Estimating the Delay Between Onset and Diagnosis of Type 2 Diabetes From the Time Course of Retinopathy Prevalence

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OBJECTIVE

By correlating known diabetes duration with the prevalence of retinopathy, more than 10 years have been estimated to lapse between the onset and diagnosis of type 2 diabetes. Such calculations, however, assumed a linear model, included stages of retinopathy not specific to diabetes, and allowed 5 years for retinopathy to occur after the onset of diabetes. We calculated the duration of undiagnosed type 2 diabetes in outpatients screened for retinopathy in a hospital-based diabetes clinic after correcting these assumptions.

RESEARCH DESIGN AND METHODS

Diabetic patients (*n* = 12,074; 35,545 fundus examinations) were stratified into younger onset (YO; age at onset <30 years) or older onset (OO; age at onset ≥30 years), insulin treated (IT) or not IT (NIT), and with mild/more severe diabetic retinopathy (AnyDR) or moderate/more severe diabetic retinopathy (ModDR). The best-fitting equation correlating known duration among the OO-NIT group with the prevalence of ModDR was used to extrapolate time from appearance of retinopathy to diagnosis of type 2 diabetes. Time for retinopathy to develop after diabetes was calculated from the equation correlating the duration among the YO-IT group with appearance of ModDR.

RESULTS

There were 1,719 patients in the OO-NIT group with AnyDR and 685 with ModDR and 756 in the YO-IT group with AnyDR and 385 with ModDR. A linear model showed ModDR appeared 2.66 years before diagnosis among those in the OO-NIT group. A quadratic model suggested that ModDR appeared 3.29 years after diagnosis among those in the YO-IT group. The resulting estimate was 6.05 years (2.66 + 3.29) between the onset and diagnosis of diabetes, compared with 13.36 years using standard criteria.

CONCLUSIONS

Using best-fitting models and stratifying by glucose-lowering treatment and severity of retinopathy substantially lowers the estimated duration of undiagnosed type 2 diabetes.

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Type 2 diabetes is a chronic condition characterized by increased blood glucose concentrations resulting from a progressive insulin secretory defect on the background of insulin resistance (1). About 15% of adults in the U.K. have impaired glucose regulation (2), and 5–12% of them progress to type 2 diabetes each year (3). Because of this gradual, asymptomatic onset, type 2 diabetes may remain undiagnosed for years, during which micro- and macrovascular complications progress unchecked, and the prevalence of diabetic retinopathy (DR) at diagnosis ranges from 10% to 37% in different reports of white populations (4–7). The latter observation prompted some authors to estimate the time elapsing from onset of diabetes to its clinical diagnosis through the correlation between known duration of type 2 diabetes and the prevalence of DR. Assuming that such a correlation is linear and that DR appears after diabetes, extrapolating the regression line before the time of diagnosis estimated the duration of unknown retinopathy between 4 and 9 years (6,7). Since it was assumed that DR needs another 5 years to appear after the onset of diabetes, the total estimated duration of unrecognized type 2 diabetes extended to well beyond 10 years.

However, there were limitations in those studies: *1*) the correlations between diabetes duration and prevalence of retinopathy were calculated including mild and very mild lesions (isolated microaneurysms, hemorrhages, or cotton wool spots), which were later shown to be detectable in up to 10% of the general nondiabetic, nonhypertensive population and in people with prediabetes (5,8–11); *2*) the linearity of the correlation has been questioned recently (7); and *3*) the plausibility of such a long duration of undiagnosed diabetes also is questionable, at least in countries with structured health care systems in which blood glucose concentrations are supposedly measured more often than every 10 years for routine or elective purposes.

In this study we used prospective data collected while screening for DR to estimate the duration of undiagnosed type 2 diabetes in a large ambulatory patient population in a hospital-based diabetes clinic. In particular, we were able to *1*) differentiate patients with any retinopathy from those with moderate or more severe DR, which is more specific to, and more likely to develop after the onset of, diabetes; *2*) apply the best-fitting linear or more complex models to the correlations between known duration and different severities of DR; and *3*) verify such correlations among patients with type 1 diabetes mellitus (T1DM), in whom the date of onset is well defined.

