

Postchallenge Hyperglycemia Is Positively Associated With Diabetic Polyneuropathy

The KORA F4 study

BRENDA W.C. BONGAERTS, PHD¹
WOLFGANG RATHMANN, MD¹
BERND KOWALL, PHD¹
CHRISTIAN HERDER, PHD²

DORIS STÖCKL, MD³
CHRISTA MEISINGER, MD³
DAN ZIEGLER, MD^{2,4}

OBJECTIVE—To assess the prevalence of distal sensorimotor polyneuropathy (DSPN) in an older population and to examine its relationship with prediabetes.

RESEARCH DESIGN AND METHODS—Glucose tolerance status was determined in 61- to 82-year-old participants ($n = 1,100$) of the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 Survey (2006–2008). Clinical DSPN was defined as bilaterally impaired foot-vibration perception and/or foot-pressure sensation.

RESULTS—Prevalence of clinical DSPN was similar in subjects with known diabetes (22.0%) and subjects with combined impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (23.9%). Among prediabetic subgroups, IFG-IGT, but not isolated-IFG and -IGT, was associated with a higher risk of clinical DSPN, compared with normal glucose tolerance. A J-shaped association was observed between clinical DSPN and quartiles of 2-h postchallenge glucose, but not with fasting glucose and HbA_{1c} levels.

CONCLUSIONS—Subjects with IFG-IGT and known diabetes had a similar prevalence of clinical DSPN. Elevated 2-h postload glucose levels appeared important for disease risk.

Diabetes Care 35:1891–1893, 2012

Distal sensorimotor polyneuropathy (DSPN) is an important complication of type 2 diabetes. It is still unclear whether nerve disorders are already manifest in subjects with prediabetes (1).

The aim of the current study was to evaluate the prevalence of DSPN in a representative sample of the older population and to study the association between prediabetes and DSPN. In addition, we examined the relationship between glucose (fasting and 2-h postload) and HbA_{1c} levels and the disorder.

RESEARCH DESIGN AND METHODS

The current study is performed using the follow-up data of the Cooperative Health Research in the Region of Augsburg (KORA) S4 Survey (1999–2001): the KORA F4 Survey (2006–2008) (2). Of the 1,209 participants, 923 participants subsequently completed an oral glucose tolerance test (OGTT) (according to World Health Organization criteria) (3), and self-reported diabetes was validated for 177 participants. Clinical DSPN was defined as bilaterally impaired foot-vibration

perception (tuning fork) and/or bilaterally impaired foot-pressure sensation (10-g monofilament). Details on a validation study of the DSPN definition are provided in the Supplementary Data online.

Age- and sex-adjusted differences in characteristics were evaluated for the different categories of glucose tolerance using ANOVA. Multivariate logistic regression models were fitted to study associations between diabetes, prediabetes (combined impaired fasting glucose [IFG] and impaired glucose tolerance [IGT], isolated IFG [i-IFG], and isolated IGT [i-IGT]), and the presence of clinical DSPN. In addition, relationships between glucose concentrations, HbA_{1c}, and clinical DSPN were studied. Analyses were performed with STATA (version 11; StataCorp, College Station, TX).

RESULTS—The results are based on 1,100 participants with complete information on glucose tolerance status, clinical DSPN, and other covariables. The study population included 577 subjects with normal glucose tolerance (NGT), 55 with i-IFG, 183 with i-IGT, 46 with IFG-IGT, 62 with undiagnosed diabetes, and 177 with known diabetes. Participants with known and undiagnosed diabetes were physically less active and had a larger waist circumference, a higher prevalence of hypertension, and prior cardiovascular events compared with subjects with NGT.

The prevalence of clinical DSPN was similar among participants with IFG-IGT (23.9% [95% CI 12.6–38.8]) and those with known diabetes (22.0 [16.2–28.9]). Prevalence in subjects with NGT, i-IFG, i-IGT, and undiagnosed diabetes was 11.1 (8.6–13.9), 5.5 (1.1–15.1), 14.8 (10.0–20.7), and 16.1 (8.0–27.7), respectively. Subjects with clinical DSPN were slightly older, taller, and physically less active than subjects without DSPN and had a larger waist circumference and higher HbA_{1c} levels.

The total prediabetic group did not show statistically significantly increased odds of having clinical DSPN compared

From the ¹Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany; the ²Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany; ³Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany; and the ⁴Department of Metabolic Diseases, Düsseldorf University Hospital, Düsseldorf, Germany.

