Identification and Characterization of Patients With Rapid Progression of Diabetic Retinopathy in the Danish National Screening Program

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Screening for diabetic retinopathy (DR) is needed for identification and treatment of patients with sight-threatening stages prior to irreversible visual loss. For avoidance of unnecessary screening, prolonged screening intervals have been proposed and implemented in Denmark and other countries (1). A potential argument against extended screening intervals is the risk of rapid progression of DR, which has been described anecdotally. Kohner coined the term "florid DR" as rapidly developed advanced stages of proliferative DR (PDR) and reported unfavorable clinical outcomes in 34 patients identified during an 8-year span (2). While individualized screening with prolonged screening intervals might serve the vast majority of patients, it would be important not to risk irreversible visual loss in the minority at risk for rapid progression. Hence, we aimed to quantify the risk of rapid progression of DR and evaluate associated risk factors in a national screening program of DR.

In Denmark, screening for DR is nationally implemented and offered for free for all patients with diabetes. According to national guidelines, screening is predominantly performed by fundus photography and level of DR is given by the International Clinical Retinopathy Disease Severity Scale as levels 0 (no DR), 1–3 (mild, moderate, and severe nonproliferative DR [NPDR]), and 4 (PDR) (1). Since 2013, results have been registered in a national quality database (DiaBase) (3). For the current study, we included data between 2 January 2013 and 30 April 2018 (Table 1).

We compared patients with rapid progression of DR in both or either eyes with patients free of DR. Including only patients with at least two episodes of screening, we defined rapid progression as a DR three-step increment or more in both or either eye within 2 years with no subsequent DR regression. For control subjects, we included patients with level 0 in both eyes at all screening episodes and at least 2 years of observation. For all patients, we only included data provided by the same screening facility to minimize the effect of grading discrepancy. At the time of the first DR screening, factors potentially associated with rapid progression of DR were registered in the Danish National Patient Register, the Danish National Prescription Registry, and the Danish Civil Registration System.

The current study was part of the Ocular and Systemic complications In diabetic retinopathy Study (OASIS) (4). It was performed according to the tenets of the Declaration of Helsinki, and relevant permissions were obtained from the Danish Data Protection Agency and the Danish Clinical Registries.

From a total number of 207,200 patients in DiaBase, 106,629 were eligible for rapid progression to severe NPDR or PDR. Among these, we identified 507 patients (0.48%) with rapid progression of DR in both ($n = 135$) or either ($n = 372$) eye. For comparison, we identified 74,016 patients free of DR (level 0) in any eyes at all screening episodes (control subjects) (Table 1).

In comparison with control subjects, patients with bilateral and unilateral rapid progression had a longer duration

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Table 1—Characteristics for patients screened for DR in the Danish Registry of Diabetic Retinopathy, as stratified by group of rapid progression or control

	Rapid progression of DR			
	Both eyes	Either eye	Control*	*P*
Number of patients, *n*	135	372	74,016	
Male sex, *n* (%)	79 (58.5)	222 (59.7)	40,785 (55.1)	0.153
Age, years	63.6 (53.1–70.5)	63.9 (52.9–72.2)	66.2 (57.3–72.6)	0.001
Type of diabetes, *n* (%)†				<0.001
Type 1 diabetes	40 (29.6)	123 (33.1)	3,854 (5.2)	
Type 2 diabetes	44 (32.6)	86 (23.1)	61,975 (83.7)	
Unknown	51 (37.8)	163 (43.8)	8,187 (11.1)	
Duration of diabetes, years‡	18.6 (11.8–20.6)	19.3 (15.2–20.5)	5.6 (2.7–10.0)	<0.001
Type 1 diabetes	20.0 (19.2–21.5)	20.2 (19.4–21.5)	9.4 (4.1–18.1)	
Type 2 diabetes	11.3 (5.9–15.6)	12.4 (5.8–19.0)	5.0 (2.4–8.8)	
Unknown	18.9 (15.8–21.1)	19.3 (16.5–20.4)	10.7 (6.3–15.3)	
Marital status, *n* (%)				0.001
Never married	31 (23.0)	51 (13.7)	8,963 (12.1)	
Married	74 (54.8)	211 (56.7)	45,640 (61.7)	
Widowed or divorced	30 (22.2)	110 (29.6)	19,413 (26.2)	
Charlson Comorbidity Index score, *n* (%)§				<0.001
0 (low)	64 (47.4)	147 (39.5)	58,403 (78.9)	
1 (moderate low)	54 (40.0)	140 (37.6)	7,247 (9.8)	
2 (moderate high)	9 (6.7)	41 (11.0)	5,851 (7.9)	
≥3 (high)	8 (5.9)	44 (11.8)	2,515 (3.4)	
Use of medication, *n* (%)‖				
Insulin	109 (80.7)	338 (90.9)	23,319 (31.5)	<0.001
Glucose-lowering treatment, excl. insulins	79 (58.5)	181 (48.7)	62,750 (84.8)	<0.001
Antihypertensive drugs	126 (93.3)	346 (93.0)	62,934 (85.0)	<0.001
Cholesterol-lowering drugs	120 (88.9)	331 (89.0)	64,524 (87.2)	0.490
Screening facility, *n* (%)				<0.001
Practicing ophthalmologist	93 (68.9)	140 (37.6)	64,244 (86.8)	
Hospital	42 (31.1)	232 (62.4)	9,772 (13.2)	
Geographical distribution, *n* (%)				<0.001
North Denmark Region	19 (14.1)	29 (7.8)	8,321 (11.2)	
Central Denmark Region	24 (17.8)	51 (13.7)	13,461 (18.2)	
Region of Southern Denmark	40 (29.6)	70 (18.8)	25,349 (34.2)	
Capital Region of Denmark	36 (26.7)	195 (52.4)	16,284 (22.0)	
Region Zealand	16 (11.9)	27 (7.3)	10,599 (14.3)	
Months of screening interval given, *n* (%)				<0.001
3	20 (14.8)	82 (22.0)	416 (0.6)	
6–9	42 (31.1)	84 (22.6)	2,163 (2.9)	
12	58 (43.0)	115 (30.9)	64,353 (86.9)	
18–48	<5	11 (3.0)	5,527 (7.5)	
Missing	13 (9.6)	81 (21.8)	1,557 (2.1)	

