Peripheral sensory neuropathy associates with micro- or macroangiopathy. Results from a population based study of patients with type 2 diabetes in Sweden.

Running title: Complications in a type 2 diabetes population

Lars Kärvestedt¹, Eva Mårtensson², Valdemar Grill, PhD¹,³. Stig Elofsson, PhD⁴, Gunvor v Wendt, PhD⁵, Anders Hamsten, PhD⁶, Kerstin Brismar, PhD¹.

Dept of Molecular Medicine and Surgery Karolinska Institutet¹, Kronan Primary Health Care Centre², Cancer research and Molecular Medicine Norwegian University of Science and Technology and St Olof Hospital, Trondheim, Norway³, Institution for Social Work, University of Stockholm⁴, Dept of Vitreoretinal Diseases, S:t Eriks Eye Hospital⁵, Atherosclerosis Research Unit Dept of Medicine, Karolinska Institutet⁶.

Corresponding author:
Lars Kärvestedt
E-mail lars.karvestedt@stockholmsjukhem.se

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Objective: To assess associations between peripheral sensory neuropathy (PSN) and other diabetes-related complications.

Research Design and Method: In an area-based cohort of type 2 diabetes we investigated 156 subjects, age 61.7 ± 7.2 years, diabetes duration of 7.0 ± 5.7 years by questionnaires, clinical examinations, blood and urine sampling and by review of medical records.

Results: Prevalence of PSN assessed by monofilament and neurothesiometer, increased with severity of retinopathy, (50% frequency in moderate, 100% in severe or proliferative retinopathy, p=0.02). Vibration Perception Threshold (VPT) was higher in subjects with retinopathy 25.6 ± 8.9 vs. 20.5 ± 8.9 (V), p=0.007. PSN was more common in overt nephropathy with higher VPT than in subjects without overt nephropathy. Subjects with PSN and no retinopathy had twice as much peripheral vascular disease (PVD) (52%PVD), as subjects with PSN in conjunction with retinopathy (19%PVD), p=0.05. In subjects with PSN alone PVD was increased three-fold (52%PVD) compared with no PSN (16%PVD), p=0.001. In multivariate analyse PSN was independently associated with PVD, OR 2.31 p=0.007, age, OR 1.12 p=0.008, male OR 2.01 p=0.02, HDLc, OR 0.21 p<0.05, and tended to be independently associated with IGFBP-1, OR 1.03 p=0.05, but not with diabetes duration or HbA1c.

Conclusions: In a representative population of type 2 diabetes, PSN is related to microvascular or macrovascular pathology. PSN is possibly affected by the IGF-axis.
Peripheral sensory neuropathy (PSN) is a well known complication of diabetes attributed to chronic hyperglycemia (1, 2). However, the risk of PSN is also increased by advancing age and affected by height and possibly gender (3) and poorly defined factors, such as processes coupled to regulation of insulin-like growth factor -1 (IGF-1) (4, 5). This makes it difficult to distinguish a specific diabetic component of the neuropathy. Retinopathy on the other hand is a specific complication of diabetes with a strict coupling to metabolic control and is also more easily investigated (1). It could be conjectured that metabolic control would be a strong determinant of PSN in subjects with both retinopathy and neuropathy but less so in diabetic subjects with neuropathy alone. It follows that other risk factors for neuropathy would be important in the last mentioned patients. However, this concept has, to our knowledge not been fully investigated in a representative population of type 2 diabetes.

In order to analyze PSN in relation to other complications and disease conditions, we investigated the prevalence of clinical and biochemical signs of vascular and neurological dysfunction at foot examination in type 2 diabetes in a population defined geographically to Sundbyberg, a suburb of Stockholm. A standardized foot examination protocol based on international consensus statements, which have been in use since 1993, was used. Further, we examined and recoded all retinal examinations available, thus enabling a comparison in subjects having neuropathy with and without concurrent retinopathy. Lastly, we tested for associations between PSN and abnormalities of the IGF-1 and its binding proteins.

MATERIALS AND METHODS

Subjects: Subjects from the geographically defined urban area of Sundbyberg, a suburb to Stockholm was asked to participate. In the area of the study 89% of the population had their health care served by three primary health care centres. Men and women, 40-70 years of age, with type 2 diabetes diagnosed after the age of 35 were included. LADA subjects were excluded based on assays of GAD antibodies.

