Age at onset and the risk of proliferative retinopathy in type 1 diabetes

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Objective: Age at onset of type 1 diabetes influences the risk of microvascular complications. However, the long-term risk of proliferative retinopathy within the wide spectrum of age at onset of type 1 diabetes is less well known.

Research design and methods: A sample of 1117 consecutively recruited patients was drawn from the FinnDiane Study population (4800 patients). Type 1 diabetes was defined as age at onset ≤ 40 years, insulin treatment initiated within one year and C-peptide ≤ 0.3 nmol/l. Retinopathy status was graded based on ophthalmic records and/or fundus photographs. The risk of proliferative retinopathy was studied in age at onset groups 0-4, 5-14 and 15-40 years.

Results: The mean durations to proliferative retinopathy were 24.3 (22.7-25.9) years in 0-4 group, 20.1 (19.2-21.1) years in 5-14 group and 21.6 (19.8-23.3) years in 15-40 group (P<0.001). In a Cox-regression model, with HbA1c, blood pressure, sex and body mass index as covariates, the highest risk of proliferative retinopathy was observed in 5-14 group (HR 1.90 [95% CI 1.45-2.48], P<0.001). Diabetes onset 0-4 vs. 5-14 years had no difference in the long-term risk of proliferative retinopathy (P=0.2). When split into two groups, age at onset <15 years was associated with a higher long-term risk than age at onset ≥15 years (HR 1.82 [95% CI 1.40-2.36], P<0.001).

Conclusions: Age at onset significantly modifies the long-term risk of proliferative retinopathy. The highest risk is in age at onset group 5-14 whereas the lowest risk is in the age at onset group 15-40 years.
Proliferative retinopathy is a severe microvascular complication in patients with type 1 diabetes. After 20 years of diabetes, almost all patients with type 1 diabetes and 58% of patients with type 2 diabetes show signs of retinopathy. When retinopathy worsens, severe visual loss eventually threatens 5-10% of the patients (1). The most severe form of retinopathy is proliferative retinopathy and most of the patients with this complication will become blind after 5-10 years without treatment (2). The prevalence of proliferative retinopathy varies between 13 and 50% after 15-25 years of diabetes in patients that need insulin (3;4).

Several risk factors for diabetic retinopathy have already been identified. The prevalence of any retinopathy is strongly related to duration of diabetes and glycaemic control (1;4). Poor glycaemic control increases both the incidence and the progression of retinopathy (5). Male sex and high blood pressure further increases the risk of retinopathy (3). Genetic factors are also likely to play a major role (6). It is of note that the age at onset of diabetes may modify the metabolic phenotype of the patients and thus predispose certain patients to diabetic retinopathy. Especially, diabetes onset before the age of 5 years may have a protective effect on the development of retinopathy (7;8). Thus it can be hypothesized that since the incidence of type 1 diabetes is on the rise and the increase has been greatest in children aged 0-4 years (9), this may possibly lead to a decrease in the overall risk of retinopathy. The studies so far have not focused on the onset of type 1 diabetes in the adulthood and therefore the number of patients with late onset diabetes has been rather small and not large enough to study the effect of late age at onset on the risk of proliferative retinopathy. Furthermore, it is not yet known whether young age at onset is a protective factor in the long run, or whether it only delays the onset of proliferative retinopathy. Therefore, the aim of this study was to elucidate how the age at onset of type 1 diabetes influences the long term risk of proliferative retinopathy in patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**

The present study is a retrospective cohort study, undertaken as part of the ongoing FinnDiane Study (Finnish Diabetic Nephropathy Study), which has since 1997 collected comprehensive data from patients with type 1 diabetes at 92 centers throughout Finland, including primary care as well as secondary and tertiary care hospitals with the aim to identify genetic and environmental risk factors for diabetic complications. All adult patients with type 1 diabetes at these centers have been invited to participate in the FinnDiane Study and 78% have responded positively (10). The recruitment strategy is random as the only inclusion criteria is type 1 diabetes and every patient at the recruiting centers have been invited. The FinnDiane Study has to date recruited 4800 patients with type 1 diabetes and although it is not by strict definition a population based study, the distribution of the patients closely follows the distribution of the general population in Finland. Thus there is no bias in the sampling procedure regarding the geographic location or selection of patients in the recruiting centers. The protocol is in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the Helsinki University Central Hospital.

