Clinical Management of Diabetic Neuropathy

CONTEMPORARY ENDOCRINOLOGY

P. Michael Conn, SERIES EDITOR

8. ***Clinical Management of Diabetic Neuropathy,*** edited by *ARISTIDIS VEVES,* 1998
7. ***Gastrointestinal Endocrinology,*** edited by *GEORGE H. GREELEY JR.,* 1998
6. ***G Proteins, Receptors, and Disease,*** edited by *ALLEN M. SPIEGEL,* 1998
5. ***Natriuretic Peptides in Health and Disease,*** edited by *WILLIS K. SAMSON AND ELLIS R. LEVIN,* 1997
4. ***Endocrinology of Critical Diseases,*** edited by *K. PATRICK OBER,* 1997
3. ***Diseases of the Pituitary:*** *Diagnosis and Treatment,* edited by *MARGARET E. WIERMAN,* 1997
2. ***Diseases of the Thyroid,*** edited by *LEWIS E. BRAVERMAN,* 1997
1. ***Endocrinology of the Vasculature,*** edited by *JAMES R. SOWERS,* 1996

Clinical Management of Diabetic Neuropathy

Edited by

Aristidis Veves, MD
Beth Israel Deaconess Medical Center
and Harvard Medical School, Boston, MA

SPRINGER-SCIENCE+BUSINESS MEDIA, LLC

Originally published by Humana Press in 1998
Softcover reprint of the hardcover 1st edition 1998

This publication is printed on acid-free paper. ♾
ANSI Z39.48-1984 (American National Standards Institute)
Permanence of Paper for Printed Library Materials.

Clinical management of diabetic neuropathy/edited by Aristidis Veves.
p. cm.—(Contemporary endocrinology; 8)
Includes bibliographical references and index.
ISBN 978-1-4612-7296-0 ISBN 978-1-4612-1816-6 (eBook)
DOI 10.1007/978-1-4612-1816-6
1. Diabetic neuropathies. II. Veves, Aristidis. II. Series: Contemporary endocrinology (Totowa, NJ); 8
[DNLM: 1. Diabetic Neuropathies—therapy. 2. Diabetes Mellitus—complications. WK 835 C641 1998]
RC422.D52C55 1998
616.4'62—dc21
DNLM/DLC
for Library of Congress 97-49683
CIP

PREFACE

Diabetic neuropathy is one of the most common long-term complications of diabetes and can affect almost every organ or system of the human body. Peripheral somatic neuropathy is directly related to foot problems and, along with peripheral vascular disease, is the main cause for foot ulceration and lower extremity amputation, the commonest reason for hospital admission among diabetic patients. On the other hand, autonomic neuropathy is involved in the development of silent cardiac ischemia and cardiac arrhythmia and can be a major contributory factor in the increased cardiovascular morbidity and mortality observed in diabetic patients.

Although the majority of practicing physicians are aware of the above effects of diabetic neuropathy, other features of the disease may remain unrecognized despite their significant impact on the patient's daily life activities. Impotence can affect up to half of the diabetic male population and can have a severe impact not only on patients' lives, but also on the lives of their partners. However, since both patients and physicians may feel uncomfortable in discussing this problem, it is not surprising that it is often left untreated despite the ready availability of inexpensive, uncomplicated, and easily accessible therapeutic options. Finally, a variety of gastrointestinal conditions that are related to autonomic neuropathy can also cause significant problems that may ultimately require hospitalization and intensive treatment.

Clinical Management of Diabetic Neuropathy has been written for the greater audience of physicians who are treating diabetic patients, and who encounter neuropathy-related problems in their daily practice. The family practitioner, internist, endocrinologist, podiatrist, cardiologist, neurologist, urologist, and gastroenterologist are all members of the team that cares for diabetics and may greatly benefit from *Clinical Management of Diabetic Neuropathy.* It was therefore felt that this volume could only be successful if it concentrated more on the clinical aspects of diabetic neuropathy and its current management, and concisely detailed the causes that are, or are presumed to be, responsible for the various clinical syndromes. Special emphasis is also given to the detailed description of treatments that are currently available, or are expected to become available in the near future. The detailed bibliography at the end of each chapter will, it is hoped, prove helpful to the reader who would like a more detailed picture of any specific topic discussed.

