Age 85+ Years Accelerates Large-Fiber Peripheral Nerve Dysfunction and Diabetes Contributes Even in the Oldest-Old: The Women’s Health and Aging Study

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Background. Both diabetes mellitus and advancing age are associated with peripheral nerve dysfunction (PND). However, the independent and potentially synergistic effects of these factors in old age are poorly described, especially among the oldest-old and among people with an existing disability.

Methods. A total of 894 women aged 65+ years participating in the Women’s Health and Aging Study received a baseline home interview and clinical examination during which PND was evaluated by the Vibratron II. Age and diabetes were examined in relation to the level of PND (normal, mild, moderate, or severe). Height, alcohol consumption, smoking, report of neurologic symptoms, and diabetes duration were examined as potential confounders.

Results. Eighteen percent of the sample reported diabetes, 42% had normal nerve function, and 23.9%, 14.5%, and 19.5% had mild, moderate, and severe PND, respectively. Women aged 85+ years had 6.5, 7.5, and 13.3 times the odds of mild, moderate, and severe PND relative to women aged 65–74 years, adjusted for diabetes and height. Women who reported diabetes had 1.8, 2.4, and 1.6 times the risk of mild, moderate, and severe PND relative to those who did not, adjusted for age and height. No interaction between age and diabetes was observed.

Conclusions. Age is strongly associated with decrements in large-fiber peripheral nerve function in disabled women aged 65+ years, with greatly accelerated risk among those aged 85+ years. Despite the overwhelmingly strong effects of advancing age on PND in this cohort, diabetes remains a significant correlate of PND. Future studies may determine whether prevention or control of diabetes is effective in reducing the occurrence of PND in old age and whether a reduction in PND will translate into reduced disability in this age group.
served independently of age and that advancing age and diabetes would have synergistic effects on PND. We show that large-fiber PND occurs with advancing age and accelerates rapidly after age 85 years and that diabetes contributes to PND even in very old age.

**Methods**

**Study Design and Cohort Selection**

The Women’s Health and Aging Study (WHAS) is a prospective study of the causes and course of disability in older women, developed and supported by the National Institute on Aging (16,17). The cohort consists of 1002 moderately to severely disabled women aged ≥65 years. Participants were recruited from an age-stratified random sample of community-dwelling Medicare beneficiaries residing in 12 contiguous zip codes in the Baltimore, Maryland area. Eligibility was determined from an in-person screening interview conducted at participants’ homes. All participants were self-respondents; no proxies were used. The WHAS received approval from the Institutional Review Board of the Johns Hopkins University, and participants provided informed consent.

**Classification of Diabetes Status**

WHAS participants received an extensive home interview that included questions about physician-diagnosed medical conditions and about symptoms characteristic of a number of conditions. Each participant was asked “Has a doctor ever told you that you had diabetes?” Women responding “yes” to this question were described as having “reported” diabetes. Participants with reported diabetes were also asked, “How old were you when you were first told that you had diabetes?” Duration of reported diabetes was calculated from the year the participant reported being diagnosed with diabetes and her age at the baseline exam. Age at diabetes diagnosis was used as a selection criterion: If the age at diagnosis was ≤30 years, the subject was excluded due to the possibility that the diabetes she reported was type 1 rather than type 2.

Five questions related to peripheral neuropathy were asked, the first being a screening question: “Is your sensation or sense of feeling normal or abnormal?” If the subject reported that her sense of feeling was abnormal, four additional questions were asked: “Is your abnormal sensation found in your legs or feet?”; “Have you ever burned your self without feeling pain?”; “Do you have a prickly-asleep- numbness feeling of the feet, like when your hand goes to sleep from lying on it?”; and “In your feet, do you have dead-asleep-numbness, like novocaine, without prickling?”

