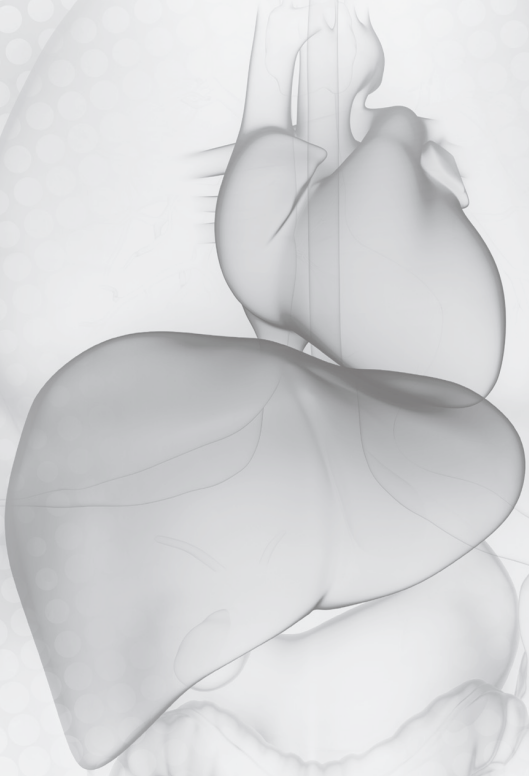
Chapter 7

Exercise in type 2 diabetes mellitus induces tissue-specific changes in fat distribution



J.T. Jonker, P. de Mol, S.T. de Vries, R.L. Widya, S.Hammer, L.D. van Schinkel, R.W. van der Meer, R.O.B. Gans, A.G. Webb, H.E. Kan, E.J.P. de Koning, H.J.G. Bilo, H.J. Lamb

Submitted

ABSTRACT

Background

Ectopic fat accumulation in type 2 diabetes (T2DM) is associated with insulin resistance and increased risk for cardiovascular disease. Exercise is generally considered beneficial to reduce T2DM associated morbidity and mortality. The effects of exercise on ectopic fat accumulation in different tissues are not well known. Therefore, the present study aimed to determine effects of an exercise intervention on organ specific fat accumulation and cardiac function in T2DM.

Methods

Twelve patients with T2DM were included (age 46 ± 2 years; BMI 28.7 ± 1.2 kg/m2, mean ± SEM). Patients were studied before and after a 6-month individualized exercise program. Abdominal fat, pericardial and paracardial fat volume and cardiac function were measured using magnetic resonance (MR) imaging. Myocardial, hepatic and myocellular triglyceride (TG) content were measured using proton-MR spectroscopy at 1.5 and 7 Tesla.

Results

Exercise significantly reduced visceral abdominal fat volume from 348 ± 57 mL (mean ± SEM) to 219 ± 33 mL ($P<0.01$), while subcutaneous abdominal fat volume remained unchanged. Exercise decreased hepatic TG content from 6.8 ± 2.3% to 4.6 ± 1.6% ($P<0.01$) and paracardial fat volume from 4.6 ± 0.9 mL to 3.7 ± 0.8 mL ($P=0.02$). Exercise did not change epicardial fat volume (4.7 ± 0.4 mL to 4.7 ± 0.4 mL), myocardial TG content (0.61 ± 0.13% to 0.60 ± 0.13%, $P>0.5$), intramyocellular lipid content (0.58 ± 0.12% to 0.68 ± 0.11%, $P>0.05$), nor cardiac function.

Conclusion

A 6-month exercise intervention in type 2 diabetes decreases hepatic triglyceride content, visceral abdominal and paracardial fat volume, which are all associated with increased cardiovascular risk. Subcutaneous fat, epicardial fat, intramyocellular and myocardial TG content did not change. Therefore, the present study demonstrates tissue-specific exercise-induced changes in body fat distribution in subjects with type 2 diabetes mellitus.

INTRODUCTION

A sedentary lifestyle increases the risk of type 2 diabetes mellitus (1). Moderate and highly active people live longer, and diabetes occurs later in life as compared to sedentary people (2). In patients with type 2 diabetes, both aerobic and resistance exercise have been shown to improve metabolic control and reduce cardiovascular risk. Therefore the American College of Sports Medicine and the American Diabetes Association recommend that patients with type 2 diabetes (T2DM) perform exercise at a moderate intensity for minimally 150 minutes per week (3).

