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Chapter 6

Sustained cardiac remodeling after a 16-week very low calorie diet in type 2 diabetes mellitus

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ABSTRACT

Background

A VLCD in T2DM patients results in cardiac remodeling and improved diastolic function. However, it is unknown how long these effects sustain after reintroduction of a regular diet. The objective of current study is to assess the long-term effects of initial weight loss by a very low calorie diet (VLCD) on cardiac dimensions and function in patients with type 2 diabetes mellitus (T2DM).

Methods

Fourteen patients with insulin-dependent T2DM (mean $\pm$ SEM: age 53 ± 2 years; body mass index (BMI) 35 ± 1 kg/m²) were treated by a VLCD (450 kcal/day) during 16 weeks. Cardiac function was measured by magnetic resonance imaging before and after the 16-week VLCD and again after 14 months of follow-up on a regular diet.

Results

BMI decreased from 35 ± 1 kg/m² to 28 ± 1 kg/m² after the VLCD and increased again to 32 ± 1 kg/m² at 18 months (both $P < 0.05$ vs. baseline). Left ventricular (LV) end-diastolic volume index increased after the 16-week VLCD (80 ± 3 to 89 ± 4 mL/m², $P < 0.05$) and remained increased after 14 months of follow-up (90 ± 3 mL/m²; $P < 0.05$ vs. baseline) at comparable filling pressures. VLCD decreased the LV mass/ LV end-diastolic volume ratio and remained decreased after 14 months of follow-up. (0.67 ± 0.03 at baseline to 0.59 ± 0.03 at 16 weeks and 0.56 ± 0.03 at 18 months resp. (both $P < 0.05$ vs. baseline)). The improvement in LV diastolic function after the 16-week VLCD, was sustained after 14 months of follow-up (early (E)/ atrial (A) diastolic filling phase ratio: 0.96 ± 0.07 (baseline); 1.12 ± 0.06 (after VLCD); 1.06 ± 0.07 (18 months, $P < 0.05$ vs. baseline)).

Conclusion

Weight reduction by a 16-week VLCD in T2DM patients results in sustained cardiac remodeling and improved diastolic function after 14 months of follow-up, despite weight regain on a regular diet.

INTRODUCTION

Diastolic dysfunction in type 2 diabetes mellitus (T2DM) is associated with an increased risk of development of heart failure and mortality, independent of coronary disease and hypertension (1). Moreover, even well-controlled patients with uncomplicated T2DM have significantly lower left ventricular (LV) end-diastolic volume indices compared to age-matched healthy controls (2). Accordingly, cross-sectional data from the Framingham Offspring cohort have indicated an association between increased insulin resistance and concentric remodeling (3). Several mechanisms underlying diastolic dysfunction in T2DM have been proposed including: hypertension, fibrosis and deposition of advanced glycation end products (AGEs), altered calcium handling and myocardial lipotoxicity (4,5).

Weight loss and lifestyle alteration are important cornerstones in the treatment of T2DM. In obesity, diet-induced weight loss not only improves insulin resistance, but also diastolic cardiac function (6-8). In obese patients with T2DM, we showed that a 16-week VLCD improves diastolic function, associated with a decrease in myocardial triglyceride (TG) content (9). There are no data available on long-term effects of diet-induced initial weight loss on cardiac function and myocardial TG content, particularly in T2DM. Therefore, we performed a 14 month follow-up study after completing a 16-week very low calorie diet (VLCD) in obese patients with insulin-dependent T2DM. We assessed cardiac function by cardiac MR imaging and myocardial triglyceride (TG) content by MR spectroscopy.