The study was approved by the local ethics committee at the Karolinska University Hospital. All participants gave informed consent.

Experimental protocol: Data assembled on examination day—Patients were examined at the Unit for Metabolic Control or the Clinical Research Centre at Karolinska University Hospital after an overnight fast. No medication was taken on the morning of admission. Patients who were treated with insulin omitted injections after 22:00 p.m. the day preceding examination.

Before the visit the patients had received questionnaires on their social situation, diabetes and relevant medical data. The resulting medical history was later verified by review of medical records.

Height and weight were measured with the subject wearing light in-door clothing without shoes. Waist index was calculated as measured waist (cm) divided with 94 for men and 80 for women (the limits for overweight).

Blood pressure was measured in the supine position after 5 minutes of rest. An ECG was registered after another 15 minutes.

A urine sample was secured from the night preceding the examination. Blood samples were taken in the overnight fasted state between 9 and 10 a.m. Samples, except those analysed by routine, were processed immediately, aliquoted into 0.5 ml micro tubes and frozen at -70°C until assay.

Foot examination (n=150)—Vibration Perception Threshold (VPT) was assessed at the metatarsophalangeal joint dig I
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using a neurothesiometer (Horwell, NEU1501, U.K.) in a two step manner, first starting from 50V with decreasing stimulation and then starting from 0V with increasing stimulation. The subject stated when he/she lost or began to feel vibration. The mean of the two measurements in the most insensitive foot were used in further analyses (2).

Sensibility to touch was tested using monofilament (10 gram Touch Test 5.07 Novo Nordisk, Copenhagen, Denmark) at four points on each foot, three on the plantar and one on the dorsal side. The procedure was repeated once. Three mistakes out of four were considered pathological (2).

Peripheral sensory neuropathy was defined as VPT $\geq 25$V and/or inability to feel the monofilament.

Foot pulses (aa dorsalis pedis and tibialis posterior) were palpated. Both pulses were required to be palpable for a normal macrocirculation.

Assessment of retinopathy—Records were available for most of the study patients in terms of retinal photography (n=111) and opthalmoscopy (n=21). The photographic records were reviewed and the severity of retinopathy assessed by an experienced retina ophthalmologist (GvW). Assessment of retinopathy was based on the most afflicted eye or on one eye only when the photographs of only one eye were assessable or available. Retinopathy was classified using an international diabetes retinopathy (DRP) classification (6) using five categories, no retinopathy, mild non-proliferative retinopathy, moderate non-proliferative retinopathy, severe non-proliferative retinopathy and proliferative retinopathy. Subjects in whom records of such investigations were lacking were excluded from the retinopathy part of the study.

Other classifications and definitions—Cardiovascular disease (CVD) was defined as a history of myocardial infarction, angina pectoris or ischemic heart disease, ongoing treatment with drugs prescribed for cardiovascular disease or the presence of a pathological electrocardiogram according to the Minnesota code. A cerebrovascular lesion (CVL) was considered present if diagnosed according to medical records or if a pathological finding on a CT of the brain had been registered.

Peripheral vascular disease (PVD) was defined as clinical macroangiopathy (no pulses) present at foot examination, or a medical history of symptoms typical of intermittent claudication.

Overt nephropathy was defined as albuminuria $\geq 300 \text{ mg/L}$ and/or serum creatinine $>100$ for women and $>110 \text{ mmol/L}$ for men. Incipient nephropathy was defined as albuminuria $\geq 30 \text{ mg/L} < 300 \text{ mg/L}$.

Hypertension was defined as $\geq 140/\geq 90 \text{ mmHg}$ at examination or presence of antihypertensive treatment.

Hyperlipidemia was considered present when lipid lowering drugs were in use or when samples at admission showed total cholesterol $\geq 5 \text{ mmol/L}$ or triglycerides $\geq 1.7 \text{ mmol/L}$. (In Sweden lipid lowering drugs are prescribed to achieve total cholesterol <4.5 mmol/L and LDLc <2.6 mmol/L)

Late autoimmune diabetes of the adult (LADA) was defined as presence of glutamic acid decarboxylase (GAD) antibody $\geq 9.5 \text{ U/L}$. GAD antibody titers were determined with Diamyd Anti-GAD65 RIA (Diamyd Diagnostics AB Stockholm, Sweden) (7, 8).

