Timing Is Everything: Age of Onset Influences Long-Term Retinopathy Risk in Type 2 Diabetes, Independent of Traditional Risk Factors

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OBJECTIVE — To test the hypothesis that age of type 2 diabetes onset influences inherent susceptibility to diabetic retinopathy, independent of disease duration and degree of hyperglycemia.

RESEARCH DESIGN AND METHODS — Retinopathy data from 624 patients with a type 2 diabetes duration of 20–30 years (group A) were analyzed by stratifying patients according to age of onset of diabetes and glycemic control. Retinopathy status was scored clinically as per a modified Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. To obviate possible bias due to a higher attrition from comorbidities in those with later-onset diabetes and retinopathy, 852 patients with type 2 diabetes of shorter duration (10–12 years, group B) were similarly studied.

RESULTS — Prevalence and severity of retinopathy was significantly higher in the younger-onset, group A patients. When further stratified according to mean A1C, retinopathy risk remained increased in younger-onset patients. The greatest impact was seen in those with a mean A1C >9% (odds ratio [OR] for retinopathy 16.6, 7.5, and 2.7 for age of diagnosis <45, 45–55, and >55 years, respectively, $P = 0.003$). By logistic regression, earlier type 2 diabetes onset is associated with increased retinopathy risk, independent of traditional risk factors (OR of retinopathy 1.9, 1.1, and 1 for age of onset <45, 45–55, and >55 years, respectively). Similar results were found in group B patients.

CONCLUSIONS — These data suggest an increased inherent susceptibility to diabetic retinopathy with earlier-onset type 2 diabetes. This further supports the importance of delaying development of diabetes and also implies a need for more stringent metabolic targets for younger individuals.

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Superimposed on the worldwide epidemic of diabetes that we are currently facing is the demographic trend to an ever younger age of diagnosis of type 2 diabetes (1). In recent studies, type 2 diabetes constitutes up to 45% of incident pediatric diabetes, and 7–22% of adolescent diabetes presents with diabetes-specific complications at diagnosis (2,3). To date, few studies have examined long-term outcomes as a function of age of diagnosis in type 2 diabetes, and even fewer have looked at the development of retinopathy specifically. There is some limited data suggesting that young-onset diabetes is associated with an increased risk for complications compared with later-onset diabetes (4) and that the development and progression of complications might be particularly rapid in early-onset disease (2). What is hitherto unknown is whether the increased prevalence of complications associated with early-onset disease is simply a consequence of the longer duration of disease, a consequence of a more severe metabolic phenotype, or in fact something specific to the diabetic milieu in younger patients that makes tissues more inherently susceptible to hyperglycemic damage.

We therefore explore the hypothesis that in type 2 diabetes, susceptibility to retinopathy is dependent on age of diabetes onset. The isolated effect of age of diabetes onset on long-term retinopathy status was examined independent of duration of diabetes and glycemic control, the two most important risk factors for retinopathy.

RESEARCH DESIGN AND METHODS

Data from 8,301 patients with type 2 diabetes referred to the Royal Prince Alfred Hospital Diabetes Centre in Sydney, Australia, from 1989 to 2007 were available for study. These patients had a full complications assessment, and data were collected following a standardized protocol as described previously (5). Specific information collected at each assessment includes demographic details, age of diagnosis, A1C, BMI, lipids, blood pressure, and albuminuria. Retinopathy status was assessed by direct fundoscopy through dilated pupils or from report by the treating ophthalmologist (in 10% of cases). Severity of retinopathy was scored as per a modified Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale (6) into the following categories: *1*) nil, *2*) nonproliferative (minimal, mild-moderate, or severe), or *3*) proliferative, each with or without *4*) macular edema. Those with either of the last two categories were considered as having "vision-threatening retinopathy."

To assess the impact of age of onset on long-term retinopathy status, independent of duration, data from 624 patients with duration of 20–30 years of known type 2 diabetes at last follow-up, were analyzed (group A). To obviate possible bias due to a higher attrition from comorbidities in those with later-onset diabetes and

retinopathy, 852 patients with type 2 diabetes of shorter duration (10–12 years, group B), and therefore younger in age, were similarly studied.

Data were analyzed by grouping patients according to the presence or absence of retinopathy at the last visit and then further stratified by age of onset and mean A1C over all visits (mean ± SD visits: group A 3.8 ± 3.2 and group B 2.8 ± 2.3). Other clinical data were taken from the patient's last visit. The presence of metabolic syndrome was defined by World Health Organization criteria (7).

