Is Peripheral Neuropathy Associated With Retinopathy and Albuminuria in Individuals With Impaired Glucose Metabolism?

The 1999–2000 AusDiab

ELIZABETH L.M. BARR, MPH[1]
TIEN Y. WONG, MD, PHD[1,2]
ROBYN J. TAPP, PHD[1]
C. ALEX HARPER, MD[2]
PAUL Z. ZIMMET, MD, PHD[1]
ROBERT ATKINS, MSC, MD[3]
JONATHAN E. SHAW, MD[1]
ON BEHALF OF THE AUSDIAB STEERING COMMITTEE

Individuals with impaired glucoses tolerance (IGT) or impaired fasting glucose (IFG) are at substantially increased risk of developing diabetes and cardiovascular disease (1). The extent to which individuals with IGT/IFG are also at risk of microvascular complications, such as neuropathy, retinopathy, and nephropathy, has not been as well defined. Some (2,3), but not all (4–7), studies have shown that microvascular complications are more common in individuals with IGT/IFG than those with normal glucose metabolism.

Peripheral neuropathy, a common microvascular complication of diabetes (8), is often associated with concomitant retinopathy (9) and albuminuria (9,10). Whether peripheral neuropathy is also associated with retinopathy and albuminuria in people with IGT/IFG is unclear and is examined in the current study.

RESEARCH DESIGN AND METHODS — The Australian, Diabetes, Obesity, and Lifestyle Study (AusDiab) is a population-based survey of Australian adults aged ≥25 years (11). Glucose tolerance status was determined by a 75-g oral glucose tolerance test (12). The prevalence of diabetes in the AusDiab was 7.4%, while 16.4% had IGT or IFG (13). All participants with diabetes, IGT, IFG, and a random sample of normal control subjects were invited for complications testing (6). This analysis is based on the 1,154 individuals with IGT or IFG who attended the complications screening.

Neuropathy was classified by *1*) the modified neuropathy symptom score (NSS), *2*) the modified neuropathy disability score (NDS), *3*) the pressure perception score (PPS), and *4*) a postural systolic blood pressure drop score of ≥20 mmHg. The NSS measured symptoms such as burning and numbness. The NDS examined ankle reflexes, vibration perception on the great toe, pin-prick perception on the dorsal surface of the great toe, and temperature perception on the dorsal surface of the metatarsals. The PPS assessed pressure perception on the plantar surface of both feet, at the great toe and the first and fifth metatarsal heads using a 10-g monofilament. Postural hypotension was determined by subtracting standing (taken after standing for 60 s) from supine systolic blood pressure. An NSS >4, an NDS >5, a PPS <6 (each site scored as 1 if normal and 0 if abnormal), and a fall in systolic blood pressure of ≥20 mmHg were considered abnormal. An overall abnormal neuropathy score was defined as abnormal if two or more of the four scales were abnormal (6,14–16).

Nonmydriatic retinal photographs (macula centered and nasal-to-disc) of each eye were taken (Canon CR6–45NM) (7) and graded according to a simplified version of the Wisconsin grading system (17). The presence of retinopathy (at least one definite retinal hemorrhage and/or microaneurysm) was determined for each eye, and individual classification was based on grading of the worst eye. Random regrading showed a high level of intrarater agreement ($\kappa = 0.73$).

A spot morning urine specimen was used to determine urinary albumin and creatinine levels (Olympus AU600 analyzer). Albuminuria was defined as presence of microalbuminuria (an albumin-to-creatinine ratio of 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women) or macroalbuminuria (albumin-to-creatinine ratio of ≥25 mg/mmol). Participants also had other laboratory measures and answered questionnaires on health status. Ethics committee approval and informed consent were obtained (11).

Statistical analysis

The proportions of participants with concomitant complications were assessed. Multiple logistic regressions were used to estimate the odds of neuropathy associated with retinopathy and albuminuria, while controlling for potential confounders. Analyses were performed with SPSS (SPSS 11.5; Chicago, IL).

RESULTS — Of 1,154 subjects with IGT or IFG, 1,150 had complete data regarding their neuropathy status, 1,027 had gradable eye photos, and 1,104

From the [1]International Diabetes Institute, Melbourne, Australia; the [2]Centre for Eye Research, University of Melbourne, Melbourne, Australia; and the [3]Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia.

Address correspondence and reprint requests to Tien Yin Wong, MD, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne St., Victoria 3002, Australia. E-mail: twong@unimelb.edu.au.

Received for publication 15 December 2005 and accepted in revised form 15 February 2006.