Inclusion of the patients into the present study was based on the ascending order of the FinnDiane patient identification numbers. Thus, the consecutively recruited patients from the very beginning of the FinnDiane-study were the first to be included in the study. This approach has two
advantages. First the sampling frame should be as random as possible with regards to ophthalmic status, and the treatment of diabetes and its complications. Secondly, these patients had the longest duration of type 1 diabetes as they were the first ones to participate in the FinnDiane study.

We obtained fundus photographs and/or records of fundus examinations performed by a specialist in ophthalmology for 1117 consecutively recruited patients. These patients were required to have onset of diabetes at the age of 40 years or less, C-peptide 0.3 nmol/l or less (11) and insulin treatment initiated within one year of diagnosis. For 972/1117 (87%) patients, the C-peptide concentrations were below 0.033 nmol/l, which represents the detection limit of the assay (Human C-peptide RIA Kit, Linco Research Inc., MO, USA). Records of fundus examinations by a specialist in ophthalmology were available for 917/1117 (82%) patients and fundus photographs were available for 851/1117 (76%) patients. The patients that had fundus photographs available (n=851) had been photographed a total of 2792 times, on a median of 3 (IQR 1-5) times per patient. Both records and photographs were available for 651/1117 (58%) patients. All available data were used to score the severity and progression of retinopathy, a procedure handled by an ophthalmologist (KH) unaware of the demographic data and the presence or absence of other complications. The ETDRS-grading scale was used, where 10 represents no retinopathy, 61 and upwards proliferative retinopathy and 81-85 advanced retinopathy (12). The eye with the more severe retinopathy was used to represent the overall retinopathy severity for the particular patient. In this study laser-treatment alone was not taken as evidence of proliferative retinopathy as severe non-proliferative retinopathy is also an indication for scatter laser photoagulation.

Data on medication, cardiovascular status, diabetic complications, hypertension and cardiovascular disease were obtained using a standardised questionnaire, which was completed by the patient’s attending physician. Blood pressure (BP) was measured twice in the sitting position using a mercury sphygmomanometer after a rest of at least 10 min. Mean arterial blood pressure was calculated according to the formula: MAP = diastolic BP + 1/3(systolic BP - diastolic BP). Anthropometric data, such as height and weight were recorded, and blood was drawn for the laboratory measurements, including HbA1c. Data on all-cause mortality were obtained from a national registry maintained by the Population Register Centre of Finland.

**Statistical Analysis:** Data are presented as means and 95% confidence intervals (CI) for continuous, normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Standard errors (SE) are given for mean differences. Kaplan-Meier survival analysis was used to estimate time without proliferative retinopathy and Mantel-Cox Logrank Test to compare survival distributions among different age at onset groups. The risk of proliferative retinopathy within the age at onset groups was estimated with a Cox proportional hazards model, controlling for clinically significant covariates. One-way anova, adjusted for multiple comparisons (Sidak), was used to compare the mean differences of these groups. Proportions were compared with Kruskal-Wallis tests. A previously published macro for SAS statistical software (SAS®, Cary, NC, USA) was used to compute the cumulative incidence of PDR and cumulative mortality before the development of PDR accounting for competing events (13). All other statistical calculations were performed with SPSS 15.0 (SPSS, Chicago, IL, USA).

