically recognized as a complication of long-standing diabetes, with risk factors including increased duration of diabetes and poor glycemic control (2,3). However, accumulating evidence suggests that the prevalence of peripheral neuropathy is markedly elevated at the time of diabetes diagnosis, with estimates varying from 11.5 to 48% in population-based observational studies (4,5). In contrast, a recent study using British and German administrative databases showed that peripheral neuropathy based on diagnostic codes was present in only 2.4–5.7% of patients with newly diagnosed diabetes in primary care practices (6). These discrepancies in the prevalence of peripheral neuropathy in new-onset diabetes could be related to differences in the methods used to ascertain this condition.

The presence of peripheral neuropathy in newly diagnosed diabetes and the time gap between the onset of diabetes and clinical diagnosis (7) support the notion that neuropathic changes could be initiated in the early stages of diabetes pathogenesis. In the Cooperative Health Research in the Region of Augsburg (KORA) F4 study, the prevalence of peripheral neuropathy defined as bilaterally impaired foot vibration perception and/or foot pressure sensation was similar in patients with known diabetes (22%) and in those with impaired fasting glucose and impaired glucose tolerance (24%) (8). The U.S. National Health and Nutrition Examination Study (1999–2004) reported that the prevalence of peripheral neuropathy, as measured by at least one insensate area on 10-g monofilament testing, was 11.9% in individuals with impaired fasting glucose (9). Using the Michigan Neuropathy Screening Instrument (MNSI), peripheral neuropathy was found in 13.0% of subjects with impaired glucose tolerance and 11.3% of those with impaired fasting glucose in the MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases)/KORA Augsburg Surveys (10). However, these studies were limited by the lack of oral glucose tolerance testing to ascertain glycemic status in the National Health and Nutrition Examination Survey (9) and the relatively small sample size in the MONICA/KORA Augsburg Surveys (10).

Age, sex, ethnicity, height, duration of diabetes, and glycemic control are established risk factors for diabetic neuropathy (2,3). However, the risk factors for peripheral neuropathy in prediabetes are not well documented. Emerging evidence suggests that components of the metabolic syndrome, in particular abdominal adiposity and dyslipidemia, are associated with peripheral neuropathy in patients with prediabetes (10,11). In the current study, we aimed to describe the prevalence of peripheral neuropathy and nerve dysfunction and to investigate the association of glucose tolerance status and metabolic syndrome with these neurological changes using data from the Prospective Metabolism and Islet Cell Evaluation (PROMISE) study, a well-characterized cohort of individuals at high risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The study population comprised participants in PROMISE, a prospective observational study that explores the longitudinal relationships of insulin resistance and pancreatic β-cell dysfunction with known and emerging risk factors in individuals at high risk for type 2 diabetes. Between May 2004 and December 2006, PROMISE recruited 712 participants without diabetes from Toronto and London, Ontario, Canada, based on the presence of one or more risk factors for type 2 diabetes, including obesity, hypertension, family history of diabetes, and history of gestational diabetes or birth of a macrosomic infant (12). Among these participants, 496 returned for the 3-year follow-up examination, when assessments of neuropathy and nerve dysfunction were conducted. There were no significant differences in BMI or measures of glucose homeostasis in participants who attended the follow-up examination compared with those who did not. After excluding participants in whom diabetes developed after baseline and before the 3-year follow-up examination (n = 7), those with missing data on glucose tolerance status at the 3-year follow-up examination (n = 2), and those with missing data on measurements of peripheral neuropathy and nerve function (n = 20), the sample size of the current analysis was 467 participants without known diabetes at the time of the 3-year examination who had peripheral neuropathy and nerve function measurements. The study procedures detailed in this article were performed at the 3-year examination, and the data were analyzed cross-sectionally. The institutional review boards at each study center approved the study protocol, and all participants provided written informed consent.

