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/m²) 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 ± 1.1 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 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.

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Introduction

The strong association between heart failure, age, BMI, dysglycaemia and insulin resistance together with the prevalence of overweight and obesity and insulin resistance together with the prevalence of overweight and obesity and insulin resistance together with the prevalence of overweight and obesity 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.
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 antiatherogenic insulinoergic 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 cross-over 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 pharmacoeutletic 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/m²) 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 glyemic 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.

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 Helmeyer [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 glyemic 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-

Table 1

| 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/m²)     | 36 ± 6   | 33 ± 6  | 0.25 |
| Waist cir. (cm)             | 116 ± 15 | 113 ± 15| 0.54 |
| Hypertension (%)            | 81       | 63      | 0.25 |
| Hyperlipidaemia (%)         | 50       | 69      | 0.36 |
| Smoking (%)                 | 13       | 24      | 0.38 |
| Oral glycaemic control medications (%) | 62       | 62      | 1.0  |
| Metformin [% in dose in mg] | 62 [111] | 44 [120]| 0.30 |
| Sulfonylurea [% in dose in mg]| 38 [3]   | 31 [5]  | 0.72 |
| Glitazone [% in dose in mg]  | 6 [30]   | 6 [30]  | 1.0  |
| ACE or AT2 receptor blocker (%) | 75       | 56      | 0.28 |
| Calcium antagonist (%)      | 31       | 38      | 0.72 |
| HMCo Co-A reducect inhibitor (%) | 25   | 19      | 0.68 |
| Glucose (mg/dl)             | 69 ± 0.8 | 74 ± 1.6| 0.23 |
| Insulin (pmol/l)            | 150 ± 28 | 158 ± 54| 0.62 |
| 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.
and interassay coefficients of variation (CV) below 5%. Frozen samples of serum (−80°C) were kept until further analysis. Immunoassays were used for determination of insulin (Chemiluminescence, Invitron Ltd, Wyastone Leys, UK, CV < 5%), intact proinsulin [18] (TECO® human Proinsulin ELISA Kit, TECOmedical AG, Sissach, Switzerland, CV < 5%), nitrotyrosine [19] (Chemiluminescence, Millipore upstate, Molsheim, Germany, CV < 10%), and OxLDL [20] (Immundiagnostik AG, Bensheim, Germany, CV 2.5 and 9.4% for intra- and inter-assay assessment respectively). Insulin resistance was calculated by homeostatic model of assessment (HOMA-IR) [21] and, additionally, by the tri-glyceride/HDL ratio [22].

Cardiac function

Two experienced echocardiographers obtained ultrasound data with a commercially available system (ALOKA Alpha 10, Tokyo) using traditional echocardiography of cardiac structures, Doppler of the transmitral inflow velocities and Doppler tissue imaging for the quantification of cardiac function as systolic (S') and diastolic (E') myocardial velocities in cm/s as previously described [23]. Given the steep decline of early diastolic myocardial velocity E' by 1% every year with ageing in normal people, individual patients were assigned to diastolic dysfunction if the actual measured velocity E' was smaller than the calculated age related cut off level for normal velocity [8].

Statistics

Sample size calculation: Based on increases of E' in previous interventional studies [11], we anticipated detecting also group differences in change of E' of at least 1 cm/s. Assuming less than one half of the variability in changes of E' (SD < 0.85), 12 patients per group were necessary to detect this clinically relevant effect size at a two-sided level of significance of 5% with 80% power. Expecting a drop-out proportion of up to 25%, 16 patients were recruited for each intervention arm.

Statistical analysis was performed using the SPSS version 16.0 software package (SPSS Inc., Chicago, IL). The difference between postprandial and fasting values was calculated as postmeal increase (Δ) and treatment effects as change from baseline. In the low-fat crossover group, statistical interaction tests were applied to assess possible carry over effects considering a p value >0.2 as no evidence for interaction. Significant, diet associated, within person changes were assessed by ANOVA for repeated measurements and post hoc tests (Bonferroni). Students’ t-test or non-parametric tests were used for evaluation of within person changes in the low-carbohydrate group, and to assess differences between the matched pair designated groups where appropriate. To compare frequency data between independent study groups, the chi-square test or Fisher’s exact test was used as appropriate. Bivariate relationship of quantitative data was assessed by using Pearson’s- or if appropriate, Spearman’s correlation coefficient. All statistical tests were conducted two-sided and a p-value < 0.05 was considered to indicate statistical significance.