RESEARCH DESIGN AND METHODS

Data from 35,545 screening episodes performed in 12,074 patients (6,751 males [55.91%] and 5,323 females [44.09%]) between 1 January 1991 and 31 December 2010 were evaluated. The patients subjected to screening were almost totally of European origin, with few patients of African, Asian, or South American descent included in the later years. Data were collected prospectively using dedicated software called SEE (Save Eyes in Europe; Elilan, Turin, Italy), which was specifically designed to record episodes according to the 1990 European Working Party screening protocol (12). All study participants gave their informed consent, and the investigations were carried out in accordance with the Declaration of Helsinki.

Details of the retinal screening procedure, grading, and quality assurance in this population were described previously (13). In brief, screening occurred using color retinal photographs of two 45° retinal fields for each eye—one centered on the macula and the other nasal to the optic disc—taken by trained medical or nursing personnel and graded by diabetes specialists according to the 1990 European Working Party protocol (14).

Patient Classification

Patients were classified as having any retinopathy (AnyDR) if they had mild lesions (microaneurysms, isolated larger hemorrhages, isolated cotton wool spots, or all three) equivalent to an Early Treatment Diabetic Retinopathy Study (ETDRS) level ≤20 (15) or worse. Those with DR equivalent to an ETDRS level >20 or worse (moderate nonproliferative, preproliferative, proliferative, or photocoagulated DR or advanced diabetic eye disease with or without macular involvement) were classified as having moderate nonproliferative DR or worse (ModDR). For patient classification, severity of DR in the worst eye was considered.

The patients were divided into younger onset (YO) if age at diagnosis of diabetes was <30 years and older onset (OO) if age at diagnosis was ≥30 years; they were further stratified into insulin treated (IT), either alone or with oral agents, and noninsulin treated (NIT), that is, using diet alone or oral agents. Age at diagnosis was self-reported and checked via medical records whenever possible. There were 7,298 patients in the OO-NIT group (58.4% males, age 63.1 ± 10.3 years, known diabetes duration 6.4 ± 7.4 years); 2,945 in the OO-IT group (52.9% males, age 63.1 ± 11.8 years, known diabetes duration 13.3 ± 10.1 years); 1,725 in the YO-IT group (50.7% males, age 30.1 ± 14.6, known diabetes duration 15.2 ± 11.2); and 106 in the YO-NIT group (50.9% males, age 40.0 ± 16.0 years, known diabetes duration 17.4 ± 14.8 years). Because of its limited size, the latter group was not further considered.

Calculations

The relationships between known duration of diabetes and prevalence of AnyDR or ModDR were evaluated separately for the OO-NIT, OO-IT, and YO-IT groups. Patients with more than one follow-up screening were included as separate observations, with the severity of retinopathy observed at each different time point. The nil prevalence of retinopathy for each group was estimated using a simple linear regression analysis (prevalence = a + b × known duration of diabetes) as the first model. Then a quadratic term, evaluated by the likelihood ratio test, was introduced in the model. Akaike information criterion and coefficient of determination (R^2) were used to choose the best-fitting model. For patients in the YO-IT group with AnyDR, a logistic model was fitted because neither linear nor quadratic models fit adequately. The time from onset of retinopathy to clinical diagnosis of diabetes was calculated as a point estimate by extrapolating the intercept of the best-fitting regression line with the horizontal axis.

RESULTS

Prevalence of AnyDR and ModDR increased up to 20 years' known duration then tended to plateau (data not shown). Hence, further calculations were performed, taking into account the first 20

years' known duration of diabetes. Table 1 summarizes the best fits estimated for the different models.

