Peripheral Sensory Neuropathy Associates With Micro- or Macroangiopathy

Results from a population-based study of type 2 diabetic patients in Sweden

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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 diabetic subjects, we investigated 156 subjects (age 61.7 ± 7.2 years and diabetes duration 7.0 ± 5.7 years) by questionnaires, clinical examinations, blood and urine sampling, and review of medical records.

RESULTS — Prevalence of PSN, assessed by monofilament and neurothesiometer testing, increased with severity of retinopathy (50% frequency in moderate and 100% in severe or proliferative retinopathy; $P = 0.02$). Vibration perception threshold was higher in subjects with retinopathy (25.6 ± 8.9 vs. 20.5 ± 8.9 V; $P = 0.007$). PSN was more common in subjects with overt nephropathy, with higher vibration perception thresholds, than in subjects without overt nephropathy. Subjects with PSN but no retinopathy had twice the prevalence of peripheral vascular disease (PVD) (52%) as subjects with both PSN and retinopathy (19%; $P = 0.05$). In subjects with PSN alone, PVD was three times more likely (52%) than in subjects without PSN (16%; $P = 0.001$). In multivariate analysis, PSN was independently associated with PVD (odds ratio 2.31; $P = 0.007$), age (1.12; $P = 0.008$), male sex (2.01; $P = 0.02$), and HDL cholesterol (0.21; $P < 0.05$) and tended to be independently associated with IGF-1 binding protein (1.03; $P = 0.05$) but not with diabetes duration or A1C.

CONCLUSIONS — In a representative population of type 2 diabetes, PSN is related to microvascular and macrovascular pathology. PSN is possibly affected by the IGF axis.

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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 by sex (3) and poorly defined factors, such as processes coupled to regulation of IGF-1 (4,5). This makes it difficult to identify specific diabetes components of neuropathy. Retinopathy, on the other hand, is a complication of diabetes strictly coupled 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 latter subjects. However, this concept has, to our knowledge, not been fully investigated in a representative population of type 2 diabetic patients.

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 during foot examinations of type 2 diabetic patients from a population near 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 records available, thus enabling a comparison of neuropathic subjects with and without concurrent retinopathy. Lastly, we tested for associations between PSN and abnormalities of the IGF-1 and its binding proteins.

RESEARCH DESIGN AND METHODS

— Subjects from the urban area of Sundbyberg, a suburb of Stockholm, were asked to participate. In the area where the study was performed, 89% of the population had their health care served by three primary health care centers. Men and women, 40–70 years of age, diagnosed with type 2 diabetes after the age of 35 were included. Latent autoimmune diabetes in adults (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

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with insulin discontinued injections after 2200 h on the day preceding the examination.

Before their visit, the patients had received questionnaires concerning 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 indoor clothing without shoes. Waist index was calculated as waist circumference (cm) divided by 94 for men and 80 for women (the limits for overweight). Blood pressure was measured in the supine position after 5 min of rest. An electrocardiogram was registered after another 15 min. A urine sample was secured on the night preceding the examination. Blood samples were taken in the overnight fasting state between 0900 and 1000 h. Samples, except those analyzed by routine, were processed immediately, aliquoted into 0.5 ml microtubes, and frozen at −70°C until assay.

Foot examination

Vibration perception threshold (VPT) was assessed at the metatarsophalangeal joint dig I using a neurothesiometer (Horwell, NEU1501, U.K.) in a two-step manner starting from 50 V with decreasing stimulation and then starting from 0 V with increasing stimulation. The subjects (n = 150) stated when they began to feel or stopped feeling vibration. The mean of the two measurements for the least sensitive foot was used in further analyses (2). Sensitivity to touch was tested using a monofilament (10 g 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 ≥25 V or inability to feel the monofilament. Foot pulses (dorsalis pedis and tibialis posterior arteries) 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 ophthalmoscopy (n = 21). The photographic records were reviewed and the severity of retinopathy assessed by an experienced retina ophthalmologist (G.v.W.). 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. The condition of retinopathy was classified into five categories using an international system of classification (6): absence of retinopathy, mild nonproliferative retinopathy, moderate nonproliferative retinopathy, severe nonproliferative retinopathy, and proliferative retinopathy. Subjects for 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 CVD, or the presence of a pathological electrocardiogram according to the Minnesota code. A cerebrovascular lesion was considered present if diagnosed according to medical records or if a pathological finding by computed tomography of the brain had been registered.