Each patient remained unaware about the assumed cardiac and metabolic effects of the study diets. The study coordinators and clinical advisors remained unaware of the outcome data before the end of the interventions. Measurements and analysis of ultrasound and of metabolic variables were performed by applying single measurement of variables or mean values as specified in the methods section by staff blinded to the patients’ diet assignment and study protocol.

Results

The baseline data of the parallel treatment groups were comparable (Table 1). As expected, most patients had increased markers of insulin resistance. With regard to the primary and secondary outcome measures, there have been neither clinically relevant nor statistically significant interaction effects in the cross-over low-fat group.

Within all 32 patients receiving low-carbohydrate diet, diastolic cardiac function improved in 24 (75%), remained unchanged (absolute difference less than 0.1 cm/s) in 1 and decreased in 7 (22%). Within the 16 patients receiving low-fat diet in contrast, only 6 (38%) patients improved diastolic function, 4 (25%) remained unchanged and 6 (38%) deteriorated (p = 0.013). Diastolic dysfunction as defined by the age related normal value of E' [8] was assigned to 16/32 patients before receiving low-carbohydrate diet. From these, 13 (81%) improved diastolic function compared to 5 such improvements (62%) amongst the 8/16 patients with diastolic dysfunction before receiving low-fat diet.

With any diet in the parallel groups, there were similar and significant improvements of weight, long term and fasting glucose and cholesterol (Table 2). Similarly with both diets, there were neither clinically relevant nor statistically significant changes in LV diameter, wall thickness, atrial size and the traditional parameters of diastolic function, the mitral inflow velocities E and A, their ratio E/A and the LV end-diastolic pressure calculated as E/E’ (data not shown).

The changes from baseline were significantly different between both treatment arms with greater benefit from low-carbohydrate diet for diastolic cardiac function (Fig. 1A), systolic blood pressure (Fig. 1B) and, as a trend, for waist circumference (Table 2), fasting insulin and the postmeal ratio triglyceride/HDL (Fig. 2A and B). The following variables remained nearly unchanged by low-fat diet but significantly improved by low-carbohydrate diet in the parallel group: diastolic

| Table 2
Changes by low-carbohydrate and low-fat diet in the parallel groups.

|                      | Low carb | Low fat | p change | P T2 |
|----------------------|----------|---------|----------|------|
| Wmax (watt)          | 10 ± 16 * | 5 ± 11  | 0.337    | 0.725|
| Rate pressure product (mmHg/min) | −933 ± 1104 ** | 540 ± 1201 | 0.143 | 0.075 |
| Weight (kg)          | −2.6 ± 3.3 ** | −1.6 ± 2.2 * | 0.495 | 0.301 |
| Waist circ. (cm)     | −4.4 ± 3.5 ** | −2.4 ± 2.3 ** | 0.069 | 0.79  |
| HbA1c (%)            | −0.3 ± 0.2 *** | −0.3 ± 0.4 ** | 0.953 | 0.163 |
| Glucose (mmol/l) fa  | −17 ± 32 ** | −30 ± 20 *** | 0.127 | 0.576 |
| Glucose (mmol/l) pp  | −16 ± 32 | −32 ± 73 | 0.465 | 0.445 |
| HOMA-IR              | −0.9 ± 2.4 * | −0.1 ± 1.4 | 0.277 | 0.309 |
| Cholesterol (mmol/l) fa | −22 ± 30 * | −30 ± 43 * | 0.525 | 0.445 |
| Cholesterol (mmol/l) pp | −16 ± 31 * | −34 ± 30 * | 0.174 | 0.433 |
| HDL (mmol/l) fa      | −1 ± 6 | −3 ± 8 | 0.455 | 0.709 |
| HDL (mmol/l) pp      | 0 ± 5 | −3 ± 6 | 0.238 | 0.903 |
| LDL (mmol/l) fa      | −14 ± 29 (*) | −26 ± 21 *** | 0.229 | 0.692 |
| LDL (mmol/l) pp      | −14 ± 26 (*) | −26 ± 20 *** | 0.156 | 0.724 |
| Uric acid (mmol/l)   | −0.5 ± 0.8 * | −0.9 ± 1.5 * | 0.341 | 0.586 |

