Vibrotactile sense in median and ulnar nerve innervated fingers of men with type 2 diabetes and with normal and impaired glucose tolerance

Running title: Vibrotactile sense in hands and type 2 diabetes

LB Dahlin[1], S Thrainsdottir[2], R Cederlund[1], NOB Thomsen[1], KF Eriksson[3], I Rosén[4], T Speidel[5] and G Sundqvist[2]†

From the Departments of Clinical Sciences in Malmö ([1]Hand Surgery, [2]Diabetes epidemiology and neuropathy and [3]Angiology), Malmö University Hospital, Lund University, Malmö, and in Lund ([4]Neurophysiology) and [5]PID AB, Malmö

Corresponding author: Lars B. Dahlin, Department of Hand Surgery, Malmö University Hospital, SE-205 02 Malmö. Tel: +46 40 33 67 69. Fax: +46 40 92 88 55. E-mail: lars.dahlin@med.lu.se.

Word count: Abstract: 241 + main text 3208

Abstract

Aims To investigate vibrotactile sense [large fibre neuropathy] at different frequencies in index and little fingers [median and ulnar nerves, respectively] of subjects with diabetic, impaired and normal glucose tolerance.

Methods Vibration thresholds [tactilometry at seven frequencies (8, 16, 32, 64, 125, 250 and 500 Hz)] and median nerve function [electrophysiology] were examined in men (age 73.4 ± 0.12; n=58) with constant normal (NGT; n=28) and impaired glucose tolerance (IGT; n=7) or with type 2 DM (n=23) for >15 years.

Results HbA1c-values were increased and vibrotactile sense (sensibility index) was impaired in index and little fingers in men with type 2 DM. Vibration thresholds were particularly increased at 16, 250 and 500 Hz in the little finger (ulnar nerve). Type 2 DM subjects showed electrophysiological (gold standard) signs of neuropathy in the median nerve. Although subjects with constant IGT had higher HbA1c-values they had no deterioration of vibrotactile sense or electrophysiology. HbA1c did not correlate with vibrotactile sense or electrophysiology, but the latter two correlated with regard to Z-score (sign of neuropathy) in forearm (NGT) and at wrist level (NGT and DM).

Conclusions Vibration thresholds are increased in finger pulps of hands in type 2 DM subjects, particularly at specific frequencies in ulnar nerve innervated finger pulps. IGT does not to induce neuropathy. Tactilometry, with a multi-frequency approach, can be a sensitive technique to screen for large fibre neuropathy in type 2 DM. Frequency-related changes may mirror dysfunction of various receptors.

Key words vibrotactile sense, neuropathy, type 2 diabetes, median nerve, ulnar nerve

Abbreviations IGT, impaired glucose tolerance; DM, diabetes mellitus; FA, fast adapting receptors; SA, slowly adapting receptors; SI, sensibility index

Introduction

The tactile surface of finger pulps in humans is important for our ability to explore the environment needed for activity of daily living. The ability to feel vibration is reflected by function in large nerve fibres and delicate receptors located in finger pulps (1, 2). Fast adapting receptors (FA), like the Meissner's end organs (FA1; epidermal papillae) and Pacini end organs (FA2; subcutaneously), in contrast to slowly adapting receptors (SA), are sensitive to fast and repeated deformation of skin. Threshold tests, (usually only 125 Hz) as vibrometry, is used to detect disturbance of vibrotactile sense and assess large fibre neuropathy in legs and feet of diabetic patients (3-9). However, knowledge about occurrence and extent of neuropathy in arm and hand is crucial, particularly as related to function of individual nerve, in view of ulnar nerve affection in diabetic patients (10). Few studies have recorded vibratory perception in finger pulps (11) in contrast to several studies reporting vibration thresholds at non-tactile surfaces (8, 9, 12) in legs, feet and hands in patients with different age, a factor to be considered (12, 13).

Vibration exposed workers have impaired vibration perception, recorded at several frequencies (e.g. not only 125 Hz) thereby covering a larger spectrum of the receptors (14), due to structural changes in nerves. Thus, a multi-frequency approach may be a sensitive method (15) to detect large fibre neuropathy also in diabetes. Our aim was to analyse vibration thresholds at seven different frequencies (tactilometry), in accordance with audiometry, from the finger pulps of the index and little fingers [median and ulnar nerves function, respectively (14)] in defined groups of men with a constant condition of type 2 DM, impaired and normal glucose tolerance for around 15 years and all at a specific age.

