Cross-sectional survey of diabetic neuropathy in Kanagawa and clinical significance of a touch test using tissue paper

Yasuyuki Jin1, Akira Kanamori1, Shogo Ito1, Kiyokazu Matoba1, Masaaki Miyakawa1, Hideaki Kaneshige1, Mitsuo Obana1, Mashiko Takai1, Hiroshi Takeda1, Hideo Machimura1, Nobuaki Minami1, Takahiro Kawata1, Shin Honda1, Sachio Aoyagi1, Hikaru Amemiya1, Nobuo Sasaki1, Michio Nakayama1, Yoshikazu Naka1, Yasuo Terauchi2, Ikuro Matsuba1*

ABSTRACT
Aims/Introduction: The prevalence of diabetes mellitus is increasing rapidly in Japan, and diabetic neuropathy is a major factor decreasing diabetic patients’ quality of life, as well as a risk factor for sudden death. The present study aimed to determine the prevalence of diabetic neuropathy and raise awareness about it among patients and their physicians.

Materials and Methods: Diabetic outpatients (N = 5077) at 249 medical institutions within Kanagawa Prefecture, Japan, were surveyed by questionnaire and underwent foot examinations. The questionnaire included 10 questions about sensory abnormalities of both feet, muscle cramps and autonomic symptoms. Foot examinations included testing for vibratory perception of the medial malleolus, Achilles tendon reflexes and touch sensation of the bottom of the great toe using tissue paper.

Results: Of the 5077 patients surveyed, 70.4% reported symptoms. Overall, 75.4% of the patients underwent vibratory perception testing, of whom 44.9% had abnormal thresholds (≤10 s). On the tissue paper touch test, performed in 94.6% of patients, 11.9% had no touch sensation. Of the 2803 type 2 diabetic patients with known background factors who underwent foot examinations, 49.4% had diabetic neuropathy. There was a high prevalence of diabetic neuropathy (36.1%) in patients with <5-year history. Of the patients with no touch sensation on the tissue paper test, 81.3% had diabetic neuropathy.

Conclusions: The present study identified the prevalence of diabetic neuropathy in Kanagawa Prefecture. The tissue paper test is a simple and excellent method of evaluating decreased superficial sensation that can help evaluate the severity of diabetic neuropathy.

(J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00174.x, 2012)

KEY WORDS: Diabetic neuropathies, Diagnosis, Epidemiology

INTRODUCTION
According to a National Health and Nutrition Survey conducted in 20077, the number of persons strongly suspected of having diabetes, compared to a Diabetes Survey conducted 10 years earlier in 19972, increased by 2 million to about 8.9 million, and when persons in whom the possibility of diabetes could not be ruled out were also included, the number increased by 8.4 million, to about 22.1 million3. Recognizing the need to deal aggressively with this dramatic increase in diabetes, the Kanagawa Physicians Association established a Diabetes Committee in 2000, began educational activities for healthcare professionals and patients, and initiated survey research on diabetes. The aim of the present study was to investigate the prevalence of diabetic neuropathy (DN) and raise awareness about DN among patients and their physicians. This survey on DN was conducted independently by the Diabetes Committee of the Kanagawa Physicians Association.

Leg numbness and pain due to DN markedly decrease patient QOL4. As peripheral neuropathy progresses, this numbness and pain is lost, hypoesthesia (diminished sensation) develops, and the risk of diabetic foot lesions increases. If autonomic neuropathy progresses, not only is QOL diminished, but this becomes a risk factor for sudden death4–6. To prevent decreased QOL due to DN, and to prevent development of diabetic foot lesions and sudden death, DN must be diagnosed at a mild stage and treated appropriately7,8. The diagnosis of DN requires comprehensive evaluation, which besides a patient’s subjective symptoms, includes objective tests such as Achilles tendon reflexes, vibration perception thresholds and peripheral nerve conduction. Testing of Achilles tendon reflexes is convenient, useful, and performed on a relatively widespread basis, but testing of vibratory perception using a tuning fork is not widely performed. In addition, besides vibratory perception, testing of touch,
pressure, temperature, and pain sensation is not usually routinely performed in clinical practice.

Therefore, in this study, in addition to the Achilles tendon reflex and vibratory perception, which have been traditionally used in the clinical diagnosis of DN, a simple touch test using tissue paper was also performed, and its significance and usefulness in diagnosing DN were examined.