Corresponding author: Wolfgang Rathmann, rathmann@ddz.uni-duesseldorf.de.

Received 19 October 2011 and accepted 8 April 2012.

DOI: 10.2337/dc11-2028

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-2028/-/DC1>.

C.M. and D.Z. share senior authorship.

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

with the NGT group (Table 1). When the subgroups were examined separately, a positive association was observed between IFG-IGT and clinical DSPN (odds ratio [OR] 2.82 [95% CI 1.29–6.10]). Compared with NGT subjects, participants with diabetes (undiagnosed and diagnosed) had increased odds of having clinical DSPN (1.54 [1.01–2.42]). This elevated risk was largely attributable to subjects with known diabetes, given that no association was observed for subjects with undiagnosed diabetes.

A J-shaped relationship was observed between quartiles of 2-h postload blood glucose and the presence of clinical DSPN (Table 1). There was no relationship between quartiles of fasting blood glucose and quartiles of HbA_{1c} levels and the disorder. In addition, there was no association

between (components of) metabolic syndrome and clinical DSPN (data not shown).

CONCLUSIONS—The present population-based study showed a similar prevalence of clinical DSPN in participants with IFG-IGT and those with known diabetes. Among the prediabetic subgroups, only IFG-IGT was positively associated with having clinical DSPN, while the total prediabetic group was not related to having the disorder. A J-shaped relationship was observed between quartiles of 2-h postload glucose and the presence of clinical DSPN. No associations were seen with fasting glucose and HbA_{1c} levels.

In the current literature, the prevalence of DSPN varies between 18 and 42% for populations with known diabetes (4,5) and between 4 and 19% for populations

with prediabetes (6–10). The prevalence found in the current study for both diabetic groups is in concordance with the literature. Published prevalences for subjects with prediabetes, or IGT only, ranged from 5 to 16% (4,7,11,12). The proportion of clinical DSPN that we found in subjects with IGT is in line with these observations. Occurrence of DSPN in IFG was reported less frequently (11–13) yet was within a range of 5.7–11.3% comparable with our study estimate. Prevalence of clinical DSPN in individuals suffering from IFG-IGT has not been published before. Our findings indicate that participants with IFG-IGT were similar to participants with diabetes regarding characteristics and frequency of clinical DSPN. Consequently, subjects with IFG-IGT represent a high-risk group for DSPN.

Considering glycemia, 2-h postload glucose concentrations appeared more important for DSPN risk than fasting glucose levels. Risk of clinical DSPN was increased at postload glucose concentrations that were still within the normal range of the glycemetic metabolism according to the World Health Organization (3). Previous studies show similar curvilinear relationships between 2-h postload glucose concentrations and risk of (cardiovascular) mortality (14,15). Altogether, these results suggest an important role of postprandial glucose levels, including those below the diagnostic threshold, in the development of diabetes complications.

The current study has some limitations. Since there is no uniform consensus on a definition of DSPN for use in epidemiological studies, we may have under- or overestimated the true prevalence of DSPN. However, a validation study of our clinical DSPN definition showed excellent diagnostic performance (see Supplementary Data online). Additional adjustment of our analyses for other risk factors of DSPN (smoking and diseases causing neurologic damage) did not change the results. Finally, stratified analyses resulted in some small subgroups.

An important methodological strength of the current study, as opposed to other previous population-based studies, is the use of the OGTT. This enables studying the entire spectrum of glucose disorders through identification of subjects with undiagnosed diabetes and prediabetes. Another strength of the study is the use of different neurologic bedside tests, facilitating a relatively accurate definition of clinical DSPN.

Replication of the present findings in large, well-defined, population-based

Table 1—Adjusted ORs* and 95% CIs for clinical DSPN† according to oral glucose tolerance status and blood concentrations: KORA F4 (2006–2008)