Peripheral vascular disease (PVD) was defined as clinical macroangiopathy (no pulses) present during a foot examination or a medical history of symptoms typical of intermittent claudication. Overt nephropathy was defined as albuminuria ≥300 mg/l or serum creatinine >100 μmol/l for women and >110 μmol/l for men. Incipient nephropathy was defined as albuminuria 30–299 mg/l. Hypertension was defined as ≥140/90 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 ≥5 mmol/l or triglycerides ≥1.7 mmol/l. (In Sweden, lipid-lowering drugs are prescribed to achieve total cholesterol <4.5 mmol/l and LDL cholesterol <2.6 mmol/l.)

LADA was defined by the presence of GAD antibodies ≥9.5 units/l. GAD antibody titers were determined with diamyd anti-GAD65 radioimmunoassay (RIA) (Diamyd Diagnostics AB, Stockholm, Sweden) (7,8).

Assays

IGF-1 (μg/l) was determined by RIA after separation from IGF-binding proteins (IGFBPs) by acid-ethanol extraction and cryoprecipitation. To minimize the interference of the remaining IGFBPs, des(1–3) IGF-1 was used as the radioligand. The intra-assay and interassay coefficients of variation (CVs) were 4 and 11%, respectively.

IGFBP-1 (μg/l) was determined by RIA according to the method of Póvoa et. al (9). The sensitivity of the RIA was 3 μg/l, and the intra- and interassay CVs were 3 and 10%, respectively.

IGFBP-3 (μg/l) was determined with a solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite 2000 IGFB-3; DPC, Los Angeles, CA). According to the manufacturer, the assay is highly specific with low cross-reactivity, and analytical sensitivity is 100 μg/l. Intra- and total assay CVs were 4.2 and 7.2%, respectively.

High-sensitive C-reactive protein (hsCRP) was determined with immunonephelometry (OQIY N High-sensitive CRP; Dade Behring, Schwalbach, Germany). The expected normal value of hsCRP is <2 mg/l.

Lipoproteins were processed with 12-h preparative ultracentrifugation, after which the VLDL cholesterol fraction was separated and analyzed. After precipitation of LDL cholesterol, HDL cholesterol was separated and analyzed. LDL cholesterol was calculated according to the Friedewald 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, Schwalbach, Germany). The normal interval of cystatin C is 0.53–0.95 mg/l.

A1C (ref. <5.2%) was determined with the immunological Mono-S method using Unimate (Roche Diagnostics, Indianapolis, IN). Fasting plasma glucose (ref. 4.0–6.0 mmol/l), S-creatinine (ref. >100 μmol/l for women and >110 μmol/l for men), and urinary albumin (ref. <30 mg/l) were analyzed by routine methods at the hospital laboratory.

Statistical analysis

All results are expressed as mean ±SD, unless otherwise stated. Parameters with nonnormal distributions were transformed, and log-normalized values were used for significance testing. If log-normalization was not acceptable, 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's χ^2 test was used. Student's t test and one-way ANOVA were used for parametric variables classified in two groups or more. Logistic regressions

Table 1—*Relations between prevalence of diabetic complications*

	PSN			Retinopathy			Overt nephropathy		
	−	+	*P*	−	+	*P*	−	+	*P*
Cardiovascular disease	57/95 (60)	33/49 (67)	NS	54/94 (57)	26/38 (68)	NS	84/140 (60)	10/13 (77)	NS
Pathological electrocardiogram	12/81 (15)	14/45 (31)	0.04	17/82 (21)	9/32 (28)	NS	22/118 (19)	4/12 (33)	NS
Cerebrovascular lesion	10/95 (11)	5/49 (10)	NS	10/94 (11)	4/38 (11)	NS	14/140 (10)	3/13 (23)	NS
PVD	16/95 (17)	20/49 (41)	0.002	26/94 (28)	11/38 (29)	NS	36/140 (26)	4/13 (31)	NS
Foot ulcer	2/95 (2)	7/49 (14)	0.008	7/94 (7)	4/38 (11)	NS	9/140 (6)	2/13 (15)	NS
PSN	—	—	—	27/85 (32)	16/35 (46)	0.1	41/128 (32)	8/13 (62)	0.06
Retinopathy	19/77 (25)	16/43 (37)	0.1	—	—	—	31/120 (26)	7/10 (70)	0.007
Overt nephropathy	5/92 (5)	8/49 (16)	0.06	3/92 (3)	7/38 (18)	0.007	—	—	—

Data are frequencies (%) unless otherwise indicated. *P* refers to Fisher's exact two-tailed test values. PSN is defined as pathological filament or VPT ≥25 V.

were performed with identified independent variables and factors of significance previously reported to study independent associations.