Materials and Methods

Patients

The patients were men from representative subgroups of an original cohort of 6956 subjects, initially residents of Malmö, Sweden, that agreed to participate in a glucose tolerance test 1975-1979 (16), 1989-1991 (3) and 2003-2005 (17). Among the population 58 men (mean age ±SEM: 73.4 ± 0.12 years; groups not different) had a constant diagnosis between 1989-1991 and 2003-2005 (i.e. around 15 years) based on an oral glucose tolerance test (NGT= normal glucose tolerance, n=28; IGT=impaired glucose tolerance, n=7; and DM=diabetes mellitus, n=23) (17). Hand function and sensibility index (SI) have previously been described in a larger population of these subjects (17).

We particularly analysed vibration thresholds at different frequencies in the men with a constant diagnosis(>15 years). Blood samples were also taken [HbA1c, cobalamin, folate, homocysteine, thyroid function (plasma thyroid stimulating hormone (TSH) and free thyroxine) and C-peptide]. The study was approved by the human ethic committee of Lund University.

Tactilometry

Vibrotactile thresholds at seven different frequencies [8, 16, 32.5, 64, 125, 250 and 500 Hz; ascending order; similar to an audiogram] were measured by a tactilometer (14) (PID AB, Malmö, Sweden), in a room with stable temperature. Sinusoidal vibrations were delivered to the pulps of index and little fingers, reflecting function of median and ulnar nerves, respectively. The vibrating probe was applied to the pulp of the investigated finger. For each investigated frequency the patient controlled the vibration amplitude by pressing a hand switch. At the beginning the vibration amplitude was increased until the subject perceived the vibration. The subject pressed and held the switch while the vibration amplitude was decreased until the subject no longer perceived a vibration stimulus. This sequence was

repeated four times for each frequency while the vibration amplitude was increased or decreased at a constant rate of 3 dB/s (until the subject responded). The vibration perception threshold value was calculated as the arithmetic mean of the peak (ascending) and bottom (descending) thresholds for each frequency. The values of the levels were expressed in dB [relative 10^{-6} ms^{-2}; method referred to as a von Bekesy up/down psychophysical algorithm; ISO13091-1].

A tactilogram, resembling an audiogram, was obtained from each finger (Fig. 1). Data from each patient was stored [MS Access Database, propriety database client software, VSM, VibroSense Meter]. The tactilogram was graphically displayed on an inverted scale with low intensity (amplitude) at top and high intensity at bottom (Fig. 1). The vibration thresholds were higher at 64 and 500 Hz. A normal tactilogram has a form of a slope interrupted by peak at 125 and 250 Hz (Fig. 1a). In patients with impaired vibrotactile sense there was a change in shape of the curve where the highest frequencies were the first one to be affected (Fig. 1b). By recording the vibrotactile threshold at several frequencies each frequency can by analysed individually. Vibrotactile thresholds in the pulps of the index and little fingers of both hands were recorded. A sensibility index was calculated (see Strömberg et al (14)), where the area beneath the curve was divided by the area of the curve from a healthy reference population [index = 1 = normal function; index < 0.8 = pathological (14)]. Values of sensibility index of a larger population of the present subjects, although those subjects did not have a constant diagnosis as the present subjects, have been presented earlier and are included in the present data (17).

Electrophysiology

Conduction studies of the median nerve were performed on the right side as previously described (3). Variables were measured to examine signs of large fibre neuropathy in forearm [motor and sensory conduction velocity in forearm] and neuropathy at wrist level [i.e. signifying nerve compression; distal latency and sensory conduction velocity at wrist]. A Z score for each individual was calculated for a) motor conduction velocity in forearm, b) sensory conduction velocity in forearm, c) sensory conduction velocity at wrist and d) distal latency [i.e. c) and d) reflecting conduction over carpal tunnel] using the formula:

Z-score = individual value of subject – mean value of control group (NGT subjects) divided by standard deviation of mean value for control group.