Assays: Insulin-like growth factor-1 (IGF-1) ($\mu$g/L) was determined by radioimmunoassay after separation from IGF-binding proteins (IGFBP:s) by acid-ethanol extraction and cryoprecipitation. To minimize interference of the remaining IGFBP:s, des (1-3) IGF-1 was used as the radioligand. The intra- and interassay CV were 4% and 11% respectively.

IGFBP-1 ($\mu$g/L) was determined by RIA according to the method of Pövo et.al (9). The sensitivity of the RIA was 3$\mu$g/L and
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IGFBP-3 (μg/L) was determined with a solid-phase, enzyme-labeled chemiluminescent immunometric assay, IMMULITE 2000 IGFB-3 (DPC, Los Angeles, USA). According to the manufacturer, the assay is highly specific with low cross-reactivity and the analytical sensitivity is 100 μg/L. Intra- and total-assay CV were 3% and 7.2%, respectively.

Highsensitive CRP (hsCRP) was determined with immunonephelometry, N Highsensitive-CRP, OQIY (Dade Behring, Germany). Expected normal value is <2 mg/L.

Lipoproteins were processed with 12 h preparative ultracentrifugation after which the VLDL fraction was separated and analysed. After precipitation of LDL, HDL was separated and analysed. LDL was calculated according to Friedewald’s formula. Cholesterol and triglyceride levels were determined after extraction with dichloromethane and methanol.

Cystatin C was determined with N Latex Cystatin C, OQNM (Dade Behring, Germany). The normal interval is 0.53-0.95 mg/L.

HemoglobinA1c (ref. <5.2%) was determined with immunologic MonoS method, Unimate (Roche Diagnostics). Fasting plasma glucose (ref 4.0-6.0 mmol/L), S-Creatinine (ref for women >100 and men >110 μmol/L) and Urinary albumin (ref <30 mg/L) were analyzed by routine methods at the hospital laboratory.

Statistical analysis: All results are expressed as mean and standard deviation (SD), unless otherwise stated. Parameters with none-normal distribution were transformed and log-normalised values were used for significance testing. If not acceptable as log-normalised, the Mann Whitney U-test or Kruskal Wallis ANOVA was used. Levels of significance were tested with Fisher’s exact two-tailed test for simple frequency when n<10, otherwise Pearson Chi-Square was used. T-test and One-way ANOVA was used for parametric variables classified in two groups or more. Logistic regressions were performed with identified independent variables, and factors previously reported of significance, to study independent associations.

RESULTS

Study population: Prevalence of type 2 diabetes in the area within the age range 40-70 years that we studied was 3.5% (sum of participants and non-participants). The participation rate was 68%.

Participants and non-participants were comparable as to gender, age, diabetes duration, antidiabetic treatments, glucose control and diabetic complications. However, according to the review of medical records more patients of non-participants had a diagnosis of CVD and hypertension compared with participants, 31% vs. 16% for CVD p=0.05 and 47% vs. 30% for hypertension, p=0.06, respectively, hence the study population had somewhat less macrovascular complications.

Characteristics of participating subjects—The study population was 95% Caucasian, 61% men and 39% women. Mean age was 61.7 ± 7.2 years with diabetes duration 7.0 ± 5.7 years, BMI 29.2 ± 4.8 kg/m² and HbA1c 6.4 ± 1.3%. There were no correlation between age and diabetes duration and no differences in relation to gender (data not shown). Antidiabetic treatment consisted of diet alone 28%, antidiabetic agent 44%, insulin 19% and a combination of antidiabetic agent and insulin 8%. Metformin was used by 21% and sulfonylurea drugs by 44%. Sixty-three % of the subjects were hypertensive at examination and 51% received antihypertensive treatment. Hyperlipidemia affected 69% of the population, treated and untreated. Women were affected more frequently than men, 87% women vs. 59% men (p=0.0002). Twenty-six % of the whole...
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Thirty-one percent were present smokers and 33% were former smokers, men being more often former smoker. Six percent had experienced some problem with alcohol over consumption according to medical records. The prevalence of macrovascular complications was CVD 62%, PVD 26% and CVL 11%, no difference between genders.

Neuropathy, univariate correlations (Table 1 and online Appendix Table A1 (online appendix available at http://care.diabetesjournals.org)): Peripheral Sensory Neuropathy (PSN) affected 34% of the subjects. Men were more often affected than women, 43 vs. 20%PSN, p=0.006.