Figure 1 shows the regression lines between known duration of diabetes and prevalence of AnyDR in the OO-NIT, OO-IT, and YO-IT groups. Both linear (Fig. 1*A*) and quadratic models (Fig. 1*B*) are shown for AnyDR and OO-NIT, confirming that a quadratic model provides the best fit. The best fits for AnyDR and OO-IT and YO-IT were provided by linear (Fig. 1*C*) and logistic equations (Fig. 1*D*), respectively. The intercepts on the horizontal axis for AnyDR were –8.46 years (linear model, Fig. 1*A*) and –3.89 years (quadratic model, Fig. 1*B*) for OO-NIT and –4.27 years for OO-IT (quadratic model, Fig. 1*C*). In the case of YO-IT (Fig. 1*D*), the intercept was estimated as not different from zero.

Figure 2*A*–*C* shows that the best fits between known duration of diabetes and prevalence of ModDR in the OO-NIT, OO-IT, and YO-IT groups were provided by linear, quadratic, and quadratic equations, respectively. The resulting intercepts between known duration of diabetes and ModDR were –2.66 years for OO-NIT, –3.36 years for the OO-IT, and +3.29 years for the YO-IT groups.

Since we and others previously demonstrated that the appearance of DR is delayed when onset of diabetes occurs during the prepubertal years (16,17), estimations in the YO-IT group were repeated for a subgroup of patients (n = 829) in whom age at onset was >12 years if males (n = 415) and >11 years if females (n = 414). The resulting best fit was also a quadratic equation, with the intercept on the x-axis at 1.73 years (Table 1 and Fig. 2*D*).

The above data suggest that AnyDR had started to develop 3.89 years before the clinical diagnosis of diabetes in the OO-NIT groups, whereas data in the YO-IT group do not allow a reliable estimation of time from the onset of diabetes to the start of AnyDR, making it impossible to work out an estimate for unknown duration of type 2 diabetes when using AnyDR as a model.

ModDR started to develop in the OO-NIT group an estimated 2.66 years before diagnosis of type 2 diabetes and 3.29 years after the onset of diabetes in the YO-IT group, or 1.73 years if only patients with diabetes onset after puberty are considered. The OO-IT group behaved somewhat in between the OO-NIT and YO-IT groups (Table 1 and Figs. 1 and 2), suggesting that this group may include individuals with later onset (after age 30) T1DM. Consequently, this group was not considered further.

Assuming that time to appearance of ModDR in the YO-IT group indicates the time elapsing from the onset of diabetes to the start of DR, the total time from onset to diagnosis of type 2 diabetes was estimated at 5.95 years (2.66 + 3.29). Restricting the model to data from patients with onset of T1DM after puberty brought the estimate down to 4.39 years (2.66 + 1.73).

CONCLUSIONS

This article suggests that type 2 diabetes may arise 4–6 years before a clinical diagnosis is reached—a much shorter length of time than previous estimates, putting this interval at longer than 10 years (6,7,18,19). Applying previous approaches from the literature to our population, that is, a linear model with AnyDR as an indicator and assuming 5

Table 1—Estimated best fits for the correlations between prevalence of retinopathy and known duration of diabetes according to the Akaike information criterion, coefficient of determination (R^2), and likelihood ratio test

DR by model	Akaike information criterion	R^2	Intercept on x-axis (years)	Likelihood ratio test
AnyDR				
OO-NIT				
Linear	98.43	0.96	−8.46	
Quadratic	82.82	0.98	−3.89	<0.0001
OO-IT				
Linear	119.3	0.97	−4.27	
Quadratic	118.8	0.97	−2.84	0.12
YO-IT				
Linear	138.4	0.94	1.6	
Quadratic	137.8	0.94	1.0	0.11
Logistic	116.7	0.99	0	Not applicable
Postpubertal YO-IT				
Linear	144.3	0.93	0.28	
Quadratic	144.9	0.93	0.89	0.25
Logistic	127.5	0.98	0	Not applicable
ModDR				
OO-NIT				
Linear	91.7	0.94	−2.66	
Quadratic	93.2	0.94	−3.85	0.46
OO-IT				
Linear	119.3	0.97	−0.74	
Quadratic	114.1	0.98	−3.36	0.007
YO-IT				
Linear	141.5	0.85	3.79	
Quadratic	124.4	0.94	3.29	<0.0001
Postpubertal YO-IT				
Linear	124.3	0.86	2.85	
Quadratic	120.5	0.90	1.73	0.02