The Z score for motor and sensory conduction velocity (compound Z score forearm) was added to reflect signs of large fibre neuropathy in forearm. The Z score for sensory conduction velocity at wrist and distal latency (compound Z score wrist; negative value during calculation of compound Z score for compensation) was also added.

Statistical analysis

Values from blood samples, vibration thresholds and electrophysiological data are expressed as median [IQR; interquatrile range]. The non-parametric one-way analysis of variance by ranks (Kruskal-Wallis) was used to compare the different categories of patients (NGT, IGT and DM). If $p<0.05$ specific complimentary analyses using Bonferroni correction or Mann Whitney were done (14). Correlations were done by Spearman correlation test ($r>0.3$ required and $p<0.05$).

Results

Values of blood samples and clinical symptoms

The HbA1c values differed between the type 2 DM and the other two groups (Table 1). Values of cobalamin, folate, homocysteine, thyroid function (plasma thyroid stimulating hormone (TSH) and free thyroxine) or C-peptide did not differ between groups. No subjects, except one individual with NGT and one with DM operated for a carpal tunnel syndrome bilaterally, had any symptoms of tingling, numbness and paresthesiae in median or the ulnar nerve innervated areas or any clinical signs of nerve compression.

Sensibility and vibration thresholds

There were no differences between the results of vibration thresholds (dB), acceleration$_{rms}$ and spatial amplitude. Therefore, only values expressed in dB are presented (12, 13). Tactilogram curves from an individual with NGT and with DM are shown in Figure 1, indicating increased vibrotactile thresholds in the latter. Sensibility index (SI) [data from subpopulation of patients from Cederlund et al (17); for calculation see Strömberg et al (14)], which reflect overall dysfunction of the tactilogram, showed a significant difference between the three groups [type 2 DM patients and NGT and IGT subjects; Kruskal-Wallis p=0.04 or less, Table 1], where vibrotactile sense was examined in index and little fingers. SI values were significantly lower in type 2 DM than in NGT subjects in the right and left little finger and in the left index finger, while only significant between IGT subjects and type 2 DM in right index finger. Thus, the lower SI among type 2 DM indicated dysfunction of vibrotactile sense in median and ulnar nerve innervated finger pulps bilaterally. In contrast, there were no differences between the SI in NGT and IGT subjects (Table 1).

Vibration thresholds in subjects with NGT and IGT and patients with DM were analysed separately at each frequency in each finger. There was no significant difference between any groups at 32 and 64 Hz in index or little fingers bilaterally. In contrast, the finger pulp of the right and left little fingers in subjects with DM, reflecting the function of the ulnar nerve, showed increased vibration thresholds at 16, 250 and 500 Hz compared to subjects with NGT (Kruskal Wallis p=0.04 or less; Table 1). In the left little finger 8 Hz also showed a significant difference between type 2 DM and NGT. The index finger showed increased vibration thresholds only at 125 Hz (left side, difference between DM and the other two groups) and at 500 Hz (right side; difference IGT and DM). Again, NGT and IGT subjects did not differ at any frequency (8, 16, 32, 64, 125, 250 and 500 Hz) in any finger. Thus, results indicate a more pronounced dysfunction, involving specific frequencies, in the ulnar nerve than in the median nerve in DM, but no dysfunction in IGT.

Electrophysiology

Electrophysiology showed significant impairment in right median nerve function in type 2 DM patients (Table 2). Values for motor and sensory conduction velocity in forearm (reflecting large fibre neuropathy in forearm) and distal latency and conduction velocity at wrist (reflecting neuropathy at wrist) together with Z scores are presented in Table 2. Type 2 DM differed significantly from NGT and IGT. The Z score of the motor and sensory conduction velocity in forearm (large fiber neuropathy in forearm) and at levels (distal latency and conduction velocity at wrist) were significantly different in patients with type 2 DM from the other two groups (Table 2). Again, subjects with NGT and IGT were not different. Thus, large fibre neuropathy in median nerve was present in type 2 DM (forearm and wrist; Table 2), but not in IGT.

