Vibration Perception Threshold as a Measure of Distal Symmetrical Peripheral Neuropathy in Type 1 Diabetes: Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)

**Running Title:** Vibration perception threshold in type 1 diabetes

Catherine L. Martin, M.S.¹, Barbara H. Waberski, M.S.², Rodica Pop-Busui, M.D., Ph.D.¹, Patricia A. Cleary, M.S.², Sarah Catton, R.N.³, James W. Albers, M.D., Ph.D.¹, Eva L. Feldman, M.D., Ph.D.¹, William H. Herman, M.D., M.P.H.¹, and The DCCT/EDIC Research Group*

¹ University of Michigan, Ann Arbor MI  
² The George Washington University Biostatistics Center, Rockville MD  
³ University of Washington Medical Center, Seattle WA

**Address correspondence:**  
Catherine L. Martin  
Email: [martinc@med.umich.edu](mailto:martinc@med.umich.edu)

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Objective: To describe the sensitivity, specificity, positive predictive value, and negative predictive value of vibration perception threshold (VPT) testing in subjects with type 1 diabetes relative to gold-standard assessments of peripheral neuropathy.

Research Design and Methods: VPT was determined in 1,177 adults with type 1 diabetes 13 to 14 years after participating in a study of intensive (INT) vs. conventional (CONV) diabetes treatment. Abnormal VPT was defined by values exceeding 2.5 SD above age-specific normal values. Signs and symptoms of peripheral neuropathy were assessed and electrodiagnostic studies were performed to establish definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy (the presence of both definite clinical neuropathy and abnormal nerve conduction).

Results: Thirty-seven percent of subjects had definite clinical neuropathy, 61% had abnormal nerve conduction, and 30% had confirmed clinical neuropathy. Abnormal VPT was more common among former CONV than INT subjects (64% vs. 57%, p < 0.05) and was associated with older age. VPT was a sensitive measure of confirmed clinical neuropathy (87%) and of definite clinical neuropathy (80%), and a specific measure of abnormal nerve conduction (62%). Higher VPT cutpoints improved test sensitivity and lower cutpoints improved specificity. Areas under the ROC curves ranged from 0.71 to 0.83 and were higher for older compared to younger subjects and highest for confirmed clinical neuropathy.

Conclusions: VPT was a sensitive measure of peripheral neuropathy. Future studies may choose to select VPT cutpoints for defining abnormality based on the population studied and clinical outcome of interest.

RESEARCH DESIGN AND METHODS
Study Sample. At baseline, the DCCT studied 1,441 subjects between 13 and 39 years of age with type 1 diabetes for 1 to 15 years who were generally in good health. Subjects were randomly assigned to intensive (INT) or conventional (CONV) therapy and
were followed for a mean of 6.5 years (1). The EDIC study enrolled 1,375 of the surviving DCCT subjects in 1994 (687 INT, 688 CONV). During EDIC 13/14, VPT studies were performed on 624 (94%) of former INT and 601 (91%) of former CONV subjects (4). Characteristics of subjects with VPT assessment did not differ from those who did not have VPT assessment performed (data not shown). Concurrent DSPN assessments were performed on 1,177 subjects.

**Vibration Perception Threshold.** VPT was assessed using the Vibratron II (Physitemp Instruments Inc., Clifton NJ). The device produces vibration amplitudes from 0.005 to 200 microns, expressed as vibration units (VU; 0.005 microns = 0.1 VU; 200 microns = 20.0 VU), with higher VU indicating worse performance or greater sensory dysfunction. A forced-choice algorithm was used to determine VPT at the dominant index finger and dominant great toe. The examiner controlled which of two metal posts (labeled A and B) was vibrating and controlled the VU using a pre-determined algorithm. The subject placed his or digit (finger or toe) first on post A, then on post B using light pressure for about one second and was asked to state which was vibrating. Subjects were encouraged to guess if uncertain and were not told if they were correct or incorrect. Subjects were positioned to prevent them from seeing the device settings. Vibration intensity was increased by 10% following incorrect responses and was decreased by 10% following correct responses. Stimuli at VU of 1.0 and less were repeated before increasing or decreasing the vibration intensity. The test was stopped when the subject made 5 errors over a minimum of 18 trials. VU corresponding to the subject’s first five errors and the five lowest correctly identified VU were rank ordered, the highest and lowest of these 10 were discarded. The average of the remaining 8 values was recorded as the VPT.

