Decline in the Cumulative Incidence of Severe Diabetic Retinopathy in Patients With Type 1 Diabetes

Janne P. Kytö, md[1,2]
Valma Harjutsalo, phd[2,3,4]
Carol Forsblom, dmsc[2,4]
Kustaa Hietala, md[1,2]
Paula A. Summanen, md, dmsc, febo[1]
Per-Henrik Groop, md, dmsc[2,4,5]
on behalf of the FinnDiane Study Group

OBJECTIVE—To determine if the cumulative incidence of severe retinopathy in patients with type 1 diabetes has changed.

RESEARCH DESIGN AND METHODS—The study looked at 3,781 patients diagnosed with type 1 diabetes (1939–2005), median age at onset 13 (interquartile range [IQR] 9–21) years, and duration of diabetes 19 (IQR 13–27) years. The severe retinopathy was based on a history of laser treatment. Patients were divided into <1975, 1975–1979, 1980–1984, and ≥1985 cohorts according to the diagnosis of diabetes.

RESULTS—The cumulative incidence of severe retinopathy has declined ($P < 0.0001$). After 20 years of duration, the cumulative incidence was 23% (95% CI 21–25) and 33 (30–35) in the earliest cohorts, 18 (15–21) in the next cohort, and 6 (4–9) in the recent cohort. After 30 years, the cumulative incidence was 52 and 48% in the earliest cohorts, while it was 62% after 40 years in the earliest cohort.

CONCLUSIONS—The cumulative incidence of severe retinopathy has declined in patients with type 1 diabetes.

Diabetes Care 34:2005–2007, 2011

Studies have demonstrated a declining incidence in severe diabetic retinopathy (SDR) or proliferative diabetic retinopathy (PDR) in patients with type 1 diabetes (1–3). Limited data are, however, available on the relationship between the period of diagnosis of type 1 diabetes and the cumulative incidence of PDR.

RESEARCH DESIGN AND METHODS

—All subjects participated in the nationwide, multicenter FinnDiane study (4). Type 1 diabetes was defined as onset before age 40 years and permanent insulin initiated within 1 year of diagnosis. A total of 3,781 patients' data on potential laser photocoagulation were available. The study protocol was approved by the ethics committees of the participating centers. Patients signed informed consent.

At the baseline visit (1997–2006), information including age at diagnosis, insulin use, and diabetes complications was obtained from the medical records using a standardized form. Laser treatment was defined as history of laser photocoagulation. Treatment was mostly due to PDR but also due to macular edema and severe nonproliferative retinopathy. Laser treatment was a surrogate end point for SDR.

Follow-up started at diagnosis of diabetes and ended at the time of the first laser treatment. Patients without laser treatment contributed to the follow-up until their baseline visit. Patients were divided into cohorts <1975, 1975–1979, 1980–1984, and ≥1985 based on the time of diagnosis of diabetes. Cumulative incidence of SDR was estimated using the Kaplan-Meier method dividing data by diagnosis years. Differences between groups were tested using the log-rank test.

Univariate and multivariate analyses were performed using Cox proportional hazards modeling. Variables were adjusted for sex, age at onset, as well as interactions. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

—Patients were divided into diagnosis cohorts: <1975 (1,440 patients); 1975–1979 (517 patients); 1980–1984 (506 patients); and ≥1985 (1,318 patients). Median age at onset was the highest in the most recent cohort, 18.3 years; it was 10.8, 12.6, and 12.7 years in the diagnosis cohorts <1975, 1975–1979, and 1980–1984, respectively. Patient characteristics are presented in more detail in Supplementary Table 1.

Laser photocoagulation was performed in 1,219 subjects (32%). There were few events during the first 10 years, after which the cumulative incidence increased and was 62% (95% CI 61–64) at 40 years. This was subdivided by year of diagnosis and revealed a declining trend ($P < 0.0001$, log-rank test) (Fig. 1). The 30-year cumulative incidence was 52% (95% CI 50–53) in those diagnosed <1975 and 48 (45–51) in those diagnosed in 1975–1979.

The cumulative incidence at 20 years was 23% (95% CI 21–25) and 33 (30–35) in the earliest cohorts, 18 (15–21) in the 1980–1984 cohort, and 6.4 (4.0–8.7) in the ≥1985 cohort.

There was a gradual decrease in hazard ratio (HR) by a later year of diagnosis. Risk of SDR decreased by 47% (HR = 0.53, [95% CI 0.42–0.67]) and 64 (0.36 [0.26–0.51]) in the 1980–1984 and ≥1985 cohorts compared with the <1975 cohort. Adjustment for sex and age at onset had no influence on the results.