Correlations between HbA1c, vibrotactile sense and electrophysiology

HbA1c values did not correlate with sensibility index or electrophysiological parameters among any investigated subjects. There were significant correlations between Z-scores (compound Z scores) in forearm (NGT 0.63, 0.001; r and p-value; Spearman correlation test) and at wrist (NGT 0.63, 0.001; DM 0.60, 0.006) and sensibility index. Sensibility index did correlate to conduction velocity in forearm (motor NGT 0.57, 0.003 and sensory NGT 0.48, 0.01), distal latency (NGT -0.40, 0.04; DM -0.58, 0.008) and conduction velocity at wrist (NGT 0.61, 0.001; DM 0.55, 0.01). However, there were no significant correlations among all subjects or among subjects with IGT between electrophysiological parameters and vibrotactile sense.

Discussion

Vibrotactile sense was impaired in finger pulps of index and little fingers in men at a specific age with type 2 DM for more than 15 years, but not in subjects with constant IGT or NGT during the same time period (>15 years) in spite of significant differences between HbA1c values between the groups. Particularly, the little finger was affected at three frequencies (16, 250 and 500 Hz) bilaterally when vibration thresholds were analysed individually, indicating a predilection for ulnar nerve dysfunction in type 2 DM. Investigation of vibrotactile sense in finger pulps (sensibility index) is important to detect any large fiber neuropathy in hands in diabetes, since such subjects may have neurological symptoms which sometimes may be overseen in clinical practise. Disturbance in vibrotactile sense in legs, previously investigated ideally at a single (125 Hz) frequency (9), is an indicator for neuropathy, sometimes even more sensitive than electrophysiology of sural nerve (18); a gold standard of large fibre peripheral diabetic neuropathy (15, 19). Interestingly, only the vibration threshold at 125 Hz, the common frequency investigated clinically, in the left index finger were significantly altered. We did not investigate thresholds for heat and cold (small fiber function) since our intention was solely to detect large fiber neuropathy.

We used electrophysiology as the gold standard to detect and verify large fibre neuropathy in upper extremity showing differences between type 2 DM and NGT and IGT (20). The Z-score from forearm indicated large fibre neuropathy in type 2 DM. Furthermore, Z-score at wrist was also different between the groups indicating neuropathy at wrist among type 2 DM, i.e. sign of nerve compression, in accordance with previous studies (20), although no subjects had any symptoms of nerve compression. Unfortunately, we have no electrophysiologic data for ulnar nerve function. Our purpose was only to verify that diabetic patients had signs of neuropathy in the arm using the gold standard (electrophysiology).

Vibrotactile sense (sensibility index) correlated with electrophysiology (e.g. Z score for neuropathy in forearm and at wrist). In contrast, although HbA1c differed significantly between the groups, it did not correlate to vibrotactile sense or electrophysiology. In long standing diabetes, nerve physiologic variables improve with more intense insulin treatment resulting in decreasing HbA1c levels (21).

We did not find any significant differences in vibrotactile sense or electrophysiologic function (right median nerve) between subjects with IGT and with NGT (17) although HbA1c differed. The question of neuropathy and IGT is debatable (22). Recent studies have indicated that at least some cases with idiopathic neuropathy can be due to a underdiagnosed IGT (23, 24) and that subjects with IGT can have signs of neuropathy. In contrast, our study, using vibrotactile sense or electrophysiology (median nerve) as measures, does not point towards a clear connection between a constant diagnosis of IGT for more than 15 years and neuropathy. A weak point is the limited number of IGT subjects (n=7), but these subjects had constant IGT for at least 15 years. In another cohort of patients from the same population (17) with a short duration of diabetes (diagnosis 2003-2005) 22 of 23 cases had IGT since the screening 1989-1991 (results not shown). When comparing such 22 IGT cases who developed DM with the present 28 cases with constant NGT, still there is no detectable difference in vibrotactile sense (true also if present seven cases included; results not shown), indicating that IGT does not impair vibrotactile sense or affect electrophysiologic function. In summary, IGT does not induce a disturbed vibrotactile sense in finger pulps or impaired electrophysiological function, i.e. in reality does not induce large fibre neuropathy.

