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Prevalence of micro- and macrovascular diabetes complications at time of type 2 diabetes diagnosis and associated clinical characteristics: A cross-sectional baseline study of 6958 patients in the Danish DD2 cohort

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ABSTRACT

Aims: To examine the prevalence of micro- and macrovascular complications and their associated clinical characteristics at time of type 2 diabetes (T2D) diagnosis.
Methods: We examined the prevalence of complications and associated clinical characteristics among 6958 newly diagnosed T2D patients enrolled in the prospective Danish Center for Strategic Research in T2D cohort during 2010–2016. We calculated age- and gender-adjusted prevalence ratios (aPRs) of complications using log-binomial and Poisson regression.
Results: In total, 35% (n = 2456) T2D patients had diabetic complications around diagnosis; 12% (n = 828) had microvascular complications, 17% (n = 1186) macrovascular complications, and 6% (n = 442) had both. HbA1c levels of ≥7% were associated with microvascular complications [HbA1c 7%–8%; aPR: 1.35, 95% confidence interval (CI): 1.12–1.62] but not macrovascular complications [aPR: 0.91, 95% CI: 0.76–1.08]. High C-peptide ≥ 800 pmol/L was associated with macrovascular [aPR 1.34, 95% CI: 1.00–1.80] but not microvascular [aPR 0.97, 95% CI: 0.71–1.33] complications. Macrovascular complications were associated with male sex, age > 50 years, obesity, hypertriglyceridemia, low HDL cholesterol, smoking, elevated CRP levels, and antihypertensive therapy. Microvascular complications were associated with high blood pressure, hypertriglyceridemia, and absence of lipid-lowering therapy.
Conclusions: One-third of patients with T2D had diabetes complications around time of diagnosis. Our findings suggest different pathophysiological mechanisms behind micro- and macrovascular complications.

1. Introduction

It is a major clinical and public health problem that a variable proportion of individuals with T2D remains undiagnosed and untreated before developing diabetes complications.[1] Many patients with T2D thus present with complications already at time of diagnosis,[1] as the various pathophysiological abnormalities associated with T2D, such as hyperglycemia, dyslipidemia, and hypertension may have existed for several years.[2,3]

Recent data on the prevalence of diabetes-related complications at time of diagnosis are scarce. Many studies that examined this issue are 10–20 years old, and generally showed high prevalences of complications,[4] e.g., a ~36% prevalence of retinopathy in the UKPDS study.[4] Diabetes case-finding has been increasing in populations-at-

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risk,[5] likely leading to earlier diabetes diagnoses and possibly a lower prevalence of complications at onset.[6,7] For example, Thomsen et al.[6] found that the median baseline hemoglobin A1c (HbA1c) measurement before initial glucose-lowering treatment in Denmark declined from 8.9% in 2000–2003 to 7.0% in 2010–2012, suggesting earlier diagnosis and therapy.

It is not well understood at present whether pathogenic processes leading to micro- and macrovascular T2D complications differ.[8] Hyperglycemia per se seems to be an important risk factor for microvascular outcomes but less so for macrovascular outcomes, for which traditional cardiovascular risk factors may play a greater role.[4,9] Moreover, several recent randomized clinical trials (RCTs)[10–13] have found that newer diabetes drugs exert a CVD protective effect beyond their glucose-lowering effect.[9] In this context, we hypothesized that clinical characteristics at baseline may differ between T2D patients presenting with micro- and macrovascular complications, with dysglycemia-related factors being more important for microvascular complications and metabolic syndrome-related factors more important for macrovascular complications. In the present study, we examined the prevalence of micro- and macrovascular complications and associated characteristics among newly diagnosed T2D patients in a large prospective Danish cohort.

2. Materials and methods

2.1. Study population

We conducted this cross-sectional study using information from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project, which includes a nationwide cohort of newly or recently diagnosed type 2 diabetes mellitus (T2D) patients enrolled from general practitioners' (GPs) offices and hospital specialist outpatient clinics in Denmark since November 2010.[14] The implementation and logistics of the DD2 project, patient enrollment, and the DD2 biobank[15] have been described in detail previously.[16] In brief, GPs or hospital physicians provide detailed interview and clinical examination data for each DD2 patient at time of enrollment. This information is recorded in the DD2 database together with each patient's civil registration number (CPR number). Blood samples (fasting) and urine samples are obtained from each patient, either on the day of the interview or later.[17]

