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The prevalence of retinopathy in patients with type 1 diabetes treated with education-based intensified insulin therapy and its association with parameters of glucose control

Katja Hatz [a,b,c,1], Anna Elisabeth Minder [d,1], Roger Lehmann [e,1], Tilman Drescher [f], Bianca Gerendas [c], Ursula Schmidt-Erfurth [c], Alexandra Kaider [g], Christian Pruente [h,b,*], Henryk Zulewski [d,i,j,*]

[a] Vista Klinik Binningen, Binningen, Switzerland
[b] Department of Ophthalmology, University of Basel, Basel, Switzerland
[c] Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Vienna, Austria
[d] Division of Endocrinology & Diabetes, Stadtspital Triemli, Zürich, Switzerland
[e] Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zürich, Switzerland
[f] Division of Endocrinology & Diabetes, Kantonsspital St. Gallen, St. Gallen, Switzerland
[g] Center for Medical Statistics, Informatics and Intelligent Systems, Section for Clinical Biometrics, Medical University of Vienna, Vienna, Austria
[h] Department of Ophthalmology, Kantonsspital Baselland, Liestal, Switzerland
[i] Department Biosystems Science and Engineering (D-BSSE), ETH Zürich, Mattenstrasse 26, Basel, Switzerland
[j] Faculty of Medicine, University of Basel, Switzerland

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ABSTRACT

Aim: Prevalence of retinopathy (DR) in patients with type 1 diabetes treated with education-based intensified insulin therapy (EBIIT) and its association with parameters of glucose control.

Methods: 151 patients with mean diabetes duration of 14.3 years [SD ± 5.8]) were analyzed. Eyes were examined using standardized 7 field ETDRS (Early Treatment Diabetic Retinopathy Study) settings and images analyzed by a professional external reading center. The glucose exposure over time was defined as HbA1c years, i.e. the sum of the differences between annual mean HbA1c (in %) minus the ideal HbA1c of 6.0% (42 mmol/mol) for each diabetes year (e.g. HbA1c of 8% (64 mmol/mol) over 6 years gives an excess HbA1c of 2.0% (22 for mmol/mol) for 6 years, resulting in 12 HbA1c years (or 131 for mmol/mol)).

Results: The median (interquartile range) of individual mean HbA1c was 7.3% (6.8–7.8) [56 mmol/mol (51–62)]. and the median HbA1c years was 16.8 (9.1–29.1) [183 mmol/mol (99–319)]. No evidence for DR was found in 59 patients (39%), stage 1 DR in 43 (28.5%), stage 2 in 41 (27.2%), stage 3 in 7 (4.6%) and proliferative DR stage 4 in 1 patient. The best

* Corresponding authors at: Department of Ophthalmology, Kantonsspital Baselland, Liestal, Switzerland (C. Pruente). Division of Endocrinology & Diabetes, Stadtspital Triemli, Zürich, Switzerland (H. Zulewski).
E-mail addresses: christian.pruente@unibas.ch (C. Pruente), henryk.zulewski@unibas.ch (H. Zulewski).
[1] Equal contributing authors.
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correlation between severity of DR and diabetes control measures was found for HbA1c years (Pearson r = 0.41, p < 0.001).
Conclusions: In type 1 diabetes EBIIT is associated with good diabetes control and a low prevalence of DR. The cumulative glucose exposure over time given as HbA1c years is the best predictor for development of DR.
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1. Introduction

Diabetic retinopathy (DR) is the most specific microvascular complication in people with type 1 diabetes. Depending on the severity of retinal changes it may lead to vision threatening retinopathy (VTDR) in up to 42% [1]. In 1984 the first large study on the prevalence of DR in young-onset diabetic adults, the Wisconsin epidemiologic study of diabetic retinopathy (WESDR), described a prevalence of any form of DR of 97.5% after ≥15 years of diabetes and proliferative retinopathy (PDR) in 67% of patients with more than 35 years diabetes duration [2].