MATERIALS AND METHODS

Subjects

This study was conducted between September 2004 and May 2006 and involved 5077 diabetic outpatients at 249 clinics and hospitals in Kanagawa Prefecture, Japan. The present study was carried out in accordance with the Declaration of Helsinki and its amendments. The Ethics Committee of the Kanagawa Physicians Association gave its approval for the study. The subjects’ written, informed consent was not required by the approved protocol; subjects gave their oral consent before any procedures were undertaken.

Methods

Before undertaking this study, we conducted more than 20 lectures in order to control and standardize the testing procedures and maintain the quality of this prefecture-wide study. After attending these lectures, participating physicians were supplied with photographs and DVDs of the procedures for conducting the tissue paper test and measuring Achilles tendon reflexes and vibration perception.

A questionnaire survey of subjective symptoms and examination of the feet were performed. The questionnaire about subjective symptoms included a total of 10 questions about sensory abnormalities of both feet (tips and soles) (numbness/tingling, pain, cold sensation, hypoesthesia, dysesthesia, paresthesia), muscle cramps, and autonomic symptoms (dizziness, gastrointestinal symptoms, sudomotor dysfunction). Each question had four potential responses: ‘none,’ ‘mild,’ ‘moderate,’ or ‘severe’ (see Supporting Information).

Examination of the feet included vibratory perception of the medial malleolus using a C128 tuning fork, Achilles tendon reflexes while assuming a tall kneeling position, and touch sensation of the bottom of the great toe using tissue paper.

For vibratory perception of the medial malleolus using a C128 tuning fork, the results were considered abnormal if the time after application of the tuning fork until vibration was no longer felt was ≤10 s. If the Achilles tendon reflex was decreased or absent, the results were considered abnormal.

The tissue paper test was performed according to the method of Kurita et al.7,9. In brief, a single tissue was folded twice lengthwise. Holding the center, the paper tip was used to lightly touch the bottom of the great toe. Instructions about the test procedure, including photographs, were provided. The results were reported in three categories: ‘usual sensation (normal),’ ‘slight sensation (diminished),’ and ‘no sensation (loss of touch sensation).’

A total of 2803 type 2 diabetic patients who answered the questionnaire about subjective symptoms, were examined for vibratory perception of the medial malleolus using a C128 tuning fork, Achilles tendon reflexes, and the tissue paper test. The background factors of these patients such as sex, age, and duration of disease were known. The presence or absence of DN was judged based on the ‘Abbreviated Diagnostic Criteria for Diabetic Polyneuropathy,’ proposed by the Diabetic Neuropathy Study Group in Japan.10 This was compared with patient profiles and clinical features.

Specifically, DN was diagnosed if any two of the following three criteria were met: on the questionnaire for subjective symptoms, there was a sensory abnormality, other than cold sensation, of both feet (numbness/tingling, pain, hypoesthesia, paresthesia, dysesthesia); bilateral Achilles tendon reflexes were decreased or absent; and vibratory perception of the medial malleolus using a C128 tuning fork was ≤10 s.

The results are shown as mean ± standard deviation. Statistical analysis was performed using the chi-square test or the Mann–Whitney U test. The level of significance was <5%. HbA1c is expressed by National Glycohemoglobin Standardization Program (NGSP) units.

RESULTS

Patient Profiles

Table 1 shows the patient profiles. There were 145 patients (2.9%) with type 1 diabetes, 4182 (82.4%) with type 2 diabetes, and 750 (14.8%) with type unknown (14.8%). Thus, the majority of patients had type 2 diabetes. There were 2721 males (53.6%) and 2302 females (45.3%). The mean age was 64 ± 12 years, and the duration of diabetes was 10 ± 8 years. The mean BMI was 24.2 ± 3.9 kg/m², including 1842 (36.3%) overweight or obese patients with a BMI ≥25 kg/m². The mean HbA1c was 7.8% ± 1.5% in NGSP units. Treatment for diabetes included diet and exercise therapy alone in 915 patients (18.0%), an oral hypoglycemic agent in 3300 (65.0%), and insulin in 862 (17.0%). In addition, 852 patients (16.8%) were receiving medication for neuropathy.

Subjective Symptoms

The questionnaire regarding subjective symptoms (Table 2) was completed by all 5077 patients. Of the seven questions about sensory abnormalities, the most frequent response was cold sensation (33.8% of patients). This was followed by numbness/tingling (26.2%) and hypoesthesia (17.8%), which were also relatively frequent.

