Onset of NIDDM Occurs at Least 4–7 Yr Before Clinical Diagnosis

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OBJECTIVE — To investigate duration of the period between diabetes onset and its clinical diagnosis.

RESEARCH DESIGN AND METHODS — Two population-based groups of white patients with non-insulin-dependent diabetes (NIDDM) in the United States and Australia were studied. Prevalence of retinopathy and duration of diabetes subsequent to clinical diagnosis were determined for all subjects. Weighted linear regression was used to examine the relationship between diabetes duration and prevalence of retinopathy.

RESULTS — Prevalence of retinopathy at clinical diagnosis of diabetes was estimated to be 20.8% in the U.S. and 9.9% in Australia and increased linearly with longer duration of diabetes. By extrapolating this linear relationship to the time when retinopathy prevalence was estimated to be zero, onset of detectable retinopathy was calculated to have occurred ~4–7 yr before diagnosis of NIDDM. Because other data indicate that diabetes may be present for 5 yr before retinopathy becomes evident, onset of NIDDM may occur 9–12 yr before its clinical diagnosis.

CONCLUSIONS — These findings suggest that undiagnosed NIDDM is not a benign condition. Clinically significant morbidity is present at diagnosis and for years before diagnosis. During this preclinical period, treatment is not being offered for diabetes or its specific complications, despite the fact that reduction in hyperglycemia, hypertension, and cardiovascular risk factors is believed to benefit patients. Imprecise dating of diabetes onset also obscures investigations of the etiology of NIDDM and studies of the nature and importance of risk factors for diabetes complications.

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RECEIVED FOR PUBLICATION 10 JULY 1991 AND ACCEPTED IN REVISED FORM 3 DECEMBER 1991.

Non-insulin-dependent diabetes mellitus (NIDDM) affects >12 million adults in the U.S., ~50% of whom are undiagnosed (1,2). It is widely believed that onset of the disease occurs years before clinical diagnosis, but this has never been documented. The period between onset and diagnosis is particularly important if significant morbidity develops during this interval, because people with undiagnosed diabetes are treated for neither their hyperglycemia nor for the specific microvascular complications of diabetes. Risk factors for macrovascular disease may also be receiving less than vigorous attention. In addition, determining the time of onset accurately should have important implications for understanding the etiology of NIDDM and the need for screening for the presence of undiagnosed diabetes. Furthermore, duration of diabetes is an established risk factor for the microvascular complications of NIDDM, but the strength of this association and its relationship to other putative risk factors would be clarified if duration of diabetes could be measured more accurately. To investigate these issues, we examined the prevalence of retinopathy in two population-based groups of white NIDDM patients. We found that a clinically significant frequency of diabetic retinopathy was present at diagnosis of diabetes in both patient groups, and prevalence of retinopathy increased linearly with increasing time after diagnosis. By extrapolating these data, we derived estimates of the length of time between actual onset of diabetes and its clinical diagnosis.

RESEARCH DESIGN AND METHODS

— The methods of identification and description of the two patient populations have appeared in detail in previous reports (3–8). The U.S. group was drawn from lists of all diabetic patients seen from 1 July 1979 to 30 June 1980 in the practices of 452 of 457 physicians who provided primary care in an 11-county area of southern Wisconsin. Eligibility criteria included a diagnosis of