Statistical analyses

Data were analyzed using NCSS 2004 software. Data for group A and group B were each grouped according to age of diagnosis of diabetes: <45, 45–55, and >55 years. A1C was also categorized: <7.0, 7.0–9.0, and >9.0%. These A1C categories were chosen to represent those with good, suboptimal, and very poor glycemic control. Continuous data were checked for normality and are presented as mean or median. Kruskal-Wallace ANOVA was used to compare means or medians. Categorical data were presented as percentage and 95% CI. χ^2, Fisher's exact test, and odds ratios were used to compare the groups. To assess whether there was any increasing or decreasing trend between the groups, a trend test was performed. Logistic regression was used to determine the independent predictors for retinopathy both as continuous and categorical variables. Independent determinants used were age, age of diagnosis (as a categorical variable in model 1 and as a continuous variable in model 2), A1C, weight, metabolic syndrome (as individual factors and as a dichotomous variable), duration of diabetes, sex, ethnicity, and family history of diabetes. A stepwise forward method was used, and variables that were significant using the log likelihood method were included in the final model. Interactions were tested between the independent variables.

RESULTS

Increase in the prevalence and severity of retinopathy in those with a younger age of diabetes onset

The demographic profile of those with a long duration (group A) and those with a moderate duration (group B) of diabetes, stratified by age of diagnosis, is shown in Table 1. For group A, there was an approximate threefold excess of retinopathy

Table 1—Demographic and clinical profile by group and age of diagnosis of type 2 diabetes

| | Group A (duration of diabetes 20–30 years, n = 624) | | | | Group B (duration of diabetes 10–12 years, n = 852) | | | |
| | Age of diagnosis (years) | | | | Age of diagnosis (years) | | | |
	<45	45–55	>55	P	<45	45–55	>55	P
n	322	232	70		236	293	323	
Age at last examination (years)	63.0 (53.8–66.4)	72.8 (70.2–75.4)	80.8 (78.8–83.0)	<0.0001	50.2 (46.3–52.9)	61.9 (59.4–64.0)	71.8 (69.3–75.4)	<0.0001
Duration (years)	24.2 (21.7–27.2)	22.8 (20.9–25.2)	22.1 (20.7–23.7)	<0.0001	10.9 (10.5–11.5)	11.1 (10.5–11.6)	10.9 (10.5–11.4)	0.3
Male (%)	55.0	53.9	57.1	0.9	59.8	58.0	51.1	0.08
Retinopathy (%)	61.8	50.0	40.0	0.0006	39.8	42.3	24.8	<0.0001
OR (95% CI)	2.4 (1.4–4.1)	1.5 (0.9–2.6)	1	0.0001 (P_{trend})	2.0 (1.4–2.9)	2.2 (1.6–3.1)	1	<0.0001 (P_{trend})
Vision-threatening retinopathy (%)	26.4	20.3	12.2	0.03	11.0	10.2	5.9	0.06
OR (95% CI)	2.4 (1.2–5.1)	1.7 (0.8–3.7)	1	0.009 (P_{trend})	2.0 (1.1–3.7)	1.8 (1.0–3.3)	1	0.03 (P_{trend})
Mean A1C (%)	8.4 ± 1.7	8.0 ± 1.3	8.2 ± 1.6	0.006	8.7 ± 1.8	8.2 ± 1.6	7.9 ± 1.6	<0.0001
Metabolic syndrome (%)	77.0	72.0	73.5	0.5	64.7	71.2	68.8	0.5
Systolic blood pressure (mmHg)	132 (120–150)	138 (125–152)	138 (128–152)	0.2	128 (117–140)	136 (126–149)	138 (127–153)	<0.0001
Diastolic blood pressure (mmHg)	72 (70–80)	70 (65–80)	70 (68–80)	0.051	80 (72–86)	80 (70–85)	76 (70–85)	0.002
Blood pressure Rx (%)	74.0	74.6	59.7	0.051	51.6	72.2	78.8	<0.001
Albuminuria (mg/l)	23.7 (10.0–86.9)	24.2 (10.0–92.0)	26.7 (10.0–99.0)	0.9	23.3 (9.0–83.3)	16.5 (8.2–51.1)	33.0 (11.0–104.3)	0.002
BMI (kg/m²)	30.0 (26.2–34.2)	28.3 (25.5–32.1)	27.6 (22.5–30.4)	<0.0001	30.1 (26.5–33.5)	29.7 (26.6–33.4)	29.5 (26.1–32.6)	0.09
HDL (mmol/l)	1.2 (1.0–1.4)	1.2 (1.0–1.6)	1.2 (1.0–1.6)	0.8	1.2 (0.9–1.4)	1.1 (1.0–1.4)	1.2 (1.0–1.5)	0.01
Triglycerides (mmol/l)	1.8 (1.2–2.7)	1.5 (1.1–2.2)	1.7 (1.0–2.5)	0.06	2.0 (1.3–2.9)	1.7 (1.2–2.7)	1.8 (1.3–2.6)	0.1