From the [1]Department of Ophthalmology, Helsinki University Central Hospital, Helsinki, Finland; the [2]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland; the [3]Diabetes Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland; the [4]Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland; and the [5]Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia.
Corresponding author: Per-Henrik Groop, per-henrik.groop@helsinki.fi.
Received 20 December 2010 and accepted 27 March 2011.
DOI: 10.2337/dc10-2391
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-2391/-/DC1.

See accompanying editorial, p. 2130.

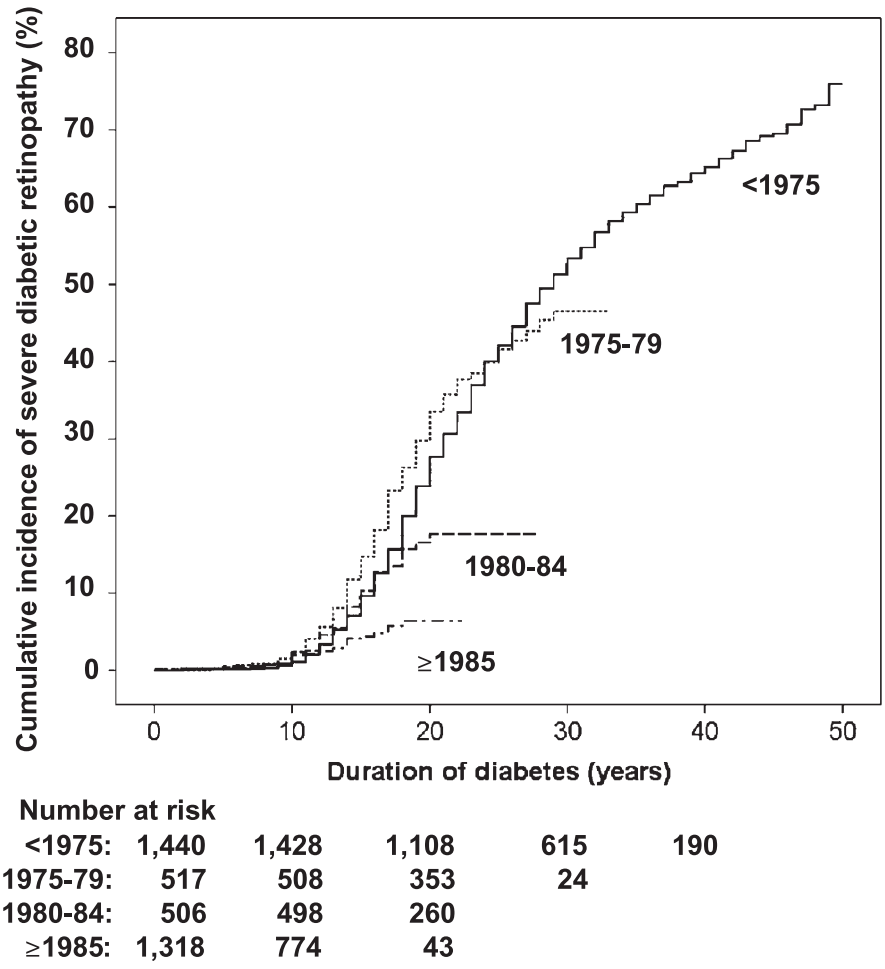

Figure 1—*The cumulative incidence (%) of SDR in patients with type 1 diabetes by duration and period of diagnosis in the FinnDiane study. The numbers of patients in each cohort who were evaluated at years 0, 10, 20, 30, and 40 are shown below the graph.*

CONCLUSIONS—We observed a declining trend in the cumulative incidence of SDR after 20–30 years of diabetes, in line with other Scandinavian studies, when patients were divided by period of diagnosis (1–3). The 30-year incidence of 48% in the 1975–1979 cohort and 52% in the <1975 cohort was similar to the 41 and 51% observed in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) population (5).

The Diabetes Control and Complications Trial (DCCT) showed that intensive insulin therapy reduced the risk of laser treatment (6). In Finland, patients have had access to insulin and self-monitoring blood glucose devices free of charge or at low cost, but only 750 patients (2%) with type 1 diabetes used pumps in 2003 (7). Contrastingly, carbohydrate counting to adjust mealtime insulin has long been a routine. These developments in diabetes care may have influenced the cumulative incidence of SDR.

Earlier, when PDR could not be laser treated, most patients became blind within 5–10 years (8,9). In Finland, the argon laser device was introduced in 1973 without uniform screening procedures. Some patients were screened for PDR by ophthalmologists using a biomicroscope, but the majority were screened by internists or general practitioners using a direct ophthalmoscope. Due to the shortage of ophthalmologists in some parts of the country, patients were not screened with equal quality. This changed in 1992 when national guidelines for screening using fundus photography were introduced (10). The photography screening was more equal, and instead of examining fundi, ophthalmologists could perform laser treatment.