The metabolic pathways involved in the pathogenesis of insulin resistance and cardiovascular risk are complex. Insulin resistance is associated with increased lipolysis from the adipose tissue. The increased flux of fatty acids can be taken up by different organs such as the liver, muscle and heart (4). The accumulation of triglycerides in tissues, other than adipose tissue, is called ectopic fat accumulation. Ectopic fat accumulation in the muscle and liver is involved in the pathophysiology of insulin resistance (5-7). Pericardial fat is the fat around the heart, which can be divided in the epicardial and paracardial fat layer. Hepatic steatosis, myocardial triglyceride accumulation and pericardial fat have been associated with cardiovascular complications (4,8,9). Therefore, strategies to limit ectopic fat accumulation are a rational approach to improve glucose homeostasis and potentially reduce cardiovascular risk.

Most intervention studies regarding the effects of exercise on fat accumulation have focused on visceral and subcutaneous fat in obese and T2DM subjects, both exercising and losing weight. However, little is known about the effect of exercise alone without diet on ectopic fat accumulation in T2DM patients.

Several studies have shown an association between epicardial fat and visceral fat volume (10,11). If this association holds a causal relationship, we expect that an exercise-induced decrease in visceral abdominal fat will be accompanied by a decrease in epicardial fat volume. Lastly, exercise in healthy and obese subjects showed that hepatic triglyceride content decreases (12,13).

In the present study we aimed to assess whether exercise without dietary intervention in T2DM subjects can decrease the following ectopic fat depositions: hepatic TG content, epicardial fat, paracardial fat, intramyocellular (IMCL) and myocardial triglyceride (TG) content. Because of the association of myocardial TG content with diastolic cardiac function (14-17), we additionally assessed cardiac function.

METHODS

Patients

Twelve patients with type 2 diabetes were included (mean age: 46±2 years). Patients were recruited by advertisement to take part in the Atlas Diabetes Challenge (18), a trekking expedition to Mt. Toubkal in Morocco organized by the Bas van de Goor Foundation for which exercise training was required. All patients underwent screening at inclusion, approximately 3 months prior to the start of the training program, consisting of physical examination, electrocardiography (ECG), echocardiography, maximal exertion cycle ergometer testing and blood analysis. Exclusion criteria were: age >70 years, complications of diabetes (retinopathy, neuropathy, nephropathy), hypertension (systolic blood pressure >165 mmHg and/or diastolic blood pressure >95 mmHg), BMI >35 kg/m^2, smoking, cardiac disease: abnormal ECG, cardiomyopathy, coronary or valvular disease, use of drugs, claustrophobia or any other contra-indication for magnetic resonance imaging (MRI). Written informed consent was obtained from all participants. The protocol was approved by the medical ethics committee of the Leiden University Medical Center and performed in compliance with the Declaration of Helsinki.

Study design

All patients underwent a 6-month individualized training program, followed by a 13-day trekking expedition to Mt Toubkal in Morocco. Patients received a training program at the beginning (-180 days) and were advised to perform two endurance and two resistance training sessions per week, in total 3.5-6 hours per week. The aim of the program was to achieve a normal estimated workload capacity after 6 months and improved general physical fitness. The training program served as a guide and patients trained unsupervised, albeit they kept in contact with the expedition physicians. Patients were studied on two occasions: at the start of the training program and after the expedition. The second study was performed at least one week after patients returned from the climbing expedition. During both study times, MR measurements were obtained in the post absorptive state (at least 4 hours after the last meal). Before the MR measurements, anthropometric measurements were performed (bodyweight, blood pressure) and blood was drawn.

At inclusion and after 6 months of exercise the maximal exercise capacity ($Watt_{max}$) was determined using an incremental cycle ergometer test to exhaustion. Maximal estimated oxygen uptake ($VO_{2\,max}$) was calculated using a formula described by Storer et al. (15). Energy expenditure was assessed using a SenseWear Pro Armband™ (Bodymedia, Pittsburgh, USA) during one week of every month of the training period, and all days of the expedition (19). During this week of energy expenditure assessment, patients recorded their food intake for estimation of their dietary intake.

Subcutaneous and visceral abdominal fat

A 1.5 Tesla MR scanner (Gyroscan ACS/ NT 15; Philips Medical Systems, Best, The Netherlands) was used for all MR imaging. Patients were scanned in a supine position. Abdominal fat was imaged using a turbo spin echo imaging sequence (20). Three transverse slices of 10 mm thick were scanned at the fifth lumbar vertebrae during breath-holds (Figure 1). Imaging parameters were: echo time (TE) of 11 ms, repetition time (TR) of 168 ms and a flip angle of 90 degrees. Contours were drawn around the visceral and subcutaneous abdominal fat deposits using MASS® software (Medis, Leiden, the Netherlands). The area of each individual slice was multiplied by the slice thickness to estimate the volume and the volumes of all three slices were summed.

