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Divergent development of autonomic and peripheral somatic neuropathies in NIDDM

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Summary There is no information on the mutual occurrence and the development of autonomic and peripheral somatic neuropathies based on long-term follow-up of patients with non-insulin-dependent diabetes mellitus (NIDDM). We investigated the relation between the changes in autonomic function values and electrodiagnostic values, and the relation between the occurrence of autonomic neuropathy and peripheral somatic polyneuropathy in a group of patients with newly diagnosed NIDDM ($n = 133$, aged 45–65 years) at baseline and 5 and 10 years later. Parasympathetic autonomic neuropathy was diagnosed on the basis of heart rate variability during deep-breathing and sympathetic autonomic neuropathy on the basis of fall in systolic blood pressure while changing from supine to standing. Polyneuropathy was diagnosed on the basis of both clinical criteria and electrodiagnostic studies (nerve conduction velocity and response-amplitude values). In 10 years 36 patients died, mainly from cardiovascular causes. Altogether 78 patients completed the study. At 10 years, parasympathetic autonomic neuropathy was diagnosed in 61.3 % of those with polyneuropathy and 66.7 % of those without. Likewise, the frequency of sympathetic autonomic neuropathy was similar in those with polyneuropathy (21.9 %) and those without (26.5 %). The respective figures for combined (both parasympathetic and sympathetic) autonomic neuropathy were 10.0 % and 18.8 %. The worsening of parasympathetic and sympathetic autonomic function values was not related to the worsening in electrodiagnostic results with time. In conclusion, the development of autonomic and peripheral somatic neuropathies was divergent in patients with NIDDM suggesting different pathophysiological processes for these neuropathies. [Diabetologia (1997) 40: 953–958]

Keywords Autonomic, peripheral, somatic, neuropathy, non-insulin-dependent, diabetes mellitus.

There is little information on the mutual development of autonomic and peripheral somatic neuropathies in diabetes mellitus [1], and long term follow-up studies with comprehensive measurement methods are lacking. Recently, autonomic neuropathy was found to predict cardiovascular mortality in non-insulin-dependent diabetic (NIDDM) patients [2], but peripheral somatic neuropathy showed no relationship with the mortality rates among these patients [3]. Furthermore, while hyperglycaemia predicted the worsening of both peripheral somatic and autonomic nervous function, the relationship of plasma insulin level to the development of autonomic and peripheral somatic neuropathies was the opposite suggesting partly different pathophysiological mechanisms for these two conditions [2, 3]. This gave us the impetus to examine the mutual development of autonomic and peripheral somatic neuropathies in these NIDDM patients followed-up for 10 years from diagnosis [4, 5].

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; E/I ratio, expiration/inspiration ratio.

Subjects and methods

This study is based on a 10-year follow-up study of patients with newly diagnosed NIDDM and control subjects [5]. The baseline diabetic study population consisted of 133 patients with newly diagnosed NIDDM aged 45 to 64 years, who were examined within 6 months from the detection of diabetes during the period 1 May 1979 to 31 December 1981 [4]. Approval for the study was given by the ethics committee of Kuopio University Central Hospital. Informed consent was given by all subjects studied.

The diabetic patients (70 male, 63 female) were referred to the study by general practitioners working in community health centres in the survey area. The diagnosis of diabetes was made in the clinical setting and it was confirmed by an oral glucose tolerance test using diagnostic criteria recommended by the World Health Organisation Expert Committee on Diabetes Mellitus [6]. Subjects whose fasting blood glucose had exceeded 7.0 mmol/l for more than six months as well as subjects with secondary diabetes, hypo- or hyperthyroidism, alcoholism, renal insufficiency, overt carcinoma or those in institutional care were not eligible for the study. All the diabetic patients were non-ketotic at the time of diagnosis. The formation, representativeness and methods of the baseline examination have been described previously in detail [4]. The 5- and 10-year examinations were carried out in 1985–1986 and in 1991–1992 [5, 7, 8].

Clinical and biochemical characteristics

Anthropometric measurements. Standing height and weight were measured. Body mass index was calculated as body weight (kg)/height (m) squared.

