Peripheral Neuropathy Defined by Monofilament Insensitivity and Diabetes Status

NHANES 1999–2004

JODIE G. KATON, PHD[1,2]
GAYLE E. REIBER, PHD[1,2,3]
KARIN M. NELSON, MD, MSHS[1,4,5]

OBJECTIVE—To determine whether diabetes status, including prediabetes, is associated with increased risk of peripheral neuropathy as defined by monofilament insensitivity.

RESEARCH DESIGN AND METHODS—This study used data from the 1999–2004 National Health and Nutrition Examination Survey ($n = 7,818$). Peripheral neuropathy was defined as one or more insensate sites detected by a Semmes-Weinstein 10-g monofilament. Generalized linear models were used to directly estimate relative risks (RRs) for the association of diabetes status and peripheral neuropathy.

RESULTS—After adjustment compared with no diabetes, prediabetes [RR 1.11 (95% CI 0.92–1.34)] and undiagnosed diabetes [1.08 (0.73–1.61)] were associated with modest increases in risk of peripheral neuropathy, and diabetes was associated with a 74% higher risk of peripheral neuropathy [1.74 (1.50–2.01)].

CONCLUSIONS—Diabetes is associated with increased risk of peripheral neuropathy defined by monofilament insensitivity, but prediabetes and undiagnosed diabetes may be associated with only a modest increase in risk.

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S tudies suggest that prediabetes defined as impaired fasting glucose or impaired glucose tolerance may be associated with increased risk of peripheral neuropathy. Findings are influenced by the definition of prediabetes, the population studied, and the criteria for diagnosing peripheral neuropathy (1–9). It is not known whether individuals with prediabetes, based on their A1C (5.7–6.4%) (10), are at increased risk of peripheral neuropathy. The objective of this study was to determine whether diabetes status, including prediabetes (10), is associated with risk of peripheral neuropathy as defined by monofilament insensitivity.

RESEARCH DESIGN AND METHODS

—We included all respondents from National Health and Nutrition Examination Survey (NHANES) 1999–2004 (11) aged ≥40 years; who completed the lower-extremity disease exam; had measured A1C; answered the question, "Other than during pregnancy have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"; and were not pregnant.

This study was deemed exempt from human subjects review by the Department of Veterans Affairs, Puget Sound Health Care System.

Variables and measures

Diabetes status was determined by questionnaire and A1C data (10). Those with no prior physician diagnosis of diabetes were classified as having no diabetes if their A1C was <5.7%, prediabetes if their A1C was 5.7–6.49%, and undiagnosed diabetes if their A1C was ≥6.5%. Peripheral neuropathy was defined as one or more insensate sites of three sites tested per foot based on the Semmes-Weinstein 10-g monofilament (1,12–15). The unit of analysis was the individual. Covariates included age, sex, and self-reported race/ethnicity.

Statistical methods

Generalized linear models were used to directly calculate the relative risks (RRs) for the association between diabetes status and peripheral neuropathy. Final models included covariates that were thought *1*) a priori to be associated with diabetes status and risk factors for peripheral neuropathy and *2*) unlikely to be a consequence of diabetes status or peripheral neuropathy. All analyses were weighted to account for the survey design, and statistical tests were at a two-sided α-level of 0.05. Analyses were completed using SAS software and STATA 12.

RESULTS—Between 1999 and 2004, 9,145 adults aged ≥40 years completed the NHANES survey and physical exam. We excluded 1,131 who did not complete a lower-extremity exam, 190 with unknown diabetes status, and 6 who were pregnant. The prevalence of prediabetes was 16% (95% CI 14–17), of undiagnosed diabetes 2% (1.6–2.3), and of diagnosed diabetes was 12% (11–13). After adjustment for age, sex, and race/ethnicity compared with individuals with no diabetes, those with prediabetes had 11% higher risk of peripheral neuropathy [RR 1.11

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(95% CI 0.92–1.34)], those with undiagnosed diabetes had 8% higher risk of peripheral neuropathy [1.08 (0.73–1.61)], and those with diagnosed diabetes had 74% higher risk of peripheral neuropathy [1.74 (1.50–2.01)] (Table 1). Results were unchanged when we defined peripheral neuropathy as two or more insensate sites. Further adjustment for height, alcohol use, and BMI did not appreciably change the results.