Abbreviations: AusDiab, Australian, Diabetes, Obesity, and Lifestyle Study; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NDS, neuropathy disability score; NSS, neuropathy symptom score; PPS, pressure perception score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc05-2464

Table 1—*Associations of neuropathy with retinopathy and nephropathy*

Neuropathy measure		*n*	Retinopathy			Albuminuria*		
			n†	Model 1	Model 2‡	*n*†	Model 1	Model 2‡
Abnormal overall neuropathy score§	Abnormal; normal	66; 1,084	10; 58	3.8 (1.7–8.4); 1.0; $P = 0.001$	4.0 (1.8–9.0); 1.0; $P = 0.001$	19; 98	2.3 (1.3–4.3); 1.0; $P = 0.007$	1.9 (0.9–4.1); 1.0; $P = 0.093$
Abnormal NSS	Abnormal; normal	317; 835	22; 46	1.4 (0.8–2.4); 1.0; $P = 0.241$	1.4 (0.8–2.4); 1.0; $P = 0.261$	35; 82	1.0 (0.6–1.5); 1.0; $P = 0.975$	1.0 (0.6–1.6); 1.0; $P = 0.883$
Abnormal NDS	Abnormal; normal	43; 1,110	5; 63	2.5 (0.9–7.1); 1.0; $P = 0.089$	2.6 (0.9–7.5); 1.0; $P = 0.078$	12; 105	2.2 (1.0–4.5); 1.0; $P = 0.044$	1.5 (0.6–3.9); 1.0; $P = 0.445$
Abnormal PPS	Abnormal; normal	70; 1,081	7; 61	2.1 (0.9–5.0); 1.0; $P = 0.109$	2.2 (0.9–5.2); 1.0; $P = 0.092$	16; 101	1.6 (0.9–3.1); 1.0; $P = 0.125$	1.8 (0.9–3.7); 1.0; $P = 0.114$
Abnormal postural hypotension test	Abnormal; normal	53; 1,098	8; 60	3.3 (1.4–7.6); 1.0; $P = 0.006$	2.4 (0.9–6.2); 1.0; $P = 0.066$	12; 104	1.8 (0.9–3.8); 1.0; $P = 0.098$	1.9 (0.9–4.3); 1.0; $P = 0.107$

Data are odds ratio (95% CI), unless otherwise indicated. Percentages not exact due to missing data and rounding. Model 1 is adjusted for age, sex, hypertension (blood pressure ≥140/90 mmHg or taking antihypertensive medication), total cholesterol, and lipid-lowering medication. Model 2 is adjusted for age, sex, hypertension, total cholesterol, lipid-lowering medication, and either *1*) microalbuminuria/macroalbuminuria for retinopathy or *2*) retinopathy for nephropathy. *Abnormal albumin-to-creatinine ratio defined as having either microalbuminuria or macroalbuminuria. †The number with retinopathy or albuminuria. ‡Overall neuropathy score was abnormal if two or more of NSS, NDS, PPS, or postural hypotension were abnormal. §Multivariate model based upon $n = 960$ for individuals with complete data.

had data on their urinary albumin-to-creatinine ratio.

In individuals with IGT or IFG, 21.7% had at least one microvascular complication. In those who were classified as abnormal on the overall neuropathy score, 20.4% were classified as having retinopathy and 28.8% had albuminuria (microalbuminuria or macroalbuminuria). Older age, higher systolic blood pressure, hypertension (≥140/90 mmHg or taking antihypertensive medication), lower total cholesterol, lower LDL cholesterol, use of lipid-lowering medication, and abnormal albumin-to-creatinine excretion rate were all significantly associated with an abnormal overall neuropathy score ($P < 0.05$). The associations between each of the neuropathy scales with both retinopathy and albuminuria are outlined in Table 1. The overall neuropathy score was independently associated with both retinopathy and albuminuria after adjusting for the effects of age, sex, hypertension, lipid-lowering medication use, and total cholesterol (model 1). The association between neuropathy and retinopathy persisted despite further adjustment for albuminuria (model 2); however, the relationship between neuropathy and albuminuria was no longer significant after adjustment for retinopathy. The inclusion of fasting blood glucose, postload glucose, or HbA_{1c} in the model did not alter the strength of the association between the overall neuropathy score and retinopathy or the overall neuropathy score and albuminuria (data not shown).

Finally, in a subsidiary analysis where abnormal postural hypotension was defined as a drop of 30 mmHg or higher (6), the results were largely similar, with a multivariate adjusted odds ratio associated with an abnormal hypotension score of 4.1 (95% CI 0.8–21.2; adjusting for variables in model 1) for retinopathy and 4.5 (1.2–17.4) for albuminuria.