Measurement of Peripheral Neuropathy

Peripheral neuropathy was measured using the MNSI. The MNSI consisted of two parts: a self-administered questionnaire on clinical signs and symptoms of neuropathy and a clinical examination of both feet involving 1) an inspection to detect deformities, dry skin, calluses, infection, fissures, or ulcerations; 2) a grading of ankle reflexes; 3) a semiquantitative assessment of vibration perception at the dorsum of the great toe; and 4) 10-g monofilament testing. In this analysis, we used only the clinical examination component of the MNSI, with a maximum possible score of 10. An MNSI score of >2 defined the presence of peripheral neuropathy (13). The MNSI has been validated against the Mayo Clinic Neuropathy Disability Score, nerve conduction measures, quantitative vibration threshold tests, and the Michigan Diabetic Neuropathy Score. In these validation studies, the maximum possible score was 8 because the score at that time did not include the 10-g monofilament test (14).

Measurement of Nerve Dysfunction

We used a neurothesiometer to quantify the vibration perception threshold (VPT), a measure of the severity of nerve dysfunction. The neurothesiometer is a battery-operated diagnostic instrument that assesses sensitivity thresholds at various sites on the body surface. It has been validated against nerve conduction studies (15). On the basis of the method of limits, participants were asked to indicate when they first perceived vibration sensation after stimulus was applied to the distal pulp of their left first toe. The intensity of the stimulus was gradually increased from null to a voltage at which vibration was first detected (16). Three separate tests were conducted with participants' eyes closed. The average of the three VPTs was used for analysis. A null stimulus test was added randomly to ensure participant adherence and understanding of the test requirements. Each center followed standardized procedures for the measurement of peripheral neuropathy and nerve dysfunction using identical sets of equipment. To ensure that the outcomes were measured consistently,

research assistants were trained centrally with annual review sessions.

Clinical Measurements and Procedure

Glycemic status (i.e., normal glucose tolerance, prediabetes, diabetes) was categorized using 1999 World Health Organization criteria (17). Prediabetes was defined as impaired glucose tolerance and/or impaired fasting glucose. Plasma glucose, HDL cholesterol, and triglyceride levels were measured in fasting blood samples by standard laboratory methods. We defined metabolic syndrome and its components using the International Diabetes Federation/American Heart Association harmonized criteria (18).

Anthropometric measurements, including height, weight, and waist circumference, were taken in duplicate according to standardized procedures, and the averages of these measurements were used in the analyses. BMI was calculated as weight in kilograms divided by height in square meters. Resting systolic and diastolic blood pressures were recorded twice using an automated sphygmomanometer after a 5-min rest. Information on demographics (age, sex, ethnicity), lifestyle factors (smoking, alcohol consumption), and family history of diabetes were collected in standardized questionnaires by self-report (12). Ethnicity was categorized into four groups for the analysis: Caucasian, South Asian, Hispanic, and other. An identical protocol for these clinical measurements and procedures was used at both the baseline and the 3-year follow-up examinations.

Statistical Analysis

We summarized the participant characteristics stratified by the presence or absence of peripheral neuropathy defined by an MNSI score of >2 out of a total of 10, using medians with interquartile ranges for continuous variables and percentages for categorical variables. We used ANOVA, Kruskal-Wallis, and χ^2 tests to determine whether continuous and categorical variables differed by the presence of peripheral neuropathy. We plotted the prevalence of peripheral neuropathy and the means and SEs of VPTs by glucose tolerance status and metabolic syndrome.

In light of the well-recognized variability in 2-h glucose concentrations after oral glucose tolerance test (19), we investigated the impact of glucose tolerance status on the prevalence of neuropathy using two separate approaches: 1) We categorized glucose tolerance status using data from the 3-year follow-up examination (i.e., normal glucose tolerance, prediabetes, and diabetes were categorized using glucose concentrations at the 3-year examination only), and 2) we categorized participants into four groups according to progression of glucose intolerance between the baseline and 3-year examinations (i.e., sustained normal glucose tolerance at both baseline and 3-year examination, progression to prediabetes, sustained prediabetes, progression to diabetes). Because of the small number of participants who regressed from prediabetes at baseline to normal glucose tolerance at 3-year examination (n = 1), this data point was included in the sustained normal glucose tolerance group.