During a central training session, the study coordinator or research nurse from each EDIC site was trained and was required to submit at least two VPT tests on non-EDIC subjects to demonstrate competency in test administration and scoring.

Ninety-four subjects, 2 to 6 from each clinical site, were randomly selected for repeat VPT testing of the great toe on the same day and by the same examiner as a measure of test reproducibility. Examiners were instructed to wait at least 30 minutes between tests. In the interval, subjects re-wore any footwear worn prior to the primary test (8).

VPT results were expressed both as continuous and categorical variables using age-specific normal values provided by Physitemp Instruments, Inc. (9). Values within 2.5 standard deviations (SD) of the age-specific mean were categorized as normal, and those exceeding 2.5 SD were categorized as abnormal.

**Definition of DSPN in DCCT and EDIC.** Board-certified neurologists and electromyographers were identified, trained, and certified in the EDIC study to conduct neurological evaluations and electrodiagnostic studies using the protocol used in the DCCT (1-3). Three analytic definitions were used in the DCCT and subsequently in the EDIC study to define DSPN. The first, definite clinical neuropathy, indicates the presence of symptoms and signs consistent with DSPN based on history and physical examination by a board-certified neurologist. The second, abnormal nerve conduction, represents one or more abnormal nerve conduction results (amplitude, conduction velocity, or F response latency) in two different peripheral nerves among the median (sensory or motor), peroneal motor, or sural sensory studies. Finally, confirmed clinical neuropathy was defined as the presence of both definite clinical neuropathy and abnormal nerve conduction (1-3).
**Statistical Analysis.** Groups were compared using Wilcoxon rank-sum tests for ordinal or continuous variables and contingency Chi-square tests for categorical variables. The performance of VPT in predicting definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy was assessed by determining sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Cohen’s Kappa (10) in the full cohort and separately for those 36 to 50 and 51 to 65 years of age. Sensitivity is the probability of having an abnormal VPT test in the presence of neuropathy. Specificity is the probability of having a normal VPT test in the absence of neuropathy. PPV is the proportion of subjects with neuropathy among those with abnormal VPT tests, reflecting both the sensitivity of the test and the prevalence of the condition in the population. NPV is the proportion of subjects without neuropathy among those with normal VPT tests. Cohen’s Kappa measures agreement between two methods. Kappa measures the percentage of data values in the main diagonal of a 2x2 table and then adjusts these values for the amount of agreement that could be expected due to chance alone. Perfect agreement results in the maximum value for Kappa of 1.0, values between 0.20 and 0.39 indicate fair agreement, values between 0.4 and 0.59 indicate moderate agreement, and values ≥ 0.6 indicate good agreement. Receiver Operating Characteristic (ROC) curves show the relationship between the true positive ratio (sensitivity) and false positive ratio (1-specificity) of a test and can be used to define cutpoints to define abnormal tests (11). Areas under the ROC curve (AUC) measure the performance of a test in predicting the outcome of interest. Generally, AUC values of 0.5 indicate that a test performs no better than chance, values between 0.70 and 0.79 indicate fair performance, values between 0.80 and 0.89 indicate good performance, and values ≥ 0.9 indicate excellent test performance.

**RESULTS**

Characteristics of the 1,177 participants with both DSPN and VPT assessment are shown in Table 1. DSPN was more prevalent among former CONV than former INT participants (p<0.01) using all three analytic definitions. DSPN prevalence among all participants was highest when defined by abnormal nerve conduction (61%). Definite clinical neuropathy was present in 37% of subjects, and confirmed clinical neuropathy in 30% of subjects.