Epicardial and paracardial fat quantification

To be able to quantify the epi- and paracardial fat volume, the heart was imaged using ECG gated breath-holds with a multi shot turbo spin echo sequence in a four-chamber view orientation (Figure 1). Water was suppressed using spectral inversion recovery (SPIR). Imaging parameters were: slice thickness of 4 mm, scan matrix: 251x256 pixels, flip angle of 90 degrees, TE of 1 ms and TR of 1000 ms. Because of the water suppression, adipose tissue around the heart was easily identified and contours were drawn around the epicardial and paracardial fat surrounding the ventricles and atria using MASS® software (Medis, Leiden, the Netherlands). The number of pixels were converted to square centimeters and multiplied by the slice thickness to obtain volume.

^{1}H-MRS of myocardial and hepatic TG content

^{1}H-MRS performed at 1.5 Tesla (Gyroscan ACS/ NT 15; Philips Medical Systems, Best, The Netherlands) was used to quantify myocardial and hepatic triglyceride (TG) content (Figure 2 and 3). Details on ^{1}H-MRS acquisition and post processing have been published previously (16,17,21). Myocardial and hepatic ^{1}H-MR single voxel MR spectroscopic data were acquired using a point resolved spectroscopy sequence. A voxel was placed in the liver and myocardial interventricular septum respectively. ECG triggering (only for myocardial spectra) and respiratory pencil beam navigator were used during acquisition (16). A water suppressed spectrum for triglyceride signal resonances and a spectrum without water suppression as internal standard were obtained. Scan parameters were: TE of 26 ms, TR of at least 3000 ms. For the water suppressed spectrum, 1024 data points were obtained, averaged over 128 acquisitions, using a 1000 Hz spectral width. For the spectrum without water suppression the only change was in TR which was set to 10000 ms and only four averages were acquired. Java-based MR user interface software (jMRUI version 2.2, Leuven, Belgium) was used for fitting of the spectra (21). The triglyceride content was calculated as (amplitude of the triglyceride signal/ amplitude of water signal) x 100.

^{1}H-MRS of intramyocellular lipid content

Skeletal muscle spectroscopy measurements were performed on a 7T whole-body MRI system (Philips Healthcare, Best, the Netherlands) using a custom-built quadrature half-volume Tx/Rx coil. Localized ^{1}H-MRS was performed in the left tibialis anterior muscle using a Stimulated Echo Acquisition Mode (STEAM) sequence with VAPOR water suppression and TE of 22 ms, TR of 2000 ms, TM of 28 ms, voxel 10x10x10 mm. Unsuppressed water spectra were recorded with the same parameters. The voxel was placed in the muscle on transverse and sagittal T1-weighted images of the lower leg, carefully avoiding vascular structures, tendon plates and visible fat (Figure 3). jMRUI software was used for post processing. All values were corrected for T2 relaxation times (IMCL; 80ms, H_2O; 30ms). Ratios of the CH_2 resonance of intramyocellular lipids (IMCL) at 1.3 ppm were calculated relative to the water peak.

Left ventricular cardiac function

The heart was imaged from apex to base during breath-holds in short axis view, using a balanced sensitivity-encoded turbo-field echo sequence. Imaging parameters were: TE of 1.7 ms, TR of 3.4 ms, flip angle of 35 degrees, a field of view of 400 mm^2, matrix of 256x256 pixels and a slice thickness of 10 mm with a 0 mm gap (17). To assess systolic function, epicardial and endocardial contours were manually drawn using MASS® software (Medis, Leiden, the Netherlands) (17,22). Left ventricular (LV) end-diastolic and end-systolic volume, ejection fraction, cardiac output and LV mass were determined as measures of systolic function. For assessment of LV diastolic function, transmitral flow was measured, using ECG-gated gradient echo sequence with a velocity sensitivity of 100 cm/sec. Imaging parameters were: TE of 4.8 ms, TR of 14 ms, flip angle of 20 degrees, slice thickness of 8 mm, field of view of 350 mm^2 and matrix of 256x256 pixels. FLOW® software (Medis, Leiden, the Netherlands) was used to create velocity versus time curves and to assess the peak velocity of the early diastole (E) and atrial contraction (A). Furthermore the peak deceleration gradient of E, the E/A peak ratio and LV filling pressures E/Ea were determined (23,24).

Assays

Serum C-peptide was measured with an automated immunoluminometric assay (ILMA) on an Immulite 2500 analyzer of Siemens Diagnostics (Breda, The Netherlands, intra-assay CV 6-7.5%, total CV 7-8.2% respectively). HbA1c was measured with a semi automated HPLC machine Primus Ultra 2 (Kordia, Leiden, the Netherlands). Serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltransferase (GGT), cholesterol and triglycerides were measured using a Modular P800 chemistry analyzer of Roche Diagnostics (Mannheim, Germany, total CV: <2%).