Blood pressure. The blood pressure was measured after a 5-min rest in the sitting position (cuff size 12.5 × 40.0 cm). Systolic blood pressure and diastolic blood pressure levels were measured to the nearest 2 mmHg.

Laboratory methods. Samples for fasting blood glucose were taken after a 12-h overnight fast. Venous blood glucose was analysed at baseline by the glucose oxidase method (Glox; Kabi Ab, Stockholm, Sweden) and plasma glucose at the 5-year examination was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany) and at the 10-year examination by a glucose oxidase method (Glucose Auto & Stat HGA-1120 Analyzer, Daiichi, Kyoto, Japan). Blood values were converted to respective plasma values by multiplying by 1.12. HbA_{1c} was measured by liquid cation exchange chromatography at the 5- and 10-year examinations (normal range, 4.0 to 6.0 %).

Classification of myocardial infarction. The myocardial infarction class consisted of patients with major Q-QS abnormalities (Minnesota code 1.1–2) [9], patients who had suffered myocardial infarction at the hospital, or both. All patient records were checked to verify the correct diagnosis of myocardial infarction [5].

Neurologic studies

Clinical examination. A detailed neurologic examination, including a questionnaire on symptoms and clinical examination, was performed at baseline and at 10-year follow-up examinations. At the 5-year follow-up examination, only electrophysiologic studies were performed [10]. Neuropathic pain was defined as pain in the limbs in the absence of a history of trauma or other evident external cause. Pain that arose during exercise and disappeared at rest, joint pain, and back pain radiating to legs were not considered as neuropathic pain. Bilateral pain or paraesthesias of the legs or feet were considered symptoms of polyneuropathy. The limbs were inspected for ulcerations and muscle atrophy. The patellar and Achilles-tendon reflexes were examined. Vibration sensation was tested with a tuning fork (128 Hz) on each medial malleolus. The absence of either Achilles-tendon reflexes or vibration sensation bilaterally was considered as a clinical sign of polyneuropathy. All the subjects were evaluated for carpal tunnel syndrome [3].

Autonomic nervous function tests. The autonomic function tests were performed at about 09–10.00 a. m. after 12 hours fast. The use of alcohol and smoking was prohibited for 24 h before the study. The order of the tests was the same for all subjects at 5- and 10-year examinations: deep breathing and orthostatic test. All tests were preceded by a 5 min resting period in the supine position. The lower 80 % tolerance limit for expiration to inspiration ratio (E/I = 1.105) was calculated from the baseline values of the control group. The E/I ratio ≤ 1.10 was considered as parasympathetic neuropathy. Systolic blood pressure decrease equal or more than 30 mmHg during standing in the orthostatic test was considered as sympathetic neuropathy [11, 12]. The combination of parasympathetic and sympathetic neuropathies was considered as combined autonomic neuropathy.

Orthostatic test at the 5-year and 10-year examinations. In the orthostatic test the subjects actively stood up after 5 min resting period in the supine position. Systolic and diastolic blood pressures were measured with a calibrated anaeroid sphygmomanometer (systolic as the first and diastolic as fifth phase of Korotkoff sounds) at the end of rest and at 1 and 3 min while standing.

At the baseline examination ECG was recorded with a three-channel Mingograph 34 ECG apparatus (Siemens, Elema, Sweden). The subjects breathed with maximum vital capacity at a respiratory cycle of 10 s (0.1 Hz) for 30 s in the supine position. Three breathing cycles were analysed manually with a coordinate-reader (Summagraphics 300, Fairfield, CT, USA) and the mean value of the three E/I ratios was taken as the E/I ratio [13, 14].

At the 5-year examination the subjects breathed with maximum vital capacity at a respiratory cycle of 10 s (0.1 Hz) for 60 s in the supine position. Six breathing cycles were analysed manually with a co-ordinate-reader (Summagraphics 300) and the mean value of the six E/I ratios was taken as the E/I ratio.