CONCLUSIONS — In this study, we have demonstrated associations between three microvascular complications in a population-derived sample of individuals with IGT or IFG. Compared with those without neuropathy, individuals with neuropathy were nearly four times more likely to have retinopathy and two times more likely to have albuminuria, independent of age, sex, hypertension, lipid-lowering medication use, and total cholesterol.

These results extend upon the findings of other population-based studies

that have found a relationship between neuropathy and other microvascular complications in people with diabetes (9,10). Our study suggests that neuropathy is associated with other microvascular complications among those without diabetes. It is difficult to distinguish whether these complications are associated with small- or large-fiber neuropathy deficits because although there was a lack of association of retinopathy and albuminuria with the NSS, there was a stronger association with postural hypotension. Prospective studies are required to examine the temporal relationships between risk factors and the development of these microvascular complications among people with normal and impaired glucose metabolism.

Acknowledgments— We are most grateful to the following for their support of the study: the Commonwealth Department of Health and Ageing, Abbott Australasia, Alphapharm, Aventis, AstraZeneca, Bristol-Myers Squibb, Eli Lilly (Aust), GlaxoSmithKline, Janssen-Cilag (Aust), Merck Lipha, Merck Sharp & Dohme (Aust), Novartis (Aust), Novo Nordisk, Pharmacia and Upjohn, Pfizer, Roche Diagnostics, Sanofi Synthelabo (Aust), Servier Laboratories (Aust), Bio-Rad Laboratories, HITECH Pathology, the Australian Kidney Foundation, Diabetes Australia, Diabetes Australia (Northern Territory), Queensland Health, South Australian Department of Human Services, Tasmanian Department of Health and Human Services, Territory Health Services, Victorian Department of Human Services and Health Department of Western Australia. Also, for their contribution to the field activities of AusDiab, we are grateful to Annie Allman, Marita Dalton, David Dunstan, Adam Meehan, Claire Reid, Alison Stewart, and Fay Wilson. Additional support was provided by the National Health and Medical Research Council, Australia (grant no. 350448), the Science Technology Innovation Grant, Victoria, and the Sylvia and Charles Viertel Clinical Investigator Award (to T.Y.W.).

References

1. Unwin N, Shaw J, Zimmet P, Alberti KGMM: Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 19:708–723, 2002
2. 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, 1990
3. Singleton JR, Smith AG, Russell J, Feldman EL: Polyneuropathy with impaired glucose tolerance: implications for diagnosis and therapy. *Curr Treat Options Neurol* 7:33–42, 2005
4. Klein R, Barrett-Connor EL, Blunt BA, Wingard DL: Visual impairment and retinopathy in people with normal glucose tolerance, impaired glucose tolerance, and newly diagnosed NIDDM. *Diabetes Care* 14:914–918, 1991
5. Van Leiden HA, Dekker JM, Moll AC, Nejpels G, Heine RJ, Bouter LM, Stehouwer CDA, Polak BCP: Blood pressure, lipids and obesity are associated with retinopathy. *Diabetes Care* 25:1320–1325, 2002
6. Tapp RJ, Shaw JE, de Courten MP, Dunstan DW, Welborn TA, Zimmet PZ: Foot complications in type 2 diabetes: an Australian population-based study. *Diabet Med* 20:105–113, 2003
7. Tapp RJ, Shaw JE, Harper CA, de Courten MP, Balkau B, McCarty DJ, Taylor HR, Welborn TA, Zimmet PZ: The prevalence of and factors associated with diabetic retinopathy in the Australian population. *Diabetes Care* 26:1731–1737, 2003
8. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D: Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 28:956–962, 2005
9. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ 3rd, 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
10. Savage S, Estacio RO, Jeffers B, Schrier RW: Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care* 19:1243–1248, 1996
11. Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw J, de Courten M, Jolley D, McCarty DJ: The Australian Diabetes, Obesity and Lifestyle Study (AusDiab): methods and response rates. *Diabetes Res Clin Pract* 57:119–129, 20021
12. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, Department of Noncommunicable Disease Surveillance, 1999
13. Dunstan DW, Zimmet PZ, Welborn TA, de Courten MP, Cameron AJ, Sicree RA, Dwyer T, Colagiuri S, Jolley D, Knuiman M, Atkins R, Shaw JE: The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 25: 829–834, 2002
14. Ewing D, Clarke B: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–918, 1982
15. Young M, Boulton A, Macleod A, Williams D, Sonksen P: A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 36:150–154, 1993
16. Litzelman D, Marriott D, Vinicor F: Independent physiological predictors of foot lesions with NIDDM. *Diabetes Care* 20: 1273–1278, 1997
17. Aldington S, Kohner E, Meuer S, Klein R, Sjolie A: Methodology for retinal photography and assessment of diabetic retinopathy. *Diabetologia* 38:437–444, 1995