Of the 10 specific questions regarding DN, the most frequent response was for muscle cramps in 40.7% of patients. For the three questions about autonomic neuropathy, the responses were dizziness/light-headedness in 27.6%, gastrointestinal disturbances in 31.9%, and sudomotor dysfunction in 20.8%. The prevalence of each was higher than that of hypoesthesia.
Examination of Feet

Vibratory perception of the medial malleolus

Vibratory perception of the medial malleolus (Table 2) was evaluated in 3826 patients (75.4%). Of the patients who had vibratory perception testing, 70.4% had abnormal results (≤10 s). Although not shown in Table 2, when ≤9 s was defined as abnormal, 56.5% had abnormal results.

Achilles tendon reflexes

Achilles tendon reflexes were evaluated in 5001 patients (98.5%). The results were bilaterally normal in 48.2%, unilaterally abnormal in 6.9%, and bilaterally abnormal in 44.9%.

Table 1 | Patient profiles.

|                        | n  | (%)  |
|------------------------|----|------|
| Total                  | 5077 |     |
| Type of diabetes       |    |      |
| Type 1                 | 145  | (2.9) |
| Type 2                 | 4182 | (82.4) |
| Unknown                | 750  | (14.8) |
| Sex                    |    |      |
| Male                   | 2721 | (53.6) |
| Female                 | 2302 | (45.3) |
| Unknown                | 54  | (1.1) |
| Age (years)            |    |      |
| 64 ± 12                | 54  | (1.1) |
| Duration of diabetes (years) | |      |
| 10 ± 8                 | 504  | (9.9) |
| Unknown                |    |      |
| BMI (kg/m²)            |    |      |
| ≥25                    | 1842 | (36.3) |
| <25                    | 3149 | (62.0) |
| Unknown                | 86  | (1.7) |
| HbA1c (%: NGSP)        |    |      |
| 7.8 ± 1.5              | 142  | (2.8) |
| Unknown                |    |      |
| Treatment of diabetes  |    |      |
| Diet and exercise therapy | 915  | (18.0) |
| Oral Hypoglycemic agent | 3300 | (65.0) |
| Insulin                | 862  | (17.0) |
| Medication for neuropathy |    |      |
| +                      | 852  | (16.8) |
| −                      | 4225 | (83.2) |
| Epalrestat             | 445  | (8.8) |
| Mecobalamin            | 391  | (7.7) |
| Mexiletine hydrochloride | 80   | (1.6) |
| Goshajink-gan          | 35   | (0.7) |
| NSAIDS                 | 33   | (0.6) |
| Others                 | 76   | (1.5) |

Data (age, duration of diabetes, BMI, HbA1c) are expressed as mean ± SD.

Tissue paper test

The tissue paper test was performed in 4805 patients (94.6%). The results were normal in 68.6%, diminished in 19.5%, and loss of touch sensation in 11.9%.

Diagnosis of Diabetic Neuropathy Based on the ‘Abbreviated Diagnostic Criteria for Diabetic Polyneuropathy’ and Comparison with Patient Clinical Features

Diagnosis of diabetic neuropathy based on the ‘Abbreviated Diagnostic Criteria for Diabetic Polyneuropathy’

The presence or absence of DN was judged in 2803 type 2 diabetic patients who answered the questionnaire about subjective symptoms. The patients were examined for vibratory perception of the medial malleolus using a C128 tuning fork, Achilles tendon reflexes, and the tissue paper test, and their patient profiles (sex, age, duration of diabetes, BMI, HbA1c) were known. Overall, 1384 patients (49.4%) were diagnosed with DN. Of these patients, 519 patients (37.5% of patients diagnosed with DN and 18.5% of all patients), had asymptomatic DN, without any sensory abnormalities (other than cold sensation) of both feet.

Comparison of two groups based on presence or absence of diabetic neuropathy

Table 3 compares the clinical profiles of the two groups based on the presence or absence of DN. There were no significant differences with respect to diabetes type, sex, BMI, or obesity. Patients with DN were significantly older, had longer duration of diabetes, and higher HbA1c levels. Regarding diabetes treatment, in the DN group, few patients were being treated with diet and exercise therapy alone, whereas many were receiving insulin. Medication for neuropathy, including aldose reductase inhibitors and vitamin B12, was being taken by 26.8% in the DN group, but only 7.0% in the non-DN group. Thus, prescription of medication for neuropathy was significantly more common in the DN group.