Few previous studies have considered the vibrotactile sense in finger pulps where an early reduction in a single finger pulp can be observed within the first year of diabetic disease

(11). Other studies signify deteriorated vibration thresholds of a non-significant area of the hand, i.e. dorsum of the metacarpal bone of index finger (12, 25), and that the thresholds are increased in diabetes. Our data show that the sensitive tactile finger pulps innervated by the median and particularly the ulnar nerve have increased vibration thresholds at several frequencies. Vibrotactile sense showed affection at 16, 250 and 500 Hz in the ulnar nerve innervated finger pulp and not in the corresponding area innervated by the median nerve. This may indicate a more pronounced larger fibre neuropathy in the ulnar nerve than in the median nerve in diabetic patients supporting findings in other studies with patient materials of different sex, age and treatments (10). Ulnar nerve affection in diabetes has been interpreted to be caused by trauma or ischemia (26). However, our patients with diabetes did not have any clinical signs of a nerve compression lesion of the ulnar nerve and only two patients (one NGT and one DM) had a median nerve compression at wrist (i.e. carpal tunnel syndrome; both operated and no present symptoms), although Z score at wrist was significantly different among type 2 DM signifying a compression neuropathy (20). The possibility that the function of the ulnar nerve, and to a lesser extent the median nerve, is influenced by other factors than DM is less likely even if diabetes may confer on the peripheral nerve an increased susceptibility to trauma (27). Blood parameters did not differ between the groups thereby excluding other causes of nerve dysfunction (e.g. B12 deficiency and hypothyreosis). One possibility is that the tactile innervation of the little finger is more sparse than the index finger, which results in a more severe functional affection in the former when there is a comparable (in percent) reduction of nerve fibres in the two nerve trunks by diabetes.

Pacinian corpuscles receptors are responsible for vibrotactile sense at frequencies more than approximately 80 Hz (probably at a maximum of 250 Hz) and are located deep in glabrous skin (1, 2, 28). Intracutaneous receptors of FA I type (Meissner’s) are probably more

important at lower frequencies [5-50 Hz; (1, 2)]. Slowly adapting afferent fibres in glabrous skin are also sensitive to vibration, particular to low frequencies, but are considered not to be of crucial importance for the vibrotactile sense (28, 29). Detection of vibrotactile sense is also poorer in hairy than in glabrous skin (30), but the discriminative performance shows striking similarities in the two types of skin with a possible exception at 50 Hz (28). Therefore, we decided to detect the vibrotactile sense in the finger pulps of the little and index fingers to reflect function of the two individual nerves. A multifrequency approach (8-500 Hz) may fully evaluate the vibrotactile sense in finger pulps which mediate high acuity tactile information to the brain. Affection at low (16 Hz) and high (250 and 500 Hz) frequencies of the ulnar nerve indicates that several of the receptors in the pulps, or their nerve fibres, are involved in diabetes. The frequency-related difference of the vibrotactile sense between the index and little fingers is interesting since it imply that diabetes affect the ulnar nerve more than the median nerve, although the previously used sensibility index (14), which analyses the whole tactilogram, showed a significant change in type 2 DM.

Competing interests

Toni Speidel is employed by and shareholder of PID AB. Other authors have nothing to declare.

Acknowledgements

The project was supported by grants from the Swedish Research Council (Medicine), Thelma Zoega´s Fund for Medical Research, Craafords Fund for Medical Research, Stiftelsen Svenska Diabetesförbundets forskningsfond, Diabetesföreningen Malmö med omnejd, Konsul Thure Carlsson Fund for Medical Research**,** Region Skåne and Funds from the University

Hospital Malmö, Sweden. We thank our statistician Jonas Björk, The Competence Center of Region Skåne, Lund for expert statistical advice.