RESULTS — The prevalence of type 2 diabetes among those 40–70 years of age was 3.5% in the area that we studied (including participants and nonparticipants). The participation rate was 68%.

Participants and nonparticipants were comparable as to sex, age, diabetes duration, antidiabetes treatments, glucose control, and diabetes complications. However, according to the review of medical records, more nonparticipating diabetic patients had a diagnosis of CVD and hypertension than participants (CVD 31 vs. 16%, $P = 0.05$; and hypertension 47 vs. 30%, $P = 0.06$, respectively). Hence, the study population had somewhat fewer macrovascular complications.

The study population was 95% Caucasian, 61% male, and 39% female. Mean ± SD age was 61.7 ± 7.2 years with diabetes duration 7.0 ± 5.7 years, BMI 29.2 ± 4.8 kg/m^2, and A1C 6.4 ± 1.3%. There was no correlation between age and diabetes duration or differences in relation to sex (data not shown). Antidiabetes treatments consisted of diet alone (28%), antidiabetes agent (44%), insulin (19%), and a combination of antidiabetes agent and insulin (8%). Metformin was used by 21% of the study population and sulfonylurea drugs by 44%. At examination, 63% of the subjects were hypertensive and 51% received antihypertensive treatment. Hyperlipidemia affected 69% of the population, treated and untreated. Women were affected more frequently than men (87 vs. 59%; $P = 0.0002$). Twenty-six percent of the whole population received treatment with lipid-lowering agents (statins 20% and fibrates 8%). Thirty-one percent were present smokers, and 33% were former smokers, with men more often former smokers. Six percent had experienced some problem with alcohol overconsumption according to medical records. The prevalence of macrovascular complications was 62% for CVD, 26% for PVD, and 11% for cerebrovascular lesions, with no difference between men and women.

Neuropathy, univariate correlations

PSN affected 34% of the subjects. Men were more often affected than women (43 vs. 20%; $P = 0.006$) (Table 1 and online appendix Table A1 [available at http://dx.doi.org/10.2337/dc08-1250]). Subjects with PSN were older than those without PSN (64.7 ± 5.2 vs. 59.7 ± 7.6 years; $P = 0.006$) and had longer diabetes duration (8.6 ± 6.3 vs. 6.1 ± 4.9 years; $P = 0.01$). They were more affected by nephropathy as judged by higher cystatin C (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; $P = 0.04$). Subjects with PSN had more vascular disease as judged by a twofold increase of pathological electrocardiograms (31 vs. 15%; $P = 0.04$). They also had greater incidence of PVD (41 vs. 17%; $P = 0.002$), and a history of foot ulceration was more common in connection with PSN (14 vs. 2%; $P = 0.008$) (Table 1).

Subjects with PSN had lower HDL cholesterol (1.15 ± 0.37 vs. 1.26 ± 0.38 mmol/l; $P = 0.0.07$) but comparable A1C. They also had comparable IGF-1 (PSN 120 ± 56 μg/l vs. no PSN 137 ± 65 μg/l; $P = 0.1$) but higher IGFBP-1 (33 ± 30 vs. 20 ± 17 μg/l; $P = 0.005$), a lower IGF-1–to–IGFBP-1 ratio (10.3 ± 16.5 vs. 12.6 ± 11.7; $P = 0.002$), and lower IGFBP-3 (3,168 ± 1,113 vs. 3,678 ± 1,044 μg/l; $P = 0.008$).

Insensitivity to touch as judged by monofilament testing affected 15%. Subjects with a pathological monofilament had a two- to threefold increase in prevalence of PVD (57 vs. 20%; $P = 0.0007$) and overt nephropathy (24 vs. 7%; $P = 0.03$). Also, incidence of foot ulcers was strongly associated with a pathological monofilament (pathological monofilament 33% vs. nonpathological 2%; $P = 0.00002$). Prevalence of pathological monofilaments increased with the severity of nephropathy (no nephropathy 11%, incipient nephropathy 24%, and overt nephropathy 38%; $P = 0.02$).

In summary, PSN in the study population affected men more often than women and was univariately associated with age, diabetes duration, retinopathy, nephropathy, PVD, HDL cholesterol, and abnormalities in IGF-1 and its binding proteins but not with A1C.

Retinopathy, univariate correlations

The prevalence of diabetes retinopathy at review of retinal examinations was 29%. Eleven percent had mild retinopathy, 13% moderate, 2% severe, and 2% proliferative (Table 1 and online appendix Table A1). Subjects with retinopathy were of the same age as those without (62.0 ± 6.9 vs. 61.6 ± 7.5 years, respectively; $P = 0.9$) 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 A1C (6.8 ± 1.2 vs. 6.3 ± 1.2%; $P = 0.02$), and higher urinary albumin (244 ± 554 vs. 22 ± 48 mg/l; $P = 0.03$). Blood pressure was comparable in subjects with and without retinopathy,

Table 2—*Clinical characteristics and fasting metabolic profile in subjects with or without retinopathy in association with presence of PSN, defined as pathological monofilament or VPT ≥25 V*

	No retinopathy			Retinopathy				
	PSN−	PSN+	*P*	PSN−	PSN+	*P*	*P**	*P*†s
n	58	27		19	16			
% male	48	81	0.004	58	69	NS	NS	NS
Age (years)	59.1 ± 7.6	65.3 ± 5.3	0.0001	60.5 ± 8.1	63.8 ± 5.6	NS	0.03	NS
Diabetes duration (years)	5.3 ± 4.3	7.1 ± 5.9	NS	8.8 ± 6.1	10.8 ± 7.1	NS	0.001	0.07
BMI (kg/m^2))	30.3 ± 4.9	27.9 ± 4.1	0.03	29.5 ± 4.7	29.8 ± 5.0	NS	NS	NS
Waist index	1.16 ± 0.14	1.11 ± 0.12	0.1	1.13 ± 0.16	1.15 ± 0.14	NS	NS	NS
hsCRP (mg/l)	2.60 ± 2.45	3.38 ± 4.02	NS	3.08 ± 2.46	2.55 ± 2.08	NS	NS	NS
Systolic blood pressure (mmHg)	145 ± 18	150 ± 17	NS	149 ± 21	154 ± 20	NS	NS	NS
Diastolic blood pressure (mmHg)	84 ± 9	83 ± 10	NS	79 ± 8	87 ± 13	0.07	NS	NS
Fasting plasma glucose (mmol/l)	8.8 ± 2.8	8.9 ± 3.8	NS	8.5 ± 2.4	10.2 ± 2.4	<0.05	0.05	0.1
A1C (%)	6.3 ± 1.3	6.2 ± 1.2	NS	6.7 ± 1.3	6.9 ± 1.0	NS	0.06	0.07
IGF-1 (μg/l)	130 ± 64	116 ± 55	NS	133 ± 59	138 ± 63	NS	NS	NS
IGF-1 SD	−0.92 ± 1.71	−1.03 ± 2.13	NS	−0.58 ± 1.62	−0.35 ± 1.62	NS	NS	NS
IGFBP-1 (μg/l)	18 ± 15	34 ± 34	0.04	19 ± 18	29 ± 18	0.02	0.004	NS
IGFBP-3 (μg/l)	3,670 ± 1,039	3,190 ± 861	0.04	3,724 ± 1,253	3,314 ± 1,518	NS	NS	NS
IGF-1–to–IGFBP-1 ratio	12.5 ± 11.2	13.0 ± 20.8	0.04	13.2 ± 12.3	6.4 ± 5.3	0.03	<0.05	NS
Cholesterol (mmol/l)	5.04 ± 1.01	5.13 ± 1.40	NS	4.93 ± 1.26	4.80 ± 0.86	NS	NS	NS
HDL cholesterol (mmol/l)	1.23 ± 0.35	1.15 ± 0.36	NS	1.23 ± 0.35	1.16 ± 0.44	NS	NS	NS
Triglycerides (mmol/l)	1.85 ± 1.18	2.05 ± 1.92	NS	1.57 ± 0.68	1.87 ± 1.33	NS	NS	NS
Cystatin C (mg/l)	0.68 ± 0.23	0.88 ± 0.42	0.07	0.80 ± 0.24	0.87 ± 0.31	NS	<0.05	NS
Creatinine (μmol/l)	74 ± 15	86 ± 22	0.004	73 ± 16	77 ± 23	NS	NS	0.1
UAlb (mg/l)	11 ± 11	36 ± 67	0.06	102 ± 251	463 ± 789	NS	0.004	0.1
VPT (V)	16.1 ± 5.1	30.2 ± 7.8	—	17.8 ± 3.3	35.0 ± 7.8	—	—	0.05

Data are means ± SD unless otherwise indicated. *P* refers to one-way ANOVA. IGF-1 SD is the score as calculated from healthy subjects. *No retinopathy/PSN− vs. retinopathy/PSN+. †No retinopathy/PSN+ vs. retinopathy/PSN+.

whereas in women retinopathy was associated with a higher resting pulse (74 ± 12 vs. 66 ± 9 bpm; $P = 0.02$).

A VPT ≥25 V was more common in subjects with retinopathy (45 vs. 27%; $P = 0.08$) as were higher VPTs in general (25.6 ± 8.9 vs. 20.5 ± 8.9 V; $P = 0.007$). Also, prevalence of PSN increased with the level of retinopathy, as stated above. Overt nephropathy was more common in subjects with retinopathy (18 vs. 3%; $P = 0.007$), and severity of nephropathy increased with severity of retinopathy ($P < 0.00001$) (online appendix Table A2). In summary, retinopathy was univariately associated with diabetes duration, glucose control, nephropathy, and peripheral neuropathy.

Nephropathy, univariate correlations

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 twofold increase of PSN (62 vs. 32%; $P = 0.06$) and higher VPTs (28.4 ± 12.6 vs. 20.9 ± 9.0 V; $P = 0.02$). Insensitivity to touch as assessed with monofilament testing was more common in overt nephropathy (24 vs. 7%; $P = 0.03$) and also increased in prevalence with severity of nephropathy (no nephropathy 11%, incipient nephropathy 24%, and overt nephropathy 38%; $P = 0.02$).

Retinopathy was three times as common in subjects with overt nephropathy as in those without (70 vs. 26%; $P = 0.007$), and severity of retinopathy increased with level of nephropathy ($P < 0.0001$) (online appendix Table A3). In summary, nephropathy was univariately closely linked to neuropathy and retinopathy.

PSN and retinopathy, univariate correlations

In subjects without retinopathy, PSN affected men more and was associated with higher age, higher creatinine, higher urinary albumin, and higher cystatin C, whereas diabetes duration and glucose control were comparable between subjects with retinopathy and without, as shown in Table 2 and online appendix Table A4. They also had lower BMI (27.9 ± 4.1 vs. 30.3 ± 4.9 kg/m^2; $P = 0.03$), higher IGFBP-1 (34 ± 34 vs. 18 ± 15 μg/l; $P = 0.04$), lower IGFBP-3 (3,190 ± 862 vs. 3,670 ± 1,039 μg/l; $P = 0.04$), and a higher IGF-1–to–IGFBP-1 ratio (13.0 ± 20.8 vs. 12.5 ± 11.2; $P = 0.04$).

PSN in subjects with no retinopathy was associated with a nearly threefold increase of pathological electrocardiograms (36 vs. 13%; $P = 0.03$) and PVD (52 vs. 16%; $P = 0.001$) and a sixfold increase of foot ulcers (19 vs. 3%).

Subjects with PSN but without retinopathy were comparable in age with those with both PSN and retinopathy but possibly had shorter diabetes durations (7.1 ± 5.9 vs. 10.8 ± 7.1 years; $P = 0.07$) and better glucose control (6.2 ± 1.2 vs. 6.9 ± 1.0 mmol/l; $P = 0.07$), whereas cystatin C was also comparable. VPTs were lower in subjects with PSN alone than in those with both PSN and retinopathy (30.2 ± 7 vs. 35.0 ± 7.88 V; $P = 0.05$).

PVD was twice as common in subjects with only PSN as in those with PSN and retinopathy (52 vs. 19%; $P = 0.05$), whereas overt nephropathy was possibly less common in the absence of retinopathy (7 vs. 31%; $P = 0.08$).