METHODS

Patients

We included 14 insulin-dependent T2DM patients (8 men, mean age: 53 ± 2 years, diabetes duration: 9 ± 1 years). Patients were eligible for inclusion if they: had stable weight at baseline, were non-smoking, had a normal stress electrocardiogram, had no other chronic (endocrine) disease and had sufficient residual insulin secretory capacity (defined as a fasting plasma C-peptide level greater than 0.8 ng/mL and a 2-fold increase of the basal C-peptide level in response to administration of 1 mg glucagon intravenously). The details of the initial VLCD study have been previously described (9). Patients were studied on three occasions: at baseline (within 1 week before the start of the VLCD), directly after the 16-week VLCD and at 18 months (78.9 ± 1.6 weeks) from baseline. The VLCD consisted of 3 meals per day containing 450 kcal/day and all essential micro- and macronutrients (Modifast, Nutrition & Santé, and Antwerpen, Belgium). Five out of the 14 patients additionally followed an exercise program during the 16 week VLCD; however this did not affect the outcome parameters. During the 16-week VLCD all glucose-lowering medication, including insulin therapy was discontinued. After the VLCD, patients were reintroduced to a regular diet. After 6 months

all patients were referred back to their own specialist, for regular medical care including, if necessary, reintroduction of glucose lowering medication.

This study was approved by the local ethics committee. Written informed consent was obtained from all patients and the study was performed in accordance with the Declaration of Helsinki

Cardiac function

All MR measurements were performed in the postprandial state (4 hours after the last meal) and in supine position. During MR imaging, blood pressure and heart rate were measured, using an automatic device (Dinamap, DPC100X, Freiburg, Germany).

We used a 1.5 Tesla Gyroscan ACS-NT MR imaging scanner (Philips, Medical Systems, Best, The Netherlands), with a body coil for radiofrequency transmission and 5-element synergy coil for signal receiving. A sensitivity encoding balanced steady-state free processing sequence, with ECG-gating and breath holding, was used with the following parameters: TE = 1.7 ms, TR = 3.4 ms, slice gap = 0 mm, flip angle = 35°, field of view = 400 * 320 mm, reconstructed matrix size = 256 * 256, slice thickness = 10 mm, to image the heart in short-axis orientation from apex to base with 12 slices. All images were quantitatively analyzed using dedicated software (MASS, Medis, Leiden, the Netherlands) to assess left ventricular (LV) end-diastolic volume, LV end-systolic volume, stroke volume, cardiac output, LV ejection fraction and LV mass (10). We calculated cardiac index, LV end-diastolic volume index, LV end-systolic volume index, LV stroke volume index and LV mass index, by dividing the parameters by the body surface area. Flow dynamics across the mitral valve were assessed using an ECG-gated gradient-echo sequence with velocity encoding with the following scan parameters: TE = 4.8 ms, TR = 14 ms, flip angle = 20°, slice thickness = 8 mm, field of view = 350 * 350 mm, matrix size = 256 * 256, velocity encoding = 100 cm/s and scan percentage = 80%. Flow encoded MRI data were analyzed using the FLOW software package (Medis, Leiden, the Netherlands). The early filling phase (E) and atrial contraction (A) were analyzed and the maximum flow rate of E and A were calculated to obtain an E/A peak flow ratio. Furthermore we quantified an estimation of filling pressure (E/Ea) (11).

Proton magnetic resonance spectroscopy

The body coil was used for radiofrequency transmission and a surface coil (17 cm) for signal receiving. A point resolved spectroscopy sequence was used to acquire single-voxel spectra (12). The voxel (8 mL) was placed in the interventricular spectrum and data were acquired at end-systole. Spectral parameters were: TR of at least 3000 ms, TE = 26 ms. A total of 1024 data points was collected over a 1000-Hz spectral width. Data acquisition was ECG-triggered and with respiratory echoes, to minimize breathing influences. Water-suppressed spectra with 128 averages and unsuppressed spectra with 4 averages (TR = 10000) were acquired, using the same voxel location. Spectra were analyzed using Java-based MR user interface software

(jMRUI version 2.2) as previously described (12). Myocardial triglycerides (peak at 1.3 parts per million (ppm) and 0.9 ppm were summed) were calculated as percentage of the unsuppressed water signal (TG/water*100).