We investigated the impact of the metabolic syndrome on the prevalence of neuropathy using three approaches: 1) we analyzed the metabolic syndrome as a dichotomous variable (i.e., presence vs. absence); 2) we analyzed the number of metabolic syndrome disorders (0–5); and 3) we calculated the mean of the z scores of metabolic disorders, which was analyzed as a continuous variable (20). Because the distribution of VPTs was skewed, we log$_e$-transformed this variable to achieve normality before subsequent analyses. In the subset of participants without diabetes at the 3-year follow-up examination, we used multiple regression analyses to investigate the association of glucose tolerance status and metabolic syndrome with MNSI scores and VPTs. The regression coefficients (β) for linear regression were presented along with their 95% CIs. We included covariates in the analyses if they were of a priori clinical relevance or if they were associated with both the exposure and the outcome. Covariates included age, sex, ethnicity, and height.

In sensitivity analyses, we used the original MNSI definition (>2 out of total score of 8) to define peripheral neuropathy in prevalence estimates and regression models to assess the consistency of the findings across the different definitions of MNSI. We also conducted a stepwise backward regression analysis with covariates being removed from the multivariable-adjusted model if $P > 0.05$. In the stepwise models, we substituted fasting blood glucose and 2-h postload blood glucose for prediabetes to determine their specific contributions to neuropathic outcomes. In addition, we defined peripheral neuropathy by VPT >12 V (21) and >15 V (22) and estimated its prevalence. Statistical analyses were performed using Stata 12.0 software (StataCorp, College Station, TX).

RESULTS

Of the 467 participants with data on peripheral neuropathy and nerve dysfunction at the 3-year examination, 344 had normal glycemic control (74%), 101 had prediabetes (21%), and 22 had new-onset diabetes (5%) ascertained by 75-g oral glucose tolerance test at that examination. Among these 467 participants, 73% were women and 63% reported having a family history of diabetes. The average age of the study population was 53 years (interquartile range 46–60 years), and the ethnic distribution for Caucasians, South Asians, Hispanics, and other races was 71%, 12%, 10%, and 7%, respectively. Approximately 34% of the participants had evidence of peripheral neuropathy as defined by an MNSI score >2. The prevalence of peripheral neuropathy according to increasing MNSI score was 65.7% for a score ≤2, 19.2% for a score >2–3, 11.8% for a score >3–4, 2.6% for a score >4–5, and 0.7% for a score >5–6. The median VPT was 5.7 V in all participants (interquartile range 4.0–8.3 V).

Characteristics of the study population stratified by the presence of MNSI-defined peripheral neuropathy are shown in Table 1. Participants with peripheral neuropathy were more likely to be older. They also had a higher level of fasting blood glucose and 2-h postload blood glucose as well as higher VPTs. No substantial ethnic or sex differences existed between those with and without MNSI-defined peripheral neuropathy.

The prevalence of peripheral neuropathy was 29% for participants with normal glucose tolerance, 49% for those with prediabetes, and 50% for those with newly diagnosed type 2 diabetes at the 3-year examination ($P < 0.001$) (Fig. 1A). There were significant differences in the prevalence of neuropathy across categories of glucose tolerance status progression between baseline and the 3-year examination. Specifically,

Table 1—Baseline characteristics of participants stratified by the presence of peripheral neuropathy in the PROMISE cohort

	Neuropathy −	Neuropathy +*	P value
n (%)	307 (65.7)	160 (34.3)	—
Age (years)	51 (45–58)	57 (48–64)	0.0001
Female sex	75.6	67.5	0.06
Ethnicity			0.08
Caucasian	70.4	71.9	
South Asian	5.54	8.75	
Hispanic	14.7	7.50	
Other	9.45	11.9	
Current smoker	4.6	5.6	0.3
Heavy drinker	11.8	13.1	0.7
Family history of diabetes	60.1	67.5	0.1
BMI (kg/m^2)	30.4 (26.6–34.4)	30.7 (27.8–35.1)	0.3
Height (cm)	164 (159–171)	166 (160–174)	0.07
Waist circumference (cm)	98.2 (88.3–108)	101 (91.0–110)	0.04
Systolic blood pressure (mmHg)	125 (115–135)	125 (117–136)	0.3
Plasma triglycerides (mmol/L)	1.23 (0.95–1.65)	1.27 (1.00–1.81)	0.3
HDL cholesterol (mmol/L)	1.3 (1.1–1.6)	1.3 (1.0–1.5)	0.4
Fasting blood glucose (mmol/L)	5.1 (4.8–5.6)	5.3 (4.9–5.7)	0.03
2-h postload blood glucose (mmol/L)	5.9 (4.8–7.3)	6.7 (5.4–8.5)	0.0001
VPT (V)	5.2 (3.8–7.2)	6.5 (5.1–9.9)	0.0001