Data are median (interquartile range) unless otherwise indicated. excl., excluding. *Control subjects defined as patients without DR in both eyes at all screening episodes and at least two rounds of screening. †Type of diabetes defined according to ICD-10 code for diabetes or Anatomical Therapeutic Chemical Classification (ATC) codes for treatment of diabetes. ‡Duration of diabetes was only calculated in patients with at least one ICD-10 code for diabetes or one ATC code for treatment of diabetes. §Systemic comorbidity defined according to codes from the Danish National Patient Register as given 5 years prior to the first date of entrance in DiaBase. We used the updated Charlson Comorbidity Index, with levels 0–3 reflecting increasing levels of comorbidity (5). ‖Use of systemic medication were assessed by the Danish National Prescription Registry, in accordance with the ATC system. For avoidance of potential identification of patients, exact numbers are not given for values <5.

of diabetes (18.6 vs. 19.3 vs. 5.6 years; $P < 0.001$) and were more likely to have type 1 diabetes (29.6% vs. 33.1% vs. 5.2%; $P < 0.001$), to have a Charlson Comorbidity Index score (5) >0 (52.6% vs. 60.4% vs. 21.1%; $P < 0.001$), to receive insulin (80.7% vs. 90.9% vs. 31.5%; $P < 0.001$), and to been given a screening interval <12 months at the last visit prior to progression (45.9% vs. 44.6% vs. 3.5%; $P < 0.001$). In the entire group of eyes with rapid progression, loss of vision (for any reason) from 0.80 Snellen or better to ≤0.40 only occurred in 11 of 642 (0.02%) eyes.

While the current study is a real-life presentation of an entire national screening population, limitations are important to acknowledge. Firstly, for legal reasons it was not possible to obtain important factors like glycemic control or blood pressure. Secondly, while trained ophthalmologists and certified hospital graders perform diabetic eye screening in Denmark, the study relied on data input from multiple sources. Thirdly, diabetic macular edema was not included in the analysis, since this is a binary end point, which is not well suited to evaluation regarding the concept of rapid progression.

In conclusion, in the national program for DR screening in Denmark, rapid progression of DR affected only 1 in every 210 patients and was not associated with vision loss. Patients with rapid progression were more likely to have a long duration of type 1 diabetes and a higher comorbidity score. Systematic screening for DR is important, and the slight risk of rapid progression should not discourage the use of individualized, prolonged screening intervals in patients with a favorable risk profile.

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References

1. Grauslund J, Andersen N, Andresen J, et al. Evidence-based Danish guidelines for screening of diabetic retinopathy. Acta Ophthalmol 2018; 96:763–769

2. Kohner EM, Hamilton AM, Joplin GF, Fraser TR. Florid diabetic retinopathy and its response to treatment by photocoagulation or pituitary ablation. Diabetes 1976;25:104–110

3. Andersen N, Hjortdal JO, Schielke KC, et al. The Danish Registry of Diabetic Retinopathy. Clin Epidemiol 2016;8:613–619

4. Grauslund J, Stokholm L, Ohm Kyvik K, Dornonville de la Cour M, Kessel L, Hass Rubin K. Interactions between ocular and systemic disease using national register-based data in the Danish Excellence Centre in Ophthalmic Epidemiology (DECODE-EYE): study perspective. Acta Ophthalmol 2020;98:573–578

5. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676–682