CONCLUSIONS—This study found that after adjustment, prediabetes, defined as A1C 5.7–6.5%, was associated with a modest increase in risk of peripheral neuropathy. Use of A1C for defining prediabetes may identify individuals with more severe, chronic hyperglycemia, which might explain the higher-than-expected prevalence of peripheral neuropathy among those with prediabetes in our study (1,3). Recently, Dyck et al. (8) reported no detectable association between impaired glucose (impaired fasting glucose or impaired glucose tolerance) and peripheral neuropathy, as defined by nerve conduction scores. While this study included detailed neurophysical measures, the sample size was small ($n = 542$) with low prevalence of peripheral neuropathy among those with prediabetes (12%) or diabetes (17%) (8).

Strengths of this study include the large nationally representative sample and separation of those with prediabetes, undiagnosed diabetes, and diagnosed diabetes. Limitations include classification of peripheral neuropathy and the cross-sectional study design.

We defined peripheral neuropathy as one or more insensate sites for optimum sensitivity and specificity (12,16) to ensure comparability with earlier published studies (1) and so that our results were relevant to current standards in primary care of diabetes (17). Sensitivity of the monofilament test ranges from 30 to 100%, and specificity ranges from 63 to 100% (16). If the low specificity of the monofilament test was independent of diabetes status, this would have led to an underestimation of the association of diabetes status and peripheral neuropathy. In research and clinical practice, the Semmes-Weinstein monofilament test is widely used and recommended to screen for peripheral neuropathy, since it is a rapid, comfortable, and inexpensive means of assessment and highly correlated with risk of injury, ulceration, and amputation (16–18). However, the monofilament test may primarily identify individuals at the highest risk for ulceration with large-fiber nerve damage. Therefore, our results may best be interpreted as measuring the association of diabetes status with risk of ulceration rather than peripheral neuropathy.

NHANES is a cross-sectional survey. Variables such as BMI, physical activity, or alcohol use may be influenced by diabetes status or presence of peripheral neuropathy. Therefore, these three variables were not included in our final models.

With a shift toward use of A1C for diagnosis of diabetes, it is important to determine whether diabetes status, based on A1C, is associated with risk for peripheral neuropathy. Our study is the first to examine this question, and the findings suggest that while diabetes is associated with a nearly twofold increased risk of peripheral neuropathy, prediabetes and undiagnosed diabetes are associated with only a modest increase in risk of peripheral neuropathy.

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Table 1—*Association of diabetes status and peripheral neuropathy, defined by monofilament insensitivity, among U.S. adults aged ≥40 years: NHANES 1999–2004*

	n	Peripheral neuropathy % (95% CI)[a]	$RR_{unadjusted}$ (95% CI)	$RR_{adjusted}$ (95% CI)[b]
≥1 Insensate site				
No diabetes	4,859	11 (9.6–11.7)	Reference	Reference
Prediabetes	1,470	16 (13.3–18.9)	1.51 (1.21–1.89)	1.11 (0.92–1.34)
Undiagnosed diabetes	216	18 (10.6–25.5)	1.79 (1.15–2.80)	1.08 (0.73–1.61)
Diagnosed diabetes	1,273	27 (23.6–30.1)	2.52 (2.15–2.95)	1.74 (1.50–2.01)
≥2 Insensate site				
No diabetes	4,859	4.2 (3.5–5.0)	Reference	Reference
Prediabetes	1,470	7.5 (6.0–9.1)	1.77 (1.40–2.24)	1.11 (0.87–1.43)
Undiagnosed diabetes	216	8.8 (4.6–13.0)	2.08 (1.31–3.30)	1.41 (0.88–2.25)
Diagnosed diabetes	1,273	14.7 (13.0–16.6)	3.47 (2.84–4.23)	2.14 (1.69–2.72)

[a]Weighted to the entire population. [b]Adjusted for age, sex, and race/ethnicity.

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