Statistical analyses

All statistical analyses were performed using SPSS 17.0 (SPSS Inc.Chicago, Illinois, USA). A 2-tailed probability value of 0.05 or less was considered statistically significant. Data are expressed as mean values $\pm$ standard error of the mean (SEM) or median (interquartile range). Non-normally distributed data were log-transformed and checked for normality after transformation. A general linear model for repeated measures, with time as within-subject factor was used for comparison between the three assessments. LSD post-hoc tests were used in case of a significant F-ratio. GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, USA) was used for creation of the figures.

RESULTS

Body mass index (BMI) decreased from $35 \pm 1 \text{ kg/m}^2$ to $28 \pm 1 \text{ kg/m}^2$ ($P < 0.05$) after the VLCD. Patients regained weight during the 14 months of follow-up to a BMI of $32 \pm 1 \text{ kg/m}^2$ ($P < 0.05$ vs. baseline, Table 1). At baseline, all patients used insulin, 8 patients used metformin and 3 patients a sulfonylureum (SU) - derivate. During the 16-week VLCD all patients had stopped insulin therapy and oral glucose lowering medication. Directly after the VLCD 14 patients used metformin and 3 patients a SU-derivate. At 18 months, four patients had restarted insulin therapy, 12 patients used metformin and 4 patients used a SU-derivate.

Table 1. Changes in metabolic parameters at baseline, after a 16-week very low calorie diet and after 14 months of follow-up on a regular diet

Variable	Baseline	16 weeks (after VLCD)	18 months
Body mass index (kg/m ²)	35.3 $\pm$ 1.1	27.5 $\pm$ 1.1*	31.7 $\pm$ 1.1*†
HbA1c (%)	8.4 $\pm$ 0.3	7.0 $\pm$ 0.4	7.7 $\pm$ 0.5
Glucose (mmol/L)	11.9 $\pm$ 0.6	7.8 $\pm$ 0.8*	10.4 $\pm$ 1.0†
Insulin (mU/L)	23.5 (14.3-29.3)	10.0 (6.8-12.0)*	6.5 (5.0-14.3)
Non-esterified fatty acids (mmol/L)	0.97 $\pm$ 0.07	0.76 $\pm$ 0.08*	0.68 $\pm$ 0.06*
Triglycerides (mmol/L)	2.3 $\pm$ 0.2	1.2 $\pm$ 0.1*	2.8 $\pm$ 0.6†

Data are mean $\pm$ SEM or median (interquartile range).

* $P < 0.05$ vs. baseline, † $P < 0.05$: 18 months vs.16 weeks

Hemodynamics

Systolic and diastolic blood pressures decreased from 155 ± 5 mmHg and 89 ± 3 mmHg respectively at baseline to 136 ± 4 mmHg and 80 ± 2 mmHg directly after the 16-week VLCD ($P < 0.05$, Table 2). At 18 months both systolic and diastolic blood pressures returned to baseline values (149 ± 5 mmHg and 88 ± 3 mmHg resp.). Heart rate decreased from 85 ± 2 beats/min at baseline to 69 ± 3 beats/min after the VLCD ($P < 0.05$) and remained decreased at 18 months (71 ± 3 beats/min, $P < 0.05$ vs. baseline). This resulted in a decreased rate pressure product after the VLCD and at 18 months compared to baseline (baseline: 13218 ± 636 beats/min-mmHG vs. 16 weeks: 9426 ± 550 beats/min-mmHG, $P < 0.05$; 18 months: 10592 ± 576 beats/min-mmHG, $P < 0.05$ vs. baseline). Prescription of antihypertensives did not significantly change during the study (number of classes of antihypertensives prescribed: at baseline: 2.4 ± 0.3 ; after VLCD: 1.9 ± 0.3 ; 18 months: 2.1 ± 0.3 ($P > 0.05$). Statin use did not significantly change during the study either.