At the 10-year examination ECG (Rigel MultiCare 302; Rigel Research Ltd, Morden, England) and continuous non-invasive arterial blood pressure signal from the middle finger (Finapress; Ohmeda Inc., Englewood, CO, USA) were recorded and simultaneously analogue-to-digital converted with temporal resolution of 200 Hz/channel and amplitude resolution of 12 bits [15]. The A/D converted signals were stored in an IBM PC/AT compatible microcomputer. A software QRS detection algorithm modified from Engelese and Zeelenberg [16] was used to define R peaks of QRS complexes with an accuracy of better than 2 ms. Beat-to-beat R-R intervals were recorded. All data acquisition and analysis were performed with a menu-driven software package (CAFTS; Medikro Ltd, Kuopio, Finland).

In the deep breathing test, the subjects breathed with maximum vital capacity for a respiratory cycle of 10 s (0.1 Hz) for 60 s in the supine position. Six breathing cycles were analysed. During each cycle, the ratio of the longest R-R interval to the shortest R-R interval was calculated and the mean of the six ratios was taken as the E/I ratio.

Neurophysiologic studies. Measurements of nerve conduction velocity at baseline and at the 5- and 10-year examinations were performed with a DISA 1500 electromyograph (Dantec, Skovlunde, Denmark). Conduction velocity in the median and deep peroneal motor nerves and antidromic conduction velocity in the superficial radial, median, sural, and superficial peroneal sensory nerves were measured by conventional methods with surface electrodes [14]. The measurements in the motor nerves were performed principally on the left side of the body, but the right side was used if a local nerve lesion was suspected or if a response could not be elicited on the left side. The measurements in sensory nerves were performed bilaterally, and the mean of the values for the two sides (or the value for a unilateral measurement, if a response on the other side could not be elicited) was calculated. The amplitudes of the motor and sensory responses were measured to the first negative peak. All studies of nerve conduction velocity were done at room temperature (between 22 °C and 24 °C). Skin temperatures were measured with ELLAB TE 3 thermometer (Elektrolaboratoriet, Copenhagen, Denmark) at the sites of sensory-nerve measurements [14]. Both directly measured values for nerve conduction velocity in the sensory nerves and values adjusted for the effect of temperature were analysed [17].

Definition of diabetic polyneuropathy. Altogether, six measurements of nerve function in the legs and feet were used as electrophysiologic indicators of polyneuropathy: in the peroneal motor nerves, nerve conduction velocity, ≤ 39 m per second; amplitude ≤ 1 mV; in the peroneal sensory nerves, nerve conduction velocity, ≤ 37 m per second; amplitude, ≤ 2 μV; in the sural sensory nerves, nerve conduction velocity, ≤ 43 m per second; amplitude, ≤ 3 μV – all at a skin temperature ≥ 31 °C. The subjects were classified as having definite polyneuropathy if four or more values were abnormal, if both the peroneal and sural nerves were involved, and if there were clinical symptoms of polyneuropathy (pain or paraesthesias in the legs); they were classified as having probable polyneuropathy if four or more values were abnormal and both the peroneal and sural nerves were involved but there were no symptoms, or if either of the nerves was electrophysiologically involved and there were symptoms. The subjects with definite or probable polyneuropathy were grouped together as subjects with polyneuropathy [3].

Statistical analysis. Statistical analyses were conducted with the SPSS/PC + program (SPSS Inc., Chicago, Ill., USA). Results are expressed as mean value ± SD. Normality of the distributions was assessed both graphically and with a goodness of fit test. The differences between the two groups were assessed by Student's *t*-test, chi squared test or Fisher's Exact Test while cells with expected frequency less than 5. Spearman's rank correlation coefficient (r_S) was calculated to assess the association of neurophysiological variables with autonomic nervous function parameters. A *p*-value less than 0.05 was considered as statistically significant. For technical reasons, complete data were not obtained from all subjects. Also the subjects with atrial fibrillation at autonomic testing were excluded from the analysis. Therefore, the number of subjects examined varied slightly from test to test.

