Prevalence of Polyneuropathy in Pre-Diabetes and Diabetes Is Associated With Abdominal Obesity and Macroangiopathy

The MONICA/KORA Augsburg Surveys S2 and S3

DAN ZIEGLER, MD, PHD, FRCPE[1]
WOLFGANG RATHMANN, MD, MSPH[2]
THORSTEN DICKHAUS, MSC[2]
CHRISTA MEISINGER, MD, MPH[3]
ANDREAS MIELCK, PHD, MPH[4]
FOR THE KORA STUDY GROUP

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

RESEARCH DESIGN AND METHODS — Subjects with diabetes ($n = 195$) and control subjects matched for age and sex ($n = 198$) from the population-based MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases)/KORA (Cooperative Research in the Region of Augsburg) Augsburg Surveys 1989/1990 (S2) and 1994/1995 (S3) aged 25–74 years were contacted again and assessed in 1997/1998 by the Michigan Neuropathy Screening Instrument using a score cut point >2. An oral glucose tolerance test was performed in the control subjects.

RESULTS — Among the control subjects, 46 (23.2%) had IGT, 71 (35.9%) had IFG, and 81 had NGT. The prevalence of polyneuropathy 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 diabetes vs. NGT, IFG, and IGT). In the entire population studied ($n = 393$), age, waist circumference, and diabetes were independent factors significantly associated with polyneuropathy, whereas in the diabetic group polyneuropathy was associated with age, waist circumference, and peripheral arterial disease (PAD) (all $P < 0.05$).

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

Diabetes Care 31:464–469, 2008

From the [1]Institute for Clinical Diabetes Research, German Diabetes Center, Leibniz Institute at the Heinrich Heine University, Düsseldorf, Germany; the [2]Institute of Biometrics and Epidemiology, German Diabetes Center, Düsseldorf, Germany; the [3]Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany; and the [4]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.

Address correspondence and reprint requests to Dr. Dan Ziegler, FRCPE, Institut für Klinische Diabetologie, Deutsches Diabetes-Zentrum, Leibniz-Zentrum an der Heinrich-Heine-Universität, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany. E-mail: dan.ziegler@ddz.uni-duesseldorf.de.

Received for publication 12 September 2007 and accepted in revised form 16 November 2007.

Published ahead of print at http://care.diabetesjournals.org on 26 November 2007. DOI: 10.2337/dc07-1796.

Abbreviations: CIAP, chronic idiopathic axonal polyneuropathy; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; KORA, Cooperative Research in the Region of Augsburg; MONICA, Monitoring Trends and Determinants on Cardiovascular Diseases; MNSI, Michigan Neuropathy Screening Instrument; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PAD, peripheral arterial disease.

Diabetic polyneuropathy affects 54 per 100,000 people a year in the community and represents the third most common 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 diabetes 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 toward 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 polyneuropathy ranging from 8 to 54% in type 1 diabetic patients and from 13 to 46% in type 2 diabetic patients (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 polyneuropathy. The risk factors most consistently associated with polyneuropathy in type 2 diabetic patients at the population level were increasing age, duration of diabetes, height, and poor glycemic control evidenced by A1C 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 polyneuropathy in type 2 diabetes. In type 1 diabetic subjects, low HDL cholesterol was associated with prevalent polyneuropathy (24), and hypertension was a

predictor of incident polyneuropathy (25). Moreover, in a center-based study in type 1 diabetic patients, triglycerides, BMI, and hypertension were identified as risk factors for incident polyneuropathy (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 polyneuropathy (26–29). Some epidemiological studies have reported that the prevalence of polyneuropathy is higher in individuals with IGT compared with those with normal glucose tolerance (NGT) (10,30), while 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 for 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 polyneuropathy in subjects with diabetes and those with IGT and NGT in the general population.