Table 2. Changes in hemodynamic parameters and cardiac function at baseline, after a 16-week very low calorie diet and after 14 months of follow-up on a regular diet

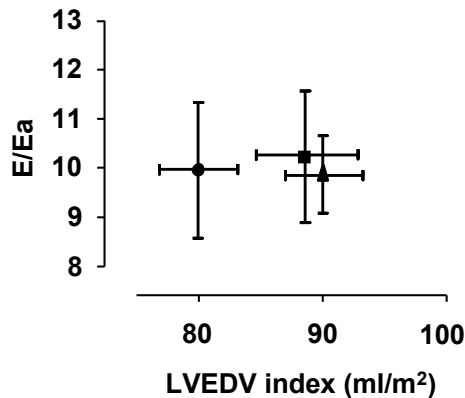
	Baseline	16-week VLCD	18 months
Hemodynamics			
Systolic blood pressure (mmHg)	155 ± 5	$136 \pm 4^*$	$149 \pm 5^†$
Diastolic blood pressure (mmHg)	89 ± 3	$80 \pm 2^*$	$88 \pm 3^†$
Heart rate (beats/min)	85 ± 2	$69 \pm 3^*$	$71 \pm 3^*$
Rate pressure product (beats/min-mmHG)	13218 ± 636	$9426 \pm 550^*$	$10592 \pm 576^{*†}$
Cardiac function and dimensions			
LVEDV (mL)	177 ± 9	177 ± 11	190 ± 9
LVEDV index (mL/m ²)	80 ± 3	$89 \pm 4^*$	$90 \pm 3^*$
LVESV (mL)	78 ± 5	75 ± 5	80 ± 4
LVESV index (mL/m ²)	35 ± 2	38 ± 2	38 ± 2
LV stroke volume (mL)	99 ± 6	102 ± 7	$110 \pm 7^*$
LV stroke volume index (mL/m ²)	45 ± 2	$51 \pm 3^*$	$52 \pm 2^*$
Cardiac index (L/min/m ²)	3.5 ± 0.2	3.3 ± 0.2	3.6 ± 0.2
Ejection fraction (%)	56 ± 2	57 ± 2	57 ± 1
LV mass (g)	119 ± 8	$102 \pm 7^*$	$109 \pm 9^{*†}$
LV mass index (g/m ²)	54 ± 3	51 ± 3	51 ± 3
LV mass/ LVEDV	0.67 ± 0.03	$0.59 \pm 0.03^*$	$0.56 \pm 0.03^*$
E/A ratio	0.96 ± 0.07	$1.12 \pm 0.06^*$	$1.06 \pm 0.07^*$
E/Ea	10.0 ± 1.4	10.2 ± 1.3	9.9 ± 0.8

* $P < 0.05$ vs. baseline, $^† P < 0.05$: 18 months vs. 16 weeks. Data are mean $\pm$ SEM. NS, not significant; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; E, early diastolic filling phase; A, diastolic atrial contraction; E/Ea, estimate of left ventricular filling pressure