However, it was not until 1993 that randomized controlled trials [3,4] unequivocally demonstrated the association between quality of diabetes control and the risk for development of DR. In the Diabetes Control and Complications Trial (DCCT) improved diabetes control with intensified insulin therapy and a HbA1c level of 7.2% (55 mmol/mol) was associated with a 54% reduction in the progression of retinopathy after 6.5 years of follow-up as compared to conventional less intensive insulin treatment resulting in a HbA1c around 9% (75 mmol/mol) [3]. In the following years intensified insulin therapy became standard of care, its implementation in real life, however, proved to be difficult mainly due to the high frequency of severe hypoglycemic events [3]. After closeout of the DCCT study all patients received intensified insulin treatment and were followed in the DCCT/EDIC trial. The documented HbA1c values increased and approached 8% (64 mmol/mol) in the following years [5]. Other cohort studies showed similar results with only moderate long term improvement in diabetes control as illustrated by the Swedish Diabetes Registry study [6] and the recently, in 2016 published follow-up of the Stockholm Diabetes Intervention Study [7] with HbA1c values between 8.0% (64 mmol/mol) and 8.4% (68 mmol/mol).

Current treatment guidelines for people with type 1 diabetes recommend a target HbA1c of 7.0% (53 mmol/mol) or less for adults [8]. Intensive patients' (and physicians') education has the potential to achieve this target while reducing the risk for severe hypoglycaemia. One of the first pioneering works describing the benefits of such an approach was published in 1983 [9] and followed by numerous other studies [10–13]. Using such an education based approach in our institutions since 1990 for patients with type 1 diabetes we have documented a median HbA1c between 7.1% (54 mmol/mol) and 7.3% (56 mmol/mol) [11,14,15]. As the true impact of such an improved diabetes control on the development of DR is not well known, the aim of our study was to analyse the prevalence of DR in those patients who received education based intensified diabetes therapy from the start.

2. Methods

Patients

This cross-sectional study consecutively recruited patients attending the outpatient clinic at the Clinics of Diabetes and Endocrinology of the University Hospital Basel, associated clinics in the Basel area and the University Hospital Zürich between August 2010 and May 2014. The study included male and female patients >18 years who had signed an informed consent, were diagnosed with type 1 diabetes mellitus at least 5 years (and less than 30 years) prior to screening and were on education based intensified insulin therapy (multiple daily insulin injections or insulin pump) from the beginning of their disease. At our centres this treatment was built on the pioneering, experimental approach by Richard Bernstein, an engineer, with type 1 diabetes who published his experience in 1980 [16]. This experimental approach became later the foundation of structured educational courses with the aim to empower patients (but also teach physicians) to learn their own, individual insulin requirements in fasting state as well as for various amounts of carbohydrates and, inversely to evaluate the needs for carbohydrates during physical activity (through experimentation) [17]. Moreover, the education program starts with the course but it continues at each follow-up visit (physician-led clinic, typically 30 min. visits) where specific problems of diabetes care are addressed using the knowledge and techniques acquired during the course. We published our experience with this type of treatment in this Journal with more detailed description of the protocol [12,18]. Patients with an inability to undergo fluorescence angiography (e.g. history of allergy to fluorescein, severe chronic renal failure, pregnancy) were excluded. The study was approved by the local ethics committee. The patients were not offered any money for compensation.

Assessments

(a) Glycemic parameters

HbA1c was measured with DCCT-standardized methods, usually the DCA 2000+ Analyzer (Bayer Diagnostics Europe, Dublin, Ireland), with a reference range between 4.2% (22 mmol/ml) and 6.5% (48 mmol/mol) for healthy individuals. For every patient all available HbA1c-values from diagnosis

of diabetes mellitus until completion of the study ophthalmological exam (±3months) were retrospectively collected searching the patient charts and contacting the treating physicians or institutions. For every year a mean HbA1c was calculated. The mean total HbA1c for every individual was determined by averaging the yearly average HbA1c-measurements. The HbA1c-years parameter was calculated by adding up the yearly difference to an HbA1c of 6% (42 mmol/mol) from diagnosis to completion of study exam (±3 months), i.e. a HbA1c of 8% (64 mml/mol) over 6 years would reflect a HbA1c-years of 12 (equals 6x(8%-6%)) or 131 for mmol/mol values. For years with no available HbA1c-measurements the most recent mean HbA1c was used to fill the blanks and calculate the HbA1c-years and mean total HbA1c.