**Examination and Evaluation of Peripheral Nerve Function**

On a separate home visit, large-fiber peripheral nerve function was evaluated by measuring vibration perception threshold (VPT) with the Vibratron II (Physitemp Instruments, Inc, Clifton, NJ). The Vibratron II measures the sensitivity of the plantar aspect of the great toe in detecting small, vibratory stimuli, thereby providing quantitative information on large-fiber peripheral nerve function. WHAS employed a standardized protocol involving a two-alternative, forced-choice procedure in which the participant indicated which of two periods of supposed stimulation was accompanied by an actual vibration. The intensity of the stimulus was reduced by approximately 10% at each trial until the participant could no longer detect the vibration. This method was derived from a standardized protocol developed by Arezzo for Physitemp Instruments (18) and has been described in detail and validated (16,19). VPT data are presented in vibration units, the actual reading displayed on the Vibratron II device. These units measure the amplitude of the stimulus and are related to “true” amplitude (measured in microns) by the following formula: $A = KX^2$, where $A$ is the amplitude in microns, $K = 0.5$, and $X$ is vibration units (20). Higher values indicate that a stronger stimulus was needed to elicit a response, reflecting worse PND.

Methodological work with the Vibratron II has provided normal, age-specific values for peripheral nerve function. For adults >65 years of age, less than 3.43 vibration units is defined as the range of normal function; 3.43 to <4.87 units indicates evidence of mild dysfunction; 4.87 to <6.31 units is evidence of moderate dysfunction, and ≥6.31 vibration units indicates severe dysfunction (18). These values are specific to the forced-choice protocol of the Vibratron II.

Of the 1002 women in the WHAS, 104 were missing VPT data. Of these, 47 initiated but did not complete the protocol, 7 were amputees or could not perform the test because of other physical problems, 5 did not understand the instructions, 43 did not comply with the instructions, and 2 refused. Following exclusion of subjects with missing VPT, 4 additional women were excluded because they reported being diagnosed with diabetes at age ≤30 years. The level of PND could therefore be determined for 894 women (89.2% of the WHAS cohort).

**Potential Confounders**

Height is related to PND with taller individuals having worse measures (7,11,12). Standing height and knee height were both measured in WHAS according to standardized protocols (16) and were investigated separately in multivariate analyses. Because old age is associated with degenerative changes in stature, we used knee height to estimate corrected standing height with a validated prediction equation for women aged 60–90 years (21). Subtraction of measured standing height from corrected standing height ($\Delta$standing height) yielded an estimate of change in stature. This variable was examined in regression analysis as an index of vertebral compression and kyphosis, both of which may be associated with PND.

Alcohol consumption has been associated with PND in older adults (13). Usual alcohol consumption was assessed during the interview with the following question: “Do you usually drink alcoholic beverages, including beer, wine, sherry, or liquor, at least once every week?” Alcohol was analyzed by contrasting women who reported any drinking to those who reported none. Current and former smokers were contrasted to never smokers.

**Statistical Analysis**

PND was analyzed as an ordinal outcome in descriptive and multivariate analyses, with the normal nerve function
group as the reference. Women with mild, moderate, or severe PND were analyzed individually as the case groups. In descriptive analyses, the chi square test was used to study the distribution of PND (normal, mild, moderate, and severe) in relation to age and diabetes (reported diabetes vs no diabetes; age: 65–74, 75–84, and ≥85 years). PND categories were also examined in relation to potentially confounding variables.

In multivariate regression analyses using the CATMOD (Categorical Model) procedure in SAS (22), effects of age and diabetes were examined in relation to the odds of having a specific level of PND (mild, moderate, or severe) relative to normal function. The combined effects (interaction) of older age and diabetes were examined to determine if the presence of both factors resulted in a synergy that increased the odds of PND beyond the effects of each factor alone. Potentially confounding variables were entered into the models to determine if the effects of age and diabetes changed following adjustment for these factors. Odds ratios (OR) ratios and 95% confidence intervals (CI) show cross-sectional associations of having a specific level of PND relative to the reference group, adjusted for potential confounders. Associations were considered statistically significant at the p < .05 level, corresponding to 95% CI excluding unity.

**Results**

Baseline characteristics of the cohort are shown in Table 1. The largest proportion of women was in the 65–74-year-old age group (40.4%), and most were white (71.8%). More than 18% of the cohort (n = 165) reported having been told by a physician that they had diabetes, and, of these, more than half reported having diabetes for 10 or more years.

Sixty-five women (7.3% of the cohort) reported having one or more neurologic symptom. Of those with symptoms, 29.2% reported one symptom, 41.5% reported two symptoms, 26.2% reported three symptoms, and 3% reported all four symptoms. Sixteen percent of the cohort reported usual alcohol consumption, 35.8% reported smoking in the past, and 12.3% were current smokers. Mean measured standing height was 156 cm, and mean knee height was 49 cm; mean corrected standing height was 157 cm, and mean Δstanding height was −0.20 cm, indicating a mean reduction in stature. Mean vibration threshold in this sample was 4.28 ± 2.23 units.

