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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RESULTS

The demographic profile of those with a younger age of diabetes onset compared with those of longer duration and those with very poor glycemic control. Continuous data were presented as mean or median. Kruskal-Wallace ANOVA was used to compare means or medians. Categorical data were presented as percentage and 95% CI.

Statistical analyses

Data were analyzed using NCSS 2004 software. Data were analyzed by grouping patients according to age of diagnosis of diabetes: <5 years, 5–15 years, 15–45 years, and >45 years. These AIC 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 medians. Categorical data were presented as percentage and 95% CI.

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 | 624 | 50.2 | 11.0 | 0.0001 | 236 | 293 | 323 | <0.0001 |
| Age at last examination (years) | 63.0 (53.8–66.4) | 50.2 (46.3–52.9) | 11.0 | 0.0001 | 8.4 (7.0–9.0) | 8.7 (7.0–9.0) | 7.9 (7.0–9.0) | <0.0001 |
| Duration (years) | 24.2 (21.7–27.2) | 12.8 (10.5–11.5) | 0.3 | 0.0001 | 1.7 (1.5–2.7) | 1.5 (1.2–2.0) | 1.7 (1.0–2.5) | 0.0001 |
| Male (%) | 55.0 | 53.9 | 59.0 | 0.9 | 30.1 (26.2–32.4) | 28.3 (25.3–32.1) | 27.6 (22.5–30.4) | <0.0001 |
| Retinopathy (%) | 61.8 | 50.0 | 40.0 | 0.0006 | 1.2 (1.0–1.4) | 1.2 (1.0–1.6) | 1.2 (1.0–1.6) | 0.8 |
| OR (95% CI) | 2.4 (1.4–4.1) | 1.5 (0.9–2.6) | 1 | 0.0001 | 2.0 (1.4–2.9) | 2.2 (1.6–3.1) | 1 | <0.0001 |
| Vision-threatening retinopathy (%) | 26.4 | 20.3 | 12.2 | 0.03 | 2.0 (1.1–3.7) | 1.8 (1.0–3.3) | 1 | 0.03 |
| OR (95% CI) | 2.4 (1.2–5.1) | 1.7 (0.8–3.7) | 1 | 0.009 | <0.0001 | 0.0001 | (P\textsubscript{trend}) | <0.0001 |
| 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 | 59.7 | 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 | <0.0001 |
| 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/m\textsuperscript{2}) | 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\textsubscript{trend} refers to trend analysis of retinopathy prevalence across the different age-of-onset subgroups. P\textsubscript{trend} refers to trend analysis of retinopathy prevalence across the different age-of-onset subgroups.
Age of diagnosis is an independent predictor of long-term retinopathy risk. Regression analysis for both duration coefficients shows that each 3.0% increase in AIC is associated with a 13.9% increase in retinopathy risk. There is a significant effect of age of diagnosis (for all age groups) as well as duration coefficients of the main cohort of interest (group A). There was a significant effect of age of diagnosis on retinopathy risk (Table 3). These findings were independent of A1C, duration of diabetes, and other risk factors. More mining risk was associated with those at younger age-of-onset. The impact of age-of-onset on retinopathy risk was also significant. These findings are consistent with the results of the Diabetes Control and Complications Trial (DCCT) and The Epidemiology of Diabetes Interventions and Complications (EDIC) trial. There was also a significant effect of age of diagnosis on retinopathy risk independent of A1C and duration of diabetes. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. However, this trend of differing retinopathy risk persists within each level of glycemic control. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. However, this trend of differing retinopathy risk persists within each level of glycemic control. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. However, this trend of differing retinopathy risk persists within each level of glycemic control. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. However, this trend of differing retinopathy risk persists within each level of glycemic control. The impact of age-of-onset on retinopathy risk was independent of A1C, duration of diabetes, and other risk factors. However, this trend of differing retinopathy risk persists within each level of glycemic control.
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 complications by being exposed to hyperglycemia at a younger age. Interestingly, levels of vascular endothelial growth factor (VEGF) and IGF-I, both potent angiogenic growth factors implicated in the development of diabetic retinopathy, have been found to vary with age in diabetes (12,13). Additionally, the VEGF expression 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, predisposing them to the development of retinopathy. 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 cohorts, 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), diabetics had been present in every subject for over 20 years. The long duration ensures sufficient time for retinopathy to develop. 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 follow-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 microvascular complications (15); however, as age of onset and duration of diabetes are so inherently 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 diabetes than in those with type 2 diabetes (20 vs. 4%); disease duration was, however, 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 retinopathy prevalence in type 1 diabetes of extreme long duration, mean age of onset was lower in the retinopathy group; although this was not found to be statistically significant, Krakoff et al. (18) found a reduced risk of retinopathy in a Pima Indian population with youth-onset diabetes compared with later-onset diabetes. Their subjects were those diagnosed before 20 years of age, a much younger onset 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)                                       | OR (95% CI)                                   |
| Model 1             |                                                   |                                               |
| Age diagnosed (years) |                                                   |                                               |
| <45                 | 1.9 (1.1–3.6)                                     | 1.8 (1.2–2.7)                                 |
| 45–55               | 1.1 (0.6–2.1)                                     | 2.2 (1.6–3.2)                                 |
| >55                 | 1                                                  | 1                                             |
| A1C (%)             |                                                   |                                               |
| <7.0                | 2.2 (1.2–3.6)                                     | 2.1 (1.4–3.1)                                 |
| 7–9                 | 3.0 (1.7–5.3)                                     | 3.6 (2.4–5.5)                                 |
| Hypertension        | 2.1 (1.3–2.7)                                     | NS                                            |
| Ethnicity           | 1.9 (1.2–2.7)                                     | NS                                            |
| Weight (kg)         | 1.01 (1.00–1.02)                                  | NS                                            |
| Model 2             |                                                   |                                               |
| Age diagnosed (years)|                                                   |                                               |
| 1.08 (0.83–0.94)    | 0.0001                                            | 0.7 (0.6–0.9)                                 |
| A1C (%)             | 1.3 (1.2–1.5)                                     | <0.0001                                       |
| Hypertension        | 2.0 (1.2–3.2)                                     | NS                                            |
| Age (years)         | 1.1 (1.0–1.2)                                     | 1.3 (1.02–1.7)                                |
| Weight (kg)         | 1.01 (1.03–1.03)                                  | NS                                            |
| Ethnicity           | 1.8 (1.2–2.7)                                     | NS                                            |
oleescent- 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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