Results

Clinical characteristics and the occurrence of autonomic and peripheral somatic neuropathies during the 10-year follow-up. Clinical characteristics of subjects are shown in Table 1. On average the diabetic patients were overweight. At the baseline, all diabetic patients were treated with diet alone. At the 5-year examination, 47% of NIDDM patients were treated with diet, 50% with oral antidiabetic drugs, and 3% with insulin. The respective figures at the 10-year examination were 18%, 59% and 23% (in 10 patients insulin was given in combination with oral drug therapy). At the baseline 8.3% and at the 10-year examination 41.9% of NIDDM patients showed peripheral polyneuropathy [3]. The respective figures for parasympathetic neuropathy were 4.9% and 65.0%. At the 5-year examination 6.8% and at 10-year examination 24.4% of NIDDM patients showed sympathetic neuropathy. The respective figures for combined autonomic neuropathy (both sympathetic and parasympathetic criteria fulfilled) were 2.1% and 15.2% [2].

Table 1. Characteristics of NIDDM patients

Baseline examination	(*n* = 133)
Men/women	70 (52.6)/63 (47.4)
Age (years)	55.7 ± 9.7
Body mass index (kg/m^2)	30.4 ± 5.2
Fasting plasma glucose (mmol/l)	12.0 ± 4.0
Systolic blood pressure (mm Hg)	150 ± 18
Diastolic blood pressure (mm Hg)	93 ± 10
Prevalence of myocardial infarction	24 (18.0)
Use of any antihypertensive drugs	69 (51.9)
Use of any diuretics	55 (41.4)
Use of any beta-blocking agents	52 (39.1)
Alcohol consumption (g/week)	47.4 ± 98.5
Smoking history (> 1 year)	62 (46.6)
5-year examination	(*n* = 121)
Body mass index (kg/m^2)	28.6 ± 4.5
Fasting plasma glucose (mmol/l)	11.9 ± 3.9
HbA_{1C} (%)	9.3 ± 2.6
10-year examination	(*n* = 92)
Body mass index (kg/m^2)	28.9 ± 4.9
Fasting plasma glucose (mmol/l)	12.2 ± 3.6
HbA_{1C} (%)	9.0 ± 2.2
Incidence of first myocardial infarction	32 (29.4)

Data are means ± SD or *n* (%)

The cross-sectional associations between autonomic and somatic nerve functions. At the baseline, no associations in nerve conduction velocities or amplitudes of any sensory or motor nerves were found with the E/I ratio in NIDDM patients (data not shown).

At the 5-year examination nerve conduction velocity in the sensory superficial peroneal nerve was associated with E/I ratio ($r_S = 0.251$, $p = 0.031$), and the respective amplitude with E/I ratio ($r_S = 0.236$, $p = 0.043$).

At the 10-year examination the nerve conduction velocity of sensory peroneal nerve was inversely associated with systolic blood pressure decrease in the orthostatic test ($r_S = –0.258$, $p = 0.020$). The nerve conduction velocities or amplitudes of other sensory or

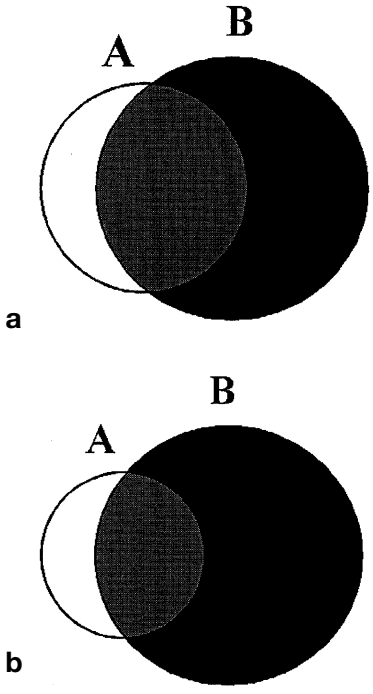

Fig. 1. A. The concomitant occurrence of autonomic neuropathy and peripheral polyneuropathy at the 10-year examination. Pure peripheral polyneuropathy was found in 10 subjects (12.8%) (area of white circle A parallels with the number of subjects), pure autonomic neuropathy (including either parasympathetic and/or sympathetic neuropathy) in 36 subjects (46.2%) (black circle B), and both autonomic and peripheral polyneuropathy in 20 subjects (25.6%) (grey area) of the total population ($n = 78$); **B.** Pure sympathetic neuropathy was found in 6 subjects (10.7%) (white circle A), pure parasympathetic neuropathy in 38 subjects (67.9%) (black circle B), and both parasympathetic and sympathetic neuropathy in 12 subjects (21.4%) (grey area) of those subjects with autonomic neuropathy ($n = 56$)

