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Low-carbohydrate/high-protein diet improves diastolic cardiac function and the metabolic syndrome in overweight-obese patients with type 2 diabetes ☆☆

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ABSTRACT

Background: Diastolic dysfunction/heart failure in the metabolic syndrome and type 2 diabetes (T2D) is an epidemic without evidence-based treatment strategies. While improved glycemic control/insulin sensitivity has been associated with augmented cardiac function in pharmacologic studies, studies on dietary intervention are scarce. Low-carbohydrate nutrition (LC) improves postprandial glucose control and insulin resistance more than standard low-fat diet (LF). We tested the hypothesis, that LC improves cardiac function in overweight-obese patients with T2D more than LF.
Methods: Two matched groups of 16 T2D patients without overt heart disease (52 ± 7 years, BMI 34 ± 6 kg/m^2) were studied in a parallel and partial cross-over design during a 3-week rehabilitation programme with either LC or LF followed by 2 weeks LC. Cardiac function was assessed as myocardial velocity during systole and early diastole (E′) using Doppler tissue imaging and metabolic control before and after a standardised breakfast.
Results: In the parallel groups, both diets induced similar and significant reductions of weight, HbA1c and cholesterol. LC considerably improved insulin resistance, fasting and postmeal triglycerides, blood pressure and diastolic cardiac function E′ (by 0.9 ± 1.4 cm/s, p = 0.023). None of these variables changed on LF, but all of them improved significantly after subsequent LC (E′ by 0.9 ± 1.1 cm/s, p = 0.023). Postprandial intact proinsulin was unchanged on LF but decreased with subsequent LC (p = 0.032).
Conclusions: These data indicate, that a low-glycaemic/high-protein but not a low-fat/high-carbohydrate nutrition modulates diastolic dysfunction in overweight T2D patients, improves insulin resistance and may prevent or delay the onset of diabetic cardiomyopathy and the metabolic syndrome.

Introduction

The strong association between heart failure, age, BMI, dysglycaemia and insulin resistance together with the prevalence of overweight and diabetes indicates that heart failure may soon reach epidemic proportions [1–3]. Of patients presenting with clinical signs of heart failure, 50% of individuals develop systolic heart failure with reduced ejection fraction (EF < 50%) HFREF and a similar proportion develops heart failure with preserved function (HFPEF) (EF > 50%) at initial hospitalization. In contrast to systolic heart failure, there have been no successful therapeutic interventional clinical trials of HFPEF or of the preceding diastolic dysfunction [4,5]. Furthermore, assessment of diastolic cardiac function has been confounded by the semi-quantitative nature of traditional Doppler echocardiographic methods. LV filling pressure is a robust measure of LV diastolic function [6,7] that can now be assessed non-invasively using Doppler tissue imaging. Although LV diastolic dysfunction improves with better glycemic control [8–11] and possibly with exercise, the effects of life style modification by dietary intervention remain scarcely known [12]. This is surprising since diet is a pivotal component in the treatment in type 2 diabetes. Low-carbohydrate diet normalises metabolic abnormalities in type 2 diabetes and in the metabolic syndrome [13–15] and as such may abort or delay the mechanisms promoting diabetic/insulin-resistance cardiomyopathy.

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[4] This author organized and measured the specifically metabolic variables of clinical chemistry and wrote the respective section of the manuscript.
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Accordingly, we assessed metabolism, hemodynamics, exercise capacity and diastolic cardiac function with Doppler tissue imaging during an inpatient rehabilitation programme with moderate physical training to test the hypothesis that in overweight type 2 diabetes patients, a low-carbohydrate diet exerts significantly greater beneficial effects on cardiac function and metabolism than a traditional iso-caloric low-fat/high-carbohydrate diet [15].

Design and methods

Study design

This study had the prespecified goal to encourage further research in metabolic and cardiovascular effects of diets with specific antithetic insulinogenic degrees as dynamic determinants of cardiovascular risk factors and LV diastolic dysfunction. The trial was designed as a prospective, controlled, matched pair parallel arm with partial crossover study for the comparison of two diets in a total 32 overweight patients with type 2 diabetes. Accordingly, the parallel arms consisted of 3 week treatment with either a low-carbohydrate or a low-fat/high-carbohydrate diet, followed in the latter group by two weeks low-carbohydrate diet in order to check similarity of metabolic and functional results between groups with small sample size. Analogous to pharmaceutic interventional studies, the study effects were assessed both as a result from the 3 interventional meals during the previous day and the subsequent nightly metabolic homeostasis mechanisms, that is in the fasting state, and acutely after the interventional test meal, that is 2 h after the breakfast. Before admission, all patients had lived according to the official dietary guideline recommendations [15]. In line with these, the test meal at baseline was composed of low-fat/high-carbohydrate diet, whereas the iso-caloric test meal at the end of any treatment period was composed in line with the respective interventional diet.

Of the in-patients who consecutively attended a weight loss programme at the rehabilitation clinic Ueberruh in Isny, Germany, 32 agreeable individuals were enrolled in the study. The inclusion criteria were age between 30 and 70 years, overweight (body-mass index >26 kg/m^2) and type 2 diabetes according to the criteria of the American Diabetes Association [16] on either dietary control or oral antidiabetic medications. Exclusion criteria were increased LV size, any history or signs of coronary or valvular heart disease, atrial fibrillation, serum creatinine > 2 mg/dl and untreated thyroid dysfunction. Patients assigned to the low-carbohydrate group were matched for age, sex and the use of antidiabetic and antihypertensive medication to the participants in the low-fat group. Baseline demographics and clinical characteristics are listed in Table 1.