(b) Ophthalmologic parameters

All ophthalmological examinations were performed by study trained physicians (Vista Klinik Binningen/Vista Diagnostics Zürich) and the same reading center certified photographer and included ETDRS 7-field color stereoscopic pairs of photographs (FF450, Zeiss, Germany) and fluorescein angiography (FA) using a standardized study protocol with 30° settings in the 7 ETDRS fields (HRA2, Heidelberg Eng., Germany). 149/151 patients finished 7-field fluorescence angiography, in 2 patients this examination had to be interrupted due to weakness after instillation of intravenous fluorescein. These patients showed a drop of blood pressure. They recovered within a few minutes after laying down and oral hydration.

Evaluations of color fundus (CF) and FA images were performed following standardized reading protocols at the Vienna Reading Center. This includes the grading of anonymized data by a trained and experienced image grader who was blinded to the study patient. The procedures also include a random supervision of the grader by a retina specialist. Classification of DR followed the international clinical diabetic retinopathy disease severity scale [19]: (0) No apparent retinopathy = no abnormalities; (1) Mild nonproliferative diabetic retinopathy = microaneurysms only; (2) Moderate nonproliferative diabetic retinopathy = more than just microaneurysms but less than severe nonproliferative diabetic retinopathy; (3) Severe nonproliferative diabetic retinopathy = any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in 2+ quadrants, prominent intraretinal microvascular abnormalities (IRMA) in 1+ quadrant; (4) Proliferative diabetic retinopathy = one or more of the following: neovascularization, vitreous/preretinal hemorrhage. The maximum DR status of both eyes of each patient was evaluated as primary endpoint. Assessment of macular edema using CF-examination was based on the international classification of macular edema by Wilkinson et al [19].

Data analysis

Normally distributed data are presented as mean (±standard deviation) or percentage, not normally distributed data (i.e. HbA1c for the population) are presented as median and interquartile range. The Pearson correlation coefficient was used to describe the association between HbA1c parameter and development of DR. The maximum DR status of both eyes was considered as primary outcome variable. P-values (2-sided) were considered significant if $p < 0.05$. All statistical analyses were performed with the software SAS version 9.4 (SAS Institute Inc., 2002–2012, Cary, NC, USA).

3. Results

The demographic characteristics are summarized in Table 1. 151 patients with diabetes mellitus type 1 (302 eyes) were included into this study. The mean duration of diabetes was 14.3 ± 5.8 years (range 5–29). The median (interquartile range (IQR)) time of follow-up at our centers was 5.8 years (IQR 3.9–7.6) with a range from 0.5 to 21 years. The median HbA1c at recruitment was 7.4% (IQR 6.8–8.1%) [57 mmol/mol (IQR 51–64)], the median of the individual mean HbA1c-values was 7.3% (IQR 6.8–7.8) [56 mmol/mol (IQR 51–62 mmol/mol)], and the median of the HbA1c-years was 16.8 (IQR 9.1–29.1), for mmol/mol 183 (IQR 99–319).

7-field color fundus (CF) evaluations for DR stages

All 151 patients underwent 7-field CF photography in both eyes (302 eyes). 102 patients (68%) presented either no signs of DR (39%) or only mild stage 1 DR (28%) while only 1 patient showed proliferative DR (stage 4), Table 2.

The individual maximal stage of DR (stage 0–4) on any eye was correlated to the quality of diabetes control (mean HbA1c $r = 0.24$, $p = 0.003$) as well as the diabetes duration ($r = 0.35 p < 0.001$) but showed the best correlation with HbA1c years ($r = 0.41$, $p < 0.001$).

Fluorescence angiography (FA)

Using FA for separate 7-field evaluation did not show any signs of DR in 48% of the patients. In 115/298 eyes (39%) with DR according to CF 7-field evaluation 7-field FA analysis showed changes attributable to a higher stage of DR than evaluated by 7-field CF. In 101 eyes without DR according to

Table 1 – Patient characteristics.

Number Patients (% male)	151 (64.9)
Age (years), mean ± SD	39.9 ± 14.0
Diabetes duration (years), mean ± SD	14.3 ± 5.8
HbA1c (median (interquartile range)	
at recruitment (%)	7.4 (6.8–8.1)
[mmol/mol]	57 (51–64)
individual overall mean (%)	7.3 (6.8–7.8)
[mmol/mol]	56 (51–62)
HbA1c years, median (interquartile range)	
(from % values),	16.8 (9.1–29.1)
(from mmol/mol values)	183 (99– 319)
BMI (kg/m^2), mean ± SD	25.2 ± 3.7
Blood pressure (mmHg), mean ± SD	
Systolic	124 ± 14
Diastolic	77 ± 10

Table 2 – HbA1c years and overall mean HbA1c according to maximum DR stage: 0 = no apparent retinopathy, 1 = mild nonproliferative diabetic retinopathy, 2 = moderate nonproliferative diabetic retinopathy, 3 = severe nonproliferative diabetic retinopathy, 4 = proliferative diabetic retinopathy.