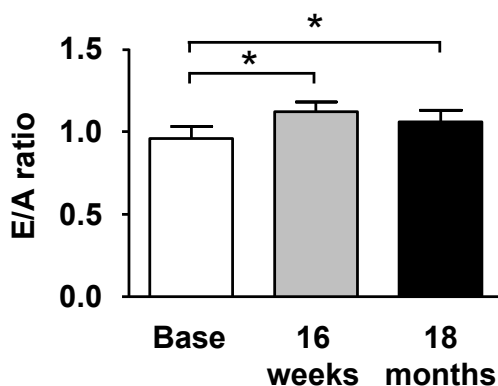
Cardiac dimensions and function

LV end-diastolic volume, end-systolic volume and end-systolic volume index did not change significantly after the 16-week VLCD and at 18 months (Table 2). End-diastolic volume index showed a sustained increase (baseline: 80 ± 3 mL/m², 16 weeks: 89 ± 4 mL/m², 18 months: 90 ± 3 mL/m² at 18 months (both $P < 0.05$ vs. baseline)). This increase occurred with unchanged filling pressures (figure 1). Simultaneously, LV stroke volume index increased from 45 ± 2 mL/m² to 51 ± 3 mL/m² after the VLCD and 52 ± 2 mL/m² at 18 months (both $P < 0.05$ vs. baseline). Cardiac index and ejection fraction did not significantly change directly after the VLCD and at 18 months compared to baseline (Table 2). LV mass showed a sustained decline from 119 ± 8 grams to 102 ± 7 grams at 16 weeks and 109 ± 9 grams at 18 months (both $P < 0.05$ vs. baseline). LV mass index was unchanged between the occasions (Table 2). A reduction in LV mass/ LV end-diastolic volume was observed (0.67 ± 0.03 at baseline to 0.59 ± 0.03 at 16 weeks and 0.56 ± 0.03 at 18 months resp. (both $P < 0.05$ vs. baseline, Figure 1)). Diastolic E/A ratio increased after the VLCD and remained increased compared to baseline at 18 months (baseline: 0.96 ± 0.07 ; after VLCD: 1.12 ± 0.06 , 18 months: 1.06 ± 0.07 , both $P < 0.05$ vs. baseline, Figure 2). E/Ea did not significantly change compared to baseline.

Figure 1. Relation of left ventricular (LV) end-diastolic volume index and LV filling pressure



Relation of LV end-diastolic volume index (LVEDVI) and E/Ea ratio (estimate of LV filling pressure) at baseline (●), after a 16-week very low calorie diet (VLCD) (■) and after an additional 14 months of follow-up on a regular diet (▲) in 14 patients with T2DM. Bars represent mean $\pm$ SEM. Note the increase in LVEDVI from 80 ± 3 mL/m² at baseline to 89 ± 4 mL/m² after a 16 week VLCD and 90 ± 3 mL/m² after an additional 14 months of follow-up on a regular diet

Figure 2. Change in left ventricular diastolic function

Changes in E/A ratio at baseline (white bar), after a 16-week VLCD (grey bar) and after an additional 14 months of follow-up on a regular diet (black bar) in 14 patients with T2DM. Note the sustainment of improved diastolic heart function at 18 months as compared to baseline. VLCD = very low calorie diet, E/A ratio = ratio between early filling phase and atrial filling phase. * $P < 0.05$ compared to baseline.

Myocardial TG content

Myocardial TG content decreased from 0.74 (0.41-1.10)% at baseline to 0.45 (0.31-0.54)% after the VLCD ($P < 0.05$ vs. baseline, based on $n = 11$ successful ^1H -MR spectroscopy measurements on all three occasions), but had returned to baseline values at 18 months (0.76 (0.65-1.32)%, $P > 0.05$ versus baseline).

DISCUSSION

This study aimed to assess the long-term effects of an initial 16-week VLCD on cardiac measures and function in obese patients with insulin dependent T2DM. Our previous study demonstrated that a 16-week VLCD decreased LV mass and improved diastolic function in insulin-dependent, obese T2DM patients (9). The present study extends these observations by showing that cardiac remodeling and diastolic function remains improved even after 14 months of follow-up on a regular diet, despite some weight regain.

Hemodynamics

Systolic and diastolic blood pressures decreased upon the use of the VLCD, but returned to baseline values after 14 months of follow-up. Nonetheless, the sustained decreased heart rate resulted in a decreased rate pressure product at 16 weeks and 18 months compared to baseline. The rate-pressure product is an estimate of myocardial oxygen consumption (13,14). In diabetic mice, cardiac efficiency is decreased, which is related to increased myocardial oxygen consumption (15). Therefore, the sustained decreased rate pressure product in

our patients may reflect improved cardiac efficiency. Accordingly, short-term clinical studies found that weight loss induced a decrement in blood pressure (6,8,16) and rate pressure product (8) in obese, non-diabetic subjects.