Data are median (interquartile range) or % unless otherwise indicated. *The presence of neuropathy was defined as >2 out of a total MNSI score of 10.

prevalence was ~29% for those with sustained normal glucose tolerance, 48% among those who progressed from normal glucose tolerance to prediabetes, 42% in those with sustained prediabetes, and 83% among those who progressed from prediabetes to diabetes (P < 0.001) (Fig. 1B). Results were similar when we defined neuropathy using the original MNSI definition (>2 out of total score of 8).

The average VPT was 6.5, 7.9, and 7.6 V for participants with normal glucose tolerance, prediabetes, and newly diagnosed type 2 diabetes, respectively (P = 0.02) (Fig. 2A). The average VPT was 6.5 V for participants who had sustained normal glucose tolerance between baseline and the 3-year examination, 7.9 V among those who progressed from normal glucose tolerance to prediabetes, 6.6 V in those who had sustained prediabetes, and 11.4 V among those who progressed from prediabetes to diabetes (P = 0.006) (Fig. 2B).

On the basis of International Diabetes Federation/American Heart Association harmonized criteria, approximately one-third of the study population had metabolic syndrome, as defined by the presence of three or more disorders. Although the prevalence of peripheral neuropathy was not significantly

different between those with and without metabolic syndrome (33% vs. 37%, respectively; P = 0.4), the average VPT was higher, specifically, 7.6 V for participants with and 6.5 V for those without metabolic syndrome (P = 0.01) (Fig. 2C). The average VPT was greater with the presence of a higher number of components of the metabolic syndrome, from 5.5 V with one component to 8.8 V with four or more components (P = 0.0005) (Fig. 2D).

Compared with those with normal glycemia, participants with prediabetes had significantly higher MNSI scores and VPTs (Table 2). In addition, progression of glucose intolerance compared with sustained normal glucose control was significantly associated with a higher risk of peripheral neuropathy and nerve dysfunction (Table 2). There was no association between metabolic syndrome and MNSI scores (Supplementary Table 1). Initial associations of metabolic syndrome with VPTs were attenuated to nonsignificance after adjusting for age, sex, ethnicity, and height (Supplementary Table 1).

In sensitivity analyses, using the original MNSI definition (>2 out of total score of 8) to define peripheral neuropathy did not change the prevalence estimates (Fig. 1) and magnitude of association in

regression models materially (data not shown). In backward stepwise multiple regression models, age, height, and prediabetes were all significant, independent positive correlates of MNSI scores and VPTs (all P < 0.05).

When prediabetes was replaced by fasting blood glucose and 2-h postload blood glucose in the stepwise regression model of neuropathic outcomes, only 2-h postload blood glucose reached a significance level of 0.05 and was retained in the final model (data not shown). We evaluated an alternative definition of peripheral neuropathy using neurothesiometer cut points of VPT >12 V and >15 V as reported previously (21,22). In the entire study sample, neuropathy prevalence was 9.7% for VPT >12 V and 5.1% for VPT >15 V, although there were no significant differences in prevalence under these definitions according to glycemic or metabolic syndrome status (data not shown).

CONCLUSIONS

In a cohort at high risk for type 2 diabetes, we observed that participants with prediabetes had a similar neuropathy prevalence as those with new-onset diabetes. In addition, the severity of nerve dysfunction, as measured objectively by a neurothesiometer, was directly proportional to the burden of metabolic syndrome disorders. In individuals without diagnosed diabetes, we observed that age, height, and prediabetes, particularly impaired glucose tolerance, were independently associated with both peripheral neuropathy and nerve dysfunction. The findings extend the current literature by documenting that the prevalence of peripheral neuropathy in individuals with prediabetes is as high as among those with new-onset diabetes and by providing additional evidence from a large, well-characterized cohort that prediabetes is an independent risk factor for neuropathy and nerve dysfunction.