Wmax = maximal exercise capacity, fa = fasting, pp = postprandial; p change = intergroup significance for change from baseline; P T2 = intergroup significance at T2; * = p < 0.05, ** = p < 0.01, *** = p < 0.001 and (*) = p < 0.1 ® 0.05 for within person change from T1 to T2.
LV function, systolic and diastolic blood pressure, maximal exercise capacity and the rate pressure product, as well as markers of insulin resistance and fasting and postmeal triglycerides (Fig. 2B and C). Furthermore, these variables also improved by the subsequent low-carbohydrate diet in the cross-over group (Table 3). Intact proinsulin remained unchanged with low-fat diet but tended to decrease after subsequent low-carbohydrate diet fasting and significantly decreased postmeal (Table 3). Within the cholesterol fractions, the low-carbohydrate diet induced less though not significantly less reduction of total cholesterol and LDL compared to the parallel low-fat group and significantly less reductions from the subsequent low-carbohydrate diet of only 2 weeks.

In the pooled data, the change of diastolic cardiac function $E'$ had a significant correlation with the change of maximal exercise capacity ($r = +0.503, p < 0.001$) (Fig. 3) and with the change of fasting glucose ($r = +0.299, p = 0.041$). In the cross-over group, the change in $E'$ had significant inverse correlations with baseline postmeal ($r = -0.371, p = 0.043$), but not with fasting intact proinsulin, and furthermore with postmeal nitrotyrosine ($r = -0.397, p = 0.030$, Fig. 3) and with the postmeal increase of nitrotyrosine ($r = -0.376, p = 0.030$) and with the postmeal (Fig. 4).

Taking the respective individual doses of antidiabetic medication at baseline as 100%, the use of these drugs was decreased in the low-carbohydrate group by 88% at T2 and by 12% in the parallel low-fat group but by a further 54% after subsequent low-carbohydrate diet.

Discussion

The main result of the present study in overweight patients with type 2 diabetes was the improvement in diastolic cardiac function with low-carbohydrate diet that was associated with increased maximal exercise capacity and improvements of insulin resistance that were not achieved by low-fat diet in spite of a similar weight loss. The strength of the study lies in the assessment of multifactorial variables potentially impacting on cardiac function including insulin resistance as well as the postmeal lipid and glucose metabolism when studying the functional changes induced by two diets of antithetic insulinogenic degree both in a parallel group and a partial cross over design.

The culprit factor causing diastolic dysfunction and heart failure has traditionally been ascribed to structural myocardial stiffness. However, increased evidence points to an additional major role played by insulin resistance and hyperglycemia [5,11,24,25] as evident from 1. the high
prevalence of diastolic dysfunction in patients with metabolic syndrome [8,26], 2. the description of an insulin resistance cardiomyopathy or diabetic cardiomyopathy [27,28] and 3. the first interventional trials reporting improved diastolic function with medical therapy that improves glycemic control or insulin resistance [8–11]. Surprisingly, the effects of life style interventions on diastolic function have been
disappointing: They were equivocal for exercise [29–31] and, with regard to nutrition, focussed on very strict caloric reduction [12], that is known to result in limited patient compliance. Dietary intervention, however, should be of greater interest because of its potential for lowering public health costs compared to pharmacologic therapy and reducing recurrent hospital admissions for heart failure in patients with metabolic syndrome [5,8,26–28,32] since the underlying insulin resistance may be modulated by more appropriate composition of nutrition. This may change the paradigm for recommending low-fat/high-carbohydrate diet [15] that has been shown to be less beneficial on all manifestations of the metabolic syndrome as compared to low-carbohydrate/high-protein nutrition [13,34,35]. In addition, the low-carbohydrate/high-protein diet is associated with a concomitant 50% reduction in antidiabetic oral or insulin

Table 3
Diet induced changes by cross-over from low-fat to low-carbohydrate.