Subjects selected for repeat VPT testing were representative of the EDIC cohort with respect to age (47.3 ± 7.3 years), gender (52% male), diabetes duration (24.8±4.3 years), frequency of confirmed clinical neuropathy (40%) and were equally distributed between treatment groups (N=50 INT, N=44 CONV). Eighty-three subjects had repeat testing. The mean primary and repeat test scores did not differ (3.8±2.7 vs. 3.9±2.8 VU, p=0.38). The calculated test-retest coefficient of reliability was 0.85.

Mean VPT was higher at both the great toe and index finger among former CONV versus INT subjects (4.03 vs. 3.53, P<0.01 at the great toe; 1.11 vs. 0.99, P<0.01 at the index finger) (Table 2). VPT at the great toe was abnormal in a majority (61%) of subjects, but abnormal at the index finger in only 6% of subjects. VPT abnormalities were more prevalent among former CONV than former INT subjects at both the toe and finger. Older age, regardless of former treatment group, was associated with higher mean VPT and greater prevalence of abnormal VPT (Table 2). Mean VPTs were higher at both the index finger (1.26 ± 0.67 vs. 1.03 ± 0.49, P<0.001) and great toe (5.86 ± 3.21 vs. 3.62 ± 2.20 P<0.001) among subjects reporting a lower extremity ulcer.
during the EDIC study compared to subjects with no reported lower extremity ulcers.

VPT was a sensitive predictor of all three DSPN outcome measures (Table 3), with the highest sensitivity noted for confirmed clinical neuropathy (87%). The sensitivity of VPT to predict definite clinical neuropathy and abnormal nerve conduction was 80% and 75% respectively. For all three outcomes, sensitivity increased with age. Specificity of VPT was highest for abnormal nerve conduction (62%) and lowest for definite (51%) or confirmed clinical neuropathy (51%) (Table 3). For all outcome measures, specificity decreased with age.

The PPV of VPT was higher for abnormal nerve conduction (76%) than for definite (49%) or confirmed clinical neuropathy (43%) and increased with age (Table 3). The NPV of VPT was higher for confirmed (90%) and definite clinical neuropathy (81%) than for abnormal nerve conduction (61%) and did not vary substantially by age (Table 3). Kappa values indicated at least fair agreement between VPT and all three outcome measures and were higher (indicating better agreement between VPT and the neurologic outcome measures) in older participants.

ROC curves were generated to plot the performance of great toe VPT against all three DSPN outcome measures. Figure 1 shows the relationship between the true-positive ratio (sensitivity) and the false-positive ratio (1-specificity) for various VPTs to predict definite clinical neuropathy (Figure 1a), abnormal nerve conduction (Figure 1b), and confirmed clinical neuropathy (Figure 1c). For the full cohort, VPT values that provided approximately 80% sensitivity were 4.30, 3.55, and 4.29 for definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy respectively. VPT values that provided approximately 80% specificity were 2.61 for definite clinical neuropathy, 2.34 for abnormal nerve conduction, and 3.31 for confirmed clinical neuropathy. AUC ranged from 0.71 to 0.83 indicating fair to good performance and were highest for confirmed clinical neuropathy. Separate ROC curves were created for subjects aged 36 to 50 and aged 51 to 65 years (together accounting for 95% of the total cohort). AUC was higher for older participants; 0.78 vs. 0.71 for definite clinical neuropathy; 0.78 vs. 0.75 for abnormal nerve conduction; 0.83 vs. 0.76 for confirmed clinical neuropathy.

CONCLUSIONS

We determined VPT and the prevalence of abnormal VPT in 1,177 subjects with type 1 diabetes during the 13th or 14th year of their participation in the EDIC study. VPT was a reliable measure of DSPN, and a sensitive and specific measure of definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy in this large cohort of patients with long-standing type 1 diabetes and a high prevalence of DSPN.

VPT at the index finger and great toe were performed concurrently with detailed neurological assessments and electrophysiologic studies. To ensure uniformity in test administration, all EDIC sites used the same devices and had centralized training. VPT testing was performed on the same day as the subject’s neurological assessment and electrophysiologic studies to minimize temporal variability when comparing results. To verify VPT test reproducibility we performed repeated, same day testing in a randomly selected subset of subjects and determined that the test-retest coefficient of reliability was good (0.85).