Each patient provided written informed consent to the study. The study was approved by the Ethical Committee of the Technische Universität München and is registered in clinical trials gov ID NCT01004757.

Clinical and metabolic parameters, hemodynamics, exercise tolerance and cardiac variables were studied at onset (T1) and end (T2) of the rehabilitation programme with either diet and, additionally in the low-fat group, after the subsequent two weeks of low-carbohydrate diet (T3). Change in myocardial diastolic function within a 2–3 weeks treatment period was considered as primary end-point outcome measure. Secondary end-point parameters were levels of triglycerides and of insulin resistance.

Diets, training and medication

The low-fat, restricted calorie diet was based on the recommendations of the European Association for the Study of Diabetes [15] and was served in a separate dining room ascribed to this diet alone. The composition of the diet was aimed at a daily energy intake of 1600–1800 kcal with 55% of calories from carbohydrates of mixed glycemic index, 20% from low-fat protein and 25% from fat including 10–15% of mono-unsaturated fat. The participants were advised to increase their consumption of low-fat grains, vegetables and fruit.

Table 1
Baseline characteristics of the study population at T1.

Characteristics	Low carb	Low fat	p T1
No	16	16	
Age (years)	52 ± 8	52 ± 7	0.80
Men (no)	5	5	1.0
Body-mass index (kg/m^2)	36 ± 6	33 ± 6	0.25
Waist circ. (cm)	116 ± 15	113 ± 15	0.54
Hypertension (%)	81	63	0.25
Hyperlipidemia (%)	50	69	0.30
Smoking (%)	13	24	0.38
Oral glycemic control medications (%)	62	62	1.0
Metformin (%) [mean dose in mg]	62 [1511]	44 [1621]	0.30
Sulfonylurea (%) [mean dose in mg]	38 [3]	31 [5]	0.72
Glitazone (%) [mean dose in mg]	6 [30]	6 [30]	1.0
ACE or AT2 receptor blocker (%)	75	56	0.28
Calcium antagonist (%)	31	38	0.72
HMG Co-A reductase inhibitor (%)	25	19	0.68
HbA1c (%)	6.9 ± 0.8	7.4 ± 1.6	0.23
Glucose (mg/dl)	150 ± 28	158 ± 54	0.62
Insulin (pmol/l)	15 ± 8	10 ± 6	0.062
HOMA-IR	5.6 ± 3.5	3.9 ± 2.6	0.13
Triglyceride/HDL ratio	3.4 ± 1.3	4.0 ± 1.7	0.74
Triglycerides (mg/dl)	150 ± 52	181 ± 78	0.21
Cholesterol (mg/dl)	208 ± 32	228 ± 61	0.25
HDL (mg/dl)	45 ± 8	48 ± 11	0.39
hsCRP (mg/l)	4.0 ± 3.9	4.8 ± 4.5	0.61
Blood pressure systolic (mm Hg)	127 ± 9	130 ± 9	0.45
Blood pressure diastolic (mm Hg)	83 ± 6	85 ± 8	0.49
Rate pressure product (mm Hg/min)	8955 ± 1302	9327 ± 1335	0.43
Maximal exercise capacity (watt)	128 ± 25	128 ± 45	1.0

Data are expressed as mean ± SD, ACE = angiotensin converting enzyme.

The non-ketogenic low-carbohydrate diet was served in the dining room of another building. This diet was based on the recommendations of Ludwig [13] as described by Heilmeyer [17]. It allowed free access to vegetable, salads, fruits, protein and plant sources of fat as provided on the food buffets, which led via the increased satiety by the latter components to an average of 1600–1800 kcal calorie intake [17]. A restricted amount of carbohydrates with low glycemic index was provided with the goal to achieve 25% of the calorie intake, 30% from protein and 45% from fat including approximately 25% of mono-unsaturated and 10% of polyunsaturated fat.

The training programme was identical for all patients (2 h daily). It consisted of heart rate controlled aerobic exercise, as determined from maximal bicycle ergometry with lactate assessment, involving endurance and resistance training. Due to the severely deconditioned status of the patients, only low intensity training was applicable, so that energy requirements were increased by 200–400 kcal/day. According to the study protocol, maintenance of antidiabetic and antihypertensive medications was intended for all patients and recorded but was adjusted, where indicated, to avoid hypoglycemia or hypotension.

Clinical outcomes

Weight was measured to the nearest 0.1 kg in the patients without their shoes. Exercise capacity was determined by maximal bicycle ergometry. Blood pressure was measured in the sitting patient after 10 minute rest.

Metabolic parameters were assessed from blood samples by venipuncture after a 12-hour fast and 2 h after the subsequent standardised breakfast (400 kcal) with low-fat composition at T1 and after low-fat diet at T2, but low-carbohydrate composition after low-carbohydrate diet at T2 and T3. Serum levels of triglycerides, total cholesterol, high-density (HDL) and low density lipoprotein (LDL) cholesterol and glucose were measured in fresh blood samples (ADVIA 2400, Siemens, Munich, Germany) and glycosylated haemoglobin (HbA1c) using the G7-HPLC Analyzer (Tosoh Europe NV, Stuttgart, Germany) with intra-