|                      | Low fat | Low carbohydrate | p ANOVA | p change |
|----------------------|---------|------------------|---------|----------|
| Wmax (watt)          | 5 ± 11  | 2 ± 7*           | 0.053   | 0.425    |
| Weight (kg)          | −16 ± 2.2* | 1.7 ± 1.4 ⬤⬤⬤⬤ | 0.000   | 0.84     |
| Waist circumference (cm) | −24 ± 2.3** | −2.3 ± 1.3 ⬤⬤⬤⬤ | 0.000   | 0.84     |
| HbA1c (%)            | −0.3 ± 0.4** | −0.3 ± 0.3 ⬤⬤⬤⬤ | 0.000   | 0.96     |
| Glucose (mmol/l)     | fa −30 ± 29** | −3 ± 27**        | 0.001   | 0.009    |
|                      | pp −32 ± 73* | −11 ± 45         | 0.029   | 0.37     |
| Cholesterol (mmol/l) | fa −30 ± 43** | −3 ± 22          | 0.047   | 0.10     |
|                      | pp −34 ± 36* | −6 ± 25          | 0.004   | 0.004    |
| HDL (mmol/l)         | fa −27 ± 7.5 | 3 ± 6            | 0.125   | 0.045    |
|                      | pp −25 ± 6.1 | 3 ± 4            | 0.077   | 0.006    |
| LDL (mmol/l)         | fa −26 ± 21*** | −1 ± 18         | 0.001   | 0.001    |
|                      | pp −26 ± 20*** | −1 ± 17        | 0.000   | 0.002    |
| Intact proinsulin (μmol/l) | fa −1 ± 8 | −6 ± 10*聽 | 0.021   | 0.445    |
|                      | pp −4 ± 15 | −8 ± 9*         | 0.004   | 0.04     |
| Nitrotyrosine (μg/ml) | fa 58 ± 180 | 8 ± 138         | 0.265   | 0.38     |
|                      | pp 16 ± 169 | 10 ± 147        | 0.813   | 0.90     |

Wmax = maximal exercise capacity, fa = fasting, pp = postprandial. Significant p values are shown in bold letters. p ANOVA for repeated measures (T1, T2 and T3), post hoc test Bonferroni.

* = p < 0.05.
** = p < 0.01.
*** = p < 0.001.

(*) = p < 0.1 – > 0.05 for intragroup significance of low-carbohydrate nutrition at T3 vs. T2.

* = p < 0.05.
** = p < 0.01.

*** = p < 0.001 for comparison with T1 either at T2 after low-fat diet or at T3 after both successive diets.

p change = interdiet significance for change from each respective baseline.

Fig. 3. In the pooled data, the correlation for the diet-induced change of diastolic cardiac function E’ with the change of exercise capacity is positive and significant. Full black dots = low carbohydrate diet in the parallel group, full grey dots = low fat diet in the respective group and black circles the subsequent cross over low carbohydrate diet of the latter group.

Fig. 4. In the pooled data of the cross-over group, the correlation for the diet-induced change of diastolic cardiac function E’ with the postmeal increase of nitrotyrosine at baseline is inverse and significant. Black dots indicate the changes after low-fat and black circles those after the subsequent low-carbohydrate diet.
Dietary function E' may translate into daily life performance as demonstrated by the positive correlation between the diet induced changes of E' and of exercise capacity in the present study population that has not been shown before. However, E' has been shown not only to be more sensitive than systolic function for detecting ischemic and other myocardial metabolic derangements, but also in detecting reversibility of diastolic dysfunction [8]. In the present study, improved myocardial energy substrate utilisation is likely to be involved given the critical limitations of myocardial energy availability in the diabetic heart [32]. Factors contributing to limited myocardial energy availability include down-regulated perfusion from endothelial dysfunction, impaired intracellular bioenergetics and reduced cardiac efficiency [28]. All of the above are based on potentially reversible metabolic derangements such as altered insulin signalling, post-meal oxidative stress and increased cytokine activity [23,25,32–35].

Theoretically, regular exercise training and a low-fat diet should improve glycemic control and reduce body weight and, accordingly, decrease insulin resistance that may translate into improvement of blood pressure and cardiac function [31]. However, this potential functional benefit may be counteracted by high carbohydrate related fluctuations in the postmeal levels of insulin, triglycerides and oxidative stress aggravating impaired insulin signalling, endothelial dysfunction and, thus, myocardial dysfunction [25,28,32]. This has been demonstrated after a single high carbohydrate test meal in overweight, diabetic patients [33]. This mechanism was also suggested by the 6/16 patients with the low-fat diet associated deterioration in left ventricular function and possibly also in earlier studies on exercise based lifestyle changes with adherence to the recommended low-fat/high-carbohydrate nutrition [29–31].

The metabolic differences between the two diets related to the specific post-prandial carbohydrate metabolism [14,34,35]. Low-carbohydrate nutrition was demonstrated to reduce insulin levels and insulin resistance that was associated with less of a burden for the beta cell as shown by the respective reduction of intact proinsulin. This confirms the potential of adequate nutrition to prevent or delay deterioration or development of type 2 diabetes. Furthermore, fasting and postmeal triglyceride levels decreased by almost 30% in spite of the higher relative percentage of fat intake, demonstrating that serum lipid levels in overweight type 2 diabetes patients do not passively mirror the amount of consumed fat. Given the myocardial triacylglycerol accumulation in diabetic cardiomyopathy [36], such a substantial reduction of dyslipidemia may be expected to augment cardiac function as confirmed by our results. The key role of postprandial glucose control in overweight type 2 diabetes with insulin resistance is corroborated by our observation that the change in diabetic function correlated inversely with markers of postmeal but not with fasting insulin resistance or oxidative stress.