On the tissue paper test, in the DN group, 29.5% had diminished sensation, and 19.8% had loss of touch sensation. Compared to the non-DN group, diminished or loss of touch sensation was significantly more frequent.

Prevalence of diabetic neuropathy by age, duration of diabetes, and HbA1c

The prevalence of DN increased with age (Table 4), reaching 58.3% in patients ≥70 years old. The prevalence of DN was high (36.2%) even in patients with diabetes <5 years, increased with longer duration of diabetes, and reached 66.8% in patients with diabetes for ≥20 years. The prevalence of DN was 41.1% with an HbA1c ≤6.0%, increased with a higher HbA1c, and reached 58.8% with an HbA1c ≥9.0%.

Diagnostic Efficiency of the Tissue Paper Test for DN

The diagnostic efficiency for DN of the tissue paper test was evaluated, with ‘loss of touch sensation’ defined as a positive test.
The sensitivity was 19.8%, the specificity was 95.6%, the positive predictive value was 81.3%, and the negative predictive value was 55.0%.

**DISCUSSION**

In this study, completed questionnaires about subjective symptoms were received from a large number of patients. Obtaining information about subjective symptoms related to DN using an interview sheet did not require much time or effort, and patient cooperation was easily obtained. This may be a useful method to diagnose DN and provide education about DN.

The questionnaire included seven subjective symptoms suggesting peripheral neuropathy, muscle cramps, and three subjective symptoms suggesting autonomic neuropathy. Muscle cramps and cold sensation were relatively frequent, and although they suggest the possibility of DN at an early stage, these symptoms are also frequent in other disorders, including intervertebral disc herniation and arteriosclerosis obliterans. To diagnose DN, a more thorough examination of objective findings is necessary.

The frequency of six subjective symptoms, excluding cold sensation, that suggest peripheral neuropathy ranged from 8.0% to 26.2%, which was lower than other objective findings. Based on these subjective symptoms alone, early diagnosis of DN would be difficult. Moreover, 37.5% of the patients who were diagnosed with DN based on the ‘Abbreviated Diagnostic Criteria for Diabetic Polyneuropathy’ had asymptomatic DN without any subjective symptoms that suggested peripheral neuropathy. Therefore, to properly diagnose DN, in addition to a history of subjective symptoms, comprehensive evaluation of various objective findings is required.

Based on the ‘Abbreviated Diagnostic Criteria for Diabetic Polyneuropathy’, 49.4% of the present patients were diagnosed with DN. In a report by the Japan Promotion Council for Diabetes Prevention, based on the same diagnostic criteria used in the present study, of 67,114 patients, 47.1% were diagnosed with DN, a prevalence rate similar to that in the present study. On the other hand, in a study of 15,000 patients by the Tohoku Diabetic Complication Forum Project, although diagnostic criteria similar to those of the present study were used, abnormal vibratory perception was defined as $<9$ s, instead of $<10$ s, and 35.8% of patients were diagnosed with DN. In the present study, when abnormal vibratory perception was defined as $<9$ s, the prevalence of patients diagnosed with DN decreased

| Table 2 | Frequency of subjective symptoms and abnormal findings on neurological examinations |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Subjective symptoms of the feet | Mild | Moderate | Severe | Total |
| $n = 5077$ | | | | |
| Symptom of sensory nervous system | | | | |
| Numbness/Tingling | 935 (18.4) | 327 (6.4) | 69 (1.4) | 1331 (26.2) |
| Pain | 308 (6.1) | 88 (1.7) | 18 (0.4) | 414 (8.2) |
| Cold | 1202 (23.7) | 413 (8.1) | 103 (2.0) | 1718 (33.8) |
| Hypoesthesia | 637 (12.5) | 206 (4.1) | 59 (1.2) | 902 (17.8) |
| Paresthesia | 318 (6.3) | 110 (2.2) | 37 (0.7) | 465 (9.2) |
| Dysesthesia | 309 (6.1) | 80 (1.6) | 18 (0.4) | 407 (8.0) |
| Symptom of motor nervous system | | | | |
| Muscle cramps | 1652 (32.5) | 346 (6.8) | 68 (1.3) | 2066 (40.7) |
| Symptom of autonomic nervous system | | | | |
| Dizziness and orthostatic hypotension | 1190 (23.4) | 177 (3.5) | 33 (0.6) | 1400 (27.6) |
| Gastrointestinal symptoms | 1206 (23.8) | 332 (6.5) | 82 (1.6) | 1620 (31.9) |
| Sudomotor dysfunction | 735 (14.5) | 255 (5.0) | 66 (1.3) | 1056 (20.8) |
| Vibration perception of medial malleolus | Normal | Abnormal (< 10 s) |
| $n = 3826$ | | | | |
| Achilles tendon reflex | Normal | Abnormal unilateral | Abnormal bilateral |
| $n = 5001$ | | | | |
| Light touch sensation of the great toe | Normal | Diminished | Loss |
| $n = 4805$ | | | | |

