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Prevalence and comorbidities of double diabetes

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ABSTRACT

Background: A growing number of people with type 1 diabetes (T1DM) are identified with features of metabolic syndrome (MS) known as "double diabetes", but epidemiologic data on the prevalence of MS in T1DM and its comorbidities are still lacking.

Background: Aim of this cross sectional study is to better estimate the prevalence of MS in T1DM, and to assess its association with comorbidities.

Methods: Data of 31,119 persons with autoimmune diabetes mellitus were analysed for signs of MS and presence of late complications. Double diabetes was defined as T1DM coexisting with MS (obesity, hypertension, dyslipidemia). Multiple linear or logistic regression analyses were performed to identify associations between double diabetes and late complications.

Results: 25.5% ($n = 7926$) of persons with T1DM presented additionally the MS. Persons with double diabetes showed significantly more macrovascular comorbidities (coronary heart disease 8.0% versus 3.0% w/o MS, stroke 3.6% versus 1.6%, diabetic foot syndrome 5.5% versus 2.1%). Also microvascular diseases were increased in people with double diabetes (retinopathy 32.4% versus 21.7%, nephropathy 28.3% versus 17.8%). Both macrovascular and microvascular comorbidities were increased independent of glucose control, even if patients with good metabolic control (HbA1c <7.0%, 53 mmol/mol) showed significantly less macrovascular (coronary heart disease 2.3% versus 1.8%, $p < 0.0001$) and microvascular problems (retinopathy 8.7% versus 6.6%, $p < 0.0001$).

Conclusions: Double diabetes seems to be an independent and important risk factor for persons with T1DM in developing macrovascular and microvascular comorbidities. Therefore,

Abbreviations: BMI, body mass index; DCCT, Diabetes Control and Complications Trial; DD, double diabetes; DPV, Diabetes-Verlaufs-Dokumentation; EDC, epidemiology of diabetes complications study; GAD-AB, glutamatdecarboxylase antibodies; HDL, high density lipoprotein; LDL, low density lipoprotein; MS, metabolic syndrome; NCEP, National Cholesterol Education Program; PAD, peripheral arterial disease; T1DM, diabetes mellitus type 1; T2DM, diabetes mellitus type 2; UKPDS, United Kingdom Prospective Diabetes Study

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patients should be identified and development of MS should be avoided. Longterm studies are needed to observe the effect of insulin resistance on patients with autoimmune diabetes.

1. Introduction

Autoimmune diabetes mellitus (type-1DM) with an autoimmune loss of insulin producing beta cells has for quite a long time been clearly separated from MS and diabetes mellitus type 2, where insulin resistance and a relative insulin deficiency is the more relevant pathophysiology [1]. During the last years increasing evidence demonstrated, that the clinical phenotype of people with T1DM presents with a broad range of clinical features and that increasing numbers of patients show signs of MS as abdominal obesity, arterial hypertension, dyslipidaemia, up to now not considered a clinical feature of diabetes mellitus type 1 [2,3]. These persons often have a family history of type 2 diabetes (T2DM) [4] or hypertension [5]. Genetic similarities are seen between obese people with autoimmune diabetes and T2DM [6]. The prevalence of persons showing signs of both diabetes forms increases significantly because of lifestyle changes in the last decades with increasing obesity and decreasing physical activity, but epidemiologic data about this phenomenon are still scarce [2,7,8]. Recently, the combined presentation of features of both type 1 and type 2 diabetes has been referred to as "double diabetes", e.g. when a person with T1DM becomes overweight/obese and insulin resistance increases [3,7,9].

Aim of the following study is to analyse the prevalence of MS – defined according to the NCEP (National Cholesterol Education Program) criteria as obesity, dyslipidaemia and arterial hypertension combined with insulin resistance – in people with T1DM [10].

2. Materials and methods

2.1. Patients and data documentation

Patients were selected from the DPV [Diabetes-Verlaufs-Dokumentation] registry, a computer-based documentation programme for all diabetes-related aspects of diagnosis and patient care. The database includes patients with all types of diabetes and is currently used by 392 specialised centres of the DPV Initiative from Germany and Austria. Prospectively documented data, after anonymisation, are transmitted twice a year from participating health care facilities to the central database in Ulm, Germany, for quality assurance and statistical analysis [11,12]. Implausible and inconsistent data are reported back to the centres of origin for verification and correction. The DPV Initiative, and analyses based on anonymised data in the DPV database, are approved by the Ethics Committee of the University of Ulm, Germany.

For the present analysis, data from patients aged ⩾18 years with a clinical diagnosis of insulin dependent T1DM were selected. Diabetes mellitus type 1 was defined as initially insulin dependent diabetes mellitus with at least one diabetes specific antibody. Data transmitted prior to September 2013 were included into this analysis. Up to this time-point, 40,046 patients ⩾18 years were registered in DPV, 32,871 showed all necessary data including BMI and insulin dose, patients who had a co-medication of sulfonylurea or who had no documented diabetes-specific antibodies were excluded (n = 1752, leaving n = 31,119 participants in the analysis). Information about gender, age, and diabetes duration was available for all subjects. For analysis of glycaemic control, individual mean HbA1c was standardised to the Diabetes Control and Complications Trial (DCCT) normal range by the "multiple of the mean method" [13] based on the local HbA1c reference ranges, HbA1c was measured by immunological tests, LDL by ultracentrifugation.

Diabetes associated kidney diseases were classified according to the German National Diabetes Guideline [14] into microalbuminuria (albumin excretion in morning urine 20–200 mg/l) and macroalbuminuria (>200 mg/l). Dyslipidemia and arterial hypertension are defined according to the NCEP criteria [10].

MS was defined according to the NCEP criteria, if participants show at least three criteria out of obesity (waist circumference >40 inches in male, >35inches in female or BMI >30 kg/m^2), hyperglycaemia present in all participants since all are diagnosed with diabetes mellitus, dyslipidaemia or arterial hypertension [10]. Of all 31,119 documented people with T1DM, 7926 fulfilled the criteria of the MS (double diabetes, DD), the rest (n = 23,193) were considered type 1 diabetic persons without MS (T1DM w/o MS). To discriminate effects of blood glucose control from those of MS a subgroup analysis for people with well controlled diabetes as defined by HbA1c <7% (53 mmol/mol) was performed (n = 9203, double diabetes n = 1892, no double diabetes n = 7311) (Fig. 1).

2.2. Statistical analysis

For categorical variables, proportions were used for description. As not all continuous parameters were normally distributed based on QQ plots, descriptive statistics with mean values and standard error were calculated for continuous variables. For unadjusted group comparisons, Kruskal–Wallis-test for continuous variables and X^2-test for binary variables were used. Bonferroni-stepdown adjustment was used to correct p-values for multiple testing.

To consider possible confounding effects as sex, age or diabetes duration on the comparison between type-1-patients and double-diabetes-patients, linear regression models were created with treatment centre as random effect. Iterations were optimised according to Newton–Raphson, and denominator degrees of freedom were calculated by the between-within-method (SAS, proc glimmix). For binary variables, multivariable logistic regression models were created.