Maximum DR stage of both eyes	Patients (%)	Median HbA1c (IQR) in % in [mmol/mol]	Median HbA1c years (IQR) analyzed with % values [with mmol/mol values]
0	59 (39.07)	7.1 (6.6–7.7) [54 (49–61)]	13.1 (7.2–19.2) [143 (79–210)]
1	43 (28.48)	7.3 (6.8–7.7) [56 (51–61)]	19.4 (11.7–28.8) [212 (127–315)]
2	41 (27.15)	7.4 (6.9–8.2) [57 (52–66)]	23.1 (9.2–38.7) [252 (100–422)]
3	7 (4.64)	7.5 (7.3–8.2) [58 (56–66)]	33.5 (16.5–60.6) [369 (173–662)]
4	1 (0.66)	9.7 [83]	74.9 [818]

CF 7-field evaluation 7-field FA analysis showed any changes attributable to DR, mostly attributable to microaneurysms which were not detected by CF but by FA. The single case of mild PDR at CF 7-field evaluation was confirmed by showing neovascularization of the disc at FA field 1. Compared with CF 7-field evaluation 7-field FA analysis was less sensitive in detecting intraretinal hemorrhages.

7-field color fundus (CF) evaluations for diabetic macular edema evaluation

No evidence for macular edema was present in 93.4% of the examined eyes. 6.6% reached the level of “diabetic macular edema apparently present”. Due to the location of the hard exudates in two eyes (0.7%) the criterium for “severe diabetic macular edema” was fulfilled, while the others were graded as “mild diabetic macular edema”.

4. Discussion

Using a standardized assessment of retinopathy including analysis of the photographs by a centralized professional ophthalmic reading center [19] we found a very low prevalence of DR in patients with type 1 diabetes who were treated from the beginning with an education based intensified insulin therapy. This is the first report describing the long term impact of such treatment on DR after a mean diabetes duration of 14.3 yrs. While two thirds of the patients presented no (39%) or mild stage 1 DR (28.5%) only one patient (0.66%) had proliferative DR. Only two eyes (0.7%) showed “severe diabetic macular edema” as a sight-threatening sign of DR. The median of individual mean HbA1c values was 7.3% (56 mmol/mol) and this may have contributed to these favorable results, indeed 60% of our patients achieved an HbA1c of 7.5% (58 mmol/mol) or less. Similar HbA1c values were reported by our group and others describing the value of an educational program on diabetes control [11–14,20], however, its true impact on the prevalence of DR has not yet been established.

The best predictive parameter for the development of DR was HbA1c-years which represents an integral for the quality of diabetes control and duration of diabetes (Table 2, Fig. 1). The concept of HbA1c years was originally described by Orchard in the Pittsburg epidemiology study [21]. In contrast to diabetes duration this value takes periods of different levels of diabetes control into account. When calculating HbA1c-years of a trial, this number is largely responsible for most of the so-called metabolic memory and for the retardation of late complications reported in the DCCT/EDIC trial. Here, the difference in HbA1c during the active trial between standard group and intensive group was 1.8% (9.0% versus 7.2% [75 mmol/mol vs 55 mmol/mol]). Calculated over a period of 6.5 years, the difference in HbA1c years would be approximately 11.7 (or 128 for mmol/mol). Based on our results such a difference in HbA1c years could account for an increase in the DR severity from stage 0 to DR stage 2 (Table 2).