Data are numbers of patients and percentage in parentheses.

© 2011 Asian Association for the Study of Diabetes and Blackwell Publishing Asia Pty Ltd
to 45.3%, but this was still slightly higher than the previous report (35.6%)\textsuperscript{12}.

In the Tohoku study\textsuperscript{12}, age (64.2 ± 11.9 years), BMI (24.4 ± 4.2 kg/m\textsuperscript{2}), duration of diabetes (9.7 ± 7.7 years), and HbA1c (7.8% ± 2.5%) did not differ greatly from our study. However, in the present study, the prevalence of DM was examined in a population limited to type 2 diabetic patients in whom subjective symptoms, vibratory perception, Achilles tendon reflex, tissue paper test results, and patient profiles (sex, age, duration of diabetes, BMI, and HbA1c) were all known. Therefore, many patients with severe neuropathy may have been included.

Meanwhile, in a study of DN by the Japan Physicians Association Research Group\textsuperscript{13}, of 12,821 patients with diabetes, 36.7% were diagnosed with DN based on evaluation by their attending physician without any specific criteria. Based on diagnostic criteria using a scoring method established by the Japan Physicians Association Research Group\textsuperscript{13}, 28.2% of all patients were diagnosed with DN, including 32.2% of type 1 diabetic patients and 27.9% of type 2 diabetic patients. Because of differences in diagnostic criteria, a direct comparison cannot be made, but with regard to the prevalence of DN based on duration of diabetes, an already high rate of 15% in type 2 diabetes with <1-year duration and up to 62% in type 2 diabetes with ≥30-year duration have been reported\textsuperscript{11}. Thus, as in the present study, a high prevalence of DN, compared to other complications, was demonstrated early in the disease history, with a marked increase in prevalence as the duration of the disease increased.

In the present study, 35% of the patients were ≥70 years old. In older persons, taking into account decreased vibratory perception with aging, vibration abnormalities should be assessed. However, because evaluation criteria by age group do not exist, in this study, vibratory perception of the medial malleolus for ≤10 s was uniformly considered abnormal. This is probably the main reason for the high rate of vibration abnormalities. If we limit the cases to the 1816 patients <70 years of age, 51.9% had abnormal vibration perception, 42.1% had abnormal Achilles tendon reflexes, and the prevalence of neuropathy decreased to 44.5%.

Simple touch tests performed at the bedside have included use of a brush or absorbent cotton, but the tissue paper test is also a touch test, which, like others, is convenient and can be easily performed by anyone. In the present study, like the Achilles tendon reflexes, this test was performed in ≥90% of patients.