Table 2. The associations between autonomic neuropathy and peripheral polyneuropathy in NIDDM patients at the 10-year examination

	Polyneuropathy	No polyneuropathy	p-value
Parasympathetic neuropathy	19/31 (61.3)	32/48 (66.7)	0.628
Sympathetic neuropathy	7/32 (21.9)	13/49 (26.5)	0.637
Combined autonomic neuropathy	3/30 (10.0)	9/48 (18.8)	0.353

Data are n (%), Chi-squared test or Fisher's Exact Test

motor nerves did not show any significant associations with E/I ratio or with systolic blood pressure decrease in the orthostatic test at 5- or at 10-years examinations.

The longitudinal associations between the development of autonomic and somatic nerve dysfunctions. No significant associations were found in the difference between the baseline and the 10-year examination in any sensory or motor nerve conduction velocities or amplitudes with the respective difference in E/I ratio in NIDDM patients.

The changes between the 5- and 10-year examinations in nerve conduction velocity of the sensory peroneal nerve ($r_S = 0.2873$, $p = 0.048$), and in the amplitude of the radialis nerve ($r_S = -0.3784$, $p = 0.002$) showed associations with the respective changes of systolic blood pressure measures (i.e. systolic blood pressure change) in the orthostatic test. No other associations were found in the changes of other sensory or motor nerve velocities or amplitudes with autonomic function changes between the 5- and 10-year examinations.

The mutual associations of autonomic and peripheral somatic neuropathies at the 10-year examination. At the 10-year examination the frequencies of both parasympathetic and sympathetic autonomic neuropathies were similar in diabetic patients with and without peripheral polyneuropathy indicating independent appearance of autonomic and peripheral somatic neuropathies (Table 2, Fig. 1). At the 10-year examination only three patients showed both combined autonomic neuropathy and peripheral somatic polyneuropathy simultaneously. At the 10-year examination the frequencies of parasympathetic, sympathetic and combined autonomic neuropathies were similar in diabetic patients with and without sensorimotor polyneuropathy classified either by electrophysiologic values (four or more abnormal values in peroneal or sural nerves) ($p = 0.431$–0.850) or by clinical symptoms ($p = 0.215$–0.549). Parasympathetic neuropathy did not associate with sympathetic neuropathy (of those with parasympathetic neuropathy 12 of 51 (23.5%) showed sympathetic neuropathy and of those without parasympathetic neuropathy 6 of 28 (21.4%) showed sympathetic neuropathy, $p = 0.831$).

Discussion

In this prospective study of newly diagnosed NIDDM subjects, we demonstrated a marked divergence in the development of autonomic and peripheral somatic neuropathies during the 10-year follow-up from the diagnosis. At the 10-year examination the frequencies of parasympathetic and sympathetic autonomic neuropathies were similar in diabetic patients with and without peripheral polyneuropathy.

There is no gold standard for classifying different types of neuropathies, and all criteria can be criticized [18]. The diagnostic criteria of both autonomic and peripheral somatic neuropathies are based on the distributions of each parameter in the population. The particular strength of our study was that we also had a non-diabetic control population which gave us a unique opportunity to create criteria for peripheral

somatic neuropathy on the basis of data obtained from the non-diabetic population also followed-up for 10 years [3]. The criteria for parasympathetic and sympathetic autonomic neuropathies used in our study were similar to those commonly used [11, 12, 19]. At baseline few positive cases for both autonomic parasympathetic neuropathy and peripheral polyneuropathy were found, while at the end of the study more positive cases for parasympathetic autonomic neuropathy were found than that was the case for peripheral polyneuropathy. This could reflect the different sensitivities of these tests to detect abnormalities.