I would like to express my gratitude to the authors, all internationally distinguished in their field, who accepted my invitation to contribute to this project. I am also indebted to Ms. Paula Smakowski, MS, PT, for her valuable editorial assistance. Finally, my sincere thanks also go to Humana Press and the series editor, Dr. P. Michael Conn, for their trust in my ability to realize such a project.

Aristidis Veves, MD

CONTENTS

CONTRIBUTORS

CAMERON M. AKBARI, MD, *Division of Vascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

ANDREW J. M. BOULTON, MD, FRCP, *The University Department of Medicine, Manchester Royal Infirmary, Manchester, UK*

EDWARD J. BOYKO, MD, MPH, *Department of Medicine, University of Washington School of Medicine, VA Puget Sound Health Care System, Seattle, WA*

JAMES S. CHRZAN, DPM, *Division of Podiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

EFTHYMIOS N. DELIARGYRIS, MD, *Department of Cardiology, University of North Carolina Hospitals, Chapel Hill, NC*

EVA L. FELDMAN, MD, PHD, *Department of Neurology, University of Michigan Medical Center, Ann Arbor, MI*

ROGER A FIELDING, PHD, *Department of Health Sciences, Sargent College of Health and Rehabilitation Sciences, Boston University, MA*

ROY FREEMAN, MD, *Autonomic and Peripheral Nerve Laboratory, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

ROBERT G. FRYKBERG, DPM, MPH, *Deaconess Joslin Foot Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

DAVID A. GELBER, MD, *Department of Neurology, Southern Illinois University School of Medicine, Springfield, IL*

JOHN M. GIURINI, DPM, *Division of Podiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

DOUGLAS A. GREENE, MD, *Division of Endocrinology and Metabolism, University of Michigan Medical Center, Ann Arbor, MI*

GEOFFREY M. HABERSHAW, DPM, *Division of Podiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

NATHAN K. LEBRASSEUR, MSPT, *Department of Health Sciences, Sargent College of Health and Rehabilitation Sciences, Boston University, MA*

FRANK W. LOGERFO, MD, *Division of Vascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

THOMAS E. LYONS, DPM, *Division of Podiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

JUAN-R. MALAGELADA, MD, *Digestive System Research Unit, Hospital General Vall d' Hebron, Autonomous University of Barcelona, Spain*

RICHARD W. NESTO, MD, *Department of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

MICHAEL PFEIFER, MD, *Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL*

BARRY I. ROSENBLUM, DPM, *Division of Podiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

GERARD SAID, MD, *Service de Neurologie, Hôpital de Bicêtre, Université Paris XI, France*

JONATHAN E. SHAW, MRCP, *The University Department of Medicine, Manchester Royal Infirmary, Manchester, UK*
ANDERS A. F. SIMA, MD, PHD, *Departments of Pathology and Neurology, Wayne State University, School of Medicine and Detroit Medical Center, Detroit, MI*
MARTIN J. STEVENS, MD, *Division of Endocrinology and Metabolism, University of Michigan Medical Center, Ann Arbor, MI*
SOLOMON TESFAYE, MD, MRCP, *Department of Medicine, Royal Hallamshire Hospital, Sheffield, UK*
THOMMEY THOMAS, MD, *Division of Endocrinology and Metabolism, University of Michigan Medical Center, Ann Arbor, MI*
ARISTIDIS VEVES, MD, *Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*
JOHN D. WARD, MD, FRCP, *Department of Medicine, Royal Hallamshire Hospital, Sheffield, UK*
LYNNE WEBSTER, MB, CHB, MSC, FRCPSYCH, *Department of Psychiatry, Manchester Royal Infirmary, Manchester, UK*
DAN ZIEGLER, MD, *Diabetes Research Institute, Heinrich Heine University, Düsseldorf, Germany*

1 The Epidemiology of Diabetic Neuropathy

Edward J. Boyko, MD, MPH

CONTENTS

INTRODUCTION

Peripheral neuropathy is a devastating complication of diabetes mellitus because of the debilitating symptoms it causes, or associated higher risk of other complications, in particular those involving the lower extremities. The epidemiology of diabetic neuropathy is not as well-understood as other complications of this metabolic disorder, including retinal, renal, and coronary artery disease. Different peripheral nerves may be damaged through a variety of pathologic processes as described in other chapters of this book. This chapter will review the prevalence, incidence, and risk factors for different types of diabetic neuropathy. The natural history of diabetic neuropathy will be briefly described with regard to foot complications.