The distributions of VPT and categories of PND are shown in Figure 1. The distribution of VPT was skewed to the right. Forty-two percent of the sample had normal peripheral nerve function, and 23.9%, 14.5%, and 19.5% had mild, moderate, and severe PND, respectively.

Figure 2 shows the distribution of PND by age group. An association between age and PND is evident. While 56% of women aged 65–74 years had normal nerve function, only 20% of women aged ≥85 years had normal nerve function; women aged 75–84 years were intermediate, with 43% having normal function. Conversely, only 13% of women aged 65–74 years had severe PND compared with 31% of women aged ≥85 years (p < .001). Reported diabetes status and level of PND are presented in Figure 3. While 66% of women with reported diabetes had PND, 56% of women without reported diabetes had PND. The prevalence of severe PND was about 20% among women with and without reported diabetes. There was no statistically significant univariate association between diabetes category and level of PND.

Results of regression analyses are presented in Table 2. Increasing age was significantly associated with greater odds of PND, and the magnitude of this association increased with increasing level of PND. Compared with women aged 65–74 years, the odds of mild PND increased 1.9-fold among women aged 75–84 years and 6.5-fold among women aged ≥85 years. The odds of severe PND in these two age groups increased dramatically to 2.6 and 13.3 compared with women aged 65–74 years. For mild and moderate PND, odds among women aged ≥85 years were more than three times that of women aged 75–84 years, and for severe PND, odds among women aged ≥85 years were more than five times that of women aged 75–84 years. These differences suggested an accelerated, nonlinear effect of age on the occurrence and severity of PND among women aged ≥85 years.

Women with reported diabetes were at significantly increased risk of mild (OR: 1.7) and moderate (OR: 2.4) PND compared with those who did not report diabetes. This association did not reach statistical significance in women with severe PND. Corrected height was associated with mild and severe PND, but this association did not reach statistical significance in the moderate PND group. Change in standing height was not associated with any level of PND when adjusted for corrected height. Smoking, alcohol use, neurologic symptoms, and duration of diabetes were not associated with any level of PND in this sample. Examination of interactions of age and diabetes revealed no significant associations with any level of PND.

**Table 1. Baseline Characteristics of Women in the Women’s Health and Aging Study, n = 894**

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74 y</td>
<td>40.4</td>
<td>361</td>
</tr>
<tr>
<td>75–84 y</td>
<td>32.0</td>
<td>286</td>
</tr>
<tr>
<td>≥ 85 y</td>
<td>27.6</td>
<td>247</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>894</td>
</tr>
<tr>
<td>Reported Diabetes</td>
<td>18.5</td>
<td>165</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 y</td>
<td>22.4</td>
<td>37</td>
</tr>
<tr>
<td>5–9 y</td>
<td>18.2</td>
<td>30</td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>55.2</td>
<td>91</td>
</tr>
<tr>
<td>Reported Neuropathy Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal sensation in feet</td>
<td>5.7</td>
<td>51</td>
</tr>
<tr>
<td>Burned feet w/o feeling pain</td>
<td>1.2</td>
<td>11</td>
</tr>
<tr>
<td>Numb feet</td>
<td>5.1</td>
<td>46</td>
</tr>
<tr>
<td>“Dead” feet</td>
<td>2.7</td>
<td>24</td>
</tr>
<tr>
<td>PND</td>
<td>7.3</td>
<td>65</td>
</tr>
<tr>
<td>Any symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 symptom</td>
<td>29.2</td>
<td>19</td>
</tr>
<tr>
<td>2 symptoms</td>
<td>41.5</td>
<td>27</td>
</tr>
<tr>
<td>3 symptoms</td>
<td>26.2</td>
<td>17</td>
</tr>
<tr>
<td>4 symptoms</td>
<td>3.1</td>
<td>2</td>
</tr>
<tr>
<td>Vibration Threshold</td>
<td>4.28 ± 2.23</td>
<td></td>
</tr>
</tbody>
</table>

*Women with valid perception data.*
DISCUSSION
We showed that the risk of having all levels of PND increases with age even after age 65 years and that the odds of having every level of PND accelerates rapidly after age 85 years. These associations were independent of diabetes status and height, two confounders of the association between age and PND. Our results are consistent with previous studies showing associations between age and decrements in nerve function (3,6,7,10–12). However, these studies are not generalizeable to the oldest-old, the fastest growing segment of the U.S. population (23). Compared with women aged 65–74 years, the risk of severe PND was 2.6 in women aged 75–84 years and 13.5 in women aged ≥85 years. The odds of being at each level of PND among women aged ≥85 years were at least threefold greater than among women aged 75–84 years.