The prevalence of peripheral neuropathy observed in individuals with prediabetes was higher than previously reported (9,10). This could be related to differences among study populations because PROMISE participants were recruited based on their risk for type 2 diabetes, and thus, potential risk factors for peripheral neuropathy (including
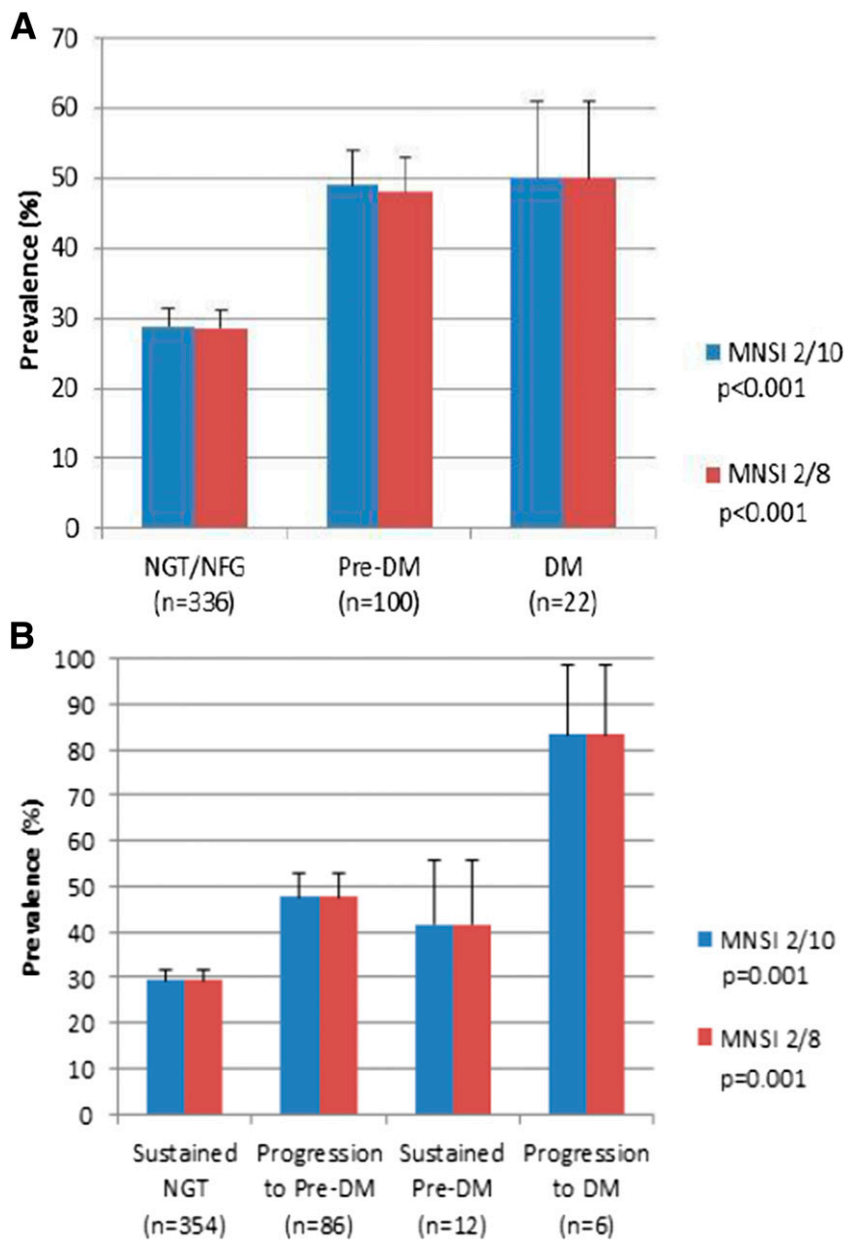
Figure 1—Prevalence of peripheral neuropathy by glucose tolerance status comparing different definitions of MNSI at 3-year follow-up (*A*) and by progression of glucose intolerance between baseline and 3-year follow-up (*B*). The *P* value refers to the overall comparison across subgroups. DM, diabetes mellitus; NFG, normal fasting glucose; NGT, normal glucose tolerance.

glycemia, a family history of diabetes, and metabolic syndrome disorders) were highly prevalent. In addition, various diagnostic criteria could account for the difference in the prevalence of neuropathy in the various subgroups of glucose abnormalities. For example, the KORA F4 study used bilaterally impaired foot vibration perception and foot pressure sensation to detect more severe peripheral neuropathy (8). A high prevalence of peripheral neuropathy was also observed in those with normal glucose tolerance, an observation that may be explained by the substantial burden of diabetes risk factors in this group.