There are six major types of diabetic neuropathy: distal symmetric polyneuropathy, autonomic neuropathy, nerve entrapment syndromes, proximal asymmetric mononeuropathy (also known as diabetic amyotrophy), truncal radiculopathy, and cranial mononeuropathy. This chapter will focus mainly on the first two types of neuropathy. Little is known regarding the epidemiology of the remaining types, probably because, with the exception of nerve entrapment syndromes, these occur infrequently.

From: *Contemporary Endocrinology: Clinical Management of Diabetic Neuropathy*
Edited by: A. Veves © Humana Press Inc., Totowa, NJ

EPIDEMIOLOGIC PRINCIPLES RELEVANT TO THE STUDY OF DIABETIC NEUROPATHY

In order to understand published research on the epidemiology of diabetic neuropathy, certain principles of epidemiologic study design must be taken into consideration. These principles guided this author in the selection of relevant citations and data presentation. Only cross-sectional or case-control studies conducted in a population-based sample (such as a defined community or health plan enrollment) were considered for this chapter based on review of MedLine citations using the keywords "epidemiology," "diabetes," and "neuropathy" from 1966 to March, 1997, review of bibliographies of the articles obtained from the MedLine search for relevant citations, and review of the author's files. Nine published studies met this criterion. Clinic-based cross-sectional or case-control studies have not been considered except in two instances, because of the potential problem of selection bias associated with these study designs *(1)*. All 11 prospective studies were considered. Prospective research is less likely to be biased because of differences in probability of subject selection based on disease (neuropathy) and risk factor presence. Prospective research is a stronger study design with regard to inferring the possibility of causation, since the presence of risk factors may be determined prior to neuropathy onset.

The problem of measurement error in the assessment of the presence or absence of diabetic neuropathy is well-recognized. Nerve conduction velocity, arguably the most objective and accurate test available for the diagnosis of this complication, is known to sometimes result in erroneous classification. For example, nerve conduction velocity may be normal in diabetic subjects with symptoms of distal symmetric polyneuropathy *(2)*. This misclassification problem becomes even more problematic when a test result is used to formulate a clinical plan for an individual patient, as compared to epidemiologic analysis where population statistics are the result of interest. When misclassification of neuropathy or risk factor status occurs nondifferentially (randomly), the net result is bias of any observed difference towards the null value *(1)*. Therefore, observed differences found in an epidemiologic analysis of risk factors for diabetic neuropathy validly reflect potential causative factors for this complication, but probably underestimate the magnitude of the risk increase. Epidemiologic studies may draw valid conclusions regarding risk factors for diabetic neuropathy even if the techniques used to measure either neuropathy or the potential risk factor are known to be inaccurate.

DISTAL SYMMETRIC POLYNEUROPATHY— PREVALENCE AND RISK FACTORS (CROSS-SECTIONAL RESEARCH)

Dyck et al. examined the prevalence of neuropathy among all clinically diagnosed diabetic subjects who resided in Rochester, Minnesota *(3)*. Only 380 of 870 eligible subjects (44%) agreed to participate, possibly caused by concern about the lengthy neurodiagnostic study protocol. Neuropathy was defined if two criteria were satisfied: abnormal nerve conduction in more than one nerve or abnormal test of autonomic function (low heart-rate variation in response to breathing or the Valsalva maneuver); and neuropathic symptom or sign or abnormal quantitative sensory testing. Median duration of diabetes was 14.5 yr for insulin-dependent diabetes mellitus (IDDM) and 8.1 yr for noninsulin-dependent diabetes mellitus (NIDDM) subjects. Although the prevalence of neuropathy was high (Table 1), most subjects with neuropathy were asymptomatic (~71%).