Data are means ± SD and median (interquartile range) unless otherwise indicated. P refers to χ^2 or ANOVA analysis of prevalence across the different age-of-onset subgroups; P_{trend} refers to trend analysis of retinopathy prevalence across the different age-of-onset subgroups.

in those with early-onset disease (<45 years), including a notable excess in vision-threatening retinopathy. For group B, the older-onset group again had the lowest prevalence of retinopathy, whereas the <45- and the 45- to 55-year onset groups were not statistically different from one another ($\chi^2 = 0.3$; $P = 0.6$). Glycemic exposure was slightly less favorable in the early-onset groups, but the differences in A1C were small, at 0.2% for group A and 0.8% for group B. There was no difference in the prevalence of the metabolic syndrome between the groups. For group A, the younger patients are receiving more antihypertensive treatment, but blood pressure remains similar between the age-of-onset groups.

Increase in the prevalence of retinopathy in those with younger age of onset: adjustment for glycemic exposure

Two approaches were used to address the extent to which excess of retinopathy in early-onset groups was due to slightly poorer glycemic control. First, retinopathy risk was stratified by average A1C. Table 2 and Fig. 1 show the prevalence and ORs of retinopathy for each age of onset at each level of glycemic exposure for the duration cohorts. The impact of the younger age of diagnosis is greatest in those with the worst long-term glycemic control (mean A1C >9%), with at least a two- to threefold increase in the OR of retinopathy for those diagnosed before 45 years of age compared with those of similar disease duration and glycemic exposure but diagnosed at >55 years of age. However, this trend of differing retinopathy prevalence according to age of onset is also seen at lower levels of glycemic exposure, even into the target range of A1C <7% (Table 2). The oldest-onset group invariably had the lowest risk of retinopathy. Second, regression analysis shows that each 1% rise in A1C is associated with a 13.9% increase in retinopathy for the main cohort of interest (group A). The small difference in A1C between the subgroups can only account for 12% of the observed difference in the prevalence of retinopathy between the youngest- and the oldest-onset group.

Age of diagnosis is an independent predictor of long-term retinopathy

Table 3 shows the results of logistic regression analysis for both duration cohorts. There is a significant effect of age of diagnosis, irrespective 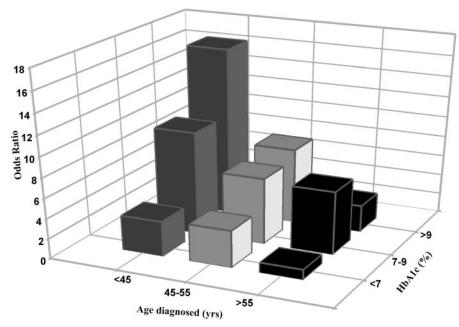of whether it was considered as a categorical variable (model 1 OR of retinopathy: 1.9, 1.1, and 1 for age of onset <45, 45–55, and >55 years, respectively, for group A with diabetes duration 20–30 years) or a continuous variable (model 2 OR of retinopathy: 0.88 [95% CI 0.83–0.94] for Group A). These findings were independent of A1C, hypertension, and other risk factors.

CONCLUSIONS — In this population with long-duration type 2 diabetes, patients with diabetes diagnosed at <45 years of age have a higher prevalence and more severe grades of diabetic retinopathy than those diagnosed later, despite matched duration of diabetes and glycemic control. Although before stratification, glycemic load was slightly more unfavorable in the youngest age-of-onset group, the difference in A1C was very small and in our opinion not sufficient to explain the rather large difference in risk of retinopathy. Moreover, the increased prevalence of retinopathy in the younger age-of-onset groups persists within each level of glycemic control. The impact of age of onset on retinopathy risk is the highest in those diagnosed before 45 years of age who have a mean A1C of >9%. Multivariate regression analysis adjusting for other traditional retinopathy risk factors indicate that the age of onset of diabetes is an independent risk factor for the development of retinopathy.

These data support earlier studies that suggest early-onset type 2 diabetes as a more aggressive disease (2,4,8). Younger patients obviously would have, on average, a longer life-time exposure to hyperglycemia and would be likely to have worse glycemic control. Both are known to be strong risk factors for retinopathy. More intriguingly, however, is the independent effect of age at onset on retinopathy risk revealed by our analysis. This suggests that there are additional factors hitherto unexplored in younger individuals that predispose to retinopathy.