Previous studies consistently demonstrated an association of age and height with diabetic neuropathy (2,23,24). In the current study, we observed that these nonmodifiable risk factors were also associated with peripheral neuropathy in prediabetes. Duration of diabetes has been shown to be a risk factor of

peripheral neuropathy, with prevalence ranging from 20.8% in patients with diabetes for <5 years to 36.8% in those with diabetes for >10 years (23). In addition, poor glycemic control increases the risk and progression of diabetic neuropathy (2,3). The PROMISE cohort comprised participants at risk for type 2 diabetes. The alarmingly high prevalence of peripheral neuropathy in individuals with prediabetes suggests that the duration and degree of dysglycemia before the clinical diagnosis of diabetes may be a crucial factor in the early initiation of neurological changes.

Despite well-established evidence regarding the risk factors for diabetic neuropathy, a literature gap exists for normal glucose tolerant and prediabetic populations. Nonglycemic parameters of the metabolic syndrome, including abdominal adiposity and dyslipidemia, have been shown to be associated with peripheral neuropathy in patients with prediabetes (10,11). In contrast, we did not observe independent associations of metabolic parameters with peripheral neuropathy or nerve dysfunction, which may be related to the high prevalence of these risk factors in the current study population. However, the findings confirm previous observations that prediabetes, in particular impaired glucose tolerance, is independently associated with both peripheral neuropathy and nerve dysfunction (25,26). Hyperglycemia may lead to neurological pathology in part through increasing oxidative stress and activation of the protein kinase C and polyol pathways, both of which exert neurotoxic effects (27,28). Besides hyperglycemia, dyslipidemia, microvascular dysfunction, and metabolic syndrome have all been shown to initiate neuropathy in prediabetes through a common mechanism of oxidative stress (29).

In clinical practice, the neurothesiometer has been used to monitor the progression of peripheral neuropathy rather than as a tool for diagnosing peripheral neuropathy. To this point, elevated VPTs have been shown to be associated with an increased risk of subsequent foot ulceration (21,22). The neurothesiometer, being minimally invasive and returning results in <3 min, may be more sensitive for the diagnosis of peripheral neuropathy, particularly in patients with mild neuropathy, such as
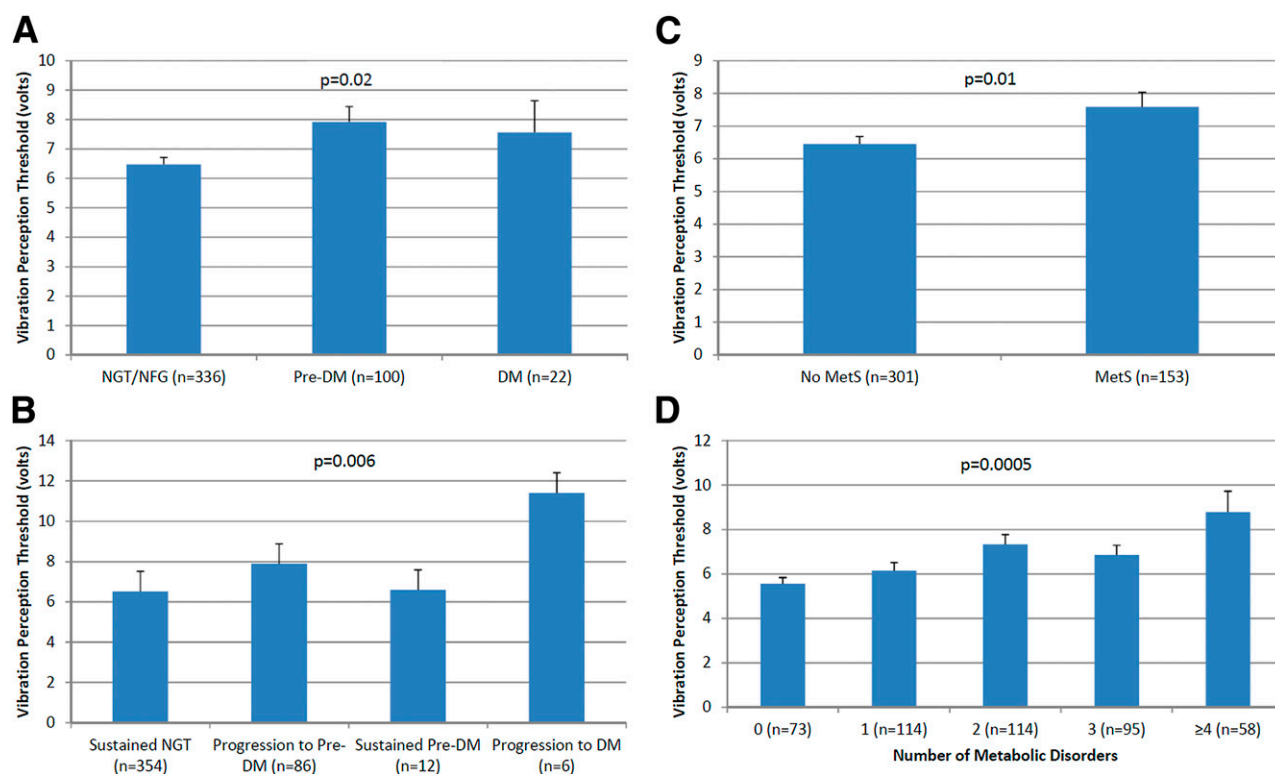
Figure 2—Severity of nerve dysfunction by glucose tolerance status at 3-year follow-up (A), by progression of glucose intolerance between baseline and 3-year follow-up (B), by the presence of the metabolic syndrome (C), and by the number of metabolic disorders (D). The P value refers to the overall comparison across subgroups. DM, diabetes mellitus; MetS, metabolic syndrome; NFG, normal fasting glucose; NGT, normal glucose tolerance.