RESEARCH DESIGN AND METHODS

The independent population-based MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases)/KORA (Cooperative Research in the Region of Augsburg) Augsburg surveys were part of the multinational World Health Organization MONICA project (35). The second MONICA Augsburg Survey 1989/1990 (S2) included 4,940 people (participation 76.9%), while the third MONICA Augsburg Survey 1994/1995 (S3) included 4,856 people (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 if they reported a diagnosis of diabetes or if they were taking antidiabetes medication. All diabetic subjects from the S2 and S3 surveys as well as nondiabetic subjects matched (1:1) for age and sex were invited again in March 1997 and assessed until July 1998 for the presence of chronic diabetes 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, six were excluded due to an incomplete dataset, leaving 195 patients in the final analysis. An oral glucose tolerance test (OGTT) was performed in those who had been invited as nondiabetic control subjects. Age- and sex-matched control subjects were defined as those who were invited as nondiabetic and confirmed in the OGTT as nondiabetic (n = 198). Thus, the entire population studied included 393 subjects, of whom 185 originated from S2 and 208 from S3. In the nondiabetic group, 81 individuals had NGT, 71 had impaired fasting glucose (IFG), and 46 had IGT. Excluded were those who were invited as diabetic but self-confirmed as control subjects (n = 16) as well as those invited as control subjects but confirmed as new diabetic (n = 23) in the OGTT.

Blood pressure, body height, and body weight were determined by trained medical staff (mainly nurses). All measurement procedures have been described in detail elsewhere (36–38). Information concerning sociodemographic variables and cardiovascular risk factors was assessed by standardized personal interviews. 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 one 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 four-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 h/week in at least one 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 for myocardial infarction or stroke (38). Total serum cholesterol and HDL and LDL cholesterol levels were measured by enzymatic methods (CHOD-PAP; Boehringer, Mannheim, Germany). Serum creatinine was measured by the para-aminophenazone (PAP) method (Boehringer). Urinary albumin (in milligrams per liter) was determined in a random morning urine sample using an immunoturbidimetric test (Tina-quant; Boehringer).

OGTTs were carried out in the morning (7:00 A.M. to 11:00 A.M.) according to the World Health Organization 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 anhydrous glucose was given (Dextro OGT; Boehringer). IFG was defined using a cut point for plasma glucose of 100–125 mg/dl according to American Diabetes Association criteria (40).

The presence or absence of polyneuropathy was determined by the Michigan Neuropathy Screening Instrument (MNSI) using a score cut point >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 at the 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 polyneuropathy was used.

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

Statistical analysis

Continuous data were expressed as the mean ± SD or geometric mean ×/÷ standard deviation factor (SDF). 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 polyneuropathy score was analyzed nonparametrically by performing the

Table 1—*Demographic and clinical variables of the subjects from the MONICA/KORA Augsburg Surveys (S2 and S3)*

	NGT	IFG	IGT	Diabetes	Overall *P*
n	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 blood pressure (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†
2-h glucose (mg/dl)	98.7 ± 19.9	104.4 ± 18.9	160.6 ± 15.8	—	<0.001†
A1C (%)	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*
Polyneuropathy (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 (%)	3.8	4.2	0	20.1	<0.001*
Foot ulcer present (%)	0	0	2.2	4.1	0.089*

Data are means ± SD and geometric mean ×/÷ SDF (standard deviation factor). ABI, ankle brachial index. *Fisher's exact test, †*F*-test, ‡log *F*-test, §Kruskal-Wallis test.

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, PAD, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, IGT, diabetes, duration of diabetes, A1C, fasting blood glucose, and 2-h 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, A1C, IGT, diabetes, and PAD. 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, A1C, albuminuria, and the prevalence of polyneuropathy, whereas 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, and absent ankle reflexes and in 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 those 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, 12 and 135 had type 1 and type 2 diabetes, respectively, and 6 had secondary diabetes, and in 42 subjects the diabetes type was not known. Diabetes treatment included oral antidiabetic agents in 86 (44.1%), insulin in 44 (22.6%), oral antidiabetic agents and insulin in 42 (21.5%), and diet only in 23 subjects (11.8%). Cardiovascular medications across the four groups studied included ACE inhibitors in a mean 6.6% (range 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 polyneuropathy 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 minus IGT, 15% (0–30); diabetes minus IFG, 17% (4–29); diabetes minus NGT, 21% (9–32); IGT minus IFG, 2% (−14 to 18); IGT minus NGT, 6% (−9 to 20); and IFG minus NGT, 4% (−8 to 16).