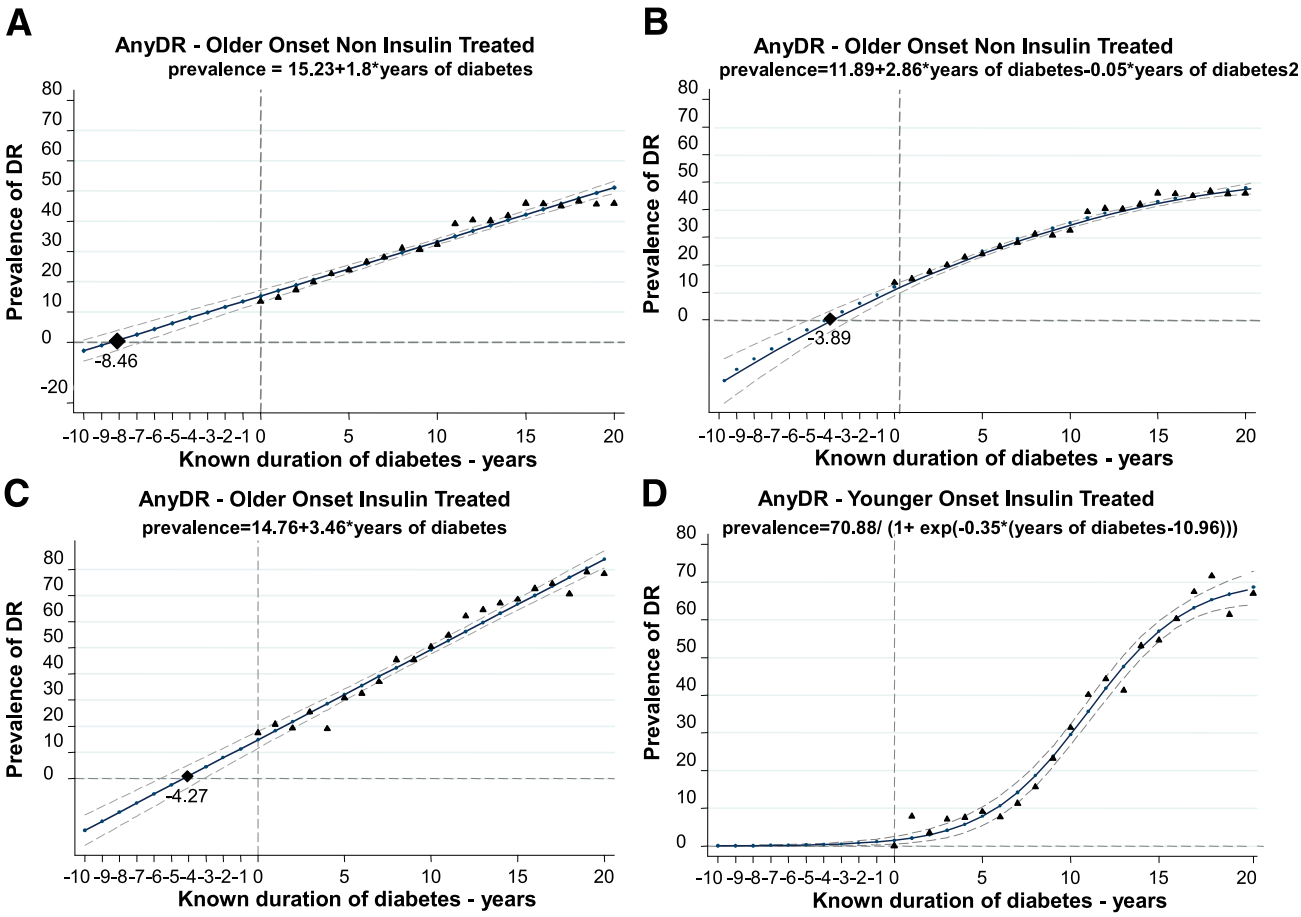

Figure 1—Best fits between known duration of diabetes and prevalence of AnyDR among patients in the OO-NIT (linear model [*A*]; quadratic model [*B*]), OO-IT (linear model [*C*]), and YO-IT groups (logistic model [*D*]).

years for retinopathy to appear, would also yield an 13.36-year (8.36 + 5) estimated interval of undiagnosed diabetes.