Cardiac dimensions and function

Previously, it was shown that T2DM patients have decreased LV end-diastolic volume indices compared to healthy controls, associated with diminished compliance (2). In this study we show that weight loss can reverse this process up to 14 months of follow-up, by a sustained decrease in LV mass/ LVEDV ratio and an increased LVEDV index at comparable estimated LV filling pressure (E/Ea, figure 1).

In accordance with our results, other studies have demonstrated a decrease in LV mass (6-8,16-18) after diet-induced weight loss in obesity, however no change in LV mass index (16-18). As insulin acts as a growth factor and can induce cardiac hypertrophy, the persistently decreased plasma insulin levels could contribute to the decrease in LV mass in our study. Accordingly, in obese rats a VLCD decreased myocardial mass, due to a decrease in myocardial cell size during weight loss and a strong association between the relative decrease in heart weight and the decrease in body weight was found (19).

The E/A ratio, a load-dependent parameter, also remained improved during long-term follow-up. However since the E/Ea ratio did not change, this change in E/A ratio most likely reflects an improvement in diastolic function. In accordance with our observation in T2DM patients, a 2-year caloric restriction study (maximum weight loss at 6 months) performed in obese, non-diabetic subjects found an improvement in diastolic function, which lasted up to 2 years after the start (6). Rider et al.(18) accordingly found an improvement in LV diastolic function after 1 year of weight loss in obese subjects without diabetes, however they did not find improvement in LV remodeling. Our study shows that weight reduction also leads to sustained improvement in diastolic function and an increase in compliance of the left ventricle in T2DM patients.

Little is known about the underlying pathophysiological mechanisms of the improved diastolic function after weight loss. Van Heerebeek et al. (20) demonstrated that heart failure in patients with normal ejection fraction is associated with an increase in cardiomyocyte diameter and a higher resting tension of the cardiomyocytes, whereas AGEs and collagen deposition were more important in patients with restricted EF. In obese diabetic mice, diet-induced weight loss also resulted in improved diastolic function, which could be partly attributed to normalization in SERCA2 activity, which determines the Ca^{2+} removal from the myofilaments (21).

Myocardial TG content

We aimed to assess changes in myocardial triglyceride content, because previous studies showed an inverse correlation between myocardial triglyceride content and cardiac function

(9,22,23). This association was explained by the concept of lipotoxicity. Accordingly, we found a decrease in myocardial TG content directly after the VLCD.

However, after 14 months of follow-up, myocardial TG content returned to baseline values, even though there was sustained improvement in cardiac function. Viljanen et al. (8) studied the effect of a 6-week VLCD in obese subjects, without diabetes and similarly found a decrease in myocardial TG content. Apparently the regain in myocardial TG content does not immediately correspond with deterioration in diastolic function, which argues against a simple relation between cardiac triglyceride content and cardiac dysfunction. In previous short-term nutritional interventions (22,23) we showed a relation between increases in myocardial TG content and deteriorated diastolic function in healthy subjects and subjects with diabetes. It could be hypothesized that the regain in myocardial TG content precedes deterioration in diastolic function. Otherwise, the contribution of the positive effects on cardiac remodeling may be more substantial to diastolic function than the regain in myocardial TG content.

A limitation of the present study is the relatively small sample size. The extensive dietary intervention, long-term follow-up and imaging protocol did not allow to include more patients. However, patients served as their own controls. Moreover, we used the highly reproducible and sensitive techniques of MRI and MRS in controlled metabolic conditions. Using this study design, we observed major short-term effects on hemodynamic and cardiac parameters, which are in line with the existing literature.

In conclusion, weight reduction by a 16-week VLCD in T2DM patients results in sustained cardiac remodeling and improved diastolic function after 14 months of follow-up, despite weight regain on a regular diet. This indicates that a beneficial cardiac effect of very low calorie diets extends far beyond the completion of those diets.

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