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Overweight, hyperglycemia and tobacco use are modifiable risk factors for onset of retinopathy 9 and 17 years after the diagnosis of diabetes – A retrospective observational nation-wide cohort study

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ABSTRACT

Background: The aims of this study were to estimate the risk for diabetic retinopathy (DR) and to identify risk factors. We investigated a nationwide population-based cohort with diabetes diagnosed at age 15–34 years.

Patients and methods: Of 794 patients registered 1987–1988 in the Diabetes Incidence Study in Sweden (DISS) 444 (56%) patients with retinal photos available for classification of retinopathy participated in a follow-up study 15–19 (median 17) years after diagnosis. Mean age was 42.3 ± 5.7 years, BMI 26.1 ± 4.1 kg/m^2, 62% were male and 91% had type 1 diabetes. A sub-study was performed in 367 patients with retinal photos from both the 9 and 17 year follow up and the risk for development of retinopathy between 9 and 17 years of follow up was calculated.

Results: After median 17 years 324/444 (73%, 67% of T1D and 71% of T2D), had developed any DR but only 5.4% proliferative DR. Male sex increased the risk of developing retinopathy (OR 1.9, 95% CI 1.2–2.9). In the sub-study obesity (OR 1.2, 95% CI 1.04–1.4), hyperglycemia (OR 2.5, 95% CI 1.6–3.8) and tobacco use (OR 2.9, 95% CI 1.1–7.3) predicted onset of retinopathy between 9 and 17 years after diagnosis of diabetes.

Abbreviations: DISS, Diabetes Incidence Study in Sweden; DN, diabetic nephropathy; DR, diabetic retinopathy; NPDR, non proliferative diabetic retinopathy; PDR, proliferative retinopathy; RAAS, renin-angiotensin-aldosterone system; T1D, type 1 diabetes; T2D, type 2 diabetes

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Conclusion: The number of patients with severe retinopathy after 17 years of diabetes disease was small. The risk of developing retinopathy with onset between 9 and 17 years after diagnosis of diabetes was strongly associated to modifiable risk factors such as glycemic control, obesity and tobacco use.

1. Introduction

The improvement in diabetes care during the past 30 years has been associated with a decrease in both prevalence and incidence of diabetic retinopathy (DR) in type 1 diabetes (T1D) [1–3]. An intensified control of blood glucose and blood pressure has been important and, in addition, the effects of lipid-lowering medications such as statins and treatments targeting the renin-angiotensin-aldosterone system (RAAS) have contributed [4–7]. In patients with type 2 diabetes (T2D) there are fewer studies and the results are not so clear-cut [8]. The prevalence of T2D is increasing worldwide and the age of onset declines, hence the risk of developing sight-threatening DR may increase [9–11]. Identifying modifiable risk factors is important to prevent DR from becoming the leading cause of blindness worldwide.

In a previous study in this cohort of patients diagnosed with diabetes at the age of 15–34 years we reported the prevalence of any DR 9 years after diagnosis to be approx 40% [12]. In that study patients with T2D had more severe DR than those with T1D and the risk factors for developing retinopathy were obesity, male sex and neuropathy [13].

The objectives of this follow up study were to estimate the 17-year cumulative incidence of diabetic retinopathy (DR) in this nation-wide and population-based cohort of 444 patients diagnosed with diabetes at ages 15–34 years in 1987–1988 and to evaluate potential clinical predictors and risk markers.

2. Methods

2.1. Patients

Since 1983 the Diabetes Incidence Study in Sweden (DISS) has aimed to register all newly diagnosed cases of diabetes, except gestational diabetes, in the age group 15–34 years [12]. In the cohort diagnosed with diabetes during 1987–88 we performed a follow up study after disease duration of mean 9 years [13–15]. In 2004 the 794 patients in the 1987–88 cohort still alive and living in Sweden were invited to participate in follow-up study on long-term diabetic complications after a disease duration of 17-years and 468/794 (59%) patients agreed to participate. The main study cohort has been described in detail previously [16]. The process of patient recruitment, type of diabetes and development of retinopathy is outlined in Fig. 1.

2.2. Baseline variables, questionnaires and laboratory samples

Baseline variables reported to the DISS register at the time of diagnosis, besides type of diabetes were age, sex and BMI. At follow up, in brief, a questionnaire was sent to their treating physicians who, between year 2004 and 2006, reported clinical data from regular follow up visits. The term diabetic nephropathy (DN) refers to persistent micro- or macroalbuminuria, thus incipient or manifest diabetic nephropathy. Identification of patients with DN was performed in two steps as previously reported [16].

Tobacco use was defined as any previous or current ongoing daily use (smoking and/or "snus"). Systolic and diastolic blood pressures at follow-up were reported in the questionnaires (mean of three measurements). The patients were also asked to provide blood samples and an over-night spot urine sample and these samples were sent to our central laboratory for analyses [16].

All HbA1c values reported in the questionnaires were measured using ion-chromatography at the local hospital laboratories using the Swedish standardized calibration by Equalis (MonoS, ref range 3.3–5.0%). These values were then converted to IFCC mmol/mol (IFCC, mmol/mol = 10.45 × Mono S, % − 10.62; www.equalis.se). At the follow up after 9 years all previous HbA1c values available from the diagnosis of diabetes up to the time-point were reported and the mean value weighted for the time between measurements was estimated for each patient [17]. At the follow up after 17 years the three latest HbA1c-values were reported and the mean of these values was calculated. In addition, HbA1c was measured centrally in available blood samples at both time-points of follow-up using ion-chromatography at Malmö University Hospital (MAS). Urinary albumin in study urine samples was analyzed with an enzyme-linked immunosorbent assay (ELISA) [18].

2.3. Classification of type of diabetes

To make a more accurate classification of type of diabetes we used islet antibody analyses (ICA and/or GADA) at diabetes diagnosis (1987–88) as previously reported [13,16]. In brief, patients were classified as having T1D; (1) if they clinically were reported as having T1D at 17 year follow-up (n = 339) or (2) if they clinically were reported as having T2D or unclassifiable diabetes but displayed any of the two antibodies, i.e. GADA or ICA, at diagnosis of diabetes (n = 89). Taken together 428 patients were classified as having T1D. Patients reported as having T2D or unclassifiable diabetes by the treating physician and lacking islet antibodies at diagnosis were considered as having T2D (n = 40). C-peptide was not considered in this reclassification since only one-third of patients had provided a blood sample in the fasting state and thus the c-peptide values were considered unreliable to use in the classification of the type of diabetes. Patients with other forms of diabetes