Subjects with PSN were older than those without PSN, 64.7 ± 5.2 vs. 59.7 ± 7.6 (year), p=0.006, and had longer diabetes duration, 8.6 ± 6.3 vs. 6.1 ± 4.9 (year), p=0.01. They were more affected by nephropathy as judged by higher CystatinC, 0.88 ± 0.42 vs. 0.71 ± 0.29 (mg/L), p=0.02, and higher albuminuria, 172 ± 483 vs. 31 ± 119 (mg/L), p=0.007. The prevalence of PSN increased with severity of retinopathy, p=0.02. Half of the subjects with moderate retinopathy and all with severe and proliferative retinopathy had PSN (online appendix Table A2).

Men with PSN had higher systolic blood pressure, 152 ± 18 vs. 144 ± 17 (mmHg), p=0.04, with vs. without PSN respectively.

Subjects with PSN had more vascular disease as judged by a two fold increase of pathological ECG, 31 vs. 15% pathological ECG, p=0.04. They also had more peripheral vascular disease, 41% vs. 17% PVD, p=0.002, and a history of foot ulceration was more common in connection with PSN, 14 vs. 2% foot ulceration, p=0.008 (Table 1).

Subjects with PSN had lower HDLc, 1.15 ± 0.37 vs. 1.26 ± 0.38 (mmol/L), p=0.07, but comparable HbA1c. They also had comparable IGF-1, 120 ± 56 vs. 137 ± 65 (μg/L), p=0.1, but with higher IGFBP-1, 33 ± 30 vs. 20 ± 17 (μg/L), p=0.005, lower IGF-1/IGFBP-1 ratio, 10.3 ± 16.5 vs. 12.6 ± 11.7, p=0.002 and lower IGFBP-3 3168 ± 1113 vs. 3678 ± 1044 (μg/L), p=0.008, PSN vs. no PSN respectively.

Insensitivity to touch as judged by monofilament affected 15%. Subjects with a pathological monofilament had a 2-3 fold increase in prevalence of peripheral vascular disease, 57 vs. 20%, p=0.0007, overt nephropathy, 24 vs. 7 %, p=0.03, and also prevalence of foot ulcers were strongly associated with a pathological monofilament, 33 vs. 2% foot ulcers, p=0.00002, with vs. without pathological monofilament. Prevalence of pathological monofilament increased with severity of nephropathy, 11% in no nephropathy, 24% in incipient and 38% in overt nephropathy, p=0.02.

In summary PSN in the study population affected males more often than women and was univariatly associated with age, diabetes duration, retinopathy and nephropathy, PVD, HDLc and abnormalities in IGF-1 and its binding proteins but not with HbA1c.

Retinopathy, univariate correlations (Table 1 and online appendix Table A1): The prevalence of diabetes retinopathy at review of retinal examinations was 29%. Eleven % had mild retinopathy, 13% moderate, 2% severe and 2% proliferative retinopathy.

Subjects with retinopathy were of the same age as those without, 62.0 ± 6.9 vs. 61.6 ± 7.5 (years) p=0.9, but had a longer diabetes duration, 10.0 ± 7.0 vs. 5.9 ± 4.9 (years) p=0.001, worse glucose control as judged by HbA1c, 6.8 ± 1.2 vs. 6.3 ± 1.2 (%) p=0.02 and higher UAlb, 244 ± 554 vs. 22 ± 48 (mg/L), p=0.03, with vs. without retinopathy respectively. Blood pressure was comparable in subjects with vs. without retinopathy while in women retinopathy was associated with higher resting pulse, 74 ± 12 vs. 66 ± 9
beats/min, \( p=0.02 \), with vs. without retinopathy.

A VPT \( \geq 25 \text{V} \) was more common in subjects with retinopathy, 45 vs. 27\% VPT\( \geq 25 \text{V} \), \( p=0.08 \), as were a higher VPT, 25.6 \( \pm 8.9 \) vs. 20.5 \( \pm 8.9 \) (V), \( p=0.007 \), with vs. without retinopathy, also prevalence of PSN increased with level of retinopathy as stated above. Overt nephropathy was more common in subjects with retinopathy, 18 vs. 3\%. \( p=0.007 \), with vs. without retinopathy and severity of nephropathy increased with severity of retinopathy, \( p<0.00001 \) (Table A2, available in an online appendix at http://care.diabetesjournals.org).