Table 1
Distal Symmetric Polyneuropathy: Prevalence, Incidence, and Risk Factors From Cross-Sectional Research Studies

Reference	*Subjects*	*Prevalence*	*Significant Risk Factors*	*Odds Ratio (95% CI)*
(3)	100 IDDM	54%	Not reported	
	259 NIDDM	45%		
(4)	277 NIDDM	27%	Age, 5-yr increase	1.2 (1.0–1.4)
	89 IGT	11%	Male gender	2.2 (1.2–4.1)
	496 NGT	4%	Diabetes duration, 5-yr increase	1.3 (1.0–1.6)
			Glycosylated hemoglobin, 2.5% increase	1.3 (1.0–1.8)
			Insulin use	2.7 (1.4–5.2)
(6)	363 IDDM	34%	Diabetes duration, 10-yr increase	1.2 (1.1–1.2)
			Glycosylated hemoglobin, 1% increase	1.4 (1.2–1.7)
			HDL cholesterol, 0.13 m*M* decrease	1.2 (1.1–1.3)
			Current smoking	2.2 (1.3–3.8)
			Any macrovascular disease	2.3 (1.0–5.4)
(10)	2405 DM	30% IDDM	Diabetes duration	not reported
	20,037 non-DM	38% NIDDM	Hypertension	not reported
			Poor glucose control	not reported
(11)	1084 DM	14%	Age at diagnosis	not reported
			Diabetes duration	not reported
			Plasma creatinine	not reported
			Insulin dose	not reported
			Orthostatic blood pressure fall	not reported
(12)	1077 (20% IDDM, 80% NIDDM)	17%	IDDM	
			Height (1-cm increase)	1.06 (1.00–1.13)
			Retinopathy	9.0 (7.7–10.3)
			NIDDM	
			Height (1-cm increase)	1.06 (1.03–1.08)
			Age (1-yr increase)	1.02 (1.00–1.05)
			Alcohol "units"/wk (1-unit increase)	1.03 (1.00–1.05)
			HbA1c (1% increase)	1.2 (1.1–1.4)
			Retinopathy	2.1 (1.7–2.6)
(13)	375 DM (78% IDDM)	[a]	IDDM	
			Age	not reported
			Diabetes duration	not reported
			NIDDM	not reported
			Height	
(14)	137 NIDDM, 139 non-diabetic controls	53–63%, depending on the test	Not reported	

[a] Not reported, since all persons with diabetes were not included in this survey.

A community-based study in San Luis Valley, Colorado, measured prevalence of neuropathy in a bi-ethnic (Hispanic and Anglo) population *(4,5)*. Neuropathy was defined if two of three criteria were satisfied: neuropathic discomfort in feet and legs; abnormal Achilles tendon reflexes; and inability to feel an iced tuning fork on the dorsum of the foot (test of thermal sensation). Subjects with NIDDM had the highest prevalence of neuropathy, whereas subjects with impaired glucose tolerance (IGT) defined according to World Health Organization criteria had a prevalence about midway between normal glucose tolerance (NGT) and NIDDM (Table 1). No IDDM subjects were included in this study. Significantly higher prevalence of neuropathy was found in relation to greater age, diabetes duration, and glycosylated hemoglobin; male gender; and insulin use. Factors not associated with neuropathy prevalence included blood pressure, height, smoking, prior alcohol use, ankle-arm index, and serum cholesterol, lipid, and lipoprotein levels.

The Pittsburgh epidemiology of diabetes complications study included 363 subjects with IDDM over 18 yr of age in a defined community (Allegheny County, Pennsylvania) *(6–8)*. Two of three of the following criteria had to be satisfied to fulfill the definition of neuropathy: abnormal sensory or motor signs on clinical examination; neuropathic symptoms; and abnormal tendon reflexes. Overall neuropathy prevalence was 34% (18% in 19–29 yr olds, and 58% in those 30 yr of age or older) (Table 1). Higher prevalence of neuropathy was associated with longer diabetes duration, higher glycosylated hemoglobin, lower HDL-cholesterol, smoking, and presence of peripheral vascular, coronary artery, or cerebrovascular disease (Table 1). Another analysis of the Pittsburgh population explored the association between physical activity and distal symmetric polyneuropathy among 628 IDDM subjects between 8–48 yr of age *(9)*. Male subjects who reported higher historical levels of leisure-time physical activity (adjusted for diabetes duration, age, and current activity levels) had a significantly lower prevalence of neuropathy. No association between historical levels of physical activity and neuropathy prevalence was seen in females.