It is interesting to note that the landmark Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) trial have demonstrated that metabolic control achieved early in the course of type 1 diabetes is effective at reducing microvascular complications risk and that the benefit extends for a considerable period beyond the time that tight glycemic control was maintained under the strict protocol of the study (9–11). Some have ascribed the "metabolic

Table 2—Prevalence and ORs of retinopathy by age of diagnosis of type 2 diabetes and mean A1C category for groups A and B with different durations of diabetes

| | Retinopathy (%) in group A: duration of type 2 diabetes 20–30 years (n = 624) | | | | Retinopathy (%) in group B: duration of type 2 diabetes 10–12 years (n = 852) | | | |
| | Age of diagnosis (years) | | | | Age of diagnosis (years) | | | |
	<45	45–55	>55	P	<45	45–55	>55	P
Mean A1C (%)								
<7	36.5	38.0	14.3	0.2	18.8	30.7	13.8	0.02
OR (95% CI)	3.5 (0.7–17.1)	3.7 (0.7–18.3)	1	0.4 (P_{trend})	1.4 (0.6–3.6)	2.8 (1.3–5.8)	1	<0.0001 (P_{trend})
7–9.0	63.1	52.3	51.2	0.1	34.4	43.4	27.3	0.02
OR (95% CI)	10.2 (2.2–47.2)	6.6 (1.4–3.0)	6.3 (1.4–31.5)	0.04 (P_{trend})	3.3 (1.6–6.6)	4.8 (2.5–9.1)	2.4 (1.2–4.5)	0.1 (P_{trend})
>9.0	73.4	55.6	30.8	0.003	55.8	52.0	36.6	0.04
OR (95% CI)	16.6 (3.5–79.2)	7.5 (1.5–36.8)	2.7 (0.4–17.9)	0.001 (P_{trend})	7.9 (4.0–15.6)	6.8 (3.3–13.8)	3.6 (1.7–7.5)	0.02 (P_{trend})

Data are % unless otherwise indicated. P refers to χ^2 analysis of retinopathy prevalence across the different age-of-onset subgroups; P_{trend} refers to trend analysis of retinopathy prevalence across different age-of-onset subgroups.

Figure 1—*Group A (duration of type 2 diabetes 20–30 years): OR for retinopathy grouped by age of diagnosis and mean A1C. Reference group is age of diagnosis >55 years and A1C <7%.*

memory" effects seen in the DCCT/EDIC trial as perhaps due to persistent suppression of inflammation and advanced glycation end product formation. In light of our data, a supplementary hypothesis could be that the age at which tissues are exposed to hyperglycemic insult is a determinant of the detrimental response. In this scenario, the DCCT control group would always be more at risk of compli- cations by being exposed to hyperglyce- mia at a younger age. Interestingly, levels of vascular endothelial growth factor (VEGF) and IGF-I, both potent angio- genic growth factors implicated in the de- velopment of diabetic retinopathy, have been found to vary with age in diabetes (12,13). Additionally, the VEGF expres- sion in response to a stimulus is lessened in older versus younger individuals (14).

Conceivably, ocular VEGF response to hypoxia and hyperglycemia may be greater in the younger patients, predis- posing them to the development of reti- nopathy. This, however, remains purely speculative and would be an interesting avenue for future research.

One of the strengths of our study is the long duration of diabetes in our co- horts, made possible by our systematic computerized database of more than 20 years of data. Even in our short-duration cohort (group B), the mean duration of diabetes was greater than 10 years, and in the longer duration cohort (group A), di- abetes had been present in every subject for over 20 years. The long duration en- sures sufficient time for retinopathy to de- velop. One previous study of newly diagnosed type 2 diabetes examined the impact of age of diagnosis on retinopathy risk (4) but did not show any relationship between retinopathy and age of diagnosis. This study, however, had a mean fol- low-up of only 3.9 years, which is too short a time to see a meaningful effect on retinopathy development. A recent study of early-onset type 2 diabetes in Asians found that diabetes duration but not age of onset was a risk factor for microvascu- lar complications (15); however, as age of onset and duration of diabetes are so in- herently linked, it is hard to demonstrate an independent effect if both are entered into a statistical model. Donaghue et al. (16) found that retinopathy was more prevalent in adolescents with type 1 dia- betes than in those with type 2 diabetes (20 vs. 4%); disease duration was, how- ever, very different between the two groups, making comparisons difficult. Our study design of comparing cohorts with equal and long duration of disease helped to tease out effects independent of disease duration and was made possible by collecting data consistently and in the same manner over a longer period of time.