References

1. Martin JH, Jessell TM. Modality coding in the somatic sensory system. In: Kandel E, Schwartz J, Jessel T, editors. *Principles of neural science*. Third ed ed. Norwalk, CT: Appleton and Lange; 1991.
2. Lundström R. Responses of mechanoreceptive afferent units in the glabrous skin of the human hand of vibration. *Scand J Work Environ Health* 1986; **12**: 413-416.
3. Eriksson KF, Nilsson H, Lindgarde F, Osterlin S, Dahlin LB, Lilja B *et al.* Diabetes mellitus but not impaired glucose tolerance is associated with dysfunction in peripheral nerves. *Diabet Med* 1994; **11**: 279-285.
4. Dyck PJ, Larson TS, O'Brien PC, Velosa JA. Patterns of quantitative sensation testing of hypoesthesia and hyperalgesia are predictive of diabetic polyneuropathy: a study of three cohorts. Nerve growth factor study group. *Diabetes Care* 2000; **23**: 510-517.
5. Gelber DA, Pfeifer MA, Broadstone VL, Munster EW, Peterson M, Arezzo JC *et al.* Components of variance for vibratory and thermal threshold testing in normal and diabetic subjects. *J Diabetes Complications* 1995; **9**: 170-176.
6. Nielsen NV, Lund FS. Diabetic polyneuropathy. Corneal sensitivity, vibratory perception and Achilles tendon reflex in diabetics. *Acta Neurol Scand* 1979; **59**: 15-22.
7. Valk GD, Grootenhuis PA, van Eijk JT, Bouter LM, Bertelsmann FW. Methods for assessing diabetic polyneuropathy: validity and reproducibility of the measurement of sensory symptom severity and nerve function tests. *Diabetes Res Clin Pract* 2000; **47**: 87-95.

8. Levy DM, Abraham RR, Abraham RM. Small- and large-fiber involvement in early diabetic neuropathy: a study with the medial plantar response and sensory thresholds. *Diabetes Care* 1987; **10**: 441-447.

9. Goldberg JM, Lindblom U. Standardized method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. *J Neurol Neurosurg Psychiatry* 1979; **42**: 793-803.

10. Fraser DM, Campbell IW, Ewing DJ, Clarke BF. Mononeuropathy in diabetes mellitus. *Diabetes* 1979; **28**: 96-101.

11. Gregersen G. Vibratory perception threshold and motor conduction velocity in diabetes and non-diabetes. *Acta Medica Scand* 1968; **183**: 61-65.

12. Lin YH, Hsieh SC, Chao CC, Chang YC, Hsieh ST. Influence of aging on thermal and vibratory thresholds of quantitative sensory testing. *J Peripher Nerv Syst* 2005; **10**: 269-281.

13. Lundström R, Strömberg T, Lundborg G. Vibrotactile perception threshold measurements for diagnosis of sensory neuropathy. Description of a reference population. *Int Arch Occup Environ Health* 1992; **64**: 201-207.

14. Stromberg T, Dahlin LB, Lundborg G. Vibrotactile sense in the hand-arm vibration syndrome. *Scand J Work Environ Health* 1998; **24**: 495-502.

15. Rahman M, Griffin SJ, Rathmann W, Wareham NJ. How should peripheral neuropathy be assessed in people with diabetes in primary care? A population-based comparison of four measures. *Diabet Med* 2003; **20**: 368-374.

16. Eriksson KF, Lindgarde F. Impaired glucose tolerance in a middle-aged male urban population: a new approach for identifying high-risk cases. *Diabetologia* 1990; **33**: 526-531.

17. Cederlund R, Thomsen N, Thrainsdottir S, Eriksson KF, Sundqvist G, Dahlin LB. Hand disorders, hand functions and activities of daily living in elderly men with type 2 diabetes. *J Diabet Compl (In press)* 2007.

18. Vinik AI, Bril V, Litchy WJ, Price KL, Bastyr EJ, 3rd. Sural sensory action potential identifies diabetic peripheral neuropathy responders to therapy. *Muscle Nerve* 2005; **32**: 619-625.

19. Vinik AI, Suwanwalaikorn S, Stansberry KB, Holland MT, McNitt PM, Colen LE. Quantitative measurement of cutaneous perception in diabetic neuropathy. *Muscle Nerve* 1995; **18**: 574-584.

20. Rota E, Quadri R, Fanti E, Isoardo G, Poglio F, Tavella A *et al.* Electrophysiological findings of peripheral neuropathy in newly diagnosed type II diabetes mellitus. *J Peripher Nerv Syst* 2005; **10**: 348-353.

21. Agardh CD, Rosen I, Schersten B. Improvement of peripheral nerve function after institution of insulin treatment in diabetes mellitus. A case-control study. *Acta Med Scand* 1983; **213**: 283-287.

22. Russell JW, Feldman EL. Impaired glucose tolerance--does it cause neuropathy? *Muscle Nerve* 2001; **24**: 1109-1112.

23. Singleton JR, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve* 2001; **24**: 1225-1228.

24. Novella SP, Inzucchi SE, Goldstein JM. The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve* 2001; **24**: 1229-1231.