**RESULTS**
Tables 1 and 2 show the clinical characteristics of the studied patients. The male/female ratio was 596/521. Mean age at onset of type 1 diabetes was 13.7 (13.1-14.1) years and the mean duration of diabetes 25.0 (24.4-25.7) years (Table 1). Proliferative retinopathy was found in 367/1117 (33 %) patients. The highest proportion of patients with proliferative retinopathy was found in age at onset group 0-4 years (47.0 % [39.5-54.6]), second highest in age at onset group 5-14 years (38.8 % [34.7-42.9]), and the lowest in age at onset group 15-40 years (18.9 % [15.0-22.7]) (Table 2). Ophthalmic follow-up data were available on a median of 10.8 (IQR 5.9-17.4) years after the diagnosis of proliferative retinopathy. Mean duration from onset of diabetes to proliferative retinopathy was 21.3 (20.6-22.1) years in all patients. The longest mean duration to proliferative retinopathy was 24.3 (22.7-25.9) years in the 0-4 group (n= 79), whereas the shortest was 20.1 (19.2-21.1) years in the 5-14 group (n= 212). In the 15-40 group the mean duration to proliferative retinopathy was 21.6 (19.8-23.3) years (n= 76) (Table 2). The mean difference in the duration of diabetes to proliferative retinopathy between the age at onset groups 0-4 and 5-14 was statistically significant (4.2 ±0.9 years, p<0.001). However, the mean difference between the other two groups did not reach statistical significance. The youngest age at onset group had the longest duration of diabetes (31.12 [29.5-32.7] years), highest Hba_{1c} (8.8 [8.5-9.0] %) and the highest proportion of patients with C-peptide below the detection limit (96.4 [92.4-98.7] %) (Table 2). Patients with proliferative retinopathy had the highest mortality (20.4%), highest body mass index (25.5 [25.1-25.9] m2/kg) and the longest duration of diabetes (33.1 [32.2-34.0] years) (Table 1).

In the Cox proportional hazards model, with potentially significant risk factors (HbA_{1c}, blood pressure, sex, body mass index) as covariates, onset of diabetes between 5-14 years of age increased the risk of proliferative retinopathy the most (HR 1.90 [95% CI 1.45-2.48], p<0.001) as contrasted to the age at onset group of 15-40 years. Similarly, patients with age at onset between 0-4 years had a higher risk of proliferative retinopathy (HR 1.61 [95% CI 1.16-2.23], p=0.002). As for the other covariates, the risk of proliferative retinopathy increased 1.5% with every unit increase in HbA_{1c} percentage (HR 1.15 [95% CI 1.07-1.23], p<0.001) and 3% with every 1 mmHg increase of mean arterial blood pressure (1.03 [95%1.02-1.04], p <0.001). Male sex and body mass index did not influence the risk of proliferative retinopathy. When the age at onset group 0-4 years was compared to the age at onset group with the highest risk (5-14 years), the long-term risk of proliferative retinopathy, adjusted for the above mentioned covariates, showed no difference (HR 0.85 [95% CI 0.65-1.10], p=0.2). The worst prognosis appears to be in the age at onset group 5-9. However, if compared to age at onset 10-14, this difference did not reach statistical significance (HR 1.29 [95 % CI 0.98- 1.70], P=0.07). Since the patients in groups 5-9 and 10-14 did not have significantly different risk, they are presented as a combined age at onset group 5-14 years in this study.

The Kaplan-Meier survival analysis stratified by various age at onset groups illustrates the progression to proliferative retinopathy (Fig 1). Median times without proliferative retinopathy were 28.9 (24.6-33.2), 29.2 (26.1-32.2) and 37.8 (32.3-43.4) years in age at onset groups 0-4 years, 5-14 years and 15-40 years respectively (P <0.001, Mantel-Cox log-rank test) (Fig 1). Despite the initial delay in the progression to proliferative retinopathy in the youngest age at onset group, the long-term risk between the age at onset groups of 0-4 years and 5-14 years was no different (p = 0.224, Mantel-Cox log-rank test) (Fig. 1). However, there was a
significant difference, when the patients were split into two groups according to the age at onset before or after 15 years of age (P <0.001, Mantel-Cox log-rank test). Median times without proliferative retinopathy were 28.9 (95% CI 26.4-31.4) for the patients with age at onset before 15 years and 37.8 (95% CI 32.3-43.4) for the patients with age at onset after 15 years of age. The risk of proliferative retinopathy was significantly higher in those patients with age at onset before 15 years vs. after 15 years, when adjusted for the above mentioned covariates (HR 1.82 [95% CI 1.40-2.36], p<0.001).