Keeping in mind the effect of different methodologies on the present results of the marked divergence concerning autonomic and peripheral somatic nervous function these data do not support the concept of exclusively similar pathophysiology for autonomic and peripheral somatic neuropathies in NIDDM. The few connections between autonomic and peripheral somatic nervous function in our study could occur by chance, and were attributable to the high number of correlations carried out.

How then could we explain the major finding regarding the divergent development of the autonomic neuropathy and peripheral somatic neuropathy in NIDDM patients? Several metabolic mechanisms [20–26] have been proposed to explain the known relationship between diabetic neuropathy and the degree and duration of hyperglycaemia in IDDM and NIDDM [2, 3, 27]. Also in our study hyperglycaemia contributed to the development of both peripheral somatic and autonomic neuropathies [2, 3]. However, our results also gave support to the notion that there could be different pathophysiological mechanisms involved in the development of autonomic and peripheral somatic polyneuropathies: while hypoinsulinaemia predicted the development of peripheral somatic polyneuropathy [3] it was hyperinsulinaemia that showed a contribution to the development of parasympathetic autonomic neuropathy in these NIDDM patients [2]. High insulin levels per se have been shown to associate with a deterioration of the blood flow in muscle tissue [28, 29], but no data are available on the impact of insulin on the microcirculation of autonomic or peripheral somatic nerve compartments or their surrounding tissues [30, 31]. Furthermore, the divergent development of autonomic and peripheral somatic neuropathies could be explained by other factors, e. g. inflammatory or immune mechanisms [32], or impact of endogenous nerve growth factors on neural tissue [33, 34].

In conclusion, the development of autonomic and peripheral somatic neuropathies were markedly divergent in NIDDM patients during 10 years of follow-up. The frequencies of autonomic parasympathetic and sympathetic neuropathies were similar with and without peripheral polyneuropathy in NIDDM patients after 10 years of follow-up.

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References

1. Young RJ, Zhou YQ, Rodriguez E, Prescott RJ, Ewing DJ, Clarke BF (1986) Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy. Diabetes 35: 192–197
2. Töyry JP, Niskanen LK, Mäntysaari MJ, Länsimies EA, Uusitupa MIJ (1996) Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM. Ten-year follow-up from the diagnosis. Diabetes 45: 308–315
3. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M (1995) Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333: 89–94
4. Uusitupa M, Siitonen O, Aro A, Pyörälä K (1985) Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged, newly diagnosed type 2 (non-insulin-dependent) diabetic subjects. Diabetologia 28: 22–27
5. Uusitupa MIJ, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K (1993) Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. Diabetologia 36: 1175–1184
6. WHO Expert Committee on Diabetes Mellitus (1980) Second report. Technical Report Series, No 646, Geneva
7. Uusitupa M, Niskanen L, Siitonen O, Voutilainen E, Pyörälä K (1990) 5-year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin-dependent diabetic and non-diabetic subjects. Circulation 82: 27–36
8. Niskanen L, Karjalainen J, Siitonen O, Uusitupa M (1994) Metabolic evolution of type 2 diabetes: a 10-year follow-up from the time of diagnosis. J Intern Med 236: 263–270
9. Rose GA, Blackburn H (1968) Cardiovascular survey methods. WHO Monograph Series No 56, Word Health Organization, Geneva
10. Lehtinen JM, Niskanen L, Hyvönen K, Siitonen O, Uusitupa M (1993) Nerve function and its determinants in patients with newly-diagnosed type 2 (non-insulin-dependent) diabetes mellitus and in control subjects – a 5-year follow-up. Diabetologia 36: 68–72
11. Ewing JE, Martyn CN, Young RJ, Clarke BF (1985) The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 5: 491–498
12. Clark CV, Mapstone R (1986) Age-adjusted normal tolerance limits for cardiovascular autonomic function assessment in the elderly. Age Ageing 15: 221–229
13. Lehtinen J (1987) Diabetic neuropathy in newly diagnosed non-insulin-dependent diabetics (academic dissertation). Series original reports 2/1987, University of Kuopio, Kuopio
14. Lehtinen JM, Uusitupa M, Siitonen O, Pyörälä K (1989) Prevalence of neuropathy in newly diagnosed NIDDM and nondiabetic control subjects. Diabetes 38: 1307–1313
15. Tahvanainen K, Länsimies E, Tikkanen P et al. (1992) Microcomputer-based monitoring of cardiovascular functions in simulated microgravity. Adv Space Res 12: 1227–1236
16. Engelese WAH, Zeelenberg C (1979) A single scan algorithm for QRS-detection and feature extraction. In: IEEE