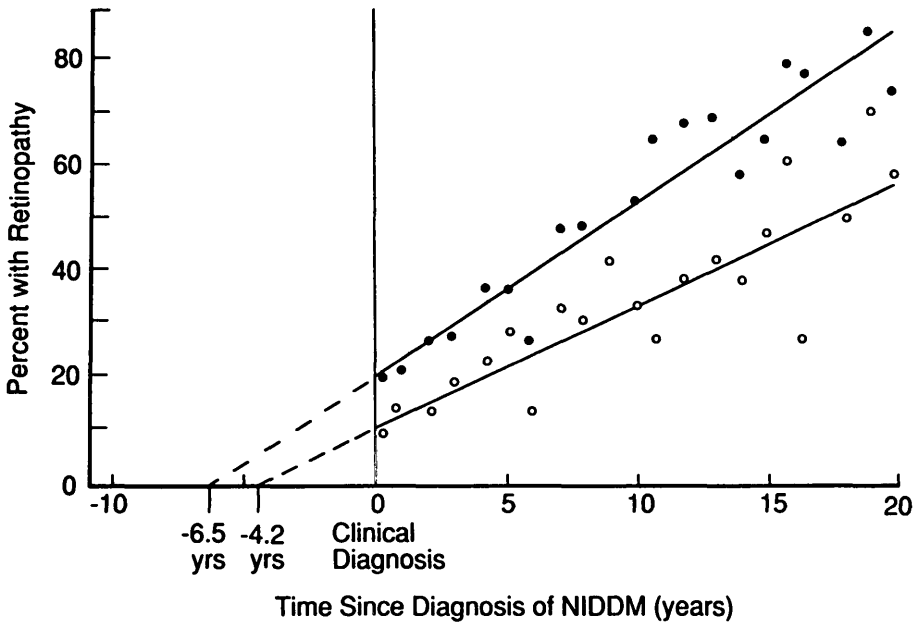

Figure 1—*Prevalence of any retinopathy according to years since clinical diagnosis of non-insulin-dependent diabetes mellitus (NIDDM) among patients in southern Wisconsin (●) and in rural Western Australia (○). Solid lines, data fitted by weighted linear regression. Lines are extrapolated to indicate the time at which onset of observable retinopathy is estimated to have occurred. R^2 = 0.89 and 0.80 for Wisconsin and Australia, respectively.*

diabetes at ≥30 yr of age by the primary-care physician, confirmed by a random or postprandial serum glucose value of ≥11.1 mM or a fasting serum glucose value of ≥7.8 mM on at least two occasions. The 5431 patients meeting these criteria were classified by duration of diabetes, and 576 patients with duration 0–4 yr and 579 with duration 5–14 yr were randomly selected for study, and all 625 patients with duration ≥15 yr. Seventy-seven percent participated in the study, and 1166 subjects with ≤20 yr of diabetes since clinical diagnosis are included in this report. Stereoscopic color fundus photographs of seven standard fields were taken through dilated pupils. Two levels of grading were conducted. First, one of two senior graders examined all photographic fields for both eyes and determined an overall retinopathy level. Second, one of several graders made a field-by-field, lesion-by-lesion evaluation of each eye with the Early Treatment of Diabetic Retinopathy adaptation of the modified Airlie House classification of diabetic retinopathy (9,10). When the two evaluations disagreed, the eye was regraded by another grader and adjudicated by the most senior grader, if necessary. Participants were classified by the more severely involved eye. Retinopathy was considered present if retinal microaneurysms, alone or with various other nonproliferative abnormalities such as blot hemorrhages, soft or hard exudates, venous beading, and intraretinal microvascular abnormalities, or signs of proliferative retinopathy, or panretinal photocoagulation treatment for proliferative retinopathy were found.

The Australian group consisted of diabetic patients in rural towns in Western Australia who participated in a community-based study of diabetes complications during 1978–1982. Based on census data and the known prevalence of diagnosed diabetes in Australia (11,12), we estimate that 70% of all diabetic subjects in these towns participated in the study. The history of diagnosis of diabetes, treatment, assessment of control, and symptoms of complications were obtained by endocrinologists. Of 1085 subjects, 904 were determined to have NIDDM on the basis of age at onset >40 yr or age at onset <40 yr but not requiring insulin therapy within 2 yr of diagnosis. Insulin or oral hypoglycemic therapy was used by 739 of 904 patients who are considered to have had symptomatic diabetes with unequivocal elevation of blood glucose levels. Of 165 NIDDM patients on diet only, 96 had unequivocal elevation of venous plasma glucose (≥11.1 mM). However, 57 had borderline venous plasma glucose values (7.8–11.0 mM) and/or elevated glycosylated hemoglobin values, and 11 had normal plasma glucose and glycosylated hemoglobin values. Consequently, it is possible that as many as 68 (57 + 11 [7.5%]) of 904 patients with NIDDM had been diagnosed by criteria that do not meet the National Diabetes Data Group/World Health Organization diagnostic criteria for diabetes (13,14). Ophthalmologic examination included expert direct and indirect opthalmoscopy and color fundus photography of eight standard 30° visual fields. Presence of any retinopathy was graded by an ophthalmologist with the criteria and standard photographs of the Diabetic Retinopathy Study Research Group (6,15). Retinopathy was considered present if microaneurysms, retinal hemorrhages, exudates, or more severe diabetic changes were found in either eye.