A total of 99 of the 1117 patients (8.9%) had died during the follow up. Of these 75/99 (75.8%) had been diagnosed with proliferative retinopathy (Table 1). The remaining 24/99 (24.2%) patients, did not have proliferative retinopathy.

CONCLUSIONS

This study shows that the patients with the youngest age at onset (0-4 years) have the longest duration of type 1 diabetes without proliferative retinopathy (24.3 [22.7-25.9] years). This observation is in line with earlier findings regarding diabetic retinopathy and nephropathy (7;8;14). However, the long-term risk of proliferative retinopathy is no different between the age at onset groups of 0-4 years and 5-14 years despite the initial advantage for those with earlier onset of diabetes. Ultimately, the survival curves for these two groups cross each other when the duration of diabetes approaches 30 years. The survival curve for those patients with age at onset of type 1 diabetes between 15-40 years appears to be consistently better than in the younger patients.

Good self-care of diabetes correlates with good metabolic control (15). It can be hypothesized that it may be easier to learn good self-care skills at a very young age as compared to the prepubertal period (14). Learning good self-care skills may take a longer time in prepubertal children as compared to the young ones, which would explain the delayed onset of proliferative retinopathy in the youngest patients. In addition to behavioral factors, hormonal changes in the puberty may contribute to worse metabolic control (16). Furthermore, the initial advantage for the younger patients may be due to more stringent management of type 1 diabetes, since this has been shown to reduce the decline in insulin production (17).

Diabetes onset at puberty has been linked to a less aggressive form of type 1 diabetes (18) and it has also been observed that β-cells are better preserved when type 1 diabetes begins in the adulthood (19). We observed a longer time without proliferative retinopathy as well as a lower risk of proliferative retinopathy for the age at onset group of 15-40 years. This finding could be explained by preservation of β-cells as these patients also had the highest C-peptide concentrations. The DCCT data indicated that patients with any residual C-peptide secretion, but especially those with the highest stimulated concentrations, had a reduced incidence of retinopathy and nephropathy (20). The role of C-peptide has been somewhat controversial, since it has not been linked to retinopathy in other studies (3). In our study those patients with a higher C-peptide concentration had less proliferative retinopathy, later age at onset, as well as lower HbA1c (Tables 1 and 2). The association of age at onset with the risk of diabetic retinopathy may not only be limited to type 1 diabetes. It has been recently noted that a higher age at onset of diabetes reduces the risk of retinopathy in type 2 diabetes patients as well (21).

An advantage of our study is that the timing of onset of proliferative retinopathy is robust, since it was based on several examinations and/or serial fundus photographs. Only in 19/367 (5.2%) patients proliferative retinopathy was discovered at
their first fundus examination by an ophthalmologist. Thus there were no available reference points for these patients before they had developed proliferative retinopathy. As all of these 19 patients comprise only 5.2% of all the patients with proliferative retinopathy, the possible inaccuracy introduced by these patients was judged to be negligible and they were kept in the study. Importantly, this also kept the original random sampling frame intact. All the other patients (N=348) had had at least one ophthalmic examination on a median of 0.7 (0.3-1.8) years prior to the diagnosis. Additionally, records of treatment and follow-up were available for nearly all (364/367) patients with proliferative retinopathy. Retinal photography has been reported to be the most sensitive screening method for diabetic retinopathy. The sensitivity is in excess of 80% in detecting proliferative retinopathy (22). Ophthalmoscopy has less sensitivity, but conversely a higher specificity. It provides good results in the hands of trained professionals such as ophthalmologists and diabetologists, especially when used in repeated examinations (22). In Finland, the national guidelines for the screening of diabetic retinopathy were published already in 1992 and updated in 2006, along the European guidelines which emphasize fundus photography as the preferable screening method (23). As a consequence of this, fundus photographs were available for as many as 851/1117 (76%) patients.