Data from the United States National Health Interview Survey were used to generate neuropathy prevalence statistics on a nationwide sample of diabetic subjects *(10)*. A total of 2405 self-reported diabetic and 20,037 self-reported nondiabetic subjects were surveyed for the presence of symptoms of neuropathy in the extremities (numbness, pain, decreased hot or cold sensation). Prevalence of symptoms was more than three times greater in diabetic vs nondiabetic subjects (Table 1). Among subjects with NIDDM, higher prevalence of symptoms was associated with longer diabetes duration, hypertension, and self-reported frequent high blood glucose, whereas age, gender, height, insulin treatment, and smoking were unrelated to this outcome.

A population-based survey in Western Australia included 1084 diabetic subjects, estimated to be 70% of the total who resided in this geographic area *(11)*. Sensory neuropathy was defined as a bilateral reduction in pinprick sensation in the feet during a sensory exam performed by endocrinologists. Neuropathy was found in 14% of subjects, and was related to greater age at diabetes diagnosis, diabetes duration, plasma creatinine, insulin dose, and orthostatic blood pressure difference (Table 1).

In a survey of 10 general practices in an English community, 1077 diabetic subjects were identified and screened for neuropathy *(12)*. Two of the following five criteria fulfilled the definition of neuropathy: neuropathic foot symptoms; loss of light touch sensation; impaired pinprick sensation; absent ankle jerk reflexes; and vibration perception threshold greater than 97.5% of an age-standardized value. A total of 16.8% of diabetic

subjects fulfilled these criteria, as compared to 750 nondiabetic controls drawn from the same general practices. Risk factors associated with higher neuropathy prevalence are shown in Table 1.

A survey of diabetic subjects in a defined community in Sweden yielded 375 subjects between the ages of 15–50 with diabetes (78% IDDM) *(13)*. A vibrameter was used to assess vibration threshold and pain sensation was evaluated with application of an electric current to the foot. Among IDDM subjects, neuropathy presence was associated with greater, age, diabetes duration, and height, although the association with height disappeared in multivariate analysis after adjustment for gender. Among subjects with NIDDM, neuropathy was associated with greater height only.

A survey of NIDDM subjects in a Dutch community revealed a high prevalence of neuropathy, but also found that a substantial proportion of nondiabetic controls also tested positive for neuropathy, probably because of the high median age of the population (70 yr) *(14)*. Proportion of diabetic and control subjects with abnormal results by test is as follows: temperature 63 vs 49%, vibration (128-Hz tuning fork) 53 vs 33%, and absent tendon reflexes 62 vs 21%. Analysis of risk factors for neuropathy was not performed.

Another community-based study that was conducted in two municipalities in Sicily will be mentioned but not discussed in detail, since only subjects who responded affirmatively to questions regarding the presence of symptoms of neuropathy were evaluated further by a neurologist *(15)*. This method likely led to considerable underascertainment of neuropathy prevalence.

Although not community-based, two other cross-sectional studies are worthy of mention because of their large sample sizes and, in one case, multinational composition. The EURODIAB IDDM complications study (A cross-sectional clinic-based study of complications from 16 European countries) examined prevalence of neuropathy, defined if two or more of the following were present: symptoms, absence of two or more ankle or knee reflexes, abnormal vibration perception threshold, and abnormal autonomic function (postural systolic blood pressure fall of 30 mmHg or more or loss of heart-rate variability as demonstrated by an RR ratio < 1) *(16)*. The factors positively correlated with neuropathy prevalence were age, diabetes duration, HbA1c, weight, current smoking, severe ketoacidosis, macroalbuminuria, and retinopathy. The UK Prospective Diabetes Study examined the association between neuropathy and potential risk factors among 2337 newly diagnosed subjects with NIDDM *(17)*. Neuropathy was defined as absence of two or more reflexes in the knees and ankles (5% of subjects), or vibration sensation greater than two standard deviations from the age-corrected mean when measured with a biothesiometer (7% of subjects). Neuropathy was significantly related to ischemic skin changes of the foot (smooth or hairless skin), but unrelated to HbAlc, fasting plasma glucose, smoking, serum lipid and lipoprotein levels, and the albumin/creatinine ratio.