In the univariate regression models including the entire population studied, significant differences between those with and without polyneuropathy were noted for the following variables: age, OR 1.08 (95% CI 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);

Table 2—*Independent variables remaining in the final multiple logistic regression models*

	OR (95% CI)	*P*
All subjects ($N = 393$)		
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
PAD (ABI <0.9)	1.88 (0.89–3.98)	0.0992
Diabetic subjects ($n = 195$)		
Age (years)	1.09 (1.04–1.14)	0.0007
Waist circumference (cm)	1.04 (1.01–1.07)	0.0183
PAD (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.

fasting glucose, 1.00 (1.00–1.01); A1C, 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 mutivariate logistic regression models included age, male sex, height, weight, waist circumference, low physical activity, log creatinine, log albuminuria, A1C, 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 polyneuropathy (all $P < 0.05$), whereas the relationship with PAD reached borderline significance ($P = 0.099$). In the diabetic subjects, independent associations with polyneuropathy 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 polyneuropathy is slightly higher in persons with IGT than in those with NGT and more than twofold higher in subjects with diabetes compared with those with IGT. We further show for the first time that the prevalence of polyneuropathy 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 in diabetic patients, apart from age, waist circumference and PAD are independently associated with prevalent polyneuropathy. This is another novel finding suggesting an interplay between polyneuropathy and both cardiovascular risk factors and macroangiopathy in the lower limbs.

The vast majority of previous population-based studies did not assess 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 polyneuropathy in diabetic patients. In the U.S. 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 OR 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 polyneuropathy in univariate analyses. Some studies have not taken measures of obesity into consideration at all when evaluating the possible risk factors of polyneuropathy (10,15,18,23). Moreover, PAD verified by ankle brachial index has not been previously reported as a risk modifier for the prevalence of polyneuropathy in diabetic patients. Thus, the present study is the first to report an independent association of prevalent polyneuropathy 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 polyneuropathy. Due to the cross-sectional nature of this study, it can be concluded that visceral obesity is not a predictor for the development of polyneuropathy and does not play a pathogenetic role, but against the background of the independent association of polyneuropathy 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 polyneuropathy in diabetic subjects. The metabolic syndrome (visceral obesity, dyslipidemia, hyperglycemia, 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 polyneuropathy 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 polyneuropathy (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 polyneuropathy in individuals with IGT compared with those with NGT, as these risk factors were associated with polyneuropathy in the entire population studied. In the San Luis Valley Diabetes Study (10) the prevalence of polyneuropathy was 3.9, 11.2, and 25.8% in subjects with NGT, IGT, and diabetes, respectively. The OR (95% CI) for the presence of polyneuropathy in individuals with IGT ($n = 89$) was 3.5 (1.5–7.9) compared with those with NGT ($n = 488$) (10). In the Hoorn Study (30) only the risk of bilateral absence of ankle reflexes (OR 1.7 [95% CI 1.1–2.8]), but not knee reflexes (1.2 [0.4–4.1]) or vibration sensation at the big toe (0.8 [0.5–1.3]) or at the medial malleoli (0.9 [0.4–2.2]), was associated with IGT as compared with NGT. Other studies have found no association be-

tween IGT and prevalent polyneuropathy (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 polyneuropathy, as compared with our study reaching only 3.9% when diagnosed by the Neuropathy Disability Score and 6.1% when diagnosed by an overall neuropathy score. However, the corresponding rates of polyneuropathy 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 polyneuropathy in individuals with IGT.

An interesting aspect in the context of a presumable "pre-diabetic 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 control subjects 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 polyneuropathy or CIAP, as some studies suggest that pre-diabetes 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 control subjects, assessment of chronic glycemic exposure and of diabetes 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 pre-diabetes compared with 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 are required. Apart from age, an important risk factor associated with polyneuropathy in diabetic patients is waist circumference, whereas PAD is a relevant associated disorder. Thus, abdominal obesity and peripheral macrovascular disease may represent important targets to prevent diabetic polyneuropathy.

Acknowledgments— The KORA (Cooperative Research in the Region of Augsburg) research platform and the MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) Augsburg studies were initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria.