The generalizability of the present results may be limited by the fact that the FinnDiane Study is not by strict definition a population based study. In any case, a possible selection bias is unlikely since the geographic distribution of the FinnDiane patients closely follows the distribution of the general population and the patient recruitment at the participating centers can be considered random. Furthermore, the diagnosis and treatment of diabetes and its complications is fairly uniform across Finland. There is only one population-based study on the prevalence of proliferative retinopathy among patients with type 1 diabetes in Finland in a sample of 1067 patients, and the results are comparable to ours (24). Another, potentially important issue is the competing risk of death. Accounting for the cumulative mortality by using a previously published SAS macro (13) did not change the outcome of either Kaplan-Meier or Cox-regression analysis. Interestingly, 75/99 patients who had died during the follow-up had developed proliferative retinopathy. The ultimate long-term risk of proliferative retinopathy appears therefore to be roughly 75% for the FinnDiane study population. Finally, there may also be a confounding cohort-effect in the present study, since the oldest patients may have a worse prognosis than the younger ones due to improvement of medical care of diabetes (Wong et al). However, we tested the data for such a cohort effect in two ways. The first way was to use the year of onset of diabetes as a continuous variable in the Cox-regression model. The other was to use the decade of onset of diabetes as a categorical variable. Both of these variables were statistically non-significant.

In conclusion, our study shows a longer time free of proliferative retinopathy in the youngest patients. It appears that this initial advantage gradually wears off in the long run. In contrast, those patients with age at onset of type 1 diabetes between ages 15-40 years may have a consistently better prognosis than any patient group with age at onset below 15 years.

ACKNOWLEDGMENTS
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acknowledge all the physicians and nurses at each center participating in the collection of patients (see appendix which can be found in an online appendix at http://care.diabetesjournals.org). The authors of this study have no relevant conflict of interest to disclose.
REFERENCES


Table 1. Clinical characteristics of patients without any retinopathy, as compared to patients with non-proliferative, and proliferative retinopathy.

<table>
<thead>
<tr>
<th>Variable (95%CI)</th>
<th>No retinopathy (n=258)</th>
<th>Non-Proliferative Retinopathy (n=492)</th>
<th>Proliferative Retinopathy (n=367)</th>
<th>All Patients (n=1117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes (years)</td>
<td>13.7 (12.6-14.7)*</td>
<td>24.9 (24.1-25.8)*</td>
<td>33.1 (32.2-34.0)*</td>
<td>25.0 (24.4-25.7)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>17.2 (16.2-18.3)*</td>
<td>14.0 (13.2-14.8)*</td>
<td>10.6 (9.9-11.3)*</td>
<td>13.7 (13.1-14.1)</td>
</tr>
<tr>
<td>HbA\textsubscript{1c} (%)</td>
<td>8.1 (7.9-8.3) ¶</td>
<td>8.5 (8.3-8.6)*</td>
<td>8.7 (8.5-8.8)*</td>
<td>8.4 (8.4-8.5)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93.7 (92.4-94.9)*</td>
<td>96.6 (95.7-97.5)*</td>
<td>102.3 (101.1-103.5)*</td>
<td>97.8 (97.2-98.5)</td>
</tr>
<tr>
<td>BMI (m\textsuperscript{2}/kg)</td>
<td>24.3 (23.9-24.7) ¶</td>
<td>25.2 (24.9-25.5)*</td>
<td>25.5 (25.1-25.9)*</td>
<td>25.1 (24.8-25.3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (1.9%)*</td>
<td>19 (3.9%)*</td>
<td>75 (20.4)*</td>
<td>99 (8.9%)</td>
</tr>
</tbody>
</table>

