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Chapter 6

Exercise and type 2 diabetes mellitus: changes in tissue-specific fat distribution and cardiac function

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ABSTRACT

Background
Ectopic fat accumulation in type 2 diabetes mellitus is associated with insulin resistance and increased risk for cardiovascular disease. The purpose of this study was to prospectively assess the effects of an exercise intervention on organ-specific fat accumulation and cardiac function in type 2 diabetes mellitus.

Methods
Written informed consent was obtained from all participants, and the study protocol was approved by the medical ethics committee. The study followed 12 patients with type 2 diabetes mellitus (seven men; mean age, 46 years ± 2 [standard error]) before and after 6 months of moderate-intensity exercise, followed by a high-altitude trekking expedition with exercise of long duration. Abdominal, epicardial, and paracardial fat volume were measured by using magnetic resonance (MR) imaging. Cardiac function was quantified with cardiac MR, and images were analyzed by a researcher who was supervised by a senior researcher (4 and 21 years of respective experience in cardiac MR). Hepatic, myocardial, and intramyocellular triglyceride (TG) content relative to water were measured with proton MR spectroscopy at 1.5 and 7 Tesla. Two-tailed paired t tests were used for statistical analysis.

Results
Exercise reduced visceral abdominal fat volume from 348 mL ± 57 to 219 mL ± 33 (P < 0.01), and subcutaneous abdominal fat volume remained unchanged (P = 0.9). 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 mL ± 0.9 to 3.7 mL ± 0.8 (P = 0.02). Exercise did not change epicardial fat volume (P = 0.9), myocardial TG content (P = 0.9), intramyocellular lipid content (P = 0.3), or cardiac function (P = 0.5).

Conclusions
A 6-month exercise intervention in type 2 diabetes mellitus decreased hepatic TG content and visceral abdominal and paracardial fat volume, which are associated with increased cardiovascular risk, but cardiac function was unaffected. Tissue-specific exercise-induced changes in body fat distribution in type 2 diabetes mellitus were demonstrated in this study.
INTRODUCTION

In patients with type 2 diabetes mellitus, both aerobic and resistance exercise have been shown to improve metabolic control and reduce cardiovascular risk. Therefore, it is recommended\(^1\) that patients with type 2 diabetes mellitus perform moderate-intensity exercise for a minimum of 150 minutes per week.

Metabolic pathways involved in the pathogenesis of insulin resistance and cardiovascular diseases 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, including in the liver, in the heart, and in muscle\(^2\). The accumulation of triglycerides (TGs) in tissues, other than adipose tissue, is called ectopic fat accumulation. Ectopic fat accumulation in the muscle and liver are involved in pathophysiologic insulin resistance\(^3-5\).

Pericardial fat is the fat around the heart that can be divided in the epicardial and paracardial fat layer. Hepatic steatosis, myocardial TG accumulation, and pericardial fat have been associated with cardiovascular complications\(^2,6,7\). Furthermore, myocardial TG accumulation has been associated with a decrease in diastolic cardiac function\(^6,9\).

Therefore, strategies to limit ectopic fat accumulation are rational approaches to improve glucose homeostasis and potentially reduce cardiovascular risk. Most intervention studies have focused on visceral and subcutaneous fat; however, to our knowledge, little is known about the effect of exercise alone without diet on ectopic fat accumulation in type 2 diabetes mellitus 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.

The purpose of our study was to prospectively assess the effects of an exercise intervention on organ-specific fat accumulation and cardiac function in type 2 diabetes mellitus.

METHODS

Patients and study design

Written informed consent was obtained from all participants, and the study protocol was approved by our medical ethics committee. Twelve patients (seven men, five women; patient age, 46 years ± 2 [standard error]) with type 2 diabetes mellitus were included. Patients were recruited by advertisements to take part in the Atlas Diabetes Challenge, a trekking expedition to Mount Toubkal in Morocco, organized by the Bas van de Goor Foundation, for which exercise training was required. At inclusion (90 days before start of training; Figure 1), all patients underwent screening that consisted of physical examination, electrocardiogra-
phy (ECG), echocardiography, maximal exertion cycle ergometer testing, and blood analysis. Exclusion criteria were patients older than 70 years, diabetic complications (i.e., retinopathy, neuropathy, or nephropathy), hypertension (systolic blood pressure > 165 mmHg and/or diastolic blood pressure > 95 mmHg), body mass index greater than 35 kg/m², smoking, known cardiac disease (i.e., abnormal ECG, cardiomyopathy, or coronary or valvular disease), use of drugs, or any contraindication for magnetic resonance (MR) imaging.

Patients underwent a 6-month individualized training program followed by a 12-day trekking expedition to Mount Toubkal (elevation, 4167 m) in Morocco. Trekking consisted of moderate-intensity exercise (walks of approximately 4-7 hours daