

Prevalence of Polyneuropathy in Prediabetes and Diabetes is Associated with Abdominal Obesity and Macroangiopathy. The MONICA/KORA Augsburg Surveys S2 and S3

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ABSTRACT

Objective: It is controversial whether there is a glycemic threshold above which polyneuropathy (PN) develops, and which are the most important factors associated with PN in the general population. The aim of this study was to determine the prevalence and risk factors of PN in subjects with diabetes, impaired fasting glucose (IFG) and those with impaired and normal glucose tolerance (IGT,NGT).

Research Design and Methods: Subjects with diabetes (n=195) and controls matched for age and sex (n=198) from the population-based MONICA/KORA Augsburg Surveys 1989/90(S2) and 1994/95(S3) aged 25-74 years were contacted again and assessed in 1997/98 by the Michigan Neuropathy Screening Instrument using a score cutpoint >2. An oral glucose tolerance test was performed in the controls.

Results: Among the controls n=46 (23.2%) had IGT, n=71 (35.9%) had IFG, and n=81 had NGT. The prevalence of PN was 28.0% in the diabetic subjects, 13.0% in those with IGT, 11.3% in those with IFG, and 7.4% in those with NGT ($p \leq 0.05$ for diabetic vs NGT, IFG, and IGT). In the entire population studied (n=393), age, waist circumference, and diabetes were independent factors significantly associated with PN, while in the diabetic group PN was associated with age, waist circumference, and peripheral arterial disease (all $p < 0.05$).

Conclusions: The prevalence of polyneuropathy is slightly increased in individuals with IGT and IFG compared to those with NGT. The association with waist circumference and peripheral arterial disease suggests that the latter and abdominal obesity may constitute important targets for strategies to prevent diabetic polyneuropathy.

Diabetic polyneuropathy (DPN) affects 54 per 100000 persons per year in the community and represents the third commonest neurological disorder surpassed only by cerebrovascular events and shingles (1). Our understanding of the epidemiology of the distal symmetric sensory or sensorimotor polyneuropathy, one of the most frequent diabetic complications, has been made difficult due to inconsistency in the selection of diagnostic procedures and referral bias (2). Numerous studies described the prevalence or incidence in hospital- or clinic-based populations, which may bias towards those patients who are more severely affected (3-7). However, it is important that the populations studied are representative of the total population being considered, and have not been subjected to significant selection biases (2).

Previous population based studies have reported prevalence rates for PN ranging from 8% to 54% in Type 1 and from 13% to 46% in Type 2 diabetic patients, respectively (8-20). Apart from inherent ethnic differences, these wide ranges may be explained by the differing criteria and diagnostic tests used to define and characterize PN. The risk factors most consistently associated with PN in Type 2 diabetic patients at the population level were increasing age and duration of diabetes, height, poor glycemic control evidenced by HbA1c as well as presence of retinopathy and nephropathy (21-23). Divergent or scant data have been reported for the role of diabetes type, insulin treatment, hypoinsulinemia, sex, hypertension, ethnicity, cigarette smoking, and alcohol use (8-23).

In contrast, frequent comorbidities of Type 2 diabetes such as the further components of the metabolic syndrome, i.e. abdominal obesity and dyslipidemia

were not hitherto identified as risk factors for PN in Type 2 diabetes. In Type 1 diabetic subjects, low HDL cholesterol was associated with prevalent PN (24) and hypertension was a predictor of incident PN (25). Moreover, in a center-based study in Type 1 diabetic patients triglycerides, BMI, and hypertension were identified as risk factors for incident PN (7).

There is now major interest in prediabetes and the closely related metabolic syndrome which are highly prevalent and enhance the risk of diabetes and macrovascular disease, but controversial discussion has recently emerged as to whether impaired glucose tolerance (IGT) may cause PN (26-29). Some epidemiological studies have reported that the prevalence of PN is higher in individuals with IGT as compared to those with normal glucose tolerance (NGT) (10,30), whilst others could not confirm such an association (9,13,31). On the other hand, several uncontrolled observational studies suggested that the chronic idiopathic axonal polyneuropathy (CIAP) is associated with IGT (27,32,33). It has been hypothesized that some components of the metabolic syndrome may play a causative role in neuropathy both for those with prediabetes, and those with otherwise idiopathic neuropathy (27,33). However, glucose intolerance is common in the elderly population, and the only study including a control group could not confirm an association between CIAP and IGT (34)

The aim of the present study was to determine the prevalence and risk factors of PN in subjects with diabetes and those with IGT and NGT in the general population.

RESEARCH DESIGN AND METHODS

Study sample. The independent population-based MONICA/KORA

Augsburg surveys were part of the multinational World Health Organization MONICA project (35). The second MONICA Augsburg Survey 1989/90 (S2) included n=4940 persons (participation: 76.9%), while the third MONICA Augsburg Survey 1994/95 (S3) included n=4856 persons (participation: 74.9%) aged 25-74 years. The surveys were approved by the local authorities. All participants gave written informed consent. Subjects were classified as having diabetes mellitus if they reported a diagnosis of diabetes or if they were taking antidiabetic medication. All diabetic subjects from the S2 and S3 surveys as well as nondiabetic persons 1:1 matched for age and sex were invited again in March 1997 and assessed until July 1998 for the presence of chronic diabetic complications including polyneuropathy. Included in the present study were cases defined as those who were invited as diabetic and confirmed as being diabetic based on self-reports (n=201). Among the diabetic subjects n=6 were excluded due to an incomplete data set, leaving n=195 patients in the final analysis. An oral glucose tolerance test was performed in persons who had been invited as nondiabetic controls. Age- and sex-matched controls were defined as those who were invited as nondiabetic and confirmed in the oral glucose tolerance test (OGTT) as nondiabetic (n=198). Thus, the entire population studied included n=393 subjects, of whom n=185 subjects originated from S2 and n=208 subjects from S3. In the nondiabetic group n=81 individuals had a normal glucose tolerance (NGT), n=71 had impaired fasting glucose (IFG), and n=46 had IGT. Excluded were persons who were invited as diabetic but self-confirmed as controls (n=16) as well as those invited as controls but confirmed as new diabetic (n=23) in the OGTT.

Data collection. Blood pressure, body height, and body weight, were determined by trained medical staff (mainly nurses). All measurement procedures have been described elsewhere in detail (36-38). Information concerning sociodemographic variables, and cardiovascular risk factors was assessed by standardized personal interviews. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. A regular smoker was defined as a subject who regularly smoked at least 1 cigarette per day. Alcohol consumption on the previous workday and during the previous weekend was calculated in grams per day. High alcohol intake was defined as ≥ 40 g/day in men and ≥ 20 g/day in women. The physical activity level was estimated by means of two separate 4-category interview questions asking about the time per week spent on sports activities during leisure time in summer and winter. The winter and summer responses were combined to define one sport variable, whereby a participant was considered physically active if he or she participated in sports in summer and in winter for more than 1 hour per week in at least 1 season. A participant was classified as inactive if he or she was less active during leisure time. Prevalent cardiovascular disease was defined as the need for hospital treatment of myocardial infarction or stroke (38). Total serum cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels were measured by enzymatic methods (CHOD-PAP; Boehringer, Mannheim, Germany). Serum creatinine was measured by the para-aminophenazone (PAP) method (Boehringer, Mannheim, Germany). Urinary albumin (mg/l) was determined in a random morning urine sample using an immunoturbidimetric test (Tina-

quant, Boehringer, Mannheim, Germany).

Oral glucose tolerance tests (OGTT) were carried out in the morning (7:00 am to 11:00 am) according to the WHO protocol as previously described (39). Participants were asked to fast for 10 h overnight, to avoid heavy physical activity on the day before examination and to refrain from smoking before and during the test. Fasting venous blood glucose was sampled and 75 g of anhydrous glucose given (Dextro OGT, Boehringer, Mannheim, Germany). IFG was defined using a cutpoint for plasma glucose of 100-125 mg/dl according to the ADA criteria (40).

The presence or absence of PN was determined by the Michigan Neuropathy Screening Instrument (MNSI) using a score cutpoint >2 as previously described (41). The clinical examination portion of this tool takes into account the inspection of the feet (deformities, dry skin, callus, infection), presence or absence of foot ulceration, ankle reflexes, and vibration perception threshold (VPT) at great toe which was measured by the calibrated Rydel Seiffer tuning fork. In addition, the MNSI questionnaire consisting of 15 questions addressing positive symptoms of PN was used.

Peripheral arterial disease (PAD) was assessed using a Mini Dopplex device (HNE Healthcare, Hilden, Germany) and defined by a ankle brachial index (ABI) <0.9 . This cutpoint has a sensitivity of 95% for the presence of PAD documented by angiography (42).

Statistical analysis. Continuous data were expressed by the mean \pm SD or geometric mean \pm SD. For continuous variables satisfying a normal distribution assumption, an ANOVA (F-test) for the comparison of the four groups was performed. For log normal variables, the ANOVA was carried out on the log scale. Binomial proportions were

compared using Fisher's exact test. The PN score was analyzed nonparametrically by performing the Kruskal-Wallis test. Associations between variables were analyzed both in the entire population studied and in the diabetic group using a stepwise procedure with MNSI >2 as the dependent variable: 1.) univariate logistic regression models where age, sex, height, weight, BMI, waist and hip circumference, systolic blood pressure, smoking, physical activity, alcohol consumption, creatinine, albuminuria, myocardial infarction, stroke, peripheral arterial disease, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, impaired glucose tolerance, diabetes mellitus, duration of diabetes, HbA1c, fasting blood glucose, and 2 hour blood glucose in the OGTT were used as independent variables. 2.) multivariate logistic regression models, 3.) stepwise and backward regression models, and 4.) final multivariate logistic regression models including age, sex, height, weight, waist circumference, physical activity, creatinine, albuminuria, duration of diabetes, HbA1c, IGT, diabetes, and peripheral arterial disease. The level of significance was set at $\alpha=0.05$. The SAS statistical package version 8.2 TS2M0 was used for all analyses.

RESULTS

The demographic variables of the subjects with NGT, IFG, IGT, and diabetes are shown in Table 1. There was a significant and steady increase in the sequence from NGT to IFG, IGT and diabetes in BMI, waist circumference, systolic blood pressure, HbA1c, albuminuria, and the prevalence of PN, while HDL cholesterol showed a corresponding decrease (all $p<0.05$). Moreover, significant differences between the four groups studied were noted for age, height, the proportions of smokers, persons with PAD, absent

ankle reflexes, and those with high alcohol consumption and low physical activity (all $p < 0.05$). Fasting and 2 h glucose in the OGTT were significantly different between persons with NGT, IFG, and IGT ($p < 0.05$). No significant differences between the groups were observed for sex, LDL cholesterol, creatinine, and the proportion of individuals with stroke, burning pain, allodynia, and foot ulcers in the lower limbs.

Among the diabetic subjects, $n=12$ and $n=135$ had type 1 and type 2 diabetes, respectively, $n=6$ had secondary diabetes, and in $n=42$ subjects the diabetes type was not known. Diabetes treatment included oral antidiabetic agents (OADs) in $n=86$ (44.1%), insulin in $n=44$ (22.6%), OADs and insulin in $n=42$ (21.5%), and diet only in $n=23$ (11.8%). Cardiovascular medications across the four groups studied (mean [range]) included ACE inhibitors in 6.6(4.7-8.0)%, β blocking agents in 4.6(2.1-9.1)%, calcium channel blockers in 5.2(3.9-5.8)%, diuretics in 5.6(5.2-6.3)%, and lipid-lowering drugs in 2.9(2.6-3.1)% of the subjects.

According to the above definition, the prevalence (95% CI) of PN was 28.0% (21.5-34.5%) in the diabetic subjects, 11.3% (5.0-31.0%) in those with IFG, 13.0% (4.9-26.3%) in those with IGT, and 7.4% (2.8-15.4%) in those with NGT. The percentage differences (95% CI) in prevalence adjusted for multiplicity were: diabetes – IGT: 15 (0-30)%; diabetes – IFG: 17 (4-29)%; diabetes – NGT: 21 (9-32); IGT – IFG: 2 (-14-18)%; IGT – NGT: 6 (-9-20)%; IFG – NGT: 4 (-8-16)%.

In the univariate regression models including the entire population studied, significant differences between persons with and without PN were noted for the following variables (OR and 95% CI): age: 1.08 (1.05-1.12), waist circumference: 1.03 (1.01-1.05), low

physical activity: 0.40 (0.21-0.78), PAD: 3.26 (1.65-6.45), diabetes: 3.99 (1.99-7.99), fasting glucose: 1.00 (1.00-1.01), HbA1c: 1.21 (1.06-1.38), log triglycerides: 1.61 (1.09-2.38), log creatinine: 5.78 (2.23-14.97), and log albuminuria: 1.24 (1.09-1.42). No differences were observed for male sex, height, weight, BMI, hip circumference, systolic blood pressure, smoking, alcohol intake, myocardial infarction, stroke, IGT, 2 h glucose, total cholesterol, LDL cholesterol, and HDL cholesterol.

The final multivariate logistic regression models included age, male sex, height, weight, waist circumference, low physical activity, log creatinine, log albuminuria, HbA1c, IGT, diabetes, and PAD. The independent variables remaining in the final multiple logistic regression models with polyneuropathy (MNSI >2) as dependent variable are listed in Table 2. In the entire population studied, age, waist circumference, and diabetes were significantly associated with PN (all $p < 0.05$), while the relationship with PAD reached borderline significance ($p=0.099$). In the diabetic subjects, independent associations with PN were noted for age, waist circumference, and PAD (all $p < 0.05$), whereas duration of diabetes did not reach statistical significance ($p=0.29$).

CONCLUSIONS

The results of this study demonstrate that in the general population the prevalence of PN is slightly higher in persons with IGT than in those with normal glucose tolerance and more than 2-fold higher in subjects with diabetes compared to those with IGT. We further show for the first time that the prevalence of PN is also slightly higher in individuals with IFG than in those with NGT and only marginally lower than in those with IGT. Moreover, both in the general population and

diabetic patients, apart from age, waist circumference and PAD are independently associated with prevalent PN. This is another novel finding suggesting an interplay between PN and both cardiovascular risk factors and macroangiopathy in the lower limbs.

The vast majority of previous population based studies have not assessed waist circumference as a potential risk factor of polyneuropathy, but did measure BMI or weight (13,16,19,21). However, these studies have not reported any association between BMI or weight and the prevalence of PN in diabetic patients. In the US National Health and Examination Survey (NHANES), weight ≥ 92 kg (4th quartile) was associated with insensate feet as assessed by the 10 g monofilament yielding an odds ratio of 2.4 (95% CI: 1.8-3.1) in the nondiabetic population, but this association was not observed in the diabetic population (19). In the Australian Diabetes Obesity and Lifestyle (AusDiab) study (17) including Type 2 diabetic patients neither BMI nor waist circumference were identified as risk factors for PN in univariate analyses. Some studies have not taken measures of obesity into consideration at all when evaluating the possible risk factors of PN (10,23,15,18). Moreover, PAD verified by ABI has not been previously reported as a risk modifier for the prevalence of PN in diabetic patients. Thus, the present study is the first to report an independent association of prevalent PN with both waist circumference and PAD in the diabetic population. An increase in waist circumference by 1 cm was associated with a 4% increase in the likelihood of PN. Due to the cross-sectional nature of this study, it neither can be concluded that visceral obesity is a predictor for the development of PN nor that it plays a pathogenetic role, but against the background of the independent association of PN with PAD reported

herein, it is tempting to speculate that visceral obesity as an important component and macroangiopathy as a frequent sequel of the metabolic syndrome may foster the risk of developing PN in diabetic subjects. The metabolic syndrome (visceral obesity, dyslipidaemia, hyperglycaemia, and hypertension), has become one of the major public health challenges worldwide. There has been growing interest in this constellation of closely related cardiovascular risk factors (43-45). Indeed, central obesity, as assessed by waist circumference, rather than BMI, was agreed as essential to define the metabolic syndrome by different panels, because of the strength of the evidence linking waist circumference with cardiovascular disease and the other metabolic syndrome components, and the likelihood that central obesity is an early step in the etiological cascade leading to full metabolic syndrome (44,45). However, whether central obesity is a harbinger of diabetic PN can only be answered by prospective studies.

This study does not confirm some previous population based studies indicating that IGT is associated with an increased prevalence of PN (10,30). While the point estimate indicates an increased prevalence, the difference did not reach statistical significance, possibly due to the relatively low sample size. On the other hand, it is conceivable that higher age and waist circumference may contribute to a higher prevalence of PN in individuals with IGT compared to those with NGT, as these risk factors were associated with PN in the entire population studied. In the San Luis Valley Diabetes study (10) the prevalence of PN was 3.9%, 11.2%, and 25.8% in subjects with NGT, IGT, and diabetes, respectively. The odds ratio (95% CI) for the presence of PN in individuals with IGT (n=89) was 3.5 (1.5-7.9) compared to those with

NGT (n=488) (10). In the Hoorn study (30) only the risk of bilateral absence of ankle reflexes (OR: 1.7 [1.1-2.8]), but not knee reflexes (OR: 1.2 [0.4-4.1]) as well as vibration sensation at the big toe (OR: 0.8 [0.5-1.3]) and the medial malleoli (OR: 0.9 [0.4-2.2]) was associated with IGT as compared to NGT. Other studies have found no association between IGT and prevalent PN (9,13,31,46). In a large sample of individuals with IGT or IFG the AusDiab study (47) recently reported a markedly lower prevalence of PN as compared with our study reaching only 3.9% when diagnosed by the Neuropathy Disability Score (NDS) and 6.1% when diagnosed by an overall neuropathy score. However, the corresponding rates of PN in a population with NGT were not reported (47). Thus, the results of the present study are compatible with the notion that the available evidence does not generally suggest a significantly elevated prevalence of PN in persons with IGT.

An interesting aspect in the context of a presumable "prediabetic neuropathy" (27,33) is the role of IGT in CIAP. Several uncontrolled observational studies have recently reported an increased prevalence of IGT in patients with CIAP (27,32,33). In the only controlled study hitherto available 32% of patients with CIAP and 14% of the controls had IGT or fasting hyperglycaemia but, after adjusting for age and sex, the difference was not significant, even in the painful neuropathy subgroup (34). A recent review has concluded that despite extensive studies it is unclear whether IFG or IGT may cause diabetic PN or CIAP as some studies suggest that

prediabetes is a common and important cause of CIAP, whereas others do not. It was judged that a considerable degree of this disparity may relate to differences in selection of patients, choice of controls, assessment of chronic glycemic exposure and of diabetic complications, and statistical power (29). There is general agreement that prospective controlled studies are required to definitively answer the question whether polyneuropathy develops more frequently and more severely in individuals with prediabetes as compared to those with NGT (26,28,29).

In conclusion, at the population level the prevalence of polyneuropathy in individuals with IGT is slightly higher than in those with NGT. To establish whether this is a true difference, larger samples would be required. Apart from age, an important risk factor associated with polyneuropathy in diabetic patients is waist circumference, while peripheral arterial disease is a relevant associated disorder. Thus, abdominal obesity and peripheral macrovascular disease may represent important targets to prevent diabetic polyneuropathy.