Significant difference (p<0.05) between two groups * ¶, or between all three groups *. One-way anova, adjusted for multiple comparisons (Sidak). Differences in proportions were compared with Kruskal-Wallis test. CI= Confidence Interval, MAP= Mean Arterial Pressure, BMI= Body Mass Index.
<table>
<thead>
<tr>
<th>Age at onset group</th>
<th>Duration of diabetes (years) (95% CI)</th>
<th>PDR % (95% CI)</th>
<th>Duration to PDR (years) (95% CI)</th>
<th>HbA1c (%) (95% CI)</th>
<th>MAP (mmHg) (95% CI)</th>
<th>C-peptide &lt; 0.033 nmol/l (%) (95% CI)</th>
<th>BMI (m2/kg) (95% CI)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset 0-4 years (n=168)</td>
<td>31.12 (29.5-32.7)*</td>
<td>47.0 (39.5-54.6) ¶</td>
<td>24.3 (22.7-25.9) ¶</td>
<td>8.8 (8.5-9.0) ¶</td>
<td>96.6 (94.9-98.3)</td>
<td>96.4 (92.4-98.7) ¶</td>
<td>24.8 (24.3-24.5)</td>
<td>(8.9 %)</td>
</tr>
<tr>
<td>Age at onset 5-14 years (n=546)</td>
<td>26.1 (25.1-27.0)*</td>
<td>38.8 (34.7-42.9) ¶</td>
<td>20.1 (19.2-21.1)*</td>
<td>8.5 (8.4-8.6)</td>
<td>97.3 (96.4-98.2)</td>
<td>89.9 (87.4-92.5)</td>
<td>24.9 (24.6-25.2)</td>
<td>(9.3%)</td>
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<tr>
<td>Age at onset &gt; 15 years (n=403)</td>
<td>21.0 (19.9-22.1)*</td>
<td>18.9 (15.0-22.7) *</td>
<td>21.6 (19.8-23.3) *</td>
<td>8.3 (8.1-8.4)*</td>
<td>99.0 (97.9-100.1)</td>
<td>79.2 (75.2-83.1)*</td>
<td>25.4 (25.0-25.8)</td>
<td>(8.2 %)</td>
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<tr>
<td>All Patients (n=1117)</td>
<td>25.0 (24.4-25.7)</td>
<td>32.9 (30.0-35.6)</td>
<td>21.3 (20.6-22.1)</td>
<td>8.4 (8.4-8.5)</td>
<td>97.8 (97.2-98.5)</td>
<td>87.0 (85.0-89.0)</td>
<td>25.0 (24.8-25.3)</td>
<td>(8.9%)</td>
</tr>
</tbody>
</table>

Significant difference (p<0.05) between two groups * ¶, or between all three groups *. One-way anova, adjusted for multiple comparisons (Sidak). Differences in proportions were compared with Kruskal-Wallis test. CI =Confidence Interval, MAP= Mean Arterial Pressure, BMI= Body Mass Index, PDR= Proliferative Diabetic Retinopathy.
Table 3. The risk of proliferative retinopathy in age at onset groups of 0-4 years (n=164) and 5-14 years (n=537), as contrasted to the age at onset group of 15-40 years (n=400). Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95 % CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age at onset 15-40 years</td>
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<td></td>
</tr>
<tr>
<td>Age at onset 0-4 years</td>
<td>1.61 (1.16-2.23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age at onset 5-14 years</td>
<td>1.90 (1.45-2.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.07 (0.86-1.33)</td>
<td>0.6</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>1.15 (1.07-1.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>1.02 (0.99-1.05)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

MAP= Mean arterial blood pressure, HR=Hazard Ratio, SE=Standard Error, CI=Confidence Interval

Figure Legend:

Figure 1. Kaplan-Meier Survival analysis of the cumulative proportion of patients without proliferative retinopathy (PDR) in 1117 patients stratified into three groups according to age at onset (P<0.001, Mantel-Cox log-rank Test).