Our main study population consisted of all 6958 incident T2D patients currently enrolled in the DD2 cohort. The unique CPR number provided to each Danish resident, at birth or upon immigration, allowed data linkage of this cohort with other Danish registries. We could thus obtain a complete hospital contact history for each DD2 participant through linkage with the Danish National Patient Registry (DNPR), which covers all Danish hospitals and contains discharge records from all inpatient hospitalizations since 1977 and all hospital outpatient clinic and emergency department visits since 1995.[18] Additionally, we obtained complete data on filled medication prescriptions for each DD2 participant through linkage with the Danish National Health Service Prescription Database (DNHSPD).[19] Through linkage with a nationwide quality-of-care database, the Danish Diabetes Database for Adults (DDDA), we were furthermore able to extract additional clinical data for a subcohort of 5115 (75%) DD2 patients.[14]

2.2. Micro- and macrovascular complications

For each cohort member, we assessed presence or absence of diabetes complications as recorded in the DNPR between 10 years before and up till 6 months after the DD2 enrolment date. The 6 months after period was included to allow for investigation and diagnosis of prevalent diabetes complications shortly after diabetes diagnosis. We categorized diabetes complications as: (1) no microvascular or macrovascular complications at enrolment; (2) microvascular complications; (3) macrovascular complications; and (4) both microvascular and macrovascular complications. Microvascular complications included a medical database history of the following conditions: retinopathy, including any diabetes-related eye disease, atherosclerotic eye disease, blindness or severely impaired vision, or use of retinal photocoagulation therapy; neuropathy, including any diabetes-related neurological complication; and nephropathy, including any diabetes-related kidney disease, albuminuria, chronic dialysis, or renal failure. Macrovascular complications included a medical registry history of any of the following conditions: history of ischemic heart disease including angina pectoris or coronary surgery; atherosclerotic cerebrovascular disease including thrombolysis and thrombectomy; atherosclerotic peripheral vascular disease including vascular surgery or amputation; or any operation for macroangiopathy (see Supplemental Table A1 for diagnosis and procedure codes).

2.3. Associated patient characteristics

From the DD2 cohort questionnaire and the linked medical databases, we extracted data on patient characteristics present at the time of DD2 enrollment. Patient characteristics of particular interest included age, sex, body mass index (BMI) ≥30 kg/m^2, central obesity (defined as waist circumference ≥ 94 cm for men and ≥80 cm for women), high waist-hip ratio (WHR) (defined as >1.0 in men and >0.85 in women), tobacco smoking, blood pressure (mm Hg), fasting blood-glucose level (mmol/L), C-peptide level (pmol/L), plasma lipid level (mmol/L), C-reactive protein (CRP) level (mg/L), and use of anti-hypertensive and lipid-lowering drugs. Data on age, sex, central obesity, WHR, physical activity, and use of lipid-lowering and anti-hypertensive drugs were available for the entire DD2 cohort, and data on HbA1c, blood pressure, BMI, tobacco smoking, and plasma lipids were available for the subcohort of 5115 patients (75%) currently linkable to the DDDA.[14] Concerning specific biomarkers, fasting blood glucose, C-peptide and CRP have currently been analyzed for the first 5563 (80%), 5800 (83%) and 1030 (15%) DD2 cohort patients in the DD2 biobank.

The DD2 project, including patient registration and sample collection, has been approved by The Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035). After receiving detailed oral and written information approved by The Regional Committees on Health Research Ethics for Southern Denmark, patients volunteer to participate in the DD2 project. Their willingness to participate is documented by a signed written informed consent document.

2.4. Statistical analysis

We characterized patients according to factors as described above. Prevalence of microvascular, macrovascular, and both micro- and macrovascular complications at baseline was calculated as proportions (percentages) of all DD2 cohort members. We calculated prevalence ratios (PRs) with 95% confidence intervals (CIs) of the different complications associated with presence of each factor using log-binomial and Poisson regression.[20] The exact pathophysiological pathways between the different dysglycemia-related and metabolic syndrome-related factors are incompletely understood and several factors may act as clusters in the same causal pathway.[21] We therefore only adjusted our estimates for age and gender in the main analysis (aPRs) to assess whether associations were independent of these two factors.[20] Because obesity and in particular abdominal obesity is thought to be a fundamental factor preceding a number of other metabolic risk factors in many individuals; we did a supplementary analysis in which