The decrease in the incidence of SDR has not been accompanied by an improvement in the present HbA_{1c}. This does not, however, rule out the possibility that patients in the earliest cohort might have been exposed to worse glycemic control over the years than patients in the recent cohort. Baseline HbA_{1c} obtained in 1997–2006 does not necessarily reflect the glycemic control decades earlier. Evidence from Sweden showed that glycemic control has improved over time (11). Notably since adults were enrolled, the proportion of those with diabetes diagnosed in early childhood was small in the most recent cohort. The age at onset, therefore, was high—a fact that might have contributed to the low cumulative incidence. Such a view is supported by our previous data, which show the highest risk of PDR in the age-at-onset group of 5–14 years and the lowest risk in the age-at-onset group of 15–40 years (12). However, the decline in the cumulative incidence of SDR remained after adjusting for age at onset.

The major strength of this study is the large number of patients, but a limitation is the fact that the diagnosis of SDR was based on the history of laser treatment rather than the review of fundus photographs. PDR was the indication for laser treatment in the great majority of patients. Most important was the fact that even self-reported laser treatment has been shown to be a reliable indicator of SDR (13). Because this study is retrospective and data on loss of vision before laser treatment were not available, potential competing risks could not be analyzed.

In conclusion, we demonstrate a decline over the last decades in the cumulative incidence of SDR in patients with type 1 diabetes.

Acknowledgments—This study was supported by grants from the Eye Foundation Finland, the Finnish Medical Foundation, the Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Kyllikki ja Uolevi Lehikoinen Foundation, Mary and Georg C. Ehrnrooth Foundation, and the Orion Research Foundation. J.P.K. has worked as Medical Advisor for Pfizer. No other potential conflicts of interest relevant to this article were reported.

The conception and design of the study was by J.P.K., V.H., C.F., K.H., P.A.S., and P.-H.G. The collection and assembly of data was by J.P.K., V.H., C.F., and K.H. The data analysis and interpretation was by J.P.K. and V.H. J.P.K. wrote the manuscript. Contributing to discussion was by J.P.K., V.H., C.F., K.H., P.A.S., and P.-H.G. Review and editing of the manuscript was by V.H., C.F., K.H., P.A.S., and P.-H.G. Final approval of the manuscript was by J.P.K. and P.-H.G.

The skilled technical assistance of Sinikka Lindh, Anna-Reetta Salonen, Anna Sandelin, Susanne Ström, Jessica Thorn, and Jaana

Tuomikangas is gratefully acknowledged. The authors also acknowledge all the physicians, nurses, and other research personnel at each center participating in the collection of patients (Supplementary Data).

References

1. Grauslund J, Green A, Sjølie AK. Prevalence and 25 year incidence of proliferative retinopathy among Danish type 1 diabetic patients. Diabetologia 2009;52:1829–1835
2. Nordwall M, Bojestig M, Arnqvist HJ, Ludvigsson J; Linköping Diabetes Complications Study. Declining incidence of severe retinopathy and persisting decrease of nephropathy in an unselected population of type 1 diabetes: the Linköping Diabetes Complications Study. Diabetologia 2004;47:1266–1272
3. Hovind P, Tarnow L, Rossing K, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003;26:1258–1264
4. Thorn LM, Forsblom C, Fagerudd J, et al.; FinnDiane Study Group. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28:2019–2024
5. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115:1859–1868
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
7. Sane T, Tulokas T, Nikkanen P, Heikkilä P, Huttunen E, Niskanen L. Insulin pump in the treatment of adult age diabetes. Duodecim 2005;121:839–845 [in Finnish]
8. Caird FI, Burditt AF, Draper GJ. Diabetic retinopathy: a further study of prognosis for vision. Diabetes 1968;17:121–123
9. Deckert T, Simonsen SE, Poulsen JE. Prognosis of proliferative retinopathy in juvenile diabetics. Diabetes 1967;16:728–733
10. Suomen Diabetesliitto ry:n retinopatiatyöryhmä (The Finnish Diabetes Association Retinopathy Work Group). Diabeettinen retinopatia: Seuranta, hoito ja näkövammautuneen diabeetikon kuntoutus. Suom Laakaril 1992;47:2199–2211 [in Finnish]
11. Bojestig M, Arnqvist HJ, Hermansson G, Karlberg BE, Ludvigsson J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. N Engl J Med 1994;330:15–18
12. Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH; FinnDiane Study Group. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. Diabetes Care 2010;33:1315–1319
13. Grassi MA, Mazzulla DA, Knudtson MD, et al. Patient self-report of prior laser treatment reliably indicates presence of severe diabetic retinopathy. Am J Ophthalmol 2009;147:501–504