VPT may provide important, clinically meaningful information about large nerve fiber dysfunction in diabetes. The neurologic impairments associated with large fiber neuropathy account for over 80% of the morbidity associated with DSPN (12).
Abnormal VPT has been shown to predict the long-term complications of ulceration and amputation (13), and has been associated with foot ulcers, gangrene, amputation, and lower extremity bypass or angioplasty in type 1 diabetes (14). Common criticisms of VPT are that it is not sufficiently specific to large fiber or even to peripheral nerve dysfunction; that the results are influenced by subject attentiveness, motivation, and fatigue (15-18); that reproducibility may vary in non-diabetic and diabetic populations; and that results may vary depending on the device used (15, 18). VPT testing has advantages of being simple, quick to perform, painless, and generally well-tolerated. VPT results are not significantly impacted by the presence of foot callus or by limb temperature (15). These advantages and the availability of standardized testing algorithms make VPT an attractive option for DSPN assessment in research settings.

The higher prevalence of abnormal VPT observed at the great toe vs. the index finger in our study was not unexpected given the characteristic length dependent (stocking distribution) pattern of DSPN. Likewise, higher mean VPTs and increased prevalence of abnormalities among older subjects is not wholly unexpected given the known effects of aging on peripheral nerve function. The higher prevalence of abnormal VPTs in former CONV than in former INT participants is consistent with the higher prevalence of definite clinical neuropathy, abnormal nerve conduction and of confirmed clinical neuropathy in the CONV group previously reported (23).

Sensitivity and specificity, PPV, NPV, and ROC curves relating VPT at the great toe to each of the analytic definitions of neuropathy used in EDIC were used to evaluate the utility of VPT to predict DSPN. VPT at the index finger was not used as less than 8% of all subjects had abnormal VPT at the finger. As a practical consideration, inclusion of the VPT test at the finger, conducted prior to testing at the toe, gives the subject an opportunity to become familiar with the test procedure and gives the examiner an opportunity to assess the subject’s attentiveness and willingness to undergo testing.

We show VPT at the great toe to be a sensitive predictor of both definite clinical neuropathy and confirmed clinical neuropathy. Because sensory examination of large nerve fibers (e.g., vibration, position sense), were components of the neurologists’ evaluation, this finding is not unexpected. VPT was a less sensitive indicator of abnormal nerve conduction. This likely reflects inclusion of upper extremity nerves in the definition of abnormal nerve conduction, and identification of subclinical neuropathy as mild abnormalities of physiological function determined by electrodiagnostic criteria but without clinically discernable signs or reported symptoms as we have previously reported (24). Specificity of VPT was greatest for abnormal nerve conduction. Overall, the sensitivities and specificities obtained in our study compare favorably to others who have reported sensitivities between 58 and 84% and specificities between 61 and 86% for VPT (19-22) measured by a variety of test devices and test methods.

The ROC curves demonstrate the clear tradeoff between sensitivity and specificity when using VPT as a predictor of DSPN. For example, to attain 90% sensitivity for VPT testing as a predictor of confirmed clinical neuropathy, the cutpoint to determine abnormal VPT would be 5.5. That would however, provide a specificity of only about 40% (Figure 1c). Optimizing specificity at 90% sets the cutpoint at 2.2, but limits sensitivity to about 40%. Using the ROC curves, cutpoints can be chosen to optimize sensitivity and/or specificity according to the outcome of interest and age group under study. The AUCs suggest that VPT performance is fair to good, with VPT best at predicting confirmed clinical neuropathy and with greater predictive value in older age groups (again, not unexpected given the known effects of aging). Using Kappa as another measure of agreement, VPT had at least fair agreement with nerve conduction studies. Abnormal nerve conduction was more prevalent than either definite clinical neuropathy or
confirmed clinical neuropathy, therefore the PPV of VPT was highest as a measure of abnormal nerve conduction. NPV was higher for confirmed clinical neuropathy and definite clinical neuropathy and lower for abnormal nerve conduction, reflecting the lower prevalence of the confirmed and definite clinical neuropathy. While these analyses do not address the utility of VPT as a measure of disease severity or the ability of VPT to measure change in neuropathy status over time, they may inform future investigations that use the same methodology, providing appropriate thresholds for determining the presence of DSPN.