The accelerated effects of age on occurrence and severity of PND in women aged ≥85 years may be associated with functional impairments in the lower extremity, potentially placing this age group at high risk of neuropathy-related disability. Supporting an association between PND and decrements in lower extremity physical abilities are several small studies of middle-aged and older adults that showed relationships between PND and gait abnormalities, loss of strength, decrements in balance, and history of falls (24–28). These factors are important for maintenance of independence in old age and highlight the potential contribution of PND to disability in elderly individuals. Evaluation of large-fiber nerve function may therefore help to identify older in-
indicated an interaction between age and diabetes, suggesting that reduced occurrence of diabetes in older adults would result in similar reductions in diabetes-associated PND across age. The oldest-old would therefore benefit as much as the young-old from a reduction in diabetes.

Long-term exposure to hyperglycemia has long been hypothesized to be causally associated with PND, but the mechanisms by which this occurs have not been fully elucidated. In this study, duration of diabetes (among the 158 women for whom these data were available) was not associated with worse PND, a finding observed in several previous studies (5,7,11). Lack of statistical power may have contributed to the absent association. An alternative explanation may be that the effects of age simply overpower the effect of diabetes duration in this elderly cohort.

Ascertainment of diabetes in the WHAS was not ideal. Because neither fasting glucose nor postchallenge glucose was measured, undiagnosed diabetes could not be categorized according to the criteria recommended by the American Diabetes Association or the World Health Organization (32,33). This is important because the prevalence of undiagnosed diabetes is known to be approximately equal to that of reported diabetes (34). Absence of data on fasting and postchallenge glucose therefore raised obvious concerns about the misclassification of diabetes. If a 50% underestimation of diabetes is assumed in this study, there might have been as many as 165 women misclassified as nondiabetic (a number equal to those who reported diabetes), and this misclassification may have underestimated the magnitude of the diabetes-PND associations observed in this study. Misclassification of diabetes could also have contributed to the absence of interaction between age and diabetes.

One hypothesized mechanism through which hyperglycemia may contribute to or enhance the progression of PND is through the pathologic effects of advanced glycation end-products (AGEs) on nerve tissues (30,35). In addition to examination of the potential role of AGEs in development and progression of PND in old age, standardized methods to examine other mechanisms, such as microvascular insufficiency, growth-factor deficiencies, and immune activity should also be developed for use in population-based studies (36).

The WHAS baseline questionnaire contained questions related to symptoms of neuropathy, including items related to hot/cold sensation and tingling. These symptoms are consistent with small- rather than large-fiber neuropathy. However, the Vibratron II evaluates large-fiber PND; WHAS did not include quantitative sensory testing for small-fiber dysfunction, such as thermal discrimination. It was therefore not surprising that the neurologic symptoms reported by WHAS subjects were not associated with PND as measured by the Vibratron II. It should be noted that screening for small-fiber dysfunction would have likely resulted in identification of more cases of nerve dysfunction, and/or more neuropathic modalities (37). This is a critical distinction because dysfunction of large and small nerve fibers does not always occur simultaneously. Further, symptoms and objective tests of nerve function are central to neuropathy classification according to criteria proposed by the San Antonio Conference (38).

Alcohol consumption and smoking were not related to PND in this study. These findings are in contrast to a previ-