The relationship between retinopathy prevalence and duration of NIDDM according to individual years of duration was assessed using weighted linear regression with weights for each year's data being inversely proportional to the binomial variance. Minimum variance unbiased estimates of regression coefficients were obtained. The confidence interval for the duration at which the prevalence of retinopathy is zero was ob-

Table 1—*Prevalence of retinopathy at clinical diagnosis of non-insulin-dependent diabetes mellitus (NIDDM)*

	With retinopathy (%)	Ref.
Patients at the Cardiff, Wales College of Medicine	29.0	20
Patients in the U.K. NIDDM Prospective Diabetes Study	23.8	21
Patients in southern Wisconsin	20.8	–
Mexican Americans in Colorado*	18.8	22
Mexican Americans in Texas*	15.7	23
Non-Hispanic whites in Colorado*	16.7	22
Non-Hispanic whites in Texas*	14.2	23
Patients in rural Western Australia	9.9	–
Patients at the Edinburgh, Scotland, Royal Infirmary Diabetes Clinic	7.4	24

*Newly diagnosed subjects detected during a screening survey for diabetes. –, this article.

tained by the inverse or fiducial method (16). All calculations were conducted with the SAS statistical package (17).

RESULTS— Figure 1 illustrates the proportion of patients who have retinopathy according to duration of diabetes. Prevalence of retinopathy at diagnosis of diabetes is estimated to be 20.8% in Wisconsin and 9.9% in Australia. In both patient groups, retinopathy prevalence increased linearly with increasing time since diagnosis of diabetes. The coefficient of determination (R^2) for both data sets was high. In Wisconsin, 89% of the variance in retinopathy prevalence was explained by duration of diabetes, and in Australia the proportion was 80%. When the linear regression lines are extrapolated to the *x*-axis, to the point at which retinopathy prevalence is 0, we can estimate the time at which retinal lesions were not detectable. This value is 6.5 yr before diabetes diagnosis in the Wisconsin group (95% confidence interval 4.1–9.9 yr) and 4.2 yr before diagnosis in the Australia group (95% confidence interval 2.1–7.4 yr).

CONCLUSIONS— Retinopathy is a common complication of diabetes and is usually the first observable vascular condition specific to diabetes to develop in diabetic patients. Our findings from representative patient groups in two health-care systems indicate that retinopathy may appear 4–7 yr before clinical diagnosis of NIDDM in these populations. It has been suggested that significant pathological changes caused by hyperglycemia precede the development of detectable retinopathy. These include biochemical alterations in various metabolic pathways including the sorbitol pathway, nonenzymatic glycosylation leading to irreversible cross-links between proteins, and abnormalities of the blood-retinal barrier and blood flow in the retinal vasculature (18). Thus, the onset of NIDDM probably occurs even earlier than 4–7 yr before clinical diagnosis.

An estimate of the minimum duration of NIDDM necessary before retinopathy becomes evident can be derived from the data of Jarrett (19). He followed 240 men in England who had impaired glucose tolerance by administering repeat oral glucose tolerance tests and clinical examinations during 10 yr. No retinopathy occurred in the 180 men who continued to have impaired glucose tolerance, and none of the 60 who developed NIDDM exhibited retinal lesions by direct ophthalmoscopy during the first 5 yr after diabetes onset. However, ~5 yr after onset, signs of diabetic retinopathy began developing in the men with NIDDM. Jarrett's findings, together with ours, suggest that NIDDM may remain undiagnosed on average for as long as 9–12 yr, i.e., 5 yr between onset of diabetes and development of measurable retinopathy and an additional 4–7 yr between development of retinopathy and clinical diagnosis of diabetes. These results in NIDDM differ from those in insulin-dependent diabetes mellitus. Among the group of patients in southern Wisconsin with age at onset of diabetes <30 yr, prevalence of detectable retinopathy was absent at diagnosis, began to increase almost immediately after diagnosis, and reached ~100% at 15 yr after diabetes diagnosis (3).