Of the five community-based cross-sectional studies reviewed of NIDDM subjects that presented data on risk factors for neuropathy, three reported a higher prevalence of this outcome with longer diabetes duration and higher glycosylated hemoglobin, and two found neuropathy prevalence correlated with age and height. The remaining risk factors reported were not reproduced by other investigators. Only three community-based cross-sectional studies addressed neuropathy prevalence in IDDM subjects in association with risk factors. Two of these investigations reported a correlation between diabetes duration and neuropathy prevalence. No other significant risk factor was

reported by more than one IDDM community-based study. Cross-sectional research affirms the importance of intensity and duration of hyperglycemia as potential risk factors for neuropathy, but also suggests other possible etiologies, as shown in Table 1.

DISTAL SYMMETRIC POLYNEUROPATHY— INCIDENCE AND RISK FACTORS (PROSPECTIVE RESEARCH)

The most important epidemiologic study of diabetic neuropathy performed to date is the Diabetes Control and Complications Trial (DCCT). Although designed to answer a therapeutic question, this trial provides much valuable information regarding the incidence of diabetic neuropathy and its relation to glycemic control. This clinical trial included 1161 patients with IDDM who were followed for 5 yr for the development and progression of neuropathy *(18)*. Subjects were randomized to intensive or control treatment groups, after being initially divided into a primary (diabetes for 5 yr or less, no microalbuminuria, no retinopathy) or secondary prevention (diabetes for 15 yr or less, moderate or less nonproliferative retinopathy, urinary albumin excretion less than 200 mg/24 h) subgroups, depending on the presence of end-point complications at baseline. Clinical neuropathy was defined as two of the three following conditions: neuropathic symptoms; sensory deficit to light touch, position, temperature, or pinprick; and abnormal deep tendon reflexes. Confirmed clinical neuropathy was defined as an abnormal clinical exam plus either abnormal nerve conduction in two or more nerves or abnormal response to autonomic testing. After 5 yr follow up, the cumulative incidence of clinical neuropathy, confirmed clinical neuropathy, and abnormal nerve conduction was lower in the intensively treated vs control groups, irrespective of presence of complications at baseline (Fig. 1). Among controls, the cumulative incidence of clinical neuropathy was 15–21%, depending on presence of baseline complications. Cumulative incidence of abnormal nerve conduction was very high among controls (40–52%). These data demonstrate the crucial role of hyperglycemia in the development of distal symmetric polyneuropathy, but also suggest that neuropathy will continue to develop even in intensively treated subjects exposed to milder degrees of hyperglycemia.

Several other prospective studies were designed to specifically define the incidence of and risk factors for diabetic neuropathy. Of 288 veterans with diabetes but no neuropathy, 20% developed neuropathy after 2 yr follow up *(19)*. Neuropathy was defined as insensitivity to the 5.07 monofilament at one or more of nine sites on either foot. Risk factors for incident neuropathy in multivariate logistic regression analysis included (OR, 95% CI): height, 2.5 cm increase 1.2 (1.1–1.4); previous foot ulcer 2.1 (1.0–4.1); age, 1 yr increase 1.04 (1.00–1.08); glycohemoglobin, 1% increase 1.2 (1.0–1.3); CAGE alcohol score *(20)*, four questions answered positively vs none 7.0 (1.7–29.0); current smoking 0.2 (0.1–0.7); and serum albumin level adjusted for serum creatinine, 1 mg/dL increase 0.3 (0.1–0.8).

Another investigation followed 231 NIDDM subjects free from distal symmetric neuropathy at baseline for a mean follow-up period of 4.7 yr to assess risk factors and incidence of this outcome *(21)*. Distal symmetric neuropathy was defined as described above for the San Luis Valley cross-sectional study *(4,5)*. Incidence of this outcome was 6.1/100 person-years (95% CI 4.7–7.8). In a logistic-regression model that included age, NIDDM duration, insulin treatment, glycohemoglobin, smoking, Hispanic ethnicity, gender, history of myocardial infarction, and angina, the following factors were