Assessment of vibratory sensation with a tuning fork at different sites in Japanese patients with diabetes mellitus

Mitsuyoshi Takahara*, Yuko Fujiwara, Fumie Sakamoto, Naoto Katakami, Taka-aki Matsuoka, Hideaki Kaneto, Iichiro Shimomura

1Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, and 2Division of Nursing, Diabetic & Foot Care Center, Osaka University Hospital, Osaka, Japan

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*Correspondence
Mitsuyoshi Takahara
Tel: 81-6-6879-3743
Fax: 81-6-6879-3739
E-mail address: takahara@endmet.med.osaka-u.ac.jp

ABSTRACT
The current study compared the vibratory sensations at different sites, using a retrospective database of 547 Japanese diabetic patients. The vibratory sensation was assessed with a 128-Hz tuning fork at the medial malleolus, the great toe, and the fifth toe. The vibratory sensations at different sites were significantly associated with one another (all \( P < 0.01 \)). The vibratory sensation at one site corresponding to 10 s at another site was calculated to be 9–11 s. Although the vibratory sensations at the three sites had different associations with the pressure sensation and the ankle reflex, they showed similar C-statistics for the impaired pressure sensation and the disappeared ankle reflex. In conclusion, the vibratory sensations at different sites were strongly associated with one another. They would be clinically acceptable alternatives to one another in the assessment of diabetic peripheral neuropathy.

INTRODUCTION
Peripheral neuropathy is a major complication of diabetes mellitus. It is not only associated with unpleasant symptoms, which impairs quality of life, but is also associated with diabetic foot, resulting in tissue loss and amputation. Its periodic assessment is clinically important in the management of diabetes mellitus.

In clinical practice, diabetic peripheral neuropathy is evaluated by the combination of several examinations, including the assessment of vibratory sensation. In Japan, vibratory sensation in diabetic patients is often assessed with a 128-Hz tuning fork at the medial malleolus, whereas it is often assessed at the great toe overseas. However, to date, few data are available about the association between the test at the medial malleolus and at the great toe in Japanese diabetic patients, which has made it difficult to compare the reports from Japan and those from overseas about vibratory sensation.

In addition, some diabetic patients will suffer from foot lesions at the very site where it is generally recommended to carry out the neurological assessment. It would be of clinical use if the assessment at some alternative sites was clinically validated.

The aim of the current study was to compare the vibratory sensations assessed by a 128-Hz tuning fork at different sites in Japanese diabetic patients.

MATERIALS AND METHODS
Study Population and Definitions
We used a retrospective clinical database of 547 Japanese patients with diabetes mellitus who had their peripheral neurological findings assessed between 2004 and 2012. The study was in accordance with Ethical Guidelines for Epidemiological Research in Japan, and was approved by the human ethics committee of Osaka University. The vibratory sensation, the Achilles tendon reflex and the pressure sensation were assessed by one certified diabetes educator. The vibratory sensation was evaluated by a 128-Hz tuning fork at the medial malleolus, the great toe and the fifth toe, as follows. The examiner stroked the end of a 128-Hz tuning fork hard enough that the sides touched, and immediately placed the vibrating tuning fork firmly on the bony prominence of the site of interest. At the same time, the examiner began counting the seconds. The patient was instructed to tell the examiner when the patient felt...
the vibration stop. The examiner recorded the time (seconds) for which the patient could perceive the vibration. The examination was repeated three times per site, and the vibratory sensation at a site was evaluated by the mean value of the three records at the site. Note that before the examinations, the examiner applied the vibrating tuning fork on the patient’s wrist, to make sure that the patient could recognize the vibration.

The pressure sensation was assessed by the Semmes Weinstein 4.31 monofilament at the planter aspects of the great toe, the first metatarsal and the fifth metatarsal. The impaired pressure sensation was determined when the patient could not perceive the applied pressure at one or more of the three sites.

The database was consecutively constructed, excluding the cases with data missing, as well as duplicative cases. We also excluded from the current analysis the patients with considerable bilateral difference in vibratory sensations (≥5 s), because the bilateral difference indicated the possibility that some neurological disorders other than diabetic peripheral neuropathy would exist. We used the neurological findings in the right lower extremity as their representative values in every patient.

**Statistical Analysis**

The differences in continuous variables and dichotomous variables between the patients with and without diabetic peripheral neuropathy were assessed by the unpaired t-test and the Fisher’s exact test, respectively. Note that the presence of diabetic peripheral neuropathy was judged according to the criteria proposed by Diagnostic Neuropathy Study Group in Japan8. The association of the vibratory sensation at one site with that at another site was assessed by calculating the Pearson’s correlation coefficient, the intraclass correlation coefficient, the corresponding value based on the univariate linear regression analysis and the C-statistic.