those with prediabetes (21). However, no standardized VPT cutoff value to define the presence of peripheral neuropathy has been published to date.

The findings of this study have important research and clinical implications. From a research perspective, although the documentation of impaired glucose tolerance in patients with idiopathic neuropathy (11) has raised the concern that clinically significant nerve dysfunction may be present before diabetes onset, the current study adds that the presence of risk factors for diabetes onset alone conveys a high risk for

neuropathy. This risk is further exacerbated by the presence of impaired glucose tolerance or new-onset diabetes. These findings emphasize the need to determine etiological factors for neuropathy onset independent of glucose metabolism and to determine the threshold of glucose exposure below that of a diagnosis of impaired glucose intolerance that may promote nerve injury. From a clinical perspective, previous evidence has suggested that older patients with diabetes or prediabetes are often unaware of their peripheral neuropathy and that they receive infrequent foot

examinations and inadequate preventive education on foot care (30). These observations coupled with the high prevalence of peripheral neuropathy and nerve dysfunction stress the urgent need for early detection and intervention not only in populations with established diabetes but also in those with risk factors such as prediabetes or metabolic syndrome.

The strengths of the PROMISE study include a well-characterized multiethnic cohort as well as detailed measurement of peripheral neuropathy and nerve dysfunction. However, several potential limitations should also be considered.

Table 2—Association of glucose tolerance status with peripheral neuropathy and nerve dysfunction in the PROMISE cohort

	MNSI score**		VPT**	
	β (95% CI)	P value	β (95% CI)	P value
Prediabetes vs. NFG/NGT (cross-sectional at 3-year follow-up)				
Unadjusted	0.38 (0.11, 0.65)	0.005	0.20 (0.076, 0.32)	0.001
Multivariable adjusted*	0.34 (0.075, 0.61)	0.01	0.14 (0.044, 0.24)	0.004
Progression of glucose intolerance vs. sustained NFG/NGT				
Unadjusted	0.40 (0.14, 0.67)	0.003	0.20 (0.085, 0.32)	0.001
Multivariable adjusted*	0.37 (0.10, 0.63)	0.007	0.15 (0.052, 0.25)	0.002

NFG, normal fasting glucose; NGT, normal glucose tolerance. *Adjusted for age, sex, ethnicity, and height. **MNSI scores (with a total score of 10) and VPTs were modeled as continuous variables.