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (SPSS Inc.Chicago, Illinois, USA). Non-normally distributed data were log-transformed and checked for normality after transformation. We used two-tailed paired t-tests to compare the two study conditions. A two-tailed probability value of 0.05 or less was considered statistically significant. Data are expressed as mean values ± standard error (SE).

RESULTS

Clinical and biochemical characteristics

The baseline characteristics are shown in Table 1. Patients increased their energy expenditure from 2965 ± 111 to 3526 ± 157 kCal/day (P=0.01). Prior to the expedition, after the training period of 6 months, VO_{2max} increased from 33.0 ± 2.2 to 36.1 ± 2.3 mL/kg/min (P<0.01). At the start of the training, seven patients used metformin, three patients a sulfonyl ureum (SU) derivate, three patients used insulin and one patient a DDP-4 inhibitor. During the training period and before the expedition, one patient stopped the use of the SU-derivate. The self reported caloric intake did not change during the exercise period (P=0.22), neither did the

Table 1. Clinical and biochemical characteristics before and after 6 months of exercise in patients with type 2 diabetes mellitus

	Baseline	After exercise
Gender (male/female) (n)	7/5	
Age (years)	46 ± 2	
Diabetes duration (years)	6.1 ± 1.4	
Height (m)	1.75 ± 0.02	
Weight (kg)	88.0 ± 3.9	83.7 ± 3.4*
Body mass index (kg/m^2)	28.7 ± 1.2	27.3 ± 1.1*
GGT (U/L)	35.1 ± 7.1	34.1 ± 5.5
ASAT (U/L)	29.8 ± 2.9	24.8 ± 4.0
ALAT (U/L)	32.8 ± 2.5	25.6 ± 3.1*
HbA1c (%)	6.7 ± 0.3	6.5 ± 0.3
C-peptide (nmol/L)	0.8 ± 0.1	0.8 ± 0.2
Cholesterol (mmol/L)	4.8 ± 0.3	4.6 ± 0.3
HDL (mmol/L)	1.5 ± 0.2	1.5 ± 0.1
Cholesterol/HDL ratio	3.9 ± 0.4	3.3 ± 0.3*
LDL (mmol/L)	2.8 ± 0.3	2.7 ± 0.3
Triglycerides (mmol/L)	1.5 ± 0.2	1.5 ± 0.2

Data are mean ± SEM. TG, triglyceride; GGT, gamma-glutamyltransferase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein. * P<0.05 after exercise compared to baseline

composition of the diet change over the exercise period. Body mass index decreased from 28.7 ± 1.2 to 27.3 ± 1.1 kg/m^2 at the end of the expedition (P<0.001). No significant change in plasma GGT, ASAT, HbA1c or c-peptide levels occurred (Table 1). Cholesterol, high density lipoprotein (HDL) or triglyceride concentrations did not change during the exercise period but there was a decrease in cholesterol/ HDL ratio (3.9 ± 0.4 at baseline to 3.3 ± 0.3 after the exercise period (P=0.01) (Table 1). There was a significant decrease in ALAT from 32.8 ± 2.5 at baseline to 25.6 ± 3.1 U/L after the exercise period (P=0.04).

Fat compartments

After the exercise intervention visceral abdominal fat volume significantly decreased (348 ± 57 at baseline to 219 ± 33mL at the end of the exercise period, P<0.01, Table 2). There was no change in subcutaneous abdominal fat volume (Table 2). Accordingly, the ratio between visceral and subcutaneous fat decreased significantly from 0.53 ± 0.11 to 0.34 ± 0.06 after the exercise intervention (P<0.01). Due to motion artifacts epi- and paracardial fat of one patient could not be measured. After exercise the paracardial fat volume decreased from 4.6 ± 0.9 to 3.7 ± 0.8 mL (n=11, P=0.02). Exercise reduced the hepatic triglyceride content (6.8 ± 2.3 at baseline to 4.6 ± 1.6 after exercise (P<0.01). Exercise did not affect myocardial triglyceride content, IMCL or epicardial fat volume (Table 2).

No significant correlation was found between the decrease in weight and the decrease in visceral abdominal fat (P=0.5), paracardial fat (P=0.3) and hepatic triglyceride content (P=0.9) respectively.

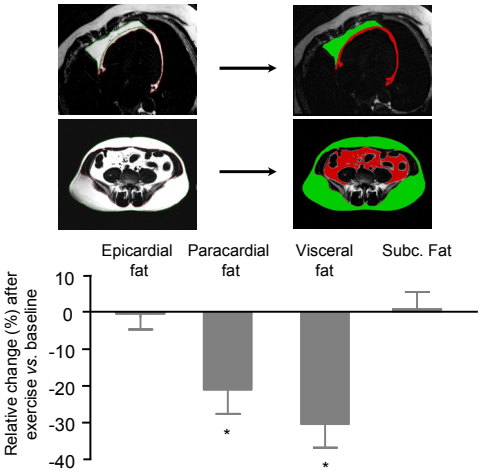
The relative changes in above mentioned fat compartments are depicted in Figure 1, 2 and 3 respectively.

