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Myocardial perfusion at rest in patients with Diabetes Mellitus Type 1 compared with healthy controls assessed with Multi Detector Computed Tomography

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ABSTRACT

Aim: Type 1 diabetes mellitus (T1DM) is associated with an increased risk of ischemic heart disease (IHD). The relative contribution of structural and functional abnormalities of the coronary circulation determining clinically manifested IHD remains unknown. The aim of this study was to assess potential differences in myocardial perfusion at rest and coronary atherosclerosis between asymptomatic T1DM patients and healthy controls.

Methods: Left ventricular (LV) myocardial perfusion at rest measured as LV myocardial Attenuation Density/LV blood pool Attenuation Density (Myo_{AD}-ratio) and coronary artery atherosclerosis were evaluated with 320-multidetector computed tomography angiography in 57 asymptomatic T1DM patients and 114 sex and age matched controls.

Results: In both groups median age was 53 years (p5,p95: 42,67) and 59.6% were men. Median duration of diabetes in the T1DM group was 35 years (p5,p95: 17,49). Median coronary calcium score was higher in T1DM patients (51 vs. 2, $p = 0.037$) compared with controls. However, a similar frequency of >50% stenosis in one or more coronary arteries was found in T1DM patients and controls (18% vs. 14%, $p = 0.49$). LV myocardial perfusion at rest

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Abbreviations: ACC, American College of Cardiology; AD, attenuation density; AHA, American Heart Association; BMI, body mass index; CACS, coronary calcium scoring; CAN, cardiovascular autonomic neuropathy; CGPS, Copenhagen General Population Study; ECG, electrocardiogram; GLM, general linear model; HU, hounsfield units; IHD, ischemic heart disease; LDL, low density lipoprotein; LV, left ventricle; MDCT, multidetector computed tomography; Myo_{AD}-, left ventricle myocardial attenuation density/left ventricle blood pool; ratio, attenuation density; NO, Nitric Oxide; SCCT, Society of Cardiovascular CT; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TPR, transmural perfusion ratio.

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(Myo_{AD}-ratio) was 18% higher in T1DM patients than controls (0.13 vs. 0.11, $p < 0.0001$). This difference was noted throughout all the LV myocardial segments. In a multiple regression analysis including diabetes, sex, age, cardiovascular risk factors, heart rate, calcium score and coronary stenosis >50%, Myo_{AD}-ratio remained significantly higher in T1DM patients ($p = 0.0001$).

Conclusions: LV myocardial perfusion at rest is higher in T1DM patients compared with controls independent of coronary atherosclerosis and cardiovascular risk factors.

1. Introduction

It is well known that type 1 diabetes mellitus (T1DM) is associated with an increased risk of ischemic heart disease (IHD). Among suggested pathogenic factors that play a role are hyperglycemia, genetic predisposition, renal disease and cardiovascular risk factors such as low density lipoprotein (LDL) cholesterol, blood pressure and smoking [1]. Early atherosclerosis and structural changes in the arterial wall is suggested by findings of increased carotid intima-media thickness in young T1DM patients. [2,3] The early effects of T1DM on atherosclerosis in the coronary arteries and especially on myocardial blood flow are not well characterized. Elevated blood flow has been described in a number of tissues in T1DM patients [4] and glycemic level as well as insulin also appears to have an effect on myocardial blood flow [5–7]. Previous studies in small groups of T1DM patients have shown a lower myocardial perfusion reserve compared with healthy controls. [5,7,8] In patients with type 2 diabetes (T2DM) a lower flow reserve was found to be due to an increased coronary blood flow at rest [9]. Whether this also apply to T1DM is unsettled. An increased resting flow has only been described as a supplementary finding in a smaller study of T1DM patients with unknown coronary anatomy using myocardial contrast echocardiography [7].

Non-invasive assessment of coronary anatomy, left ventricular (LV) myocardial perfusion and transmural myocardial perfusion gradients from epicardial to endocardial layers can now be performed using contrast-enhanced 320-multidetector computed tomography (MDCT) [10–14].

The aim of this study was to investigate potential differences in myocardial resting perfusion and coronary atherosclerosis between asymptomatic T1DM patients and a healthy group of sex and age-matched controls assessed with MDCT to obtain a better understanding of the microcirculation in T1DM that could be related to the higher risk of IHD.

2. Method

2.1. Study population

The study populations consisted of 57 T1DM patients matched with a group of healthy subjects 1:2 (N = 114) with regard to age and sex.

Patients with long-lasting T1DM, persistent normoalbuminuria, and no history of IHD defined as prior percutaneous coronary intervention, prior coronary artery bypass graft, prior myocardial infarction were recruited from the outpatient clinic cohort of T1DM patients at Steno Diabetes Center and the Diabetes Unit, Rigshospitalet as previously reported. The T1DM patients were originally recruited as part of another study in which the association between cardiovascular autonomic neuropathy (CAN) defined as two or more abnormal tests [15] and subclinical atherosclerosis was investigated [16]. Inclusion criteria were T1DM according to American Diabetes Association criteria of at least 10 years duration, age between 18 and 75 years, and HbA1 C <10%. Exclusion criteria were contrast allergy, albuminuria (urinary albumin-to-creatinine ratio >30 mg/g), elevated serum-creatinine >120 μmol/L, untreated hypertension (>140/85 mmHg), electrocardiographic (ECG) signs of heart disease (including other rhythm than sinus rhythm) and clinical symptoms of heart disease.

Healthy subjects were randomly selected from a previously studied random group of 409 participants from the MDCT Copenhagen General Population Study (CGPS) [13,17], a large ongoing cross-sectional population study, in which genotypic and phenotypic data of relevance to a wide range of health-related conditions are registered. The participants were randomly selected from the 409 people to match the T1DM group on sex and age. Inclusion criteria were age >40 years. Exclusion criteria were contrast allergy, other heart rhythm than sinus, serum-creatinine >100 μmol/L, body mass index (BMI) >35 and known IHD defined as prior percutaneous coronary intervention, prior coronary artery bypass graft, prior myocardial infarction or angina pectoris. Serving as a control group for the current study only participants from the CGPS with successful MDCT myocardial perfusion segmentation and without image artefacts (see below) were randomly selected, stratified by age and gender as described above. Cardiovascular risk factors were defined as: family history of IHD, hypertension, hypercholesterolemia and smoking. Informed content and ethical approval for both study groups had previously been obtained (#H-KF-01-144/01 and H-4-2009-091).

2.2. MDCT Scan protocol

The participants were instructed not to consume caffeine at least 18 h before the scan to maintain low heart rate. On arrival to our laboratory, blood pressure, heart rate and ECG were recorded. T1DM patients were given 5 mg ivabradine orally on the evening before and on the morning of cardiac imaging, in order to decrease heart rate for optimised image quality. Ivabradine was selected to reduce heart rate in order to ensure that hypoglycaemia was not masked by beta-adrenocepter