The first attempt to estimate the interval from onset to clinical diagnosis of type 2 diabetes was published by Harris et al. (6), who calculated the weighted linear regressions between known duration and prevalence of DR in two different white populations, one residing in Wisconsin and the other in Australia, and suggested that DR started to develop 6.5 years (95% CI 4.1–9.9) and 4.2 years (95% CI 2.1–7.4) before diagnosis, respectively. An estimated 5 years for retinopathy to develop after the onset of type 2 diabetes was added to these numbers, bringing the total duration of undiagnosed diabetes to 9–12 years. The two populations had different characteristics, both in the definitions used to assign a diagnosis of non–insulin-dependent diabetes (NIDDM) and in the methods used to detect retinopathy. In addition, patients were lumped together despite whether they were taking insulin, and any severity of retinopathy was considered. The Wisconsin cohort included patients both receiving insulin treatment or not at the time of study, and NIDDM was defined on the basis of age at diagnosis ≥30 years and no insulin treatment for at least 2 years thereafter. Their results are in between the estimates we reached for the OO-NIT and OO-IT groups using a linear model (8.46 and 4.27 years, respectively).

Using a similar approach in a South Indian outpatient population, Ramachandran et al. (18) estimated 4.1 years preceding the diagnosis of NIDDM, defined by an oral glucose load. Any retinopathy, assessed using a detailed dilated eye examination by an ophthalmologist, was plotted against known duration of diabetes, but the overall prevalence of DR was lower than in previous reports. In another study of Egyptian adults (19) using the same model, the lag time between onset of DR and clinical diagnosis of NIDDM was 2.6 years, which, by adding an assumed 5 years for retinopathy to appear after the onset of diabetes, brought the total estimated time of unknown diabetes duration to 7.6 years.

Finally, in a selected population with type 2 diabetes in Tayside, Scotland, Ellis et al. (7) extrapolated 5.77 years (95% CI 4.6–7.0 years) from the beginning of DR to a clinical diagnosis of type 2 diabetes, to which the customary 5-year time to develop retinopathy from the onset of diabetes was added. The authors, however, questioned the linearity of the correlation, citing the by then established presence of minimal retinal lesions in people without diabetes (11) and the possibility of a glycemic threshold below which retinopathy may start to appear and that might differ from current diagnostic criteria for diabetes.

This point was raised by other investigators, questioning whether current diagnostic criteria are truly indicative of a threshold glycemic level below which microvascular complications do