The present data have great potential for the dietary prevention of diabetes and cardiovascular risk analogous to the reduced risk of diabetes, hypertension and adverse cardiac events associated with the α-glucosidase inhibitor acarbose [37] that is also effective by reducing postprandial hyperglycaemia and hyperinsulinemia. A low-carbohydrate non-restricted-calorie diet may be optimal for those who cannot adhere to a restricted-calorie diet [35].

Our data with short term dietary intervention are concordant with long term studies demonstrating the beneficial effects of low-carbohydrate diets on all features of the metabolic syndrome [14,35,38]. This suggests, that causal pathophysiological mechanisms of the metabolic syndrome are successfully met by this dietary prevention of postprandial dysmetabolism implicating the potential to prevent or delay the onset of diastolic heart failure and cardiovascular disease [2,8,24,32,39]. These findings are further corroborated by the associated reduction of antihyperglycemic medication by 54–88% that is similar to previous reports [14,17,40].

Limitations

The following aspects of our study, however, deserve critical review. The partial cross over design allowed only 2 additional weeks with low-carbohydrate nutrition; this was due to financial restrictions by the management of the rehabilitation clinic and may have weakened the respective changes of the studied variables, nevertheless, the similarity of these changes to those in the parallel group excludes bias in patient selection in small samples. The small sample size may be regarded as a limitation, although the significant associations in this small study group underscore the relevance of the findings. For the sake of homogeneity in the study population, participants with overt cardiovascular disease had been excluded. However, this does not limit the relevance of our findings, because the overall relationship of glucose metabolism and insulin resistance with diastolic function has been shown to play a role independent of coronary artery disease and heart failure as mediating factors [4,9,32]. The design of the study did not allow us to elucidate and differentiate the mechanisms underlying the changes in diastolic function in overweight diabetics; likely the moderate reduction of systolic and diastolic blood pressure has contributed but cannot account for the whole range of functional cardiac improvement considering the normal range of blood pressure at baseline. Finally, the findings in this study warrant confirmation in future randomized studies to determine if these early beneficial cardiac effects are sustained long term as suggested by the respective long term effects on metabolism and cardiovascular risk factors [14,15,35,38].

This is the first study to demonstrate that dietary control of insulin resistance and postmeal glucose levels by a moderate restriction of carbohydrate intake improves diastolic dysfunction in obese patients with type 2 diabetes. This study shows that dietary modulation is the cornerstone of treatment of type 2 diabetes and the metabolic syndrome and has potential cost-savings in reducing expensive hospital admissions by delaying or preventing the onset of diastolic heart failure based on diabetic/insulin resistant cardiomyopathy. Moreover, the findings support the hypothesis that by normalizing the underlying pathophysiological mechanisms, the metabolic syndrome may be improved in all of its manifestations.

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References

[1] Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement of the American Heart Association Councils on epidemiology and prevention, clinical cardiology, cardiovascular nursing, and high blood pressure research; quality of care and outcomes research interdisciplinary working group; and functional genomics and translational biology interdisciplinary working group. Circulation 2009;117:2544–55.
[2] Thrainsdottir IS, Aspelund T, Gudnason V, et al. Increasing glucose levels and BMI predict future heart failure. Experience from the Reykjavik Study. Eur J Heart Fail 2007;9:1051–7.
[3] Ingelsson E, Sundstrom J, Amlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–41.
[4] Stahrenberg R, Edelmann F, Mende M, et al. Association of glucose metabolism with diastolic dysfunction along the diabetic continuum. Diabetologia 2010;53:1331–40.
[5] Borlaug BA, Paulus WJ. Heart failure preserved ejection fraction: pathophysiology, diagnosis and treatment. Eur Heart J 2011;32:670–9.
[6] Naghavi SF, Middleton R, Kopelev HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
[7] Paulus WJ, Tschape C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.
[8] von Bibra H, St. John Sutton M. Diastolic dysfunction in diabetes and metabolic syndrome—diagnostic and prognostic potential. Diabetologia 2010;53:1033–45.