### Table 3 | Patient profiles of the two groups

|                     | Diabetic neuropathy | P      |
|---------------------|---------------------|--------|
|                     | +                   | -      |
| 1384 (49.4)         | 1419 (50.6)         |
| Sex                 |                     |        |
| Male                | 748 (54.0)          | 757 (53.3) | ns* |
| Female              | 636 (46.0)          | 662 (46.7) |
| Age (years)         | 67 ± 11             | 62 ± 12 | 0.0001† |
| Duration of diabetes (years) | 12.2 ± 8.5   | 8.8 ± 7.4 | 0.0001† |
| BMI (kg/m\textsuperscript{2}) | 24.0 ± 3.7      | 24.2 ± 3.9 | ns†  |
| ≥23                 | 789 (57.0)          | 836 (58.9) | ns* |
| ≤23                 | 579 (41.8)          | 578 (40.7) |
| HbA1c (NGSP)        | 7.9 ± 1.5           | 7.6 ± 1.4 | 0.0001† |
| Treatment of diabetes |                    |        |
| Diet and exercise therapy | 167 (12.1)   | 344 (24.2) | <0.0001* |
| Oral hypoglycemic agent | 957 (69.1)       | 944 (66.5) |
| Insulin             | 264 (19.1)          | 131 (9.2) |
| Medication for neuropathy |                  |        |
| +                   | 371 (26.8)          | 99 (7.0) | <0.0001* |
| −                   | 1013 (73.2)         | 1320 (93.0) |
| Epalrestat          | 206 (149)           | 37 (2.6) | <0.0001* |
| Mecobalamin         | 170 (12.3)          | 49 (3.5) | <0.0001* |
| Mexiletine hydrochloride | 44 (3.2)       | 4 (0.3) | <0.0001* |
| Goshajinki-gan      | 15 (1.1)            | 3 (0.2) | <0.005* |
| NSAIDS              | 7 (0.5)             | 9 (0.6) | ns* |
| Others              | 34 (2.5)            | 23 (1.6) | ns* |
| Light touch sensation of the great toe |        |        |
| Normal              | 702 (50.7)          | 1198 (84.4) | <0.0001† |
| Diminished          | 408 (29.5)          | 158 (11.1) |
| Loss                | 274 (19.8)          | 63 (4.4) |

Data are mean ± SD, or numbers of patients and percentage in parentheses. ns, not significant.
*Chi-square test.
†Mann–Whitney U test.

### Table 4 | Prevalence of diabetic neuropathy by age, diabetes duration and HbA1C

| Age (years) | <40 | 40–49 | 50–59 | 60–69 | ≥70 |
|-------------|-----|-------|-------|-------|-----|
| n           | 71  | 198   | 623   | 924   | 987 |
| Prevalence of diabetic neuropathy n (%) | 18 (25.4) | 68 (34.3) | 255 (40.9) | 468 (50.6) | 575 (58.3) |
| Duration of diabetes (years) | 5 | 5–9 | 10–14 | 15–19 | ≥20 |
| n           | 780 | 638   | 623   | 298   | 310 |
| Prevalence of diabetic neuropathy n (%) | 282 (36.2) | 285 (44.7) | 332 (53.3) | 175 (58.7) | 310 (66.8) |
| HbA1c (% NGSP) | <6.0 | 60–69 | 70–79 | 80–89 | ≥90 |
| n           | 355 | 1000  | 742   | 352   | 354 |
| Prevalence of diabetic neuropathy n (%) | 146 (41.1) | 454 (45.4) | 364 (49.1) | 212 (60.2) | 208 (56.8) |
a result that supports the convenience of testing. In clinical settings, use of a monofilament as a method to evaluate tactile pressure sensation is well known. In particular, consensus has been reached on using a 5.07 size monofilament applied at a pressure of 10 g as a tool for screening patients with severe sensory disturbances who are at high risk for foot lesions. In addition, the authors have previously reported that, with a 4.17 size monofilament applied at a pressure of 1 g, if there is absence of sensation, there is a high likelihood of mild to moderate sensory disturbance.

The tissue paper test, which evaluates tactile pressure sensation with a force of about 0.6 g, is a method of assessing even milder sensory disturbance than with a 4.17 size monofilament. In addition, the tissue paper test, compared to Achilles tendon reflexes, is reported to correlate more strongly with distal action potentials and may be able to detect even milder peripheral neuropathy. However, besides a very weak applied force, because tissue paper has little elasticity, and the applied force can easily vary, test accuracy may be limited.

The tissue paper test, if 'loss of touch sensation' is defined as a positive test, has a high positive predictive value for diagnosing DN. In other words, with the tissue paper test, if there is 'loss of touch sensation,' DN can be diagnosed at a high rate of 82.6%, making this a useful diagnostic test. However, since the negative predictive value is low, DN cannot be ruled out if testing is negative. Therefore, based on the tissue paper test alone, diagnosing DN is difficult. Comprehensive evaluation is necessary, including subjective symptoms, Achilles tendon reflexes, and vibratory perception.

In a touch test using a monofilament, reproducibility is higher than in touch tests using tissue paper, a brush, or cotton. Furthermore, semiquantitative evaluation is possible. However, many medical clinics do not have monofilaments, and widespread use would be too costly (although much cheaper than electrophysiologic test equipment). Tissue paper, however, is available or can easily be obtained by almost all clinics. Reproducibility may be inferior compared to a monofilament, but if we limit this to 2-ply tissue paper (almost all tissue paper in Japan is this type), then as a substitute corresponding to a monofilament with a mild pressure of 0.6–1.0 g, the touch test, even in routine outpatient settings, can be easily performed.