Using a single oral glucose tolerance test to diagnose prediabetes has been shown to have low reproducibility (31). Although the neurothesiometer has been validated to assess nerve dysfunction, limited evidence supports using only VPT to assess the severity of peripheral neuropathy. In addition, we did not have information on other known causes of peripheral neuropathy or collect information on whether participants were symptomatic. Finally, the results may apply only to individuals with similar demographic and metabolic characteristics.

In conclusion, this study documents that the prevalence of peripheral neuropathy in patients with prediabetes and additional risk factors for diabetes onset is as high as in those with newly diagnosed (or early onset) diabetes and confirms that risk factors for diabetic neuropathy, such as age, height, and glycemia, are associated with peripheral neuropathy, even in the absence of a clinical diagnosis of diabetes. The results support efforts toward early detection and intervention as a means to reduce the incidence of peripheral neuropathy and its downstream consequences in high-risk populations.

References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–1724
2. Adler AI, Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Smith DG. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. Diabetes Care 1997;20:1162–1167
3. Sorensen L, Molyneaux L, Yue DK. Insensate versus painful diabetic neuropathy: the effects of height, gender, ethnicity and glycaemic control. Diabetes Res Clin Pract 2002;57:45–51
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
5. Spijkerman AM, Dekker JM, Nijpels G, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the Hoorn screening study. Diabetes Care 2003;26:2604–2608
6. Kostev K, Jockwig A, Hallwachs A, Rathmann W. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. Prim Care Diabetes 2014;8:250–255
7. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992;15:815–819
8. Bongaerts BW, Rathmann W, Kowall B, et al. Postchallenge hyperglycemia is positively associated with diabetic polyneuropathy: the KORA F4 study. Diabetes Care 2012;35:1891–1893
9. Gregg EW, Gu Q, Williams D, et al. Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. Diabetes Res Clin Pract 2007;77:485–488
10. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group. 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;31:464–469
11. Smith AG. Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. J Peripher Nerv Syst 2012;17(Suppl. 2):15–21
12. Hanley AJ, Retnakaran R, Qi Y, et al. Association of hematological parameters with insulin resistance and β-cell dysfunction in nondiabetic subjects. J Clin Endocrinol Metab 2009;94:3824–3832
13. Moghtaderi A, Bakhshipour A, Rashidi H. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. Clin Neurol Neurosurg 2006;108:477–481
14. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994;17:1281–1289
15. Bril V, Kojic J, Ngo M, Clark K. Comparison of a neurothesiometer and vibration in measuring vibration perception thresholds and relationship to nerve conduction studies. Diabetes Care 1997;20:1360–1362
16. Claus D, Mustafa C, Vogel W, Herz M, Neundörfer B. Assessment of diabetic neuropathy: definition of norm and discrimination of abnormal nerve function. Muscle Nerve 1993;16:757–768
17. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Organization, 1999
18. Alberti KG, Eckel RH, Grundy SM, et al.; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645
19. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518–523
20. Kelly AS, Steinberger J, Jacobs DR, Hong CP, Moran A, Sinaiko AR. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. Int J Pediatr Obes 2011;6:e283–e289
21. Bril V, Perkins BA. Comparison of vibration perception thresholds obtained with the Neurothesiometer and the CASE IV and relationship to nerve conduction studies. Diabet Med 2002;19:661–666
22. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. Diabetes Care 1994;17:557–560
23. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–154
24. Cheng YJ, Gregg EW, Kahn HS, Williams DE, De Rekeneire N, Narayan KM. Peripheral

insensate neuropathy—a tall problem for US adults? Am J Epidemiol 2006;164:873–880

25. Dyck PJ, Dyck PJ, Klein CJ, Weigand SD. Does impaired glucose metabolism cause polyneuropathy? Review of previous studies and design of a prospective controlled population-based study. Muscle Nerve 2007;36:536–541

26. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 2003;60:108–111

27. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: where are we now and where to go? J Diabetes Investig 2011;2:18–32

28. Dobretsov M, Romanovsky D, Stimers JR. Early diabetic neuropathy: triggers and mechanisms. World J Gastroenterol 2007;13:175–191

29. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol 2011;7:682–690

30. Bongaerts BW, Rathmann W, Heier M, et al. Older subjects with diabetes and prediabetes are frequently unaware of having distal sensorimotor polyneuropathy: the KORA F4 study. Diabetes Care 2013;36:1141–1146

31. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80