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Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-diabetes and diabetes. The KORA Myocardial Infarction Registry

Dan Ziegler [a,*], Wolfgang Rathmann [b], Christa Meisinger [c,d], Thorsten Dickhaus [b], Andreas Mielck [e], for the KORA Study Group

[a] Institute of Clinical Diabetes Research, German Diabetes Center, Leibniz Center for Diabetes Research at the Heinrich Heine University, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany
[b] Institute of Biometrics and Epidemiology, German Diabetes Center, Düsseldorf, Germany
[c] Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany
[d] Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Augsburg, Germany
[e] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany

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ABSTRACT

The lowest glycemic threshold for and the risk factors associated with neuropathic pain have not been established. The aim of this study was to determine the prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), normal glucose tolerance (NGT). Subjects aged 25–74 years with diabetes ($n = 214$) and controls matched for age and sex ($n = 212$) from the population-based KORA (Cooperative Health Research in the Region of Augsburg) Myocardial Infarction Registry were assessed for neuropathic pain by the Michigan Neuropathy Screening Instrument using its pain-relevant questions and an examination score cutpoint >2. An oral glucose tolerance test was performed in the controls. Among the controls, 61 (28.8%) had IGT (either isolated or combined with IFG), 70 (33.0%) had isolated IFG, and 81 had NGT. The prevalence of neuropathic pain was 21.0% in the diabetic subjects, 14.8% in those with IGT, 5.7% in those with IFG, and 3.7% in those with NGT (overall $p < 0.001$). In the entire population studied ($n = 426$), age, waist circumference, peripheral arterial disease (PAD), and diabetes were independent factors significantly associated with neuropathic pain, while in the diabetic group it was waist circumference, physical activity, and PAD (all $p < 0.05$). In conclusion, the prevalence of neuropathic pain is relatively high among survivors of myocardial infarction with diabetes and IGT compared to those with isolated IFG and NGT. Associated cardiovascular risk factors including abdominal obesity and low physical activity may constitute targets to prevent neuropathic pain in this population.

1. Introduction

Approximately one of three diabetic patients is affected by distal symmetric polyneuropathy which represents a major health problem, as it may present with partly excruciating neuropathic pain and is responsible for substantial morbidity and increased mortality (Forsblom et al., 1998; Daousi et al., 2004; Ziegler et al., 2008). Chronic pain associated with diabetic neuropathy exerts a substantial impact on the quality of life, particularly by causing considerable interference with daily functioning and enjoyment of life (Galer et al., 2000; Tölle et al., 2006). Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates patients to seek health care.

Hyperglycemia is a major permissive factor for the development of diabetic polyneuropathy, but evidence has emerged suggesting that vascular factors appear to play a paramount role for its pathogenesis and clinical phenotype (Cameron et al., 2001; Tesfaye et al., 2005). On the other hand, patients with peripheral arterial disease (PAD) may develop a peripheral sensory neuropathy independent of diabetes manifesting as a broad spectrum of peripheral nerve dysfunctions including pain and sensory deficiencies due to chronic ischemia mostly involving the lower limbs (Lang et al., 2006).

There is now major interest in pre-diabetes 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 or neuropathic pain (Russell and Feldman, 2001; Singleton and Smith, 2006; Kissel, 2006; Dyck et al., 2007). Some epidemiological studies have

* Corresponding author. Tel.: +49 211 33821; fax: +49 211 3382277.
E-mail address: dan.ziegler@ddz.uni-duesseldorf.de (D. Ziegler).

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reported that the prevalence of polyneuropathy is higher in individuals with IGT as compared to those with normal glucose tolerance (NGT) (Franklin et al., 1990; de Neeling et al., 1996), whilst others could not confirm such an association (Fujimoto et al., 1987; Shaw et al., 1998; Eriksson et al., 1994). Painful neuropathy affects 8–26% of the diabetic population (Daousi et al., 2006; Davies et al., 2006; Wu et al., 2007; Ziegler et al., 2008), but the prevalence neuropathic pain in subjects with pre-diabetes in relation to those with diabetes and the associated risk factors have not been hitherto determined.

The aim of the present study was to determine the prevalence and risk factors of painful neuropathy among survivors of myocardial infarction with diabetes, IGT, IFG, and NGT. Using myocardial infarction as a model of macroangiopathy we hypothesized that if vascular disease is an important determinant of neuropathic pain, the prevalence of the latter would be increased and the associated risk factors could be modified in this population.