In the elegant 50-year Medalist study by King et al. (17), which examined reti- nopathy prevalence in type 1 diabetes of extreme long duration, mean age of onset was lower in the retinopathy group; al- though this was not found to be statisti- cally significant, Krakoff et al. (18) found a reduced risk of retinopathy in a Pima Indian population with youth-onset dia- betes compared with later-onset diabetes. Their subjects were those diagnosed be- fore 20 years of age, a much younger on- set cohort than in our study. Thus, it is possible that our findings are not able to be generalized to type 1 diabetes and ad-

Table 3—*Predictors for retinopathy by logistic regression analysis*

Variable	Group A: duration of type 2 diabetes 20–30 years		Group B: duration of type 2 diabetes 10–12 years	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Model 1				
Age diagnosed (years)				
<45	1.9 (1.1–3.6)	0.04	1.8 (1.2–2.7)	0.0003
45–55	1.1 (0.6–2.1)	0.8	2.2 (1.6–3.2)	<0.0001
>55	1		1	
A1C (%)				
<7.0	1		1	
7–9	2.2 (1.2–3.6)	0.002	2.1 (1.4–3.1)	0.0003
>9.0	3.0 (1.7–5.3)	0.0002	3.6 (2.4–5.5)	<0.0001
Hypertension	2.1 (1.3–2.7)	0.003		NS
Ethnicity	1.9 (1.2–2.7)	0.004		NS
Weight (kg)	1.01 (1.00–1.02)	0.045		NS
Model 2				
Age diagnosed (years)	0.88 (0.83–0.94)	0.0001	0.7 (0.6–0.9)	0.03
A1C (%)	1.3 (1.2–1.5)	<0.0001	1.3 (1.2–1.4)	<0.0001
Hypertension	2.0 (1.2–3.2)	0.01		NS
Age (years)	1.1 (1.0–1.2)	0.002	1.3 (1.02–1.7)	0.04
Weight (kg)	1.01 (1.03–1.03)	0.03		NS
Ethnicity	1.8 (1.2–2.7)	0.005		NS

olescent- or childhood-onset type 2 diabetes, as these years may not contribute equally to risk of complications.

Our findings are not without caveats. Retinal photography is undoubtedly the gold standard for diagnosis and classification of diabetic retinopathy. While this is ideal, it would be logistically very difficult to implement in this study, particularly as the data collection span over a period of two decades and began at a time when retinal photography was not freely available as a clinical tool. Moreover, our study has the extremely stringent inclusion criteria of a very long and standardized duration of diabetes. It would be impossible to predict which patient will survive long enough to fulfill this criteria; thus, it would be difficult to photograph a manageable-sized cohort to test our hypothesis in a prospective manner. In our study, the diagnosis and classification of retinopathy was performed by a single physician (D.K.Y.) in 50–60% of cases. This physician has demonstrated and published good agreement with ophthalmologists in the detection and assessment of retinopathy (19). Due to the organizational structure of our clinics, over a period of nearly two decades, only five experienced specialist endocrinologists were responsible for examining the 30–40% of the patients not examined by either D.K.Y. or an ophthalmologist. All endocrinologists received the same training in fundoscopy and classification of retinopathy using a simple clinical guideline. There was also no evidence of a statistically significant difference in the distribution of the various examiners among the different age-groups of patients that had been studied (data not shown). Instead of relying on retrospective interpretation of clinical records, the retinal findings were prospectively categorized and entered into a purpose-designed computer database over a time span of two decades. Although differing sensitivities in the detection of retinopathy or misclassification of retinopathy cannot be completely discounted as a source of bias, it is minimized by the above-mentioned factors.

As mentioned previously, it is possible that the presence of retinopathy is associated with an excess mortality risk (20) and therefore a preferential drop out of older patients with retinopathy. This would introduce an ascertainment bias and reduce the number of later-onset individuals with retinopathy. We tried to assess the magnitude of this confounding effect by studying two cohorts with different disease durations. The group with the shorter duration of diabetes, which would be expected to have less retinopathy associated mortality, nevertheless showed the same trend of more retinopathy in the younger-onset group. We consider this as supporting evidence that what we have observed is a true phenomenon. However, we cannot discount the possibility that for younger patients, the metabolically severe cases are more likely to be diagnosed and preferentially referred to our clinic, resulting in bias toward detection of more youth with retinopathy.

In summary, this study shows that early onset of type 2 diabetes is an independent risk factor for the development of diabetic retinopathy. This suggests an increased inherent tissue susceptibility to the damaging effects of hyperglycemia at a younger age. This further supports the importance of delaying the onset of diabetes even if it cannot be completely prevented. It also implies a need for more stringent metabolic targets for younger individuals in the early years after diabetes onset.

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