Our study extends the observed reduction in the prevalence of DR as compared to older cohorts [2,22,23], as a consequence of improved diabetes control. The recently published results of a Swedish cohort of patients with 20 to 24 years of diabetes duration by Nordwall et al. [24], reported no DR in 12.5% of the patients while 13.5% had PDR or Laser therapy. In this cohort only patients with diabetes onset between 1983 and 1987 were included. Since an education based intensified insulin therapy became standard of care in the early 1990′s, some of those patients may not yet have profited from this new form of therapy during the first years of diabetes. Indeed, as mentioned above, the metabolic effect of higher glucose concentrations during the first years of diabetes treatment may continue to affect complications even years after the improvement of diabetes control, as has been described in the DCCT-EDIC trial [25,26]. The strength of our study is the standardized assessment and centralized analysis of retinopathy in a certified ophthalmic reading center, which limited the methodological variability, enhanced diagnostic accuracy and, thus, reduced the risk to underestimate the real prevalence of DR. By including only patients with intensified insulin therapy from the beginning of diabetes we also reduced the aforementioned effect of metabolic memory. Although the patients in our study were followed by different centers, all physicians and diabetes educators were trained in education based intensified insulin therapy at the clinics of

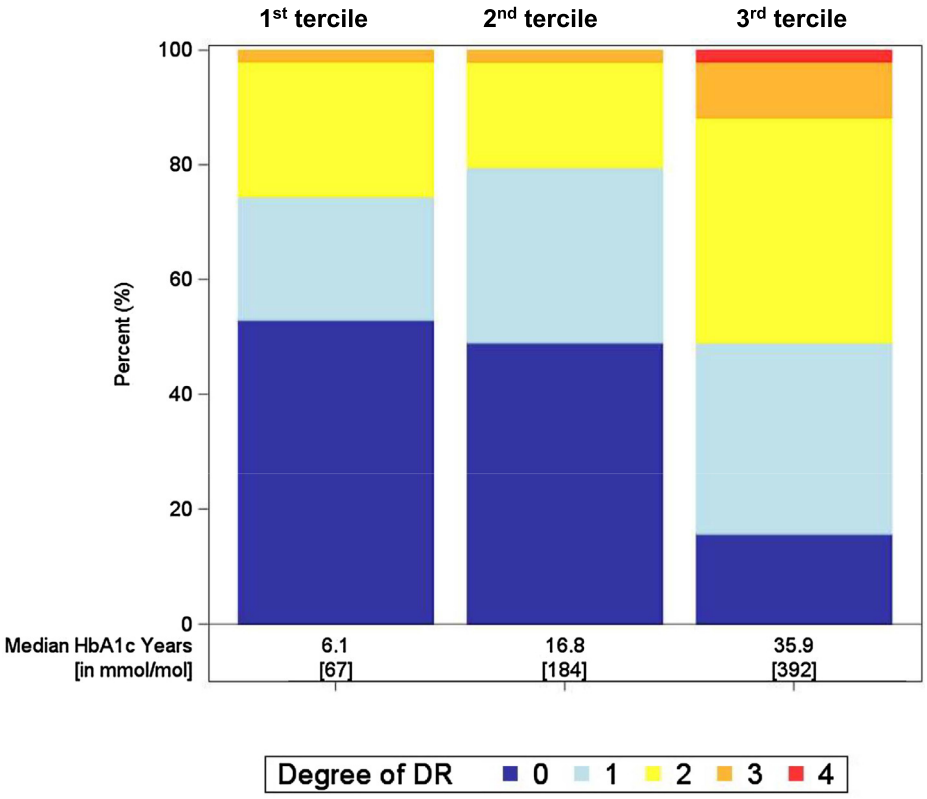

Fig. 1 – Severity of diabetic retinopathy according to the terciles of HbA1c years. Degree of severity of retinopathy 0 = no apparent retinopathy, 1 = mild nonproliferative diabetic retinopathy, 2 = moderate nonproliferative diabetic retinopathy, 3 = severe nonproliferative diabetic retinopathy, 4 = proliferative diabetic retinopathy.

Zürich or Basel and, thus, assuring the same level of patient care. One limitation is the relatively short observation period (due to the study design) as compared with some other bigger cohort studies.

In conclusion, the implementation of an education based intensified insulin therapy in routine diabetes care is not only associated with a better diabetes control but also with reduced risk for the development of diabetic retinopathy. The glucose exposure over time expressed as HbA1c-years is the best predictive parameter for the development of DR.

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Duality of interest

The authors have no conflicts of interest to report.

Contribution statement

Study design: CP, HZ, KH.

Patient recruitment and data collection: KH, RL, AM, HZ, TD.

Image analysis: BG, US.

Data analysis: AK, KH, HZ, AM.

Wrote manuscript: KH, HZ, AM, RL.

Critical revision and final preparation of the manuscript: all authors

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.016.

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