Table 2. Fat compartments at baseline and after 6 months of exercise in 12 patients with type 2 diabetes mellitus

Fat compartments	Baseline	After exercise
Visceral abdominal fat (mL)	348 ± 57	219 ± 33*
Subcutaneous abdominal fat (mL)	699 ± 71	704 ± 74
Ratio visceral / subcutaneous fat	0.53 ± 0.11	0.34 ± 0.06*
Epicardial fat (mL) (n=11)	4.7 ± 0.4	4.7 ± 0.4
Paracardial fat (mL) (n=11)	4.6 ± 0.9	3.7 ± 0.8*
Hepatic TG content (%)	6.8 ± 2.3	4.6 ± 1.6*
Myocardial TG content (%)	0.61 ± 0.13	0.60 ± 0.13
IMCL/$H_2$0 (%)	0.58 ± 0.12	0.68 ± 0.11

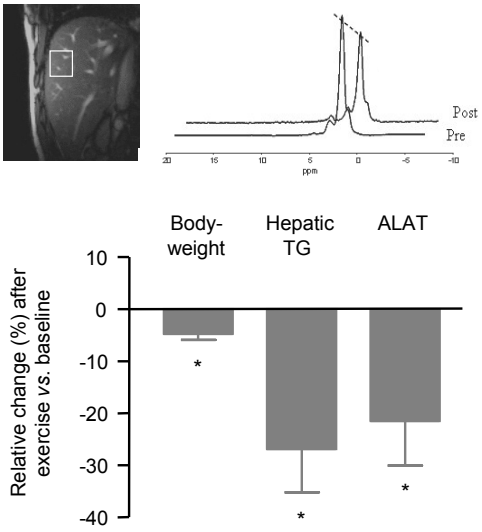
Data are mean ± SEM. TG, triglyceride; IMCL/H_2O, ratio of intramyocellular lipids and water.
* P<0.05 after exercise compared to baseline

Figure 1.



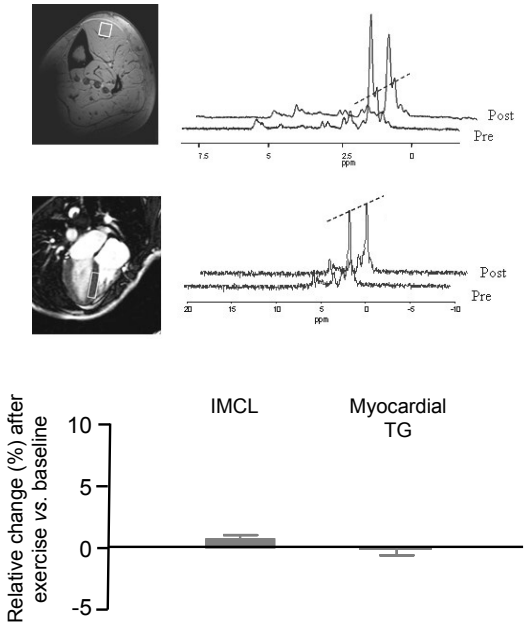
Top panel shows quantification of epicardial (red) and paracardial fat (green) volume (upper figures) and visceral (red) and subcutaneous (green) abdominal fat (lower figures).
Lower panel shows relative changes in epicardial, paracardial, visceral and subcutaneous abdominal fat volume, after 6 months of exercise compared to baseline. * P<0.05 for change after exercise compared to baseline

Figure 2.



Top panel shows placement of voxel for quantification of hepatic TG content.
Two representative ^{1}H-MRS spectra before and after exercise of a single patient.
Lower panel shows relative changes in bodyweight, hepatic TG content and ALAT after 6 months of exercise compared to baseline. * P<0.05 for change after exercise compared to baseline

Figure 3.



Top panel shows placement of voxel for quantification of IMCL in left anterior tibialis muscle and myocardial TG content in the cardiac septum. Two representative ^{1}H-MRS spectra for IMCL and myocardial TG content before and after exercise of a single patient.
Lower panel shows relative changes in IMCL and myocardial TG content. No statistically significant changes were observed

Myocardial function

As shown in Table 3, systolic and diastolic blood pressure, heart rate, left ventricular mass and diastolic function measured by the E/A peak flow and E deceleration peak did not change after exercise. Ejection fraction (baseline: 56 ± 1 to 58 ± 1% after exercise, P=0.06), cardiac output and cardiac index did not change either.