In summary retinopathy was univariatly associated with diabetes duration, glucose control, nephropathy, and peripheral neuropathy.

**Nephropathy, univariate correlations**

(Table I and Online Appendix Table A1): At examination incipient nephropathy affected 14\% and overt nephropathy 8\%. Of subjects with overt nephropathy 85\% were male (n=11).

Subjects with overt nephropathy had a two fold increase of PSN, 62 vs. 32\% PSN, \( p=0.06 \), with higher VPT, 28.4 \( \pm 12.6 \) vs. 20.9 \( \pm 9.0 \) (V), \( p=0.02 \), with vs. without overt nephropathy. Insensitivity to touch as assessed with monofilament was more common in overt nephropathy, 24 vs. 7\%, \( p=0.03 \) and also increased in prevalence with severity of nephropathy, 11\% in no nephropathy, 24\% in incipient and 38\% in overt nephropathy, \( p=0.02 \).

Retinopathy was three times as common in subjects with overt nephropathy compared to those without, 70 vs. 26\% RP, \( p=0.007 \) and also severity of retinopathy increased with level of nephropathy, incipient and overt, \( p<0.00001 \) (online appendix Table A3).

In summary nephropathy was univariatly closely linked to neuropathy and retinopathy.

**PSN and retinopathy, univariate correlations**

(Table 2 and online appendix Table A4): In subjects without retinopathy, PSN affected men more and were associated with, higher age, higher Creatinine, higher UA1b and higher CystatinC while diabetes duration and glucose control was comparable as shown in table 2. They also had lower BMI, 27.9 \( \pm 4.1 \) vs. 30.3 \( \pm 4.9 \) (kg/m2), \( p=0.03 \), higher IGFBP-1, 34 \( \pm 34 \) vs. 18 \( \pm 15 \) (\( \mu \text{g/L} \)), \( p=0.04 \), lower IGFBP-3, 3190 \( \pm 862 \) vs. 3670 \( \pm 1039 \) (\( \mu \text{g/L} \)), \( p=0.04 \) and higher IGF-1/IGFBP-1 ratio, 13.0 \( \pm 20.8 \) vs. 12.5 \( \pm 11.2 \), \( p=0.04 \), with vs. without PSN respectively.

PSN in subjects with no retinopathy was associated with a nearly three-folded increase of pathological ECG, 36 vs. 13\% pathol. ECG, \( p=0.03 \), and PVD, 52 vs. 16\% PVD, \( p=0.001 \), and a six-folded increase of foot ulcers, 19 vs. 3\% foot ulcer, with vs. without PSN respectively.

Subjects with PSN but without retinopathy were comparable with those with PSN in conjunction with retinopathy in age but had possibly shorter diabetes duration, 7.1 \( \pm 5.9 \) vs. 10.8 \( \pm 7.1 \) (years), \( p=0.07 \), better glucose control 6.2 \( \pm 1.2 \) vs. 6.9 \( \pm 1.0 \) (mmol/L), \( p=0.07 \), PSN alone vs. PSN with retinopathy, while CystatinC was comparable.

VPT was lower in subjects with PSN alone compared to those with both PSN and retinopathy, 30.2 \( \pm 7 \) vs. 35.0 \( \pm 7.88 \) (V), \( p=0.05 \).

PVD was twice as common in subjects with only PSN compared with those with PSN and retinopathy, 52 vs. 19\% PVD, \( p=0.05 \), while overt nephropathy was possible less common in absence of retinopathy, 7 vs. 31\% overt nephropathy, \( p=0.08 \), PSN without vs. with retinopathy.

In summary, PSN in subjects with no retinopathy was univariatly associated with age, gender, PVD, kidney function, macrovascular disease as judged by ECG and IGFBP:s but not with glucose control or
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We find that PSN was more common in our study population (34%) than retinopathy (29%) and nephropathy (22%). PSN affected men more than women and was related to height, age and diabetes duration. These findings confirm previous reports (3, 10, 11). However, we did not find association to the level of glucose control as measured at the time of the investigation. The latter finding is in contrast to some previously reports (12-14). However, in agreement with earlier reports we found an association between PSN and retinopathy suggesting impaired metabolic control as a cause. Comparing subjects with only PSN and subjects with both PSN and retinopathy we found that subjects with PSN alone had shorter diabetes duration and better glucose control but significantly more often PVD than subjects with both PSN and retinopathy. A finding of a close relationship between PSN and PVD has previously been reported (15). We interpret this as PVD causing relative hypoxemia as another risk factor for PSN which may be further enhanced by the presence of hyperglycemia, which in itself is a sufficient cause of PSN.