References

1. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD: The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 123:665–676, 2000
2. Shaw JE, Zimmet PZ, Gries FA, Ziegler D: Epidemiology of Diabetic Neuropathy. In *Textbook of Diabetic Neuropathy*. Gries FA, Cameron NE, Low PA, Ziegler D, Eds. Thieme, Stuttgart, New York, 2003, p. 64–82
3. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH: A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 36:150–154, 1993
4. Ziegler D, Gries FA, Mühlen H, Rathmann W, Spüler M, Lessmann F, the DiaCAN Multicenter Study Group: Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes centers. *Diabete Metab* 19:143–151, 1993
5. Fedele D, Comi G, Coscelli C, Cucinotta D, Feldman EL, Ghirlanda G, Greene DA, Negrin P, Santeusanio F, the Italian Diabetic Neuropathy Committee: A multicenter study on the prevalence of diabetic neuropathy in Italy. *Diabetes Care* 20:836–843, 1997
6. Cabezas-Cerrato J, Neuropathy Spanish Study Group of the Spanish Diabetes Society (SDS): The prevalence of clinical diabetic polyneuropathy in Spain: a study in primary care and hospital clinic groups. *Diabetologia* 41:1263–1269, 1998
7. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH; EURODIAB Prospective Complications Study Group: Vascular risk factors and diabetic neuropathy. *N Engl J Med* 352:341–350, 2005
8. Knuiman MW, Welborn TA, McCann VJ, Stanton KG, Constable IJ: Prevalence of diabetic complications in relation to risk factors. *Diabetes* 35:1332–1339, 1986
9. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes* 36: 730–739, 1987
10. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF Sensory neuropathy in non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. *Am J Epidemiol* 131:633–643
11. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'Brien PC, Melton LJ 3d, Service FJ: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 43:817–824, 1993
12. Harris M, Eastman R, Cowie C: Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population. *Diabetes Care* 16:1446–1452, 1993
13. Shaw JE, Hodge AM, de Courten M, Dowse GK, Gareeboo H, Tuomilehto J, Alberti KGMM, Zimmet PZ: Diabetic neuropathy in Mauritius: prevalence and risk factors. *Diabetes Res Clin Prac* 42:131–139, 1998
14. Verhoeven S, van Ballegooie E, Casparie AF: Impact of late complications in type 2 diabetes in a Dutch population. *Diabet Med* 8:435–438, 1991
15. Walters DP, Gatting W, Mullee MA, Hill RD: The prevalence of diabetic distal sensory neuropathy in an English community. *Diabet Med* 9:349–353, 1992
16. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, Wolz M, Burt V, Curtin L, Engelgau M, Geiss L; 1999–2000 national health and nutrition examination survey: Prevalence of lower-extremity disease in the U.S. adult population ≥40 years of age with and without diabetes: 1999–2000 National Health and Nutrition Examination Survey. *Diabetes Care* 27:1591–1597, 2004
17. Tapp RJ, Shaw JE, de Courten MP, Dunstan DW, Welborn TA, Zimmet PZ; AusDiab Study Group: Foot complications in type 2 diabetes: an Australian population-based study. *Diabet Med* 20:105–113, 2003
18. Hanley AJ, Harris SB, Mamakeesick M, Goodwin K, Fiddler E, Hegele RA, Spence JD, House AA, Brown E, Schoales B, McLaughlin JR, Klein R, Zinman B: Complications of type 2 diabetes among Aboriginal Canadians: prevalence and associated risk factors. *Diabetes Care* 28: 2054–2057, 2005
19. Cheng YJ, Gregg EW, Kahn HS, Williams DE, De Rekeneire N, Narayan KM: Peripheral insensate neuropathy—a tall problem for US adults? *Am J Epidemiol* 164:873–880, 2006
20. Koopman RJ, Mainous AG, Liszka HA, Colwell JA, Slate EH, Carnemolla MA, Everett CJ: Evidence of nephropathy and peripheral neuropathy in US adults with undiagnosed diabetes. *Ann Fam Med* 4:427–432, 2006
21. Dyck PJ, Davies JL, Wilson DM, Service