In general, VPT was best as an indicator of confirmed clinical neuropathy. This was especially true among older participants. VPT as measured in EDIC may be useful in future studies of type 1 diabetes with cutpoints selected to optimize sensitivity and specificity depending upon both the characteristics of the population studied and the clinical outcome selected.

Authors contributions. C.M. wrote the manuscript; B.W. researched data, performed analysis; R.P.B. contributed to discussion, reviewed/edited manuscript; P.C. researched data, reviewed/edited manuscript; S.C. reviewed/edited manuscript; J.A. contributed to discussion, reviewed/edited manuscript; E.F. contributed to discussion, reviewed/edited manuscript; W.H. contributed to discussion, reviewed, edited manuscript.

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Table 1. Characteristics of subjects evaluated for VPT in EDIC year 13/14 *

| Characteristic                     | Total Cohort | INT   | CONV  |
|-----------------------------------|--------------|-------|-------|
| N                                 | 1,177        | 599   | 578   |
| Age (yr)                          | 47±7         | 48±7† | 47±7† |
| Men (%)                           | 622 (53)     | 307 (51) | 315 (55) |
| Duration of diabetes (yr)         | 26±5         | 26±5  | 26±5  |
| HbA1c (%)                         | 7.8±1.2      | 7.8±1.2 | 7.8±1.2 |
| Height (cm)                       | 172±10       | 171±9 | 173±10 |
| Body Mass Index (kg/m²)           | 28.2±5.0     | 28.4±5.2 | 28.0±4.7 |
| Lower extremity ulcers (%)        | 90 (8)       | 37 (6) | 53 (9) |
| Definite clinical neuropathy (%)  | 438 (37)     | 201 (34) | 237 (41) ‡ |
| Abnormal nerve conduction (%)     | 722 (61)     | 324 (54) | 398 (69) ‡ |
| Confirmed clinical neuropathy (%) | 353 (30)     | 151 (25) | 202 (35) ‡ |

Data are means ± std or N(%).
* Data presented for same year at which VPT test performed.
† P<0.05; ‡ P<0.01 for treatment group differences by the Wilcoxon rank-sum test or contingency Chi-square.
§ Presence of signs and symptoms consistent with distal symmetrical polyneuropathy with abnormal electrodagnostic tests in at least 2 of 3 nerves tested.
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Table 2. VPT results for subjects evaluated in EDIC year 13/14 by treatment group and age category

| Characteristic                  | Treatment Group | Age Categories |
|---------------------------------|-----------------|----------------|
|                                 | Total Cohort    | INT | CONV | ≤35 | 36-50 | 51-65 |
| N                               | 1,177           | 599 | 578  | 59  | 693   | 425   |
| VPT Great Toe (vu)              | 3.78±2.35       | 3.53±2.19 | 4.03±2.47 † | 2.38±1.61 | 3.44±1.97 | 4.53±2.75 † |
| Abnormal (%)                    | 710 (61)        | 341 (57) | 369 (64) * | 20 (34) | 401 (58) | 289 (69) † |
| VPT Index Finger (vu)           | 1.05±0.51       | 0.99±0.42 | 1.11±0.58 † | 0.96±0.42 | 1.00±0.47 | 1.13±0.58 † |
| Abnormal (%)                    | 71 (6)          | 24 (4)    | 47 (8) † | 2 (3) | 41 (6) | 28 (7) |

Data are means ± std or N(%). Vu = vibration units.
*P<0.05; †P<0.01 for treatment group or age group differences by the Wilcoxon rank-sum test or contingency Chi-square.