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TABLE 1. Demographic and clinical variables of the subjects from the MONICA/KORA Augsburg Surveys (S2 and S3).

	NGT	IFG	IGT	Diabetes	Overall P-value
<i>n</i>	81	71	46	195	--
Sex (m/f)	43/38	45/26	23/23	110/85	0.47 [§]
Age (years)	63.6±9.3	66.6±8.1	69.3±7.8	66.8±9.4	0.004 [*]
Height (cm)	166.3±9.2	169.1±9.3	165.8±9.4	164.6±9.0	0.006 [*]
BMI (kg/m ²)	26.7±2.9	27.4±5.2	29.0±4.4	29.6±4.6	<0.001 ⁺
Waist circumference (cm)	91.9±10.1	96.0±11.4	99.0±12.7	100.0±12.5	<0.001 ⁺
Systolic BP (mmHg)	134±20.5	140±21.3	147±23.7	149±20.9	<0.001 ⁺
Fasting glucose (mg/dl)	92.3±6.7	107.7±6.4	107.6±9.1	--	<0.001 ⁺
2h glucose (mg/dl)	98.7±19.9	104.4±18.9	160.6±15.8	--	<0.001 ⁺
HbA _{1c} (%)	5.0±0.3	5.2±0.6	5.2±0.4	7.3±1.8	<0.001 ⁺
LDL cholesterol (mg/dl)	143.4±34.9	151.5±39.1	145.3±36.4	141.2±38.2	0.27 ⁺
HDL cholesterol (mg/dl)	59.5±16.9	58.1±17.5	56.8±13.5	48.6±14.7	<0.001 ⁺
Creatinine (mg/dl)	0.81./:1.21	0.83./:1.22	0.85./:1.22	0.88./:1.36	0.053 ^{&}
Albuminuria (mg/l)	6.10./:3.79	9.13./:4.36	12.69./:4.06	30.12./:8.27	<0.001 ^{&}
Smoking (%)	7.4	18.3	2.2	9.7	0.031 [§]
Alcohol (%)	10.0	26.8	8.7	6.7	<0.001 [§]
Low physical activity (%)	45.7	32.4	32.6	20.0	<0.001 [§]
Stroke (%)	5.1	2.8	4.3	10.4	0.143 [§]
PAD [ABI<0.9] (%)	3.7	8.5	2.2	16.2	0.0021 [§]
PN [MNSI > 2] (%)	7.4	11.3	13.0	28.0	<0.001 ⁺
Burning pain feet/legs (%)	9.9	11.3	10.9	15.5	0.619 [§]
Allodynia feet (%)	2.5	4.2	10.9	10.3	0.063 [§]
Absent ankle reflexes (%)	3.75	4.2	0	20.1	<0.001 [§]
Foot ulcer present (%)	0	0	2.2	4.1	0.089 [§]

NGT: normal glucose tolerance; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; PAD: peripheral arterial disease; ABI: ankle brachial index; BP: blood pressure; PN: polyneuropathy; MNSI: Michigan Neuropathy Screening Instrument
^{*}F-test; ⁺Kruskal-Wallis test; [§]Fisher's exact test; [&]log F-test.

TABLE 2. Independent variables remaining in the final multiple logistic regression models.

All subjects (n=393)	OR (95% CI)	P value
Age (years)	1.09 (1.05-1.13)	<0.0001
Waist circumference (cm)	1.03 (1.00-1.05)	0.0200
Diabetes	2.82 (1.55-5.13)	0.0007
Peripheral arterial disease (ABI<0.9)	1.88 (0.89-3.98)	0.0992
Diabetic subjects (n=195)		
	OR (95% CI)	P value
Age (years)	1.09 (1.04-1.14)	0.0007
Waist circumference (cm)	1.04 (1.01-1.07)	0.0183
Peripheral arterial disease (ABI<0.9)	2.76 (1.20-6.38)	0.0173
Duration of diabetes (years)	1.02 (0.99-1.05)	0.2852

ABI: ankle brachial index; OR: odds ratio