2. Methods

The study methods and MI case definition of the population-based KORA Myocardial Infarction Registry have been described in detail elsewhere (Löwel et al., 1991). To study medical outcomes of diabetes (KORA-A; Cooperative Research in the Augsburg Region, Southern Germany) (Mielck et al., 2006), 463 diabetic subjects were identified from the MI register, with 384 (82.9%) still living in the study region. Of those, 16 were not contactable, 73 refused and 21 were unable to participate, leaving 274 diabetic persons who could be included in the KORA-A study (response rate 71.4%); 41 stated afterwards that they do not have diabetes, leaving 233 who were assessed for the presence or absence of chronic diabetic complications including polyneuropathy. The KORA-A study was 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 and/or if they were taking antidiabetic medication. Included in the present study were cases defined as those who were invited as having diabetes and confirmed as being diabetic based on self-reports ($n = 233$). Among the diabetic subjects, 19 were excluded due to an incomplete data set, leaving 214 patients in the final analysis. An oral glucose tolerance test (OGTT) was performed in all persons who had been invited as nondiabetic controls. Age-matched and sex-matched controls were defined as those who were invited as nondiabetic and confirmed in the OGTT as nondiabetic ($n = 254$), i.e. 11.9% of all non-diabetic long-term MI survivors from the KORA Myocardial Infarction Registry. Due to the matching, their age and sex characteristics were different from the non-diabetic survivors (matched non-diabetic: age: 70.5 ± 6.9 years, males: 75%; all survivors: age: 66.4 ± 9.9 years, males: 77%). In this matched nondiabetic group, 81 individuals had NGT, 70 had isolated IFG, and 61 had IGT. In the IGT group, 28 persons had isolated IGT, while the remaining 33 individuals had both IGT and IFG). Excluded were persons who were invited as diabetic but self-confirmed as controls ($n = 44$). Excluded were also persons who were invited as controls but confirmed as new diabetic ($n = 42$) in the OGTT.

Blood pressure, body height, and body weight, were determined by trained medical staff (mainly nurses). All measurement procedures have been described elsewhere in detail (Keil et al., 1985; Hense et al., 1998; Meisinger et al., 2002). Information concerning sociodemographic variables, and cardiovascular risk factors was assessed by standardized personal interviews. 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 $\geqslant$40 g/day in men and $\geqslant$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 h per week in at least one season. A participant was classified as inactive if he or she was less active during leisure time. 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).

OGTTs were carried out in the morning (7:00–11:00 am) according to the WHO protocol (WHO, 1985) as previously described (Rathmann et al., 2002 and Rathmann et al., 2003). 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).

The presence or absence of neuropathic pain was determined by the Michigan Neuropathy Screening Instrument (MNSI) question 2 (Do you have burning pain or pain at rest in your lower legs and/or feet?) and question 6 (Is it painful when the bed covers touch your skin?) and clinical examination using a score cutpoint >2 as previously suggested (Feldman et al., 1994) and recently validated (Moghtaderi et al., 2006). 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. Neuropathic pain (painful neuropathy) was defined as the positive answer to question 2 and/or question 6 in presence of a MNSI score >2.

Peripheral arterial disease (PAD) was assessed using a Mini Dopplex device (HNE Healthcare, Hilden, Germany) and defined by an ankle brachial index (ABI) < 0.9. This cutpoint has a sensitivity of 95% for the presence of PAD documented by angiography (Bernstein and Fronek, 1982).

2.1. Statistical analysis

Continuous data were expressed by the mean ± SD or geometric mean $\times/\div$ 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 proportions of subjects with neuropathic pain in each of the four groups studied were analysed nonparametrically by performing the Kruskal–Wallis test. Univariate logistic regression models were performed where age, sex, height, weight, BMI, waist circumference, hip circumference, systolic blood pressure, smoking, physical activity, alcohol consumption, creatinine, albuminuria, 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 h blood glucose in the OGTT were used as independent variables. Multiple associations were studied both in the entire population and in the diabetic group using a stepwise logistic regression analysis with pain in presence of MNSI > 2 as the dependent variable. At each step of the algorithm it was possible to enter and/or remove new covariates. The

level of significance was set at $\alpha = 0.05$. The SAS statistical package version 9.1.3 (TS1M3) was used for all analyses.

3. Results

The demographic variables of the survivors of MI with NGT, IFG, IGT, and diabetes are shown in Table 1. Significant differences between the four groups studied were noted for age, BMI, waist circumference, systolic blood pressure, HbA1 c, HDL cholesterol, creatinine, albuminuria and the proportions of stroke, PAD, allodynia, absent ankle reflexes, and polyneuropathy (all $p < 0.05$). Fasting and 2 h glucose in the OGTT were significantly different between the groups with NGT, IFG, and IGT (both $p < 0.05$). No significant differences between the groups were noted for sex, height, LDL cholesterol and the proportions of smokers as well as those with high alcohol consumption, low physical activity, burning pain, and foot ulcers.

