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Risk factors for diabetic macular oedema in type 2 diabetes: A case-control study in a United Kingdom primary care setting

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ABSTRACT

Aim: To identify risk factors associated with the development of DMO among patients diagnosed with type 2 diabetes managed in a primary care setting in the UK.

Methods: A case-control study nested in a cohort of incident Type 2 diabetes identified in The Health Improvement Network database from 2000–2007. Cases were people with DMO (N = 211) and controls were a DMO-free sample (N = 2194). No age restrictions were applied. Adjusted odds ratios and 95%CIs were estimated (OR; 95%CI).

Results: DMO increased with high alcohol use (2.88; 1.49–5.55), cataracts (4.10; 2.73–6.15), HbA1c ≥7% (1.58; 1.08–2.32), systolic blood pressure ≥160 mm Hg (2.03; 1.17–3.53), total cholesterol ≥5 mmol/L (1.66; 1.15–2.39), LDL ≥3 mmol/L (1.73; 1.14–2.61), and microalbuminuria (1.78; 1.16–2.73). Diuretic drugs were associated with a reduced risk of DMO (0.68; 0.47–0.99), as did smoking (0.47; 0.28–0.77), overweight (0.53; 0.30–0.96) or obesity (0.52; 0.30–0.91) at diabetes diagnosis, and high triglyceride levels (0.51; 0.35–0.74). Patients treated with anti-diabetic drugs showed higher risk of DMO than non-treated patients, particularly those with sulphonylureas (3.40; 2.42–4.78), insulin (3.21; 1.92–5.36) or glitazones (1.88; 1.17–3.04).

Conclusion: In patients with type 2 diabetes managed in primary care, multiple factors associated with DMO were identified, such as cataracts, microalbuminuria and high levels of HbA1c, systolic BP, total cholesterol, and LDL. Diuretic drugs were associated with a reduced risk of DMO. Treated diabetes, particularly with sulphonylureas, insulin or glitazones showed highest risk of DMO. The inverse association between smoking, obesity, and triglycerides and DMO deserves further research.

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1. Introduction

Diabetic retinopathy (DR) is a leading cause of blindness in the working-age population in the United Kingdom (UK) [1]. Visual loss in the population with diabetes may be caused by diabetic macular oedema (DMO), macular ischaemia, or retinal or optic neovascularization [2]. Particularly, retinal thickening results from fluid leakage due to breakdown of the blood-retina barrier [3]. Although the risk for impaired vision increases at advanced stages of DR [4], DMO can appear at early stages of retinopathy and cause loss of vision [5].

It has been estimated that 1% of patients with type 2 diabetes will develop sight-threatening maculopathy after 9-years with diabetes [6], and 5% in a 6-year period from the first retina screening [7,8]. In a UK primary care setting, the estimated incidence rate of newly diagnosed DMO was 1.80 per 1000 p-y [9]. However, the diagnosis of DMO is challenging and the data about its incidence is inconsistent [10].

In contrast to other eye complications of diabetes, DMO is such a complicated condition in clinical practice that retinal damage persists after standard treatment with photocoagulation in a large proportion of patients [2,11]. However, there are few studies assessing DMO predictors. Epidemiological research aim at identifying and quantifying risk factors of DMO for potentially improving DMO prevention strategies. Hyperglycemia and longer diabetes duration as well as hypertension, dyslipidemia, micro- and macroalbuminuria have been associated with increased risk of DMO in persons with type 2 diabetes, whereas obesity has shown an inverse relationship [10,12,13].

The aim of this study was to identify risk factors associated with the development of DMO among patients with type 2 diabetes managed in a primary care setting in the UK.

2. Material and methods

2.1. Data source

The Health Improvement Network (THIN) is a longitudinal primary care medical records database containing anonymised data on over 3 million patients registered with participating UK primary care practices at the moment the studied was performed [14]. These patients are representative of the entire UK population with respect to age, sex, and geographic region [15]. The THIN database contains individual patient demographic and clinical information recorded by primary care practitioners (PCPs) as part of their routine care, including information such as PCP consultations, referrals, hospitalizations, laboratory test results, and prescriptions issued by PCPs. Letters from specialist visits and hospital admissions (i.e. discharge letters) are also available. Diagnoses and test procedures are recorded using Read codes [16,17]. Prescriptions written by PCPs are generated and recorded automatically in the database using a coded drug dictionary (MultiLex) [18].

2.2. Study cohort and case ascertainment

A case-control analysis nested in a cohort of patients newly diagnosed with type 2 diabetes was performed. Detailed information on the diabetic study cohort has been published elsewhere [19,20]. In summary, the study cohort comprised all patients newly diagnosed with type 2 diabetes (N = 63,226) between January 2000 and December 2007. Diabetes onset was defined as the date of the first recorded diabetes diagnosis or the first recorded anti-diabetic prescription.

The study cohort was followed from diabetes onset until the first record of diabetic maculopathy, including DMO, in the period 2000–2008 [20]. Among all identified maculopathies, potential DMO cases were ascertained through specific codes. Diagnoses of DMO were validated in a two-step procedure comprised of a manual review of computerized patient profiles including PCPs' free-text comments and responses to questionnaires sent to PCPs. DMO diagnosis was confirmed in 90% of all cases initially identified [19].

Controls were selected from the pool of patients with type 2 diabetes that were not affected by diabetic maculopathy or DMO. A group of 2194 controls was selected using density sampling by generating a random date within the study period for each potential control. If the random date for a patient was included in his/her eligible person-time (follow-up period), that person was marked as an eligible control. The index date to compare cases with controls was the first recorded date of DMO diagnosis for cases and the random date for controls.

2.3. Risk factors assessment

The following information on potential risk factors was derived from the THIN database:

1. Demographic and lifestyle factors: age, sex, body mass index (BMI, kg/m^2), smoking status and alcohol consumption (units per week; 1 unit of alcohol is equal to 10 mL (~8 g) ethanol), using the most recent status before the diabetes onset.
2. Healthcare service use: number of PCP visits and referrals and hospitalizations, from one year before to 15 days before the index date.
3. Relevant laboratory test results between the onset of diabetes and the index date: glycated haemoglobin (HbA1c, (%), the first value after diabetes diagnosis and the mean value of all available measurements), systolic and diastolic blood pressure (BP, mmHg, the last value before the index date and the mean value of all available measurements), microalbuminuria (defined as having a recorded value of urine albumin of 30–300 mg/L or 3–30 mg/mmol of creatinine), proteinuria (defined as having a recorded value of urine albumin of 300–30,000 mg/L or >30 mg/mmol of creatinine), and lipid levels (including total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL] and triglycerides, all in mmol/L, using the last values recorded before the index date).
4. Prior history of other diseases, including ocular and cardiovascular diseases, was collected at any time before index date.
5. Exposure to hypoglycaemic agents and drugs used for cardiovascular diseases was ascertained prior to the index date and classified into 3 mutually exclusive time windows: (1) current use, when the most recent prescription lasted until the index date or ended in the 30 days prior to

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