FJ, Melton LJ, O'Brien PC: Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. *Diabetes Care* 22:1479–1486, 1999
22. Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJ, Klein CJ, Rizza RA, Pach JM, Klein R, Larson TS, Melton LJ, O'Brien PC: Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. *Diabetes Care* 29:2282–2288, 2006
23. Franklin GM, Shetterly SM, Cohen JA, Baxter J, Hamman RF: Risk factors for distal symmetric neuropathy in NIDDM: The San Luis Valley Diabetes Study. *Diabetes Care* 17:1172–1177, 1994
24. Maser RE, Steenkiste AR, Dorman JS, Kamp Nielsen V, Bass EB, Manjoo Q, Drash AL, Becker DJ, Kuller LH, Greene DA, Orchard TJ: Epidemiological correlates of diabetic neuropathy: report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes* 38:1456–1461, 1989
25. Forrest KY, Maser RE, Pambianco G, Becker DJ, Orchard TJ: Hypertension as a risk factor for diabetic neuropathy: a prospective study. *Diabetes* 46:665–670, 1997
26. Russell JW, Feldman EL: Impaired glucose tolerance—does it cause neuropathy? *Muscle Nerve* 24:1109–1112, 2001
27. Singleton JR, Smith AG: Therapy insight: neurological complications of prediabetes. *Nat Clin Pract Neurol* 2:276–282, 2006
28. Kissel JT: Peripheral neuropathy with impaired glucose tolerance: a sweet smell of success? *Arch Neurol* 63:1055–1056, 2006
29. Dyck PJ, Dyck PJ, Klein CJ, Weigand SD: Does impaired glucose metabolism cause polyneuropathy? Review of previous studies and design of a prospective controlled population-based study. *Muscle Nerve* 36:536–541, 2007
30. de Neeling JN, Beks PJ, Bertelsmann FW, Heine RJ, Bouter LM: Peripheral somatic nerve function in relation to glucose tolerance in an elderly Caucasian population: the Hoorn study. *Diabet Med* 13:960–966, 1996
31. Eriksson KF, Nilsson H, Lindgärde F, Osterlin S, Dahlin LB, Lilja B, Rosén I, Sundkvist G: Diabetes mellitus but not impaired glucose tolerance is associated with dysfunction in peripheral nerves. *Diabet Med* 11:279–285, 1994
32. Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP: Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. *Arch Neurol* 63:1075–1079, 2006
33. Smith AG, Singleton JR: Idiopathic neuropathy, prediabetes and the metabolic syndrome. *J Neurol Sci* 242:9–14, 2006
34. Hughes RA, Umapathi T, Gray IA, Gregson NA, Noori M, Pannala AS, Proteggente A, Swan AV: A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy. *Brain* 127:1723–1730, 2004
35. WHO MONICA Project Principal Investigators, prepared by H. Tunstall-Pedoe: The World Health Organization MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease): a major international collaboration. *J Clin Epidemiol* 34:105–114, 1988
36. Keil U, Cairns V, Döring A: MONICA-Project, Region Augsburg, manual of operations, survey. In *GSF-Bericht 20*, Munich, Germany, Forschungszentrum für Gesundheit und Umwelt, 1985
37. Hense HW, Filipiak B, Döring A: Ten-year trends of cardiovascular risk factors in the MONICA Augsburg Region in Southern Germany: results from the 1984/85, 1989/90 and 1994/1995 surveys. *Cardiovasc Dis Prev* 1:318–327, 1998
38. Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Löwel H: Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med* 162:82–89, 2002
39. Rathmann W, Haastert B, Icks A, Löwel H, Meisinger C, Holle R, Giani G: High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening: the KORA survey 2000. *Diabetologia* 46:182–189, 2003
40. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
41. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA: A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 17:1281–1289, 1994
42. Bernstein EF, Fronek A: Current status of noninvasive tests in the diagnosis of peripheral arterial disease. *Surg Clin North Am* 62:473–487, 1982
43. World Health Organization: *Report of a WHO Consultation: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications*. Geneva, World Health Org., 1999 (Tech. Rep. Ser., no. WHO/NCD/NCS/99.2)
44. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:24–30, 2005
45. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 112:2735–2752, 2005. [Erratum in: *Circulation* 112:e297–e298]
46. Sosenko JM, Kato M, Soto R, Goldberg RB: Sensory function at diagnosis and in early stages of NIDDM in patients detected through screening. *Diabetes Care* 15:847–852, 1992
47. Barr EL, Wong TY, Tapp RJ, Harper CA, Zimmet PZ, Atkins R, Shaw JE; AusDiab Steering Committee: Is peripheral neuropathy associated with retinopathy and albuminuria in individuals with impaired glucose metabolism? The 1999–2000 AusDiab Study. *Diabetes Care* 29:1114–1116, 2006