HDLc was in this study lower in subjects with PSN, p=0.07, and in a multivariate regression analyse independently associated with PSN, p<0.05. Decreased HDLc is a risk factor for PVD in T2D (16) and also for PSN in the metabolic syndrome (17). Most of the proposed pathogenetic metabolic factors for PSN also have vascular effects (18).

Our subjects with PSN had higher IGFBP-1 as previously demonstrated in type 1 diabetes (19) and lower IGF-1/IGFBP-1 ratio and IGFBP-3 compared to subjects without PSN suggesting lower bioactive IGF-1. Autocrine and paracrine IGF-1 is postulated to be crucial for maintained nerve function and the natural decline in IGF:s with age could be a factor behind the age dependent increase of PSN (4, 20). IGFBP-1

diabetes duration. VPT was lower in subjects with PSN alone compared to those with PSN combined with retinopathy.

**Multivariate analysis:** Retinopathy was independently associated with diabetes duration, OR 1.10, p=0.01, glucose control as judged by HbA1c, OR 1.38, p=0.06 and overt nephropathy increased the risk of retinopathy two fold, OR 2.04, p=0.09 (online appendix Table A5).

Peripheral sensory neuropathy was associated with gender, men being more affected, OR 2.01, p=0.02, and increased with age, OR 1.12, p=0.008 while diabetes duration lost significance, p=0.1. Presence of PVD doubled the risk of PSN, OR 2.31, p=0.007 while an increase of HDLc diminished the risk, OR 0.21, p<0.05. Also, a high IGFBP-1 was connected to increased risk of PSN, OR 1.03, p=0.05 (Table 3).

When tobacco use was included in the model and subjects with alcohol over consumption was excluded, PSN was still associated with gender, OR 2.00, p=0.07, and PVD, OR 2.70, p=0.03 while use of tobacco turned out to be insignificant. However the interaction of male and tobacco use possibly increased the probability of PSN, OR 1.94, p=0.08 (online appendix Table A6).

In summary PSN was independently associated with gender, aging, PVD, HDLc and possibly IGFBP-1.

**DISCUSSION**

In this representative population based study where the status of non-participants was also assessed we confirm and extend associations between peripheral sensory neuropathy (PSN) and other microvascular complications in type 2 diabetes, in particular retinopathy. Importantly we demonstrate a close association of peripheral sensory neuropathy and peripheral vascular disease that seems independent of glucose control. Furthermore we report an association between the IGF-IGFBP axis and neuropathy.
is believed to down regulate the IGF:s action, hence an increase of IGFBP-1 resulting in a lower IGF-1/IGFBP-1 ratio suggests reduced IGF activity, which in turn could predispose for PSN. The higher IGFBP-1, which is regulated by insulin, suggests insulin deficiency in the liver since there was no correlation between IGFBP-1 and hsCRP (21).

Retinopathy was, as expected, associated with diabetes duration, hyperglycemia, PSN and nephropathy (14, 22-24). Further, we report that women with retinopathy has higher resting pulse than women without retinopathy, this finding could suggest a connection between retinopathy and autonomic neuropathy as reported in a pupillometri study (25). As to dyslipidemia which has been reported as a risk factor (23) we found no association.

Logistic regression models confirmed to a large extent the findings in univariate analysis. Hence there was an association of the risk for PSN with age (12%/year), IGFBP-1 (3%/µg/L), HDLc (-80%/mmol/L), gender (200% being male) and PVD (230% having PVD). Furthermore, retinopathy was independently associated with diabetes duration and HbA1c whereas overt nephropathy was independently associated with age, and retinopathy. Hence a previously known connection between retinopathy and nephropathy was confirmed.

In conclusion, we report PSN to be independently associated with PVD and HDLc in addition to the well known associations with age and gender. This means that patients with PSN without retinopathy should be suspected to have PVD. Further we report, to our knowledge, for the first time an association between PSN and IGFBP-1 in type 2 diabetes.