25. Hilz MJ, Axelrod FB, Hermann K, Haertl U, Duetsch M, Neundorfer B. Normative values of vibratory perception in 530 children, juveniles and adults aged 3-79 years. *J Neurol Sci* 1998; **159**: 219-225.

26. Schady W, Abuaisha B, Boulton AJ. Observations on severe ulnar neuropathy in diabetes. *J Diabetes Complications* 1998; **12**: 128-132.

27. Dahlin LB, Meiri KF, McLean WG, Rydevik B, Sjöstrand J. Effects of nerve compression on fast axonal transport in streptozotocin-induced diabetes mellitus. *Diabetologia* 1986; **29**: 181-185.

28. Mahns DA, Perkins NM, Sahai V, Robinson L, Rowe MJ. Vibrotactile frequency discrimination in human hairy skin. *J Neurophysiol* 2006; **95**: 1442-1450.

29. Talbot WH, Darian-Smith I, Kornhuber HH, Mountcastle VB. The sense of flutter-vibration: comparison of the human capacity with response patterns of mechanoreceptive afferents from the monkey hand. *J Neurophysiol* 1968; **31**: 301-334.

30. Merzenich MM, Harrington TH. The sense of flutter-vibration evoked by stimulation of the hairy skin of primates: comparison of human sensory capacity with the responses of mechanoreceptive afferents innervating the hairy skin of monkeys. *Exp Brain Res* 1969; **9**: 236-260.

Figure Legends

Figure 1. Tactilograms from a subject with normal glucose tolerance (a) and from a patient with type 2 diabetes > 15 years (b), where the vibrotactile thresholds (y-axis) were investigated at seven (8, 16, 32.5, 65, 125, 250 and 500 Hz) different frequencies (x-axis). The individual vibration thresholds at each frequency (top at diagram), based on the midpoint between the upper and lower limina (expressed in decibels relative to 10^{-6} m/s^2, see Methods), are written below the curve. Note the different shapes of the curves in a and b.

Table 1. Vibration thresholds in index and little fingers at seven frequencies in 58 subjects with diabetic (DM), impaired (IGT) and normal glucose tolerance (NGT) constantly during 15 years

HbA1c %	Right index finger	**8 Hz**	**16 Hz**	**32 Hz**	**64 Hz**	**125 Hz**	**250 Hz**	**500 Hz**	**SI value***
4.5	NGT	108	114	121	116	116	127	146	0.91
[0.5]	(n=28)	[12.6]	[10.8]	[10.3]	[7.6]	[13.0]	[16.9]	[20.4]	[0.39]
4.6	IGT	109	112	115	114	110	126	140	1.03
[0.5]	(n= 7)	[9.0]	[5.4]	[6.0]	[9.9]	[4.0]	[9.8]	[8.3]	[0.10]
7.2[a]	DM	110	115	120	117	118	129	154 [b]	0.83 [b]
[2.2]	(n=23)	[7.0]	[6.0]	[6.3]	[8.1]	[17]	[16.1]	[11.7]	[0.29]
0.0001	p-value	0.33	0.50	0.06	0.08	0.10	0.20	**0.03**	**0.042**

	Right little	**8 Hz**	**16 Hz**	**32 Hz**	**64 Hz**	**125 Hz**	**250 Hz**	**500 Hz**	**SI value***

finger								
NGT	107	111	119	117	118	128	143	0.92
(n=28)	[11.8]	[8.4]	[10.2]	[14.2]	[14.5]	[19.2]	[20.2]	[0.36]
IGT	110	111	117	122	118	128	151	0.85
(n=7)	[12.4]	[7.4]	[6.6]	[12.6]	[8.4]	[6.3]	[11.7]	[0.21]
DM	109	117 [a]	123	123	123	139 [c]	159 [a]	0.72 [c]
(n=23)	[9.0]	[4.3]	[6.7]	[11.9]	[17.7]	[25.0]	[9.7]	[0.28]
p-value	0.58	**0.015**	0.07	0.38	0.13	**0.04**	**0.002**	**0.03**