DISCUSSION

This study comprised a real-life setting with a 6-month training period of moderate exercise followed by a trekking expedition with, for the greater part, strenuous exercise. This exercise and trekking expedition induced a 20% decrease in visceral fat, hepatic triglyceride content and paracardial fat in patients with T2DM. We did not observe changes in subcutaneous abdominal fat, myocardial or intramyocellular triglyceride content, nor in epicardial fat volume or cardiac function.

Table 3. Hemodynamics and cardiac function at baseline and after 6 months of exercise in patients with type 2 diabetes mellitus

	Baseline	After exercise
Hemodynamics		
Systolic bloodpressure (mmHg)	142 ± 7	142 ± 7
Diastolic bloodpressure (mmHg)	87 ± 4	83 ± 4
Heart rate (beats per minute)	71 ± 2	68 ± 2
Cardiac dimensions and function		
LV mass (g)	103 ± 8	107 ± 9
LV mass index (g/m^2)	50 ± 3	53 ± 4
LV end-diastolic volume (mL)	176 ± 9	179 ± 9
LV end-systolic volume (mL)	77 ± 4	76 ± 4
LV stroke volume (mL)	99 ± 5	103 ± 5
Ejection fraction (%)	56 ± 1	58 ± 1
Cardiac index ($L/min/m^2$)	3.1 ± 0.1	3.1 ± 0.1
E/A peak flow	1.45 ± 0.16	1.31 ± 0.11
E deceleration peak ($mL/s^2 \cdot 10^{-3}$)	3.9 ± 4.3	3.9 ± 3.4
E/Ea	10.8 ± 0.64	11.4 ± 0.71

Data are mean ± SEM. LV, left ventricular; E, early diastolic filling phase; A, diastolic atrial contraction; E/Ea, estimate of left ventricular filling pressure

Epicardial and paracardial fat

Epicardial fat and visceral abdominal fat are both visceral fat depots by definition and have cross-sectionally been correlated (10,11). Therefore, it could be hypothesized that both fat compartments would be similarly affected by exercise. Interestingly, we found that a 6-month exercise program decreased visceral abdominal fat and paracardial fat, but did not change epicardial fat volume in T2DM.

Recent studies (25,26) show that paracardial fat volume is a better predictor of cardiovascular risk than epicardial fat and therefore a decrease in both visceral and paracardial fat might indicate a decreased cardiovascular risk. Kim et al. (27) found a significant reduction in epicardial fat after a 12-week exercise program in *obese men* and the change in epicardial fat correlated with the change in visceral fat. The effect of aerobic exercise on epicardial fat gene expression has been studied in pigs and showed that the epicardial fat around the coronary arteries and the epicardial fat around the myocardium respond differently with respect to the expression of inflammatory genes and that exercise did not change inflammatory gene expression in visceral fat (28). Therefore, it can be concluded that epicardial fat shows regional differences in its response to exercise. The regional differences might explain the difference in outcome of our study, compared to that of Kim et al. (27), as they measured epicardial fat thickness adjacent to the right ventricle using echocardiography, while we used MRI to measure epicardial fat volume around both ventricles and atria. Interestingly, a recent study

by Sicari et al. (25) found a cross-sectional correlation between visceral fat and paracardial fat volume, but not with epicardial fat. Apparently, exercise in T2DM has a disparate effect on visceral and epicardial adipose tissue, which resulted in a decrease in visceral and paracardial fat, but no change in epicardial fat in our study.

Hepatic triglyceride content

At baseline subjects had a mean hepatic triglyceride content of 6.8%. Hepatic steatosis is defined as a TG content >5.6% measured with ^{1}H-MRS (29). We found that exercise decreased hepatic TG content by 26% in patients with type 2 diabetes, and thereby reduced their hepatic TG content to normal values (<5.6%). This decrease was accompanied by a decrease in ALAT. Previous studies reported on the effects of exercise on hepatic TG content, but only in patients *without diabetes* (12). The exact mechanism behind the exercise induced reduction in hepatic TG content is not clear.

Although patients did have (unintended) weight loss, there was no significant correlation between change in body weight and change in hepatic TG content. It has been hypothesized that the decrease in hepatic TG content is due to a diminished flow of free fatty acids from the visceral adipose tissue, in accordance with the portal hypothesis (30). However, reduction in hepatic TG content has also been described without a reduction in visceral fat (13).

This indicates that the liver is not a passive bystander, which adapts to changes in fatty acid metabolism. Studies in rodents raise the possibility that active intrahepatic biochemical and molecular mechanisms are present, associated with aerobic fitness that affect hepatic fatty acid metabolism, and as a consequence, liver triglyceride content. This concept is supported by a study of Rector et al. (31). This study showed that sudden cessation of daily physical activity in hyperphagic/obese rats resulted in stimulation of biochemical pathways known to initiate hepatic steatosis, including decreased hepatic mitochondrial oxidative capacity, increased hepatic expression of de novo lipogenesis proteins, and increased hepatic malonyl CoA levels.