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**Table 2. Regression Analysis Relating Diabetes, Age, and Height to Level of Peripheral Nerve Dysfunction, Women’s Health and Aging Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild vs Normal</th>
<th>Moderate vs Normal</th>
<th>Severe vs Normal</th>
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<tbody>
<tr>
<td>OR</td>
<td>%95 CI</td>
<td>OR %95 CI</td>
<td>OR %95 CI</td>
</tr>
<tr>
<td>75–84 y vs 65–74 y</td>
<td>1.9 1.2–3.0</td>
<td>2.2 1.2–3.8</td>
<td>2.6 1.5–4.5</td>
</tr>
<tr>
<td>≥85 y vs 65–74 y</td>
<td>6.5 3.6–11.7</td>
<td>7.5 3.8–14.9</td>
<td>13.3 7.0–25.4</td>
</tr>
<tr>
<td>Reported diabetes vs nondiabetic</td>
<td>1.8 1.01–2.9</td>
<td>2.4 1.4–4.3</td>
<td>1.6 0.91–2.8</td>
</tr>
<tr>
<td>Height (per cm)</td>
<td>1.1 1.02–1.1</td>
<td>1.03 0.99–1.09</td>
<td>1.1 1.05–1.2</td>
</tr>
</tbody>
</table>

**Notes:** Smoking, alcohol use, neurologic symptoms, and duration of diabetes were not associated with any level of peripheral nerve dysfunction; these variables were not included in multivariate models. OR = odds ratio; CI = confidence interval.
ous study of younger subjects (39) and also to a study of older individuals (13) and may be due to the strong effects of age among the oldest-old in the WHAS. Alternatively, a selection bias may have been present in this study: Individuals with behavioral characteristics such as smoking and alcohol consumption might have been less likely to have survived until age 65 years, the minimum age at which women were eligible for inclusion in the study. Supporting this possibility is the fact that at the time of the home interview, only 16% of the sample reported usual alcohol consumption, and only 12% were current smokers.

Kyphosis and vertebral compression present methodologic difficulties in studies of older adults in which accurate measurement of height is critical for interpreting quantitative data. We addressed this problem by calculating corrected height with a validated algorithm. While corrected height predicted worse PND in most analyses, standing height was not associated with PND, suggesting that large-fiber PND is length dependent. It is interesting to note that advancing age is associated with several potentially related phenomena: kyphosis, decreased bone mineral density, and dysfunction of peripheral nerves, the latter in both the presence and absence of diabetes. Kyphosis is characterized by gradual, usually painless vertebral deformities, accompanied by bone density in the lower range of age- and sex-adjusted norms. With age, diffuse loss of bone density is observed at numerous other sites, including the lower extremity. Marked bone loss predisposing to fracture also occurs in Charcot neuroarthropathy, a chronic, progressive arthropathy related to sensory neuropathy. While mechanisms leading to development of Charcot foot are poorly understood, abnormalities of blood flow and increased bone resorption have been proposed (40,41). The relationship between general, age-related loss of bone density and age-related decrements in peripheral nerve function has not been explored. These phenomena may be linked by mechanisms similar to those hypothesized to cause the focal bone loss observed in the Charcot foot or by pathways yet to be identified.

This study has several limitations, most of which are related to the design and selection of the cohort. First, the WHAS is limited to women, preventing examination of gender effects on associations between both diabetes and age on PND. While previous studies have suggested that PND is more common among men than among women (9), this association has not been consistent among persons with and without diabetes (11) and has been absent when height is accounted for in the analysis (5). From a public health standpoint, understanding modifiable risk factors related to PND is critical for older women because women have a longer life expectancy than men and, as we have shown, the likelihood of having PND increases dramatically at advanced age. Our findings associated with the dramatic increase in PND among women aged ≥85 years is particularly important in light of current demographic trends in the United States: In the year 2050, it is estimated that there will be 4.7 million more women aged ≥85 years than men of the same age (23).

The WHAS cohort was selected on the basis of the presence of disability at the baseline examination, making it somewhat unrepresentative of the general population of women aged ≥65 years. However, the WHAS provides a unique opportunity to study peripheral nerve function in a large cohort of individuals whose existing disabilities could have masked the effects of diabetes and age on PND. Consistent with our hypotheses, however, we found that both age and diabetes independently affect PND in this cohort, indicating measurable effects of diabetes, even in the presence of considerable and comorbidity.

In summary, we have shown that both age and diabetes are independently associated with significant decrements in large-fiber peripheral nerve function in older women with existing disability and that the effects of age on PND accelerate rapidly after the age of 85 years. Despite the clear effects of age on PND and a growing body of evidence that PND may be associated with disability in old age, the effects of PND on functionally relevant outcomes in older adults have received surprisingly limited attention. Future epidemiologic studies of peripheral nerve function in old age should focus on clarifying the role of nerve dysfunction on functionally relevant outcomes.

Acknowledgments

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References