Table 3. Performance of VPT testing on the Great Toe

|                          | N * | Sensitivity  | Specificity | PPV † | NPV ‡ | % Correct | Kappa |
|--------------------------|-----|--------------|-------------|-------|-------|-----------|-------|
| % (95% CI)               |     |              |             |       |       |           |       |
| **Definite Clinical Neuropathy** |     |              |             |       |       |           |       |
| Total Cohort             | 1,170 | 80 (76-84) | 51 (47-54) | 49    | 81    | 62        | 0.271 |
| Age 36-50                | 691  | 75 (69-81)  | 50 (46-55) | 42    | 81    | 58        | 0.208 |
| Age 51-65                | 420  | 87 (82-92)  | 47 (41-54) | 59    | 80    | 66        | 0.330 |
| **Abnormal Nerve Conduction** |     |              |             |       |       |           |       |
| Total Cohort             | 1,170 | 75 (72-78) | 62 (58-67) | 76    | 61    | 70        | 0.271 |
| Age 36-50                | 691  | 72 (68-77)  | 63 (57-68) | 74    | 61    | 68        | 0.350 |
| Age 51-65                | 420  | 81 (76-85)  | 57 (48-65) | 80    | 58    | 73        | 0.377 |
| **Confirmed Clinical Neuropathy** |     |              |             |       |       |           |       |
| Total Cohort             | 1,170 | 87 (84-91) | 51 (47-54) | 43    | 90    | 62        | 0.296 |
| Age 36-50                | 691  | 84 (78-89)  | 51 (46-55) | 37    | 90    | 59        | 0.241 |
| Age 51-65                | 420  | 93 (89-97)  | 47 (41-53) | 53    | 91    | 65        | 0.348 |

* N=7 subjects are missing a great toe measurement
† Positive predictive value; ‡ Negative predictive value
FIGURE LEGENDS

Figure 1. ROC curves for the accuracy of VPT testing at the great toe for predicting definite clinical neuropathy (Figure 1a), abnormal nerve conduction (Figure 1b) and confirmed clinical neuropathy (Figure 1c) in all subjects. The ROC curves shown in Figures 1d-1f are for the accuracy of VPT in predicting definite clinical neuropathy (1d), abnormal nerve conduction and confirmed clinical neuropathy among subjects age 35 to 50, while Figures 1g-1i show ROC curves for the accuracy of VPT testing at the great toe for predicting definite clinical neuropathy (1g), abnormal nerve conduction (1h) and confirmed clinical neuropathy (1i) for subjects age 51 to 65. For each ROC curve, the VPT value corresponding to each decile of 1-specificity are shown.

A.
B. 

Approximate area under curve = 0.763

C. 

Approximate area under curve = 0.800
D. Approximate area under curve = 0.705

E. Approximate area under curve = 0.748
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\[
\text{Approximate area under curve} = 0.764
\]

\[
\begin{align*}
\text{Sensitivity} & \quad 0.0 \quad 0.1 \quad 0.2 \quad 0.3 \quad 0.4 \quad 0.5 \quad 0.6 \quad 0.7 \quad 0.8 \quad 0.9 \quad 1.0 \\
\text{1-Specificity} & \quad 0 \quad 0.1 \quad 0.2 \quad 0.3 \quad 0.4 \quad 0.5 \quad 0.6 \quad 0.7 \quad 0.8 \quad 0.9 \quad 1.0
\end{align*}
\]

\[
\text{Approximate area under curve} = 0.780
\]

\[
\begin{align*}
\text{Sensitivity} & \quad 0.0 \quad 0.1 \quad 0.2 \quad 0.3 \quad 0.4 \quad 0.5 \quad 0.6 \quad 0.7 \quad 0.8 \quad 0.9 \quad 1.0 \\
\text{1-Specificity} & \quad 0 \quad 0.1 \quad 0.2 \quad 0.3 \quad 0.4 \quad 0.5 \quad 0.6 \quad 0.7 \quad 0.8 \quad 0.9 \quad 1.0
\end{align*}
\]
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H.

Approximate area under curve = 0.780

I.

Approximate area under curve = 0.830