IMCL and myocardial triglyceride content

An increased IMCL content has been associated with peripheral insulin resistance. In contrast, endurance trained athletes have also an increased IMCL content (known as the 'athlete's paradox'). The apparent contrast may be due to the low (diabetes) versus high (athletes) capacity to oxidize those lipids. Data on the effects of exercise on IMCL content in insulin resistant subjects are inconsistent. A 16-week moderate intensity exercise program in 25 obese, insulin resistant subjects increased IMCL (13), however two studies of 10-12 weeks of exercise in overweight men and T2DM respectively found no change in IMCL (14, 15). We found no effect of a 6-month exercise program on IMCL. Although several studies focused on the effects of exercise on IMCL, only two studies studied the effect of exercise on myocardial TG content. Twelve weeks of exercise decreased myocardial TG content in healthy obese subjects (32), but

not in T2DM patients (33). Our study confirms and extends this latter result, as our 6-month exercise training did not change myocardial TG content in T2DM.

Previously, an association was found between myocardial TG content and diastolic cardiac function (14,17,20). In the current study, exercise did not change myocardial TG content, nor diastolic function. No change was found in ejection fraction, cardiac output, cardiac index, left ventricular mass nor in diastolic function. One year of home-based training in 223 T2DM patients similarly showed no significant changes in myocardial function (34). Schrauwen et al. (32) showed that 12 weeks of training in 11 overweight subjects without diabetes did not improve diastolic function, cardiac output or cardiac index; however ejection fraction increased by 2%.

A limitation of the present study is the relatively small number of patients. Therefore, multivariable analysis is not possible. However, patients act as their own control and even with the small patient number the current data show statistically significant changes in fat distribution upon exercise. Many studies examining dynamics of ectopic fat accumulation focus on the effects of diet or combined diet and exercise on weight loss in relation to changes in imaging parameters. In our study, patients did lose some weight, however, without attending to a diet. Therefore, we can assume that weight loss was achieved by training only.

In conclusion, a 6-month exercise intervention in type 2 diabetes decreases hepatic triglyceride content, visceral abdominal and paracardial fat volume, which are all associated with increased cardiovascular risk. Subcutaneous fat, epicardial fat, intramyocellular and myocardial TG content did not change. Therefore, the present study demonstrates tissue-specific exercise-induced changes in body fat distribution in subjects with type 2 diabetes mellitus.

REFERENCE LIST

1. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. JAMA. 2011; 305:2448-2455.
2. Jonker JT, De Laet C, Franco OH, Peeters A, Mackenbach J, Nusselder WJ. Physical activity and life expectancy with and without diabetes: life table analysis of the Framingham Heart Study. Diabetes Care. 2006; 29:38-43.
3. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasan-Taber L, Albright AL, Braun B. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care. 2010; 33:2692-2696.
4. McGavock JM, Victor RG, Unger RH, Szczepaniak LS. Adiposity of the heart, revisited. Ann Intern Med. 2006; 144:517-524.
5. Krssak M, Falk PK, Dresner A, DiPietro L, Vogel SM, Rothman DL, Roden M, Shulman GI. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia. 1999; 42:113-116.
6. Perseghin G, Scifo P, De CF, Pagliato E, Battezzati A, Arcelloni C, Vanzulli A, Testolin G, Pozza G, Del MA, Luzi L. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes. 1999; 48:1600-1606.
7. Samuel VT, Liu ZX, Qu X, Elder BD, Bilz S, Befroy D, Romanelli AJ, Shulman GI. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem. 2004; 279:32345-32353.
8. Greif M, Becker A, von ZF, Lebherz C, Lehrke M, Broedl UC, Tittus J, Parhofer K, Becker C, Reiser M, Knez A, Leber AW. Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 2009; 29:781-786.
9. Wong VW, Wong GL, Yip GW, Lo AO, Limquiaco J, Chu WC, Chim AM, Yu CM, Yu J, Chan FK, Sung JJ, Chan HL. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut. 2011; 60:1721-1727.
10. Ahn SG. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart. 2008; 94: e7-e11.
11. Iacobellis G. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab. 2003; 88:5163-5168.
12. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, George J. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology. 2009; 50:1105-1112.
13. Magkos F. Exercise and fat accumulation in the human liver. Curr Opin Lipidol. 2010; 21:507-517.
14. Hammer S. Short-term flexibility of myocardial triglycerides and diastolic function in patients with type 2 diabetes mellitus. Am J PHysiol Endocriinol Metab. 2008; 295:E714-718.
15. Storer TW, Davis JA, Caiozzo VJ. Accurate prediction of VO2max in cycle ergometry. Med Sci Sports Exerc. 1990; 22:704-712.