According to the above definition, the prevalence (95% CI) of neuropathic pain was 21.0% (15.8–27.1%) in the diabetic subjects, 14.8% (7.0–26.2%) in those with IGT, 5.7% (1.6–14.0%) in those with IFG, and 3.7% (0.8–10.4%) in those with NGT (overall $p < 0.001$). The percentage differences (95% CI) between the groups in prevalence of neuropathic pain adjusted for multiplicity were: diabetes minus IGT: 6.3% (−7.4% to 20.0%); diabetes minus IFG: 15.3% (5.2–25.4%); diabetes minus NGT: 17.3% (8.4–26.3%); IGT minus IFG: 9.0% (−4.6% to 22.7%); IGT minus NGT: 11.1 (−1.8% to 23.9%); and IFG minus NGT: 2.0 (−6.9% to 10.9%).

The univariate regression models including the entire population ($n = 426$) showing associations with neuropathic pain as dependent variable ($p \leqslant 0.1$) are listed in Table 2. No relationship with neuropathic pain was noted for sex, BMI, systolic blood pressure, smoking, high alcohol consumption, physical activity, proportions of stroke, fasting and 2 h blood glucose in the OGTT, HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides.

Table 2
Associations with painful neuropathy ($p \leqslant 0.1$) as dependent variable in univariate regression models including the entire population ($n = 426$)

	OR (95% CI)	*P*-value
Age (years)	1.04 (0.99–1.08)	0.105
Height (cm)	1.04 (1.00–1.08)	0.057
Weight (kg)	1.03 (1.01–1.06)	0.017
Waist circumference (cm)	1.05 (1.02–1.08)	0.004
Hip circumference (cm)	1.04 (1.00–1.08)	0.030
Peripheral arterial disease (ABI<0.9)	2.19 (1.15–4.19)	0.018
Diabetes	1.94 (0.99–3.80)	0.054
Creatinine	2.82 (1.23–6.43)	0.014
Albuminuria (mg/l)	1.14 (0.98–1.33)	0.082

ABI: ankle brachial index; OR: odds ratio.

The independent variables remaining in the final multiple logistic regression models with neuropathic pain as dependent variable are listed in Table 3. In the entire population studied, age, waist circumference, PAD, and diabetes were significantly associated with neuropathic pain (all $p < 0.05$). In the diabetic subjects, indepen-

Table 3
Independent variables remaining in the final multiple logistic regression models

All subjects ($n = 426$)	OR (95% CI)	*P*-value
Age (years)	1.06 (1.01–1.11)	0.0295
Waist circumference (cm)	1.04 (1.01–1.07)	0.0049
Peripheral arterial disease (ABI < 0.9)	3.65 (1.85–7.22)	0.0002
Diabetes	2.98 (1.44–6.14)	0.0032
Diabetic subjects ($n = 214$)	OR (95% CI)	*P*-value
Waist circumference (cm)	1.05 (1.01–1.09)	0.0054
Physical activity	0.31 (0.10–0.99)	0.0484
Peripheral arterial disease (ABI < 0.9)	5.61 (2.43–12.96)	<0.0001

ABI: ankle brachial index; OR: odds ratio.

Table 1
Demographic and clinical variables of the subjects from the MONICA/KORA Augsburg Myocardial Infarction Registry