Computers in Cardiology. IEEE Computer Society, Long Beach, CA, pp 37–42
17. Lang AH, Forsström J, Björkqvist S-E, Kuusela V (1977) Statistical variation of nerve conduction velocity: an analysis of normal subjects and uraemic patients. J Neurol Sci 33: 229–241
18. Thomas PK, Tomlinson DR (1993) Diabetic and hypoglycemic neuropathy. In: Dyck PJ, Thomas PK (eds) Peripheral neuropathy. W.B. Saunders company, Philadelphia, pp 1219–1250
19. Smith SA (1982) Reduced sinus arrhythmia in diabetic autonomic neuropathy: diagnostic value of an age-related normal range. B M J 285: 1599–1601
20. Dyck PJ, Zimmerman BR, Vilen TH et al. (1988) Nerve glucose, fructose, sorbitol, myo-inositol, and fiber degeneration and regeneration in diabetic neuropathy. N Engl J Med 319: 542–548
21. Tilton RG, Chang K, Nyengaard JR, Van den Enden M, Ido Y, Williamson JR (1995) Inhibition of sorbitol dehydrogenase: effects on vascular and neural dysfunction in streptozocin-induced diabetic rats. Diabetes 44: 234–242
22. Greene DA, Lattimer SA (1983) Impaired rat sciatic nerve sodium-potassium adenosine triphosphatase in acute streptozotocin diabetes and its correction by dietary myo-inositol supplementation. J Clin Invest 72: 1058–1063
23. Williamson JR, Chang K, Frangos M et al. (1993) Hyperglycemic pseudohypoxia and diabetes complications. Diabetes 42: 801–813
24. Vlassara H, Brownlee M, Cerami A (1981) Nonenzymatic glycosylation of peripheral nerve protein in diabetes mellitus. Proc Natl Acad Sci USA 78: 5190–5192
25. Cullum NA, Mahon J, Stringer K, McLean WG (1991) Glycation of rat sciatic nerve tubulin in experimental diabetes mellitus. Diabetologia 34: 387–389
26. Thurston JH, McDougal DB, Hauhart RE, Schulz DW (1995) Effects of acute, subacute, and chronic diabetes on carbohydrate and energy metabolism in rat sciatic nerve: relation to mechanisms of peripheral neuropathy. Diabetes 44: 190–195
27. DCCT Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329: 977–986
28. Laakso M, Edelman SV, Brechtel G, Baron AD (1990) Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man: a novel mechanism for insulin resistance. J Clin Invest 85: 1844–1852
29. Ganroth PO (1993) Insulin resistance syndrome: possible key role of blood flow in resting muscle. Diabetologia 36: 876–879
30. Sima AAF, Nathaniel V, Bril V, McEwen TAJ, Greene DA (1988) Histopathological heterogeneity of neuropathy in insulin-dependent and non-insulin-dependent diabetes, and demonstration of axo-glial dysjunction in human diabetic neuropathy. J Clin Invest 81: 349–364
31. Giannini C, Dyck PJ (1994) Ultrastructural morphometric abnormalities of sural nerve endoneurial microvessels in diabetes mellitus. Ann Neurol 36: 408–415
32. Dyck PJ (1992) New understanding and treatment of diabetic neuropathy. N Engl J Med 326: 1287–1288
33. Anand P, Terenghi G, Warner G, Kopelman P, Williams-Chestnut RE, Sinicropi DV (1996) The role of endogenous nerve growth factor in human diabetic neuropathy. Nature Med 2: 703–707
34. Dyck PJ (1996) Nerve growth factor and diabetic neuropathy. Lancet 348: 1044–1045