16. van der Meer RW, Doornbos J, Kozerke S, Schar M, Bax JJ, Hammer S, Smit JW, Romijn JA, Diamant M, Rijzewijk LJ, de Roos A, Lamb HJ. Metabolic imaging of myocardial triglyceride content: reproducibility of 1H MR spectroscopy with respiratory navigator gating in volunteers. Radiology. 2007; 245:251-257.

17. van der Meer RW, Hammer S, Smit JW, Frolich M, Bax JJ, Diamant M, Rijzewijk LJ, de Roos A, Romijn JA, Lamb HJ. Short-term caloric restriction induces accumulation of myocardial triglycerides and decreases left ventricular diastolic function in healthy subjects. Diabetes. 2007; 56:2849-2853.

18. Bas van de Goor Foundation. 2011; www.bvdgf.org

19. Berntsen S, Hageberg R, Aandstad A, Mowinckel P, Anderssen SA, Carlsen KH, Andersen LB. Validity of physical activity monitors in adults participating in free-living activities. Br J Sports Med. 2010; 44:657-664.

20. Hammer S, Snel M, Lamb HJ, Jazet IM, van der Meer RW, Pijl H, Meinders EA, Romijn JA, de Roos A, Smit JW. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. J Am Coll Cardiol. 2008; 52: 1006-1012.

21. Vanhamme L, van den Boogaart A, Van Huffel S. Improved method for accurate and efficient quantification of MRS data with use of prior knowledge. J Magn Reson. 1997; 129:35-43.

22. Paelinck BP, de Roos A, Bax JJ, Bosmans JM, van Der Geest RJ, Dhondt D, Parizel PM, Vrints CJ, Lamb HJ. Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. J Am Coll Cardiol. 2005; 45:1109-1116.

23. Lamb HJ, Beyerbacht HP, van der LA, Stoel BC, Doornbos J, van der Wall EE, de Roos A. Diastolic dysfunction in hypertensive heart disease is associated with altered myocardial metabolism. Circulation. 1999; 99:2261-2267.

24. Pattynama PM, Lamb HJ, van der Velde EA, van der Wall EE, de Roos A. Left ventricular measurements with cine and spin-echo MR imaging: a study of reproducibility with variance component analysis. Radiology. 1993; 187:261-268.

25. Sicari R, Sironi AM, Petz R, Frassi F, Chubuchny V, De MD, Positano V, Lombardi M, Picano E, Gastaldelli A. Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study. J Am Soc Echocardiogr. 2011; 24:1156-1162.

26. Thanassoulis G, Massaro JM, Hoffmann U, Mahabadi AA, Vasan RS, O'Donnell CJ, Fox CS. Prevalence, distribution, and risk factor correlates of high pericardial and intrathoracic fat depots in the Framingham heart study. Circ Cardiovasc Imaging. 2010; 3:559-566.

27. Kim MK, Tomita T, Kim MJ, Sasai H, Maeda S, Tanaka K. Aerobic exercise training reduces epicardial fat in obese men. J Appl Physiol. 2009; 106:5-11.

28. Company JM, Booth FW, Laughlin MH, rce-Esquivel AA, Sacks HS, Bahouth SW, Fain JN. Epicardial fat gene expression after aerobic exercise training in pigs with coronary atherosclerosis: relationship to visceral and subcutaneous fat. J Appl Physiol. 2010; 109:1904-1912.

29. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, Hobbs HH, Dobbins RL. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab. 2005; 288:E462-E468.

30. O'Leary VB. Exercise-induced reversal of insulin resistance in obese elderly is associated with reduced visceral fat. J Appl Physiol 2006; 100: 1584-1589.

31. Rector RS. Daily exercise vs. caloric restriction for prevention of nonalcoholic fatty liver disease in the OLETF rat model. Am J physiol Gastrointes Liver Physiol. 2011; 300: G874-883

32. Schrauwen-Hinderling VB. Improved ejection fraction after exercise training in obesity is accompanied by reduced cardiac lipid content. J Clin Endocrinol Metab 2010; 95: 1932-1938.

33. Schrauwen-Hinderling VB, Meex RC, Hesselink MK, van de WT, Leiner T, Schar M, Lamb HJ, Wildberger JE, Glatz JF, Schrauwen P, Kooi ME. Cardiac lipid content is unresponsive to a physical activity training intervention in type 2 diabetic patients, despite improved ejection fraction. Cardiovasc Diabetol. Cardiovasc Diabetol 2011; 10:47-48

34. Hordern MD, Coombes JS, Cooney LM, Jeffriess L, Prins JB, Marwick TH. Effects of exercise intervention on myocardial function in type 2 diabetes. Heart. 2009; 95:1343-1349.