	NGT	IFG	IGT	Diabetes	Overall *P*-value
n	81	70	61	214	–
Sex (m/f)	59/22	56/14	44/17	172/42	0.35[c]
Age (years)	71.1 ± 6.3	70.9 ± 6.8	72.0 ± 6.8	69.0 ± 8.1	0.010[a]
Height (cm)	167.8 ± 7.8	168.5 ± 9.0	167.5 ± 9.4	168.6 ± 8.9	0.82[a]
BMI (kg/m^2)	27.5 ± 3.9	28.1 ± 3.6	27.7 ± 3.6	29.1 ± 4.3	0.005[a]
Waist circumference (cm)	98.1 ± 9.8	98.6 ± 8.9	99.1 ± 12.3	103.5 ± 10.7	<0.001[a]
Systolic BP (mmHg)	138 ± 18.2	139 ± 19.0	141 ± 17.6	147 ± 20.6	<0.001[a]
Fasting glucose (mg/dl)	92.1 ± 5.2	107.6 ± 6.8	102.3 ± 10.3	–	<0.001[a]
2 h glucose (mg/dl)	102.7 ± 20.5	108.2 ± 19.8	160.2 ± 15.5	–	<0.001[a]
HbA1c (%)	4.8 ± 0.3	4.9 ± 0.3	4.9 ± 0.3	6.8 ± 1.6	<0.001[a]
LDL cholesterol (mg/dl)	130.7 ± 33.9	136.6 ± 39.5	137.0 ± 42.7	128.8 ± 41.3	0.35[a]
HDL cholesterol (mg/dl)	53.9 ± 12.9	52.5 ± 15.3	50.6 ± 12.4	45.7 ± 13.9	<0.001[a]
Creatinine (mg/dl)	0.93×/÷1.24	0.97×/÷1.22	0.96×/÷1.31	1.13×/÷1.46	<0.001[d]
Albuminuria (mg/l)	10.8×/÷4.14	13.5×/÷4.16	18.4×/÷5.67	36.7×/÷8.04	<0.001[d]
Smoking (%)	11.1	7.2	4.9	7.5	0.60[c]
Alcohol (%)	10.0	13.2	12.1	13.1	0.91[c]
Low physical activity (%)	40.7	36.2	32.8	26.2	0.08[c]
Stroke (%)	3.8	7.5	11.9	14.8	0.03[c]
PAD [ABI < 0.9] (%)	11.4	11.6	17.0	25.7	0.01[c]
Burning pain feet/legs (%)	13.6	13.0	21.3	22.4	0.18[c]
Allodynia feet (%)	3.7	1.5	3.3	14.8	<0.001[c]
Absent ankle reflexes (%)	8.6	4.3	3.4	25.6	<0.001[c]
Foot ulcer present (%)	1.2	0	1.7	2.9	0.61[c]
Polyneuropathy [MNSI > 2] (%)	17.3	8.7	24.6	38.6	<0.001[b]
Neuropathic pain (%)	3.7	5.7	14.8	21.0	<0.001[c]

NGT: normal glucose tolerance; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; PAD: peripheral arterial disease; ABI: ankle brachial index; BP: blood pressure; MNSI: Michigan Neuropathy Screening Instrument.

[a] F-test.
[b] Kruskal–Wallis test.
[c] Fisher's exact test.
[d] log F-test.

dent associations with neuropathic pain were noted for waist circumference, physical activity, and PAD (all $p < 0.05$).

4. Discussion

The results of this study demonstrate that the prevalence of neuropathic pain is relatively high among survivors of myocardial infarction with diabetes and IGT reaching 21.0% and 14.8%, respectively. In contrast, persons with isolated IFG showed only a minimally higher prevalence of 5.7% as compared to 3.7% in those with NGT. Moreover, this study shows that abdominal obesity and low physical activity are important risk factors associated with neuropathic pain, while PAD is an associated disorder in subjects with previous MI.

The epidemiology of polyneuropathy or neuropathic pain has not been previously addressed in patients with evidence of macroangiopathy such as coronary heart disease or MI. However, myocardial infarction or ischemia have been identified as risk factors for polyneuropathy in a primary health care population (Barbosa et al., 2001). We hypothesized that if vascular disease is an important factor in the development of polyneuropathy as recently suggested (Cameron et al., 2001; Tesfaye et al., 2005), the prevalence of the latter should be increased in patients with macroangiopathy evidenced by a MI. Indeed, the prevalence of polyneuropathy using a cutpoint of >2 for the MNSI clinical examination score in patients who survived a MI was shifted to considerably higher levels reaching 24.6% in the IGT group and 38.6% in the diabetic group compared to a lower prevalence of polyneuropathy we recently reported in the general population of 13.0% in subjects with IGT, and 28.0% in those with diabetes (Ziegler et al., 2008). The most striking result in the present MI population was that in the IGT group the prevalence of painful neuropathy was even slightly higher (14.8%) than the prevalence of polyneuropathy including the symptomatic and asymptomatic cases in the general population (13.0%). In contrast, despite the prevalence of polyneuropathy of 11.3% in persons with IFG in the general population, the prevalence of neuropathic pain in patients with previous MI and IFG was only 5.7%. Thus, in this population, IGT rather than IFG appears to foster neuropathic pain.