	Clinical DSPN		OR	95% CI
	No	Yes		
Oral glucose tolerance status				
NGT	513	64	1.00	Reference
Prediabetes (total)	243	41	1.22	0.78–1.90
i-IFG	52	3	0.33	0.10–1.13
i-IGT	156	27	1.26	0.76–2.08
IFG-IGT	35	11	2.82	1.29–6.10
Diabetes (total)	190	49	1.54	1.01–2.42
Known diabetes	138	39	1.77	1.10–2.87
Undiagnosed diabetes	52	10	1.22	0.57–2.61
Blood concentrations				
Fasting glucose (mg/dL)‡§				
Quartile 1	222	31	1.00	0.57–1.76
Quartile 2	195	29	1.00	Reference
Quartile 3	191	27	0.96	0.53–1.71
Quartile 4	200	28	0.82	0.43–1.54
2-h postload glucose (mg/dL) §				
Quartile 1	212	27	1.64	0.84–3.20
Quartile 2	208	16	1.00	Reference
Quartile 3	197	36	2.91	1.51–5.62
Quartile 4	191	36	3.64	1.56–8.48
HbA _{1c} (%)¶				
Quartile 1	281	32	0.74	0.45–1.21
Quartile 2	292	48	1.00	Reference
Quartile 3	156	21	0.82	0.46–1.45
Quartile 4	217	53	1.15	0.70–1.87

*All models were adjusted for age (years), sex, height (cm), waist circumference (cm), diastolic blood pressure (mmHg), level of physical activity (low/high), and alcohol consumption (low, moderate, high). †Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation. ‡The quartile borders for fasting glucose levels are quartile 1: 66–91 mg/dL; quartile 2: 92–97 mg/dL; quartile 3: 98–104 mg/dL; and quartile 4: 105–168 mg/dL. §Patients with known diabetes (n = 177) were excluded because they did not need to undergo an OGTT and, hence, have inadequate fasting and no postload glucose blood samples. ||The quartile borders for 2-h glucose values are quartile 1: 49–99 mg/dL; quartile 2: 100–119 mg/dL; quartile 3: 120–149 mg/dL; and quartile 4: 150–275 mg/dL. ¶The quartile borders for HbA_{1c} levels are quartile 1: 4.7–5.4%; quartile 2: 5.5–5.7%; quartile 3: 5.8–5.9%; and quartile 4: 6.0–12.1%.

studies may shed light on the developmental mechanism of DSPN and on identifying high-risk individuals.

Acknowledgments—The current study was funded by a grant from the German Research Foundation (RA-45913/3-1). The German Diabetes Center is funded by the German Federal Ministry of Health and the Ministry of Innovation, Science, Research, and Technology of the State of North Rhine-Westphalia.

No potential conflicts of interest relevant to this article were reported.

B.W.C.B. performed data analyses and wrote the manuscript. W.R. planned the study, contributed to data analyses, and wrote the manuscript. B.K., C.H., D.S., and C.M. reviewed and edited the manuscript. D.Z. planned the study, contributed to data analyses and discussion, and reviewed and edited the manuscript. W.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors are grateful to Dr. Margit Heier for performing the neurologic examinations and interviews in all participants of the KORA F4 Survey.

References

1. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? *Nat Rev Endocrinol* 2011;7:682–690
2. Rathmann W, Haastert B, Icks A, et al. High prevalence of undiagnosed diabetes mellitus in southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia* 2003;46:182–189
3. World Health Organization. *Report of a WHO Consultation: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications*. Geneva, World Health Organization, 1999
4. 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. Stuttgart, Germany, Thieme, 2003, p. 64–82
5. Herder C, Lankisch M, Ziegler D, et al. Subclinical inflammation and diabetic polyneuropathy: MONICA/KORA Survey F3 (Augsburg, Germany). *Diabetes Care* 2009;32:680–682
6. Rith-Najarian SJ, Stolusky T, Gohdes DM. Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria. *Diabetes Care* 1992;15:1386–1389
7. Herman WH, Aubert RE, Engelgau MM, et al. Diabetes mellitus in Egypt: glycaemic control and microvascular and neuropathic complications. *Diabet Med* 1998;15:1045–1051
8. Shaw JE, Hodge AM, de Courten M, et al. Diabetic neuropathy in Mauritius: prevalence and risk factors. *Diabetes Res Clin Pract* 1998;42:131–139
9. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995;333:89–94
10. Dyck PJ, Clark VM, Overland CJ, et al. Impaired glycemia and diabetic polyneuropathy: the OC IG Survey. *Diabetes Care* 2012;35:584–591
11. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes Care* 2008;31:464–469
12. 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* 2003;20:105–113
13. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. *Pain Med* 2009;10:393–400
14. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829–841
15. Kowall B, Rathmann W, Heier M, et al. Categories of glucose tolerance and continuous glycemic measures and mortality. *Eur J Epidemiol* 2011;26:637–645