Left index finger	**8 Hz**	**16 Hz**	**32 Hz**	**64 Hz**	**125 Hz**	**250 Hz**	**500 Hz**	**SI value***
NGT	106	112	118	114	109	125	142	0.99
(n=28)	[12.0]	[9.7]	[7.4]	[8.6]	[13.7]	[15.0]	[13.3]	[0.34]
IGT	110	112	116	111	112	124	144	0.99
(n=7)	[9.4]	[4.2]	[3.4]	[5.4]	[9.4]	[5.1]	[7.9]	[0.06]

DM	109	114	120	114	117 [a]	133	150	0.86 [a]
(n=23)	[8.3]	[6.6]	[4.0]	[9.0]	[10.3]	[17.7]	[19.2]	[0.26]
p-value	0.54	0.51	0.07	0.16	**0.026**	0.08	0.12	**0.04**

Left little finger	**8 Hz**	**16 Hz**	**32 Hz**	**64 Hz**	**125 Hz**	**250 Hz**	**500 Hz**	**SI value***
NGT	102	110	118	117	113	124	145	1.02
(n=35)	[10.5]	[6.9]	[9.3]	[11.6]	[8.7]	[12.8]	[14.9]	[0.25]
IGT	110	112	119	119	114	129	152	0.92
(n=)	[11.5]	[4.1]	[4.4]	[8.7]	[9.8]	[15.5]	[21.9]	[0.24]
DM	111 [c]	115 [c]	122	118	120	137 [c]	154 [c]	0.81 [c]
(n=23)	[8.9]	[9.0]	[8.2]	[13.4]	[13.1]	[13.5]	[15.8]	[0.35]
p-value	**0.009**	**0.003**	0.14	0.29	0.08	**0.003**	**0.009**	**0.007**

Results are median [IQR; interquatrile range]. Kruskal Wallis (KW) was used to calculate statistical significant differences with a subsequent Bonferroni correction or Mann-Whitney (14). P-values <0.05 is written in bold. There was no difference between NGT (n=28) and IGT (n=7) at any of the finger pulps or frequencies. The diagnosis was based on an oral glucose tolerance test 1989-1991 and 2003-2005. [a] significant between DM and the other two groups; [b] significant between DM and IGT; [c] significant between DM and NGT; * indicates the value of sensibility index (14) calculated from subgroups of subjects in a previous study (17), where a value below 0.8 is considered pathological (14).

Table 2. Electrophysiological data from subjects with diabetic (DM), impaired (IGT) and normal glucose tolerance (NGT) constantly for >15 years.

Right side	**Median nerve motor conduction velocity (m/s^2)**	**Distal latency (ms)**	**Median nerve antedrom conduction velocity forearm (m/s^2)**	**Median nerve antedrom conduction velocity wrist (m/s^2)**	**Z score (motor and sensory CV forearm)**	**Z score (distal latency and CV wrist)**
NGT	53.0	4.20	56.0	47.0	0.02	0.59
(n=28)	[5.0]	[0.45]	[7.0]	[8.0]	[1.9]	[1.47]
IGT	54.0	4.1	57.0	50.0	0.69	0.36
(n=7)	[5.3]	[0.80]	[1.5]	[7.7]	[1.19]	[1.33]
DM	49.0 [a]	4.80 [a]	52.0 [a]	43 [a]	-1.05 [a]	-0.80 [a]
(n=21)	[5.5]	[0.93]	[6.0]	[16.0]	[1.63]	[2.98]
p-value	**0.016**	**0.007**	**0.0024**	**0.012**	**0.005**	**0.02**

Results are median [IQR; interquatrile range]. Kruskal Wallis (KW) was used to calculate statistical significant differences between the groups with subsequent Bonferroni correction or Mann Whitney (14). CV=conduction velocity. P-values <0.05 is written in bold. There was no difference between NGT (n=28) and IGT (n=7) in any of the

measured variables. [a] indicates statistical significant difference between DM and the other two groups. The diagnosis was based on an oral glucose tolerance test 1989-1991 and 2003-2005. The HbA1c were statistically higher among type 2 DM than in the other two groups (p=0.0001; 7.2 % [2.2] vs. 4.5 % [0.5] and 4.5 [0.5]; KW and Bonferroni correction). Electrophysiologic recordings are from right median nerve. For calculation of Z score see text. Electrophysiological data missing in two patients with DM compared with data from Table 1. For calculation of Z score see Methods.