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Suppression of plasma free fatty acids reduces myocardial lipid content and systolic function in type 2 diabetes

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Abstract *Background and Aim:* Type 2 diabetes (T2DM) is closely associated with the development of heart failure, which might be related with impaired substrate metabolism and accumulation of myocardial lipids (MYCL). The aim of this study was to investigate the impact of an acute pharmacological inhibition of adipose tissue lipolysis leading to reduced availability of circulating FFA on MYCL and heart function in T2DM.
Methods and Results: 8 patients with T2DM (Age: 56 ± 11; BMI: 28 ± 3.5 kg/m^2; HbA1c: 7.29 ± 0.88%) were investigated on two study days in random order. Following administration of Acipimox or Placebo MYCL and heart function were measured by ^{1}H-magnetic-resonance-spectroscopy and tomography at baseline, at 2 and at 6 h. Acipimox reduced circulating FFA by −69% ($p < 0.001$), MYCL by −39 ± 41% ($p < 0.001$) as well as systolic heart function (Ejection Fraction (EF): −13 ± 8%, $p = 0.025$; Cardiac Index: −16 ± 15%, $p = 0.063$ compared to baseline). Changes in plasma FFA concentrations strongly correlated with changes in MYCL ($r = 0.707$; $p = 0.002$) and EF ($r = 0.651$; $p = 0.006$). Diastolic heart function remained unchanged.
Conclusions: Our results indicate, that inhibition of adipose tissue lipolysis is associated with a rapid depletion of MYCL-stores and reduced systolic heart function in T2DM. These changes were comparable to those previously found in insulin sensitive controls. MYCL thus likely serve as a readily available energy source to cope with short-time changes in FFA availability.

Background

Type 2 diabetes (T2DM) is a major risk factor for the development of cardiovascular disease and heart failure. Besides macrovascular complications, altered myocardial substrate metabolism in insulin resistant states might cause cardiac dysfunction even in the absence of coronary artery disease, termed diabetic cardiomyopathy (diabCMP) [1].

Metabolic dysregulation in T2DM is proposed to be the underlying pathophysiological mechanism in diabCMP. Under physiological conditions the heart is flexible to adapt to altered availability of fuels, i.e. mainly free fatty acids (FFA), carbohydrates and amino acids, according to actual energy demands. Preclinical studies suggest that this adaptive potential is impaired in insulin resistant states so that cardiomyocytes become dependent on

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Table 1 Baseline characteristics of all type 2 diabetic patients included in the experiments; PNR = patient number; BMI = body mass index.

PNR	Age (years)	BMI (kg/m^2)	HbA1c (%)	Diabetes duration (years)	Medication
1	46	29	8.7	2	Metformin 1 g once daily
2	53	25	6.7	5	Metformin 1 g twice daily, Gliclazide 30 mg twice daily, Vildagliptin 50 mg twice daily
3	62	31	7.2	6	Metformin 1 g twice daily, Gliclazide 30 mg twice daily
4	55	24	6.5	2	Diet only
5	75	26	7.5	10	Gliclazide 30 mg twice daily, Linagliptin 5 mg once daily
6	69	36	6.5	0.5	Diet only
7	38	27	6.5	2	Metformin 850 mg twice daily
8	51	29	8.7	5	Metformin 1 g twice daily, Dapagliflozin 10 mg once daily, 4 units bedtime NPH Insulin
Mean	56 ± 11	28 ± 4	7.2 ± 1	4 ± 3	

constant FFA oxidation, whereas glucose uptake and oxidation is decreased. This might result in metabolic inflexibility [2,3]. In addition, increased FFA uptake into the heart exceeds FFA oxidation, which leads to enhanced accumulation of myocardial lipids (MYCL) and toxic intermediates, altered cellular signalling and mitochondrial dysfunction, which is summarized by "lipotoxicity" [4–6]. These processes are consecutively followed by morphological changes, left ventricular (LV) hypertrophy and decreased LV compliance [5], which is associated with increased cardiovascular risk and mortality in affected patients.

Cardiac steatosis is commonly associated with T2DM [7,8] and was reported to be an independent predictor of LV diastolic dysfunction [9]. Moreover, acute effects of increased plasma FFA [10] and glucose [11] concentrations on MYCL highlight the short-term flexibility of cardiac lipid accumulation and heart function.

We have recently described that a constant and adequate availability of FFA is prerequisite for the acute catecholamine mediated response of the left ventricle to stress (hypoglycemia) in healthy subjects [12]. Against the background of impaired metabolic flexibility ascribed to the diabetic heart, we hypothesized that the myocardium of patients with T2DM might be even more susceptible to an acute depletion of circulating FFAs. This appears particularly relevant since drugs, which pharmacologically inhibit adipose tissue lipolysis like insulin or nicotinic acid, are widely used in routine care.

However, up to now acute effects of decreased plasma FFA availability on MYCL and LV function have not been studied in T2DM. Therefore the aim of this study was to investigate the impact of an acute pharmacological inhibition of adipose tissue lipolysis by a nicotinic acid analogue (Acipimox) leading to reduced availability of circulating FFA on MYCL and heart function in patients with T2DM.

Methods

8 T2DM patients (2 females/6 males, age: 56 ± 11a; BMI: 28 ± 3.5 kg/m^2; HbA1c: 7.29 ± 0.88%) were recruited from the diabetes outpatient's service at the Medical University of Vienna and asked to participate in this single-blinded, randomized, placebo controlled study after the following criteria were excluded: HbA1c >9%, insulin therapy (except bedtime insulin supported oral therapy), history of heart disease including cardiovascular disease, cardiomyopathy, history of cardiac surgery, known intolerance to niacins and general magnetic resonance (MR) contraindications (claustrophobia, metal agents in/on the body). Glucose lowering therapy was omitted during the study days. One subject was treated with very low dose of bedtime NPH insulin and omitted insulin the day before the experiments. Also statin therapy was paused the day before the experiments. Basal characteristics of all patients included are shown in Table 1.

The ethical committee of the Medical University of Vienna approved this study and written informed consent was obtained from all participating subjects. This study was registered on clinicaltrials.gov (NCT01980524).

Participants were asked to refrain from intensive physical training, to stop regular moderate exercising and to ingest an isocaloric diet (30 kcal/kg/day, carbohydrate/protein/fat: 55%/15%/30%) for three days prior to the study related experiments. They were investigated on two different study days in random order, similar to a recently published protocol in healthy subjects [12]. Each participant was studied after an overnight fast for at least 8 h. At baseline and at 180 min placebo (Aci−) or 250 mg Acipimox (Aci+) was administered orally to inhibit adipose tissue lipolysis. Myocardial lipid content (MYCL) and LV-heart function was measured by ^{1}H-magnetic-resonance-spectroscopy and tomography at time points I (0–60 min), II (180–240 min) and III (420–480 min). Blood was drawn via a venous catheter placed into an antecubital vein. Blood samples for the measurement of glucose, insulin and FFA were taken at 0, 90, 180, 270, 330 and 420 min.

Plasma glucose was determined immediately (Biosen C_line, EKF Diagnostic, Barleben/Magdeburg, Germany). Plasma ***FFA and plasma insulin*** were measured in the laboratory of the Division of Endocrinology & Metabolism (FFA: micro-fluorimetric assay; WAKO, Neuss, Germany; Insulin: ELISA Mercodia, Sweden).