We also investigated whether the vibratory sensations at different sites had any different impacts on other neurological findings. We carried out the trivariate logistic regression analysis whose dependent variable was either impaired pressure sensation or disappeared ankle reflex, and whose explanatory variables were the vibratory sensations at the three sites. Furthermore, we assessed the C-statistic of the vibratory sensation at each site for other neurological findings.

Data are given as means and standard deviation for continuous variables or as percentages for dichotomous variables. Hemoglobin A1c levels were converted to a National Glycohemoglobin Standardization Program equivalent value with the conversion equation reported by the Japan Diabetes Society.12 A P-value < 0.05 was considered to be significant and 95% confidence intervals (CI) were given when required. All statistical analyses were carried out using IBM SPSS Statistics Version 19 (SPSS Inc., Chicago, IL, USA).

**Table 1 | Characteristics of patients with and without peripheral neuropathy**

| Characteristics | Patients without neuropathy (n = 251) | Patients with neuropathy (n = 296) | P-value |
|-----------------|--------------------------------------|-----------------------------------|---------|
| Males           | 156 (62%)                            | 172 (58%)                         | 0.38    |
| Age (years)     | 62±13                                | 66±10                             | <0.01   |
| Body mass index (kg/m²) | 23.9±4.0                         | 23.8±4.1                          | 0.66    |
| Type 1 diabetes mellitus | 33 (13%)                          | 20 (7%)                           | 0.01    |
| Diabetic duration | 14±10                                | 19±12                             | <0.01   |
| Hemoglobin A1c (%) | 7.3±1.0                               | 7.5±1.4                           | 0.08    |
| Insulin use     | 99 (39%)                             | 155 (52%)                         | <0.01   |
| Vibratory sensation (s) |                                   |                                   |         |
| Medial malleolus | 12±3                                 | 8±3                               | <0.01   |
| Great toe       | 11±3                                 | 7±4                               | <0.01   |
| Fifth toe       | 11±3                                 | 7±4                               | <0.01   |
| Disappeared ankle reflex | 10 (4%)                            | 118 (40%)                         | <0.01   |
| Impaired pressure sensation | 9 (4%)                             | 89 (30%)                          | <0.01   |
| Diabetic retinopathy | 61 (24%)                            | 141 (48%)                         | <0.01   |
| Diabetic nephropathy | 60 (24%)                            | 126 (43%)                         | <0.01   |
| Hypertension    | 127 (51%)                            | 180 (61%)                         | 0.02    |
| Dyslipidemia    | 122 (49%)                            | 135 (46%)                         | 0.49    |
| Cardiovascular disease | 46 (18%)                           | 97 (33%)                          | <0.01   |

Data are mean ± standard deviation or n (%).

**Table 2 | Associations among the vibratory sensations assessed at three different sites**

| Correlation coefficient r | Medial malleolus | Great toe | Fifth toe |
|---------------------------|------------------|-----------|-----------|
|                           | n = 120 (n = 120)| n = 120   | n = 120   |
|                           | v = 0.78 (0.75, 0.81) | v = 0.75 (0.71, 0.78) | v = 0.75 (0.71, 0.78) |
|                           | v = 0.78 (0.75, 0.81) | v = 0.75 (0.71, 0.78) | v = 0.78 (0.77, 0.84) |
| Intraclass correlation coefficient | n = 120 | n = 120 | n = 120 |
| Medial malleolus | v = 0.78 (0.75, 0.81) | v = 0.75 (0.71, 0.78) | v = 0.78 (0.78, 0.84) |
| Great toe | v = 0.78 (0.75, 0.81) | v = 0.75 (0.71, 0.78) | v = 0.78 (0.78, 0.84) |
| Fifth toe | v = 0.73 (0.69, 0.77) | v = 0.78 (0.78, 0.84) | v = 0.78 (0.78, 0.84) |

| Corresponding value to 10 s at medial malleolus | n = 120 | n = 120 | n = 120 |
|-----------------------------------------------|--------|--------|--------|
| Medial malleolus | v = 9.3 (9.1, 9.5) | v = 9.1 (8.8, 9.3) | v = 9.1 (8.8, 9.3) |
| Great toe | v = 10.5 (10.3, 10.7) | v = 9.7 (9.5, 9.9) | v = 9.7 (9.5, 9.9) |
| Fifth toe | v = 10.6 (10.4, 10.8) | v = 10.0 (9.8, 10.2) | v = 10.0 (9.8, 10.2) |