In actual clinical practice, DN must not only be diagnosed, but its severity must be assessed for proper treatment. As noted in the 'Stage Classification of Diabetic Polyneuropathy' by the Japanese Study Group of Diabetic Neuropathy, in order to assess severity, besides subjective symptoms, Achilles tendon reflexes, vibratory perception, superficial sensory disturbances, autonomic neuropathy, and motor disturbances must also be evaluated. The tissue paper test is a simple and excellent method of evaluating decreased superficial sensation, and it can help evaluate the severity of neuropathy.

In conclusion, the present study identified the prevalence of DN in Kanagawa Prefecture. In the future, the aggressive use of foot examinations, including questionnaires about subjective symptoms and the tissue paper test, should be promoted. This strategy aims at earlier diagnosis and prevention of more severe diabetic neuropathy.

ACKNOWLEDGEMENTS
The authors express their sincere appreciation to the physicians and medical staff at the 249 hospitals and clinics in Kanagawa Prefecture who cooperated in this study. This research was conducted by the Diabetes Committee of the Kanagawa Physicians Association and was not supported by external funding. There is no conflict of interest in all the authors listed.

REFERENCES
1. Ministry of Health, Labor and Welfare. Outline of the Results of the National Health and Nutrition Survey (extracts). Ministry of Health, Labor and Welfare, Tokyo, Japan, 2007. Available at http://www.mhlw.go.jp/houdou/2008/12/h1225-5.html. (accessed on 2011, October 11) (Japanese).
2. Ministry of Health, Labor and Welfare. 1997 National Diabetes Survey. Ministry of Health, Labor and Welfare, Tokyo, Japan, 1997. Available at http://www.mhlw.go.jp/toukei/kouhyo/indexkk_4_1.html. (accessed on 2011, October 11) (Japanese).
3. Morimoto A, Nishimura R, Tajima N. Trends in the epidemiology of patients with diabetes in Japan. Jpn Med Assoc J. 2010; 53: 36–40.
4. Van Acker K, Bouhassira D, De Bacquer D, et al. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. Diabetes Metab. 2009; 35: 206–213.
5. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med 1980; 49: 95–108.
6. O’Brien IA, McDuffion JP, Correll RM. The influence of autonomic neuropathy on mortality in insulin-dependent diabetics. Q J Med 1991; 79: 495–502.
7. Kunita A, Takagi S, Nakai N, et al. Clinical Utility of Sensory Symptoms, Neurological Examination, and Nerve Conduction Studies of the feet for early detection of diabetic polyneuropathy. J Japan Diabetes Soc 2007; 50: 473–478 (Japanese).
8. DCCT Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. Ann Intern Med 1995; 122: 561–568.
9. Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patients with non-insulin dependent diabetes. New Engl J Med 1995; 333: 39–84.
10. 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: S178–S183.
11. Japan Promotion Council for Diabetes Prevention and Countermeasures. Report on abnormalities in foot
appearance and diabetic neuropathy in diabetes patients in Japan. Japanese Medical Association, Tokyo, Japan, 2008. Available at http://dl.med.or.jp/dl-med/tounyoubyou/diabetes080312.pdf (last accessed on 2011, October 11) (Japanese).

12. Satoh J, Baba M, Yagihashi S, et al. Frequency of Diabetic Polyneuropathy (DPN) and Clinical Significance of Achilles Tendon Reflex in Diagnosis of DPN: survey of 15,000 Patients in Tohoku, Japan. J Japan Diabetes Soc 2007; 50: 799–806 (Japanese).

13. Japan Physicians Association Research Group. Study on Diabetic Neuropathy, 2nd report: diabetic Neuropathy. J Japan Physic Assoc 2001; 16: 353–381 (Japanese).

14. Rith-Najaran SJ, Stolusky T, Gohdes DM. Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria. Diabet Care 1992; 15: 1386–1389.

15. Jin Y, Kanamori A, Fujita Y. Use of Semmes-Weinstein monofilaments for evaluating the severity of diabetic neuropathy. J Japan Diabetes Soc 2001; 44: 209–216 (Japanese).

SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:

Data S1 | Questionnaire about symptoms of diabetic neuropathy.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.