We believe these findings may have important implications. First, they suggest that undiagnosed diabetes is not a benign condition; indeed, clinically significant morbidity is present at diagnosis. In our study, 21 and 10% of patients in Wisconsin and Australia, respectively, were estimated to have retinopathy at diagnosis of NIDDM. In other reports, retinopathy was found at diagnosis in as many as 29% of patients (Table 1). Gross proteinuria was present in 11% of the Wisconsin patients with age at onset >30 yr and with <1 yr duration of diabetes, in 37% of NIDDM patients in France examined within 1 yr after diagnosis, and in 10% of subjects detected to have NIDDM during a screening survey among Mexican Americans (25–27).

The presence of diabetic microangiopathy at the time of clinical diagnosis of NIDDM indicates that complications of NIDDM are progressing while diabetes remains undiagnosed. These complications may be a consequence of untreated hyperglycemia, which is an important risk factor for retinopathy, renal impairment, and sensory neuropathy (3–7,22,23,27–32). A clinical trial is being conducted to investigate whether reduction of hyperglycemia leads to decreased incidence of microvascular complications in insulin-dependent diabetes mellitus (33). The results may not be directly applicable to NIDDM. However, if results indicate a beneficial effect,

then earlier diagnosis and treatment of diabetes may be indicated for prevention of retinopathy and other complications of NIDDM. Microvascular disease has also been associated with elevated blood pressure in some studies (22,23,25,27, 31,34), although not in all (35).

A significant percentage of new NIDDM patients also have macrovascular complications. In the Second National Health and Nutrition Examination Survey (NHANES II) of a representative sample of U.S. residents, people with NIDDM newly detected by oral glucose tolerance tests had abnormal heart findings (22%), angina (10%), peripheral vascular disease (8%), and medical history of myocardial infarction (8%) and stroke (6%) (36). Age-standardized rates were two to three times those of people with normal glucose tolerance (37). When diabetes is undiagnosed, risk factors for macrovascular disease may be neglected, including blood pressure, dyslipidemia, obesity, and cigarette smoking. Indeed, blood pressure was >160/95 mmHg in 57% of newly discovered diabetic subjects in NHANES II, and hypercholesterolemia (>240 mg/dl) was found in 77% (36,38).

A second issue concerns investigation of the etiology of NIDDM and its complications. Duration of diabetes, dated from time of clinical diagnosis, is a strong risk factor for microvascular complications (Fig. 1). However, the strength of this association and its relationship to other putative risk factors such as hyperglycemia, blood pressure, cigarette smoking, sex, race, and socioeconomic status may be clouded by imprecise dating of NIDDM onset. Comparative studies of risk factors for NIDDM complications, either among populations or between IDDM and NIDDM, are also likely to be confounded by the varying ascertainment of NIDDM and uncertainty about its time of onset. It is possible that the relationship of macrovascular disease to duration of NIDDM is also obscured, but time of onset of frank diabetes may be of lesser importance for macrovascular disease than for microvascular disease because the origin of accelerated atherosclerosis may occur at the stage of impaired glucose tolerance (37,39). Finally, it is likely that the ability to compare the etiology of diabetes among populations is severely compromised by variations in NIDDM diagnostic rates in differing health-care systems.

Some caution would be advised in considering our estimates for the time of development of detectable retinopathy. Only 77% of eligible patients in Wisconsin and 70% in Australia participated in the study. Whether patients with retinopathy were more or less likely to participate is not known. Differential survival of diabetic patients may have affected our results. Among all Wisconsin patients (with any duration of diabetes), 6-yr survival for those without retinopathy was 68% compared with 55% for subjects with any retinopathy (40). Exclusion in this study of patients with >20 yr duration of diabetes and thus more severe retinopathy should have attenuated any effect of differential mortality on prevalence of retinopathy.

Acknowledgments— This work was partially supported by Grant EY-03083 (R.K.) from the National Eye Institute (Bethesda, MD).

We thank Dr. Ian Constable for providing data on retinopathy in the Australian patients and Scot E. Moss for expert statistical advice.

This paper was presented at the International Diabetes Federation, Washington, DC, 23–28 June 1991.

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