| C-statistic for predicting | Medial malleolus | Great toe | Fifth toe |
|---------------------------|------------------|-----------|-----------|
| v < 0.05 at medial malleolus | v = 0.88 (0.85, 0.91) | v = 0.86 (0.83, 0.89) | v = 0.86 (0.83, 0.89) |
| v < 0.05 at great toe | v = 0.90 (0.87, 0.92) | v = 0.89 (0.86, 0.92) | v = 0.89 (0.86, 0.92) |
| v < 0.05 at fifth toe | v = 0.86 (0.83, 0.89) | v = 0.89 (0.86, 0.92) | v = 0.89 (0.86, 0.92) |
| Impaired pressure sensation | v = 0.80 (0.75, 0.85) | v = 0.84 (0.80, 0.88) | v = 0.82 (0.77, 0.87) |
| Disappeared ankle reflex | v = 0.75 (0.70, 0.79) | v = 0.74 (0.69, 0.79) | v = 0.73 (0.68, 0.78) |

Data are shown with 95% confidence intervals. Corresponding values were obtained from univariate linear regression models.
RESULTS

The patients were aged 64 ± 12 years and 328 (60%) were male. Diabetic duration was 17 ± 11 years and hemoglobin A1c levels were 7.4 ± 1.2%. Table 1 shows the characteristics of those with and without diabetic peripheral neuropathy.

Table 2 and Figure 1 show the association among the vibratory sensations at different sites. They were significantly correlated with one another (all \( P < 0.01 \)). The vibratory sensation at one site corresponding to 10 s at another site was calculated to be from 9 to 11 s. The C-statistics for the vibratory sensation <10 s at another site ranged from 0.86 to 0.90.

Table 3 shows the association of the vibratory sensations with other neurological findings. In logistic regression models, the vibratory sensations at the great toe and the fifth toe were independently associated with impaired pressure sensation (both \( P < 0.01 \)), but not with disappeared ankle reflex (both \( P > 0.05 \)). In contrast, that at the medial malleolus was associated with disappeared ankle reflex (\( P = 0.01 \)). Nevertheless, as shown in Table 2, the vibratory sensations at different sites demonstrated similar C-statistics for predicting the impaired pressure sensation and the disappeared ankle reflex.

DISCUSSION

The current study investigated the vibratory sensations at the medial malleolus, the great toe and the fifth toe in Japanese diabetic patients, suggesting that they are strongly associated with one another, as shown in Table 2. In contrast, they had some different associations with other neurological findings (Table 3). One possible explanation of these findings could be the closeness in distance of the sites where neurological findings were assessed. Indeed, the vibratory sensations at the toes had significantly independent associations with the pressure sensation, assessed at the toe and metatarsal. In contrast, the vibratory sensation at the medial malleolus was associated with the ankle reflex. Nevertheless, interestingly, the predictive performances of respective vibratory sensations for neurological findings were almost the same (Table 2). These findings indicate that, despite their independent associations with other neuro-
logical findings, the vibratory sensations at different sites would clinically complement one another, as to assessing peripheral neuropathy.

The current study had some limitations. First, this was a single-center study. However, the current single-center design enabled the neurological evaluation of the entire study population by one examiner, which could minimize measurement error. Second, we constructed the database in a retrospective manner, which might cause some selection biases. Future studies will be required to validate the current findings.

In conclusion, the vibratory sensations at the medial malleolus, the great toe and the fifth toe were strongly associated with one another in Japanese diabetic patients. They would be clinically acceptable alternatives to one another in the assessment of diabetic peripheral neuropathy.

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REFERENCES
1. Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333: 89–94.
2. Adler AI, Boyko EJ, Ahroni JH, et al. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. Diabetes Care 1997; 20: 1162–1167.
3. Forrest KY, Maser RE, Pambianco G, et al. Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes 1997; 46: 665–670.
4. Bakker K, Apekvist J, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012; 28(Suppl 1): 225–231.
5. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008; 31: 1679–1685.
6. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956–962.
7. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013; 36(Suppl 1): S11–S66.
8. Yasuda H, Sanada M, Kitada K, et al. Rationale and usefulness of newly devised abbreviated diagnostic criteria and staging for diabetic polyneuropathy. Diabetes Res Clin Pract 2007; 77(Suppl 1): S178–S183.
9. Jin Y, Kanamori A, Ito S, et al. Cross-sectional survey of diabetic neuropathy in Kanagawa and clinical significance of a touch test using tissue paper. J Diabetes Invest 2012; 3: 252–258.
10. Alport AR, Sander HW. Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. Continuum (Minneap Minn) 2012; 18: 13–38.
11. Cherry C, Wesselingh S, Lal L, et al. Evaluation of a clinical screening tool for HIV-associated sensory neuropathies. Neurology 2005; 65: 1778–1781.
12. Kashiwagi A, Kasuga M, Araki E, et al. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest 2012; 3: 39–40.