Previous studies have assessed the prevalence of polyneuropathy rather than neuropathic pain in persons with pre-diabetes. In the San Luis Valley Diabetes study (Franklin et al., 1990) the prevalence of polyneuropathy 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 polyneuropathy in individuals with IGT ($n = 89$) was 3.5 (1.5–7.9) compared to those with NGT ($n = 488$). In the Hoorn study (de Neeling et al., 1996) 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. On the other hand, several studies have found no association between IGT and prevalent polyneuropathy (Fujimoto et al., 1987; Shaw et al., 1998; Eriksson et al., 1994). In a large sample of individuals with IGT or IFG, the AusDiab study (Barr et al., 2006) 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. Against this background we suggest that the prevalence of both polyneuropathy and neuropathic pain in persons with IGT is increased in presence of CHD and that visceral obesity and PAD further contribute to this increase.

An interesting aspect in the context of a presumable "pre-diabetic neuropathy" is the role of IGT in chronic idiopathic axonal polyneuropathy (CIAP). It has been hypothesized that some components of the metabolic syndrome may play a causative role in neuropathy both for those with pre-diabetes, and those with otherwise idiopathic neuropathy (Singleton and Smith, 2006; Smith and Singleton, 2006). Several uncontrolled observational studies have recently reported an increased prevalence of IGT in patients with CIAP (Singleton and Smith, 2006; Hoffman-Snyder et al., 2006). However, glucose intolerance is common in the elderly population. In the only controlled study hitherto available 32% of patients with CIAP and 14% of the controls had IGT or fasting hyperglycemia but, after adjusting for age and sex, the difference was not significant, even in the painful neuropathy subgroup (Hughes et al., 2004). 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 controls, assessment of chronic glycemic exposure and of diabetic complications, and statistical power (Dyck et al., 2007). 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 as compared to those with NGT (Russell and Feldman, 2001; Kissel, 2006; Dyck et al., 2007).

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 (Shaw et al., 1998; Gregg et al., 2004; Cheng et al., 2006; Dyck et al., 1999). However, these studies have not reported any association between BMI or weight and the prevalence of polyneuropathy in diabetic patients. In the US National Health and Examination Survey (NHANES) (Cheng et al., 2006), weight $\geqslant$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. In the Australian Diabetes Obesity and Lifestyle (AusDiab) study (Tapp et al., 2003) 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 (Franklin et al., 1990; Walters et al., 1992; Hanley et al., 2005). Moreover, PAD verified by ABI has not been previously reported as a risk modifier for the prevalence of painful diabetic neuropathy.

There are several limitations of this study. First, because we assessed a survivor cohort, a bias towards the less severe cases of MI may cannot be excluded. Second, the subgroups of NGT, IFG, and IGT were relatively small as compared with the diabetic group. Third, possible selection bias due to the incomplete response rate has to be taken into account. Fourth, neuropathic pain was assessed categorically rather than by a pain severity scale. However, we presume that these limitations did not exert a major impact on our observations. Although this sample of patients is not representative of the general population, it is representative of patients in the general population who survived a myocardial infarction.

Interestingly, the present study focusing on neuropathic pain including survivors of MI is in line with our recent observation in the diabetic general population showing an independent association of prevalent polyneuropathy with both waist circumference and PAD (Ziegler et al., 2008). Thus, almost identical cardiovascular risk factors and disorders are associated with polyneuropathy and neuropathic pain in the diabetic general population and survivors of MI, in whom age was replaced by low physical activity as an additional risk factor. Due to the cross-sectional nature of this study, it neither can be concluded that visceral obesity is a predictor

for the development of neuropathic pain nor that it plays a pathogenetic role, but against the background of the independent association of painful neuropathy with PAD reported herein, it is tempting to speculate that visceral obesity as an important component and macroangiopathy as frequent sequel of the metabolic syndrome may foster the risk of developing painful neuropathy in diabetic subjects. However, whether central obesity is a harbinger of diabetic peripheral neuropathic pain can only be answered by well-designed large prospective studies.

In conclusion, the prevalence of neuropathic pain in survivors of MI with IGT and diabetes is relatively high as compared to those with IFG and NGT. An important risk factor associated with diabetic peripheral neuropathic pain is waist circumference and low physical activity, while peripheral arterial disease is a relevant associated disorder. Retrospective data indicate that multifactorial cardiovascular risk intervention may be more successful in diabetic patients without than in those with polyneuropathy (Coppini et al., 2006), although recent controlled clinical trials could not demonstrate a favourable effect of multifactorial intervention or intensive diabetes therapy on new or worsening neuropathy in Type 2 diabetic patients (Gaede et al., 2008; The ADVANCE Collaborative Group, 2008). Whether abdominal obesity and peripheral macrovascular disease may represent important targets for strategies to prevent neuropathic pain associated with IGT and diabetes remains to be established.

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