Table 3—*Binomial logit–modeled probability for PSN in the study population*

	Level of effect	OR	Estimate	*P*
Age (years)		1.12 (1.03–1.21)	0.11	0.008
Diabetes duration (years)		1.08 (0.98–1.19)	0.08	0.1
IGFBP-1 (μg/l)		1.03 (1.00–1.05)	0.03	0.05
Urinary albumin (mg/l)		1.00 (1.00–1.01)	0.00	0.2
HDL cholesterol (mmol/l)		0.21 (0.04–0.98)	−1.57	<0.05
Sex	Male	2.01 (1.10–3.67)	0.70	0.02
PVD	PVD+	2.31 (1.25–4.25)	0.84	0.007
Sex*PVD	1	1.60 (0.88–2.91)	0.47	0.1

Data are OR (95% CI) unless otherwise indicated.

In summary, PSN in subjects with no retinopathy was univariately associated with age, sex, PVD, kidney function, macrovascular disease as judged by electrocardiogram and IGFBPs but not with glucose control or diabetes duration. VPT was lower in subjects with PSN alone than in those with PSN combined with retinopathy.

Multivariate analysis

Retinopathy was independently associated with diabetes duration (odds ratio [OR] 1.10; $P = 0.01$) and glucose control as judged by A1C (1.38; $P = 0.06$), and overt nephropathy increased the risk of retinopathy twofold (2.04; $P = 0.09$) (online appendix Table A5). Peripheral sensory neuropathy was associated with sex, with men more affected (2.01, $P = 0.02$) and increased with age (1.12; $P = 0.008$), whereas diabetes duration lost significance ($P = 0.1$). Presence of PVD doubled the risk of PSN (2.31; $P = 0.007$), whereas an increase of HDL cholesterol diminished the risk (0.21; $P < 0.05$). Also, a high IGFBP-1 was connected to increased risk of PSN (1.03; $P = 0.05$) (Table 3).

When tobacco use was included in the model and subjects with alcohol overconsumption were excluded, PSN was still associated with sex (OR 2.00; $P = 0.07$) and PVD (2.70; $P = 0.03$), whereas use of tobacco turned out to be insignificant. However, the interaction of male sex and tobacco use possibly increased the probability of PSN (1.94; $P = 0.08$) (online appendix Table A6). In summary, PSN was independently associated with sex, aging, PVD, HDL cholesterol, and possibly IGFBP-1.

CONCLUSIONS — In this representative population-based study, which also assessed the status of nonparticipants, we confirm and extend associations between PSN and other microvascular complications in type 2 diabetes, in particular, retinopathy. Importantly, we demonstrate a close association of PSN and PVD that seems independent of glucose control. Furthermore, we report an association between the IGF-IGFBP axis and neuropathy.

We find that PSN was more common in our study population (34%) than retinopathy (29%) and nephropathy (22%). PSN affected men more often 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 with the level of glucose control as measured at the time of the investigation. The latter finding is in contrast to some previous 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 durations and better glucose control but also had PVD significantly more often than subjects with both PSN and retinopathy. A finding of a close relationship between PSN and PVD has previously been reported (15). Our interpretation of this is that PVD causes relative hypoxemia and so is another risk factor for PSN that, in turn, may be further enhanced by the presence of hyperglycemia, which in itself is a sufficient cause of PSN.

HDL cholesterol was in this study lower in subjects with PSN ($P = 0.07$) and in multivariate regression analysis was independently associated with PSN ($P < 0.05$). Decreased HDL cholesterol is a risk factor for PVD in type 2 diabetes (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), a lower IGF-1–to–IGFBP-1 ratio, and lower IGFBP-3 than 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 IGFs with age could be a factor behind the age-dependent increase of PSN (4,20). IGFBP-1 is believed to downregulate IGF action; hence, an increase of IGFBP-1 resulting in a lower IGF-1–to–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 because 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 have higher resting pulses than women without retinopathy—this finding could suggest a connection between retinopathy and autonomic neuropathy, as reported in a pupillometry 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 risk for PSN with age (12% per year), IGFBP-1 (3% per μg/l), HDL cholesterol (−80% per mmol/l), male sex (200% greater risk), and PVD (230% greater risk). Furthermore, retinopathy was independently associated with diabetes duration and A1C, 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 HDL cholesterol in addition to the well-known associations of PSN with age and sex. This means that patients with PSN but without retinopathy should be suspected to have PVD. Further, we report for the first time, to our knowledge, 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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