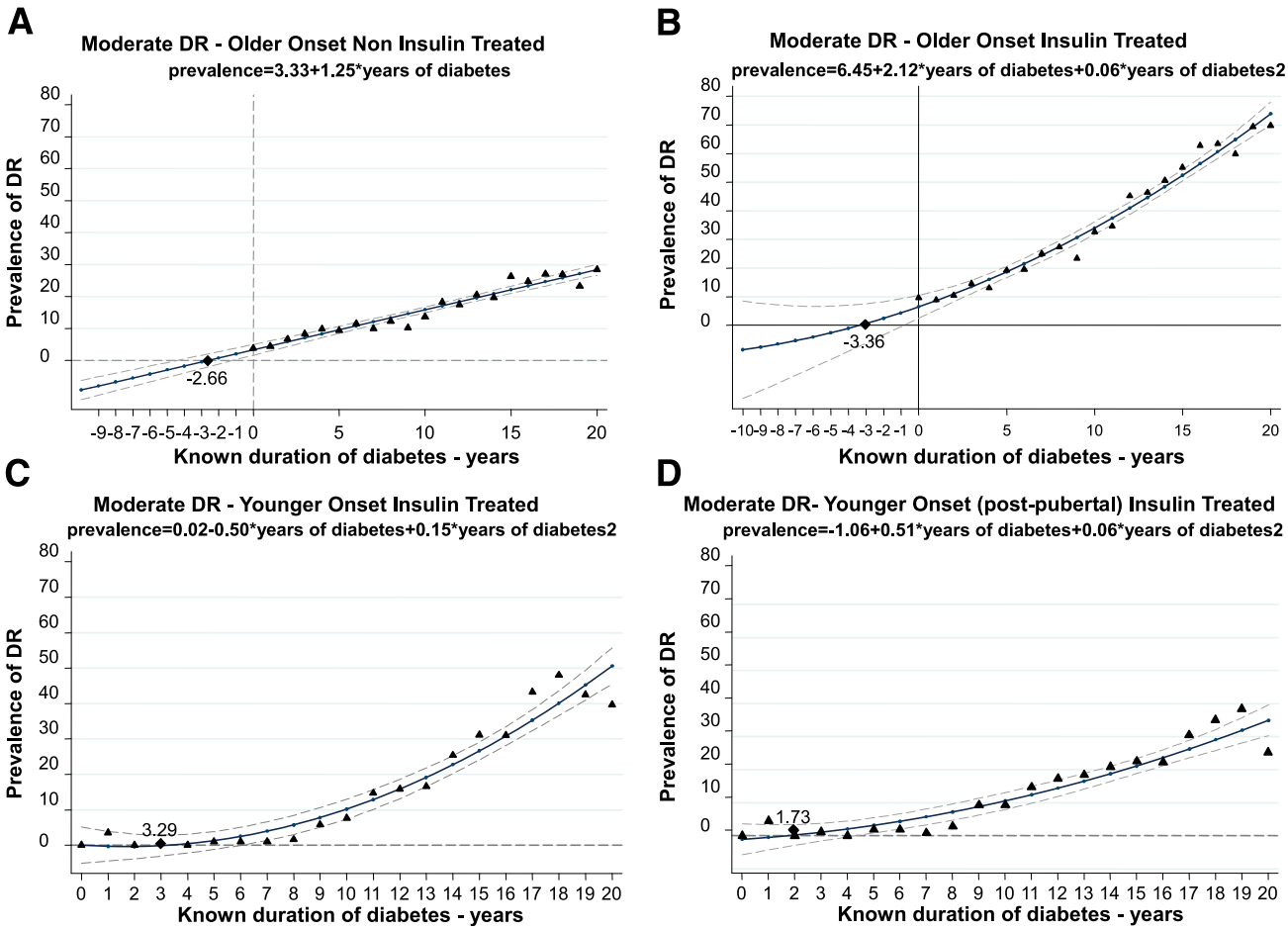

Figure 2—Best fits between known duration of diabetes and prevalence of ModDR among patients in the OO-NIT (*A*) and OO-IT groups (*B*), all patients in the YO-IT group (*C*), and patients with postpubertal onset YO-IT (*D*).

not develop. These criteria are based upon three reports suggesting that 7.0 mmol/L (126 mg/dL) represents the glycemic threshold below which DR will not appear (20), but the methodology used to detect retinopathy in those articles was later questioned (7,11). Observations in Pima Indians (21) and from the Diabetes Prevention Program showed that retinopathy may appear in people with impaired glucose tolerance (22). Wong et al. (11) examined data from three large, cross-sectional adult populations—the Blue Mountains Eye Study in Australia (n = 3,162), the Australian Diabetes, Obesity and Lifestyle Study (n = 2,182), and the Multi-Ethnic Study of Atherosclerosis in the U.S. (n = 6,079)—and could not confirm the notion of a glycemic threshold.

In this article, the problem was addressed by calculating not only the regressions between known duration of type 2 diabetes and any retinopathy, which would include carriers of less specific minimal retinal lesions, possibly independent of diabetes (5,8–11), but also those between known duration and moderate or worse DR, which is more specific to diabetes (11). The latter model yielded a shorter interval from intercept on the x-axis to time 0: −2.66 years for patients in the OO-NIT group. Data collected from the patients in the YO-IT group suggest 3.29 years for ModDR to develop after the onset of diabetes, resulting in an overall 6-year estimated interval of undiagnosed diabetes, which is shorter than previous estimates. Including only patients with postpubertal onset T1DM, in whom retinopathy may progress more rapidly (16,17), further reduced the estimate to 4.39 years.