The findings in this study are subject to the limitations of a cross-sectional study. They will be further evaluated in a prospective study of this cohort.

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REFERENCES
Table 1. Relations between prevalence of diabetic complications

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<th>Overt nephropathy</th>
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<td></td>
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<td>f %</td>
<td>p</td>
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<td>Overt nephropathy</td>
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<td>16 0.06</td>
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p refers to Fisher’s exact two tailed test, f is frequency. Peripheral sensory neuropathy is defined as pathological filament and/or VPT≥25V

Table 2. Clinical characteristics and fasting metabolic profile in subjects with or without retinopathy in association to presence or not of peripheral sensory neuropathy (PSN) defined as pathological monofilament and/or VPT≥25.

<table>
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<td>3.38(4.03)</td>
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<td>145(18)</td>
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<td>diast BP mmHg</td>
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<td>8.9(3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>6.3(1.3)</td>
<td>6.2(1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-1 μg/L</td>
<td>130(64)</td>
<td>116(55)</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-1 SD μg/L</td>
<td>-0.92(1.71)</td>
<td>-1.03(2.13)</td>
<td>NS</td>
</tr>
<tr>
<td>IGFBP-1 μg/L</td>
<td>18(15)</td>
<td>34(34)</td>
<td>0.04</td>
</tr>
<tr>
<td>IGFBP-3 μg/L</td>
<td>3670(1039)</td>
<td>3190(861)</td>
<td>0.04</td>
</tr>
<tr>
<td>IGF-1/IGFBP-1</td>
<td>12.5(11.2)</td>
<td>13.0(20.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cholesterol mmol/L</td>
<td>5.04(1.01)</td>
<td>5.13(1.40)</td>
<td>NS</td>
</tr>
<tr>
<td>HDLc mmol/L</td>
<td>1.23(0.35)</td>
<td>1.15(0.36)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides mmol/L</td>
<td>1.85(1.18)</td>
<td>2.05(1.92)</td>
<td>NS</td>
</tr>
<tr>
<td>CystatinC mg/L</td>
<td>0.68(0.23)</td>
<td>0.88(0.42)</td>
<td>0.07</td>
</tr>
<tr>
<td>Creatinine μmol/L</td>
<td>74(15)</td>
<td>86(22)</td>
<td>0.004</td>
</tr>
<tr>
<td>UAlb mg/L</td>
<td>11(11)</td>
<td>36(67)</td>
<td>0.06</td>
</tr>
<tr>
<td>VPT</td>
<td>16.1(5.1)</td>
<td>30.2(7.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

p refers to One-way ANOVA.
IGF-1 SD is the Standard Deviation score as calculated from healthy subjects.
Table 3. Binomial LOGIT Modeled probability for peripheral sensory neuropathy (PSN) in the study population.

<table>
<thead>
<tr>
<th>Level of Effect</th>
<th>OR</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>Estimate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (year)</td>
<td>1.12</td>
<td>1.03</td>
<td>1.21</td>
<td>0.11</td>
<td>0.008</td>
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<tr>
<td>diabetes duration (year)</td>
<td>1.08</td>
<td>0.98</td>
<td>1.19</td>
<td>0.08</td>
<td>0.1</td>
</tr>
<tr>
<td>IGFBP-1 (µg/L)</td>
<td>1.03</td>
<td>1.00</td>
<td>1.05</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Ualb (mg/L)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.01</td>
<td>0.00</td>
<td>0.2</td>
</tr>
<tr>
<td>HDLc (mmol/L)</td>
<td>0.21</td>
<td>0.04</td>
<td>0.98</td>
<td>-1.57</td>
<td>&lt;0.05</td>
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<tr>
<td>gender</td>
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<tr>
<td>male</td>
<td>2.01</td>
<td>1.10</td>
<td>3.67</td>
<td>0.70</td>
<td>0.02</td>
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<td>PVD</td>
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<tr>
<td>PVD +</td>
<td>2.31</td>
<td>1.25</td>
<td>4.25</td>
<td>0.84</td>
<td>0.007</td>
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<td>gender*PVD</td>
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<tr>
<td>1</td>
<td>1.60</td>
<td>0.88</td>
<td>2.91</td>
<td>0.47</td>
<td>0.1</td>
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