A progressively increasing prevalence of DR was observed within the first 20 years of known diabetes duration, followed by a plateau, suggesting that a survivor effect may take place thereafter, as DR is an established independent predictor of cardiovascular mortality (23). Hence, similar to previous studies in the literature, we limited our observation time to the first 20 years of known diabetes duration.

Strengths of this article include a large population database obtained prospectively from a screening program that uses a defined consensus protocol (13,14) and software that forces operators to collect all required information without missing data. Grading criteria allowed us to discriminate mild from more severe DR on a scale compatible with ETDRS classifications (15). Finally, information on glucose-lowering therapy at the time of screening allowed us to separate OO patients into those who were not taking insulin, a supposedly "pure" population of type 2 diabetes, and an equally virtually "clean" group of patients with T1DM (YO-IT), in whom certainty

about the date of diabetes onset provided information on the incidence and progression rates of DR. In particular, the curves of the cumulative prevalence of nonproliferative and preproliferative DR (data not shown) were virtually superimposable with those reported in EURODIAB, a survey of complications in patients with T1DM across Europe (24). The OO-IT group was not included in these calculations because it may include a mix of patients with both late-onset T1DM and long-standing type 2 diabetes. Data from Table 1, however, show that their inclusion would have resulted in even shorter estimates for unknown diabetes duration.

Weaknesses include a lack of information on HbA_{1c} and blood pressure, two major determinants of DR incidence and progression; this is a problem shared with other large screening programs (25). In addition, the patients in this study were subjected to screening for DR over a 20-year period, and their type 2 diabetes had been diagnosed at different times using current criteria. Also, retinal photography used two-field, nonstereo, 45° images rather than standard ETDRS seven-field 30° stereos (15). However, our photographic protocol was based upon the EURODIAB procedure, which had been previously validated and found to perform as well as the ETDRS in detecting mild and moderately severe DR (26). In any event, figures for the prevalence of DR at diagnosis in our different groups are consistent with previous data in the literature, suggesting that our results can be generalized at least to other white populations. Finally, we extrapolated data obtained from patients with T1DM, in whom the date of onset is certain, to estimate the time from the onset of diabetes to the appearance of retinopathy in patients with type 2 diabetes because there are no recent data on the appearance of moderate or more severe retinopathy in patients who are not treated with insulin. The 5-year time for retinopathy to develop, as used in the literature, derived from prospective observation studies of mixed populations of patients with NIDDM who were treated with insulin and not treated with insulin in Wisconsin and the U.K. (6), and included any mild lesion (not necessarily specific for DR). Our approach may be problematic because there are no direct comparisons of the incidence rates of moderate/more severe retinopathy in T1DM and type 2 diabetes. If anything, our own data suggest that the cumulative prevalences of ModDR in the OO-NIT group (Fig. 2*A*) and the postpubertal YO-IT group (Fig. 2*D*) are similar in slope, although they are described by linear and quadratic functions, respectively. A possible interpretation is that, while metabolic control is usually worse in the early years of T1DM, age and higher blood pressure could contribute to more rapid progression of retinopathy in patients with type 2 diabetes, resulting in overall similar rates of development in the two conditions.

In conclusion, this study suggests that metabolic abnormalities may precede clinical diagnosis of NIT type 2 diabetes by 4 to 6 years, which is much less than previous estimates. Whether such metabolic abnormalities coincide with current diagnostic criteria for type 2 diabetes remains to be established. That about 15% of the adult population may suffer from impaired glucose regulation without having full-blown type 2 diabetes (2) and that impaired glucose tolerance is associated with increased risk for DR (19,20) suggest that part of those "hidden" years may be spent in a prediabetic state (1), accounting at least in part for delayed and incomplete diagnoses of diabetes. Sorting out these issues will provide a more solid basis upon which to determine the feasibility of and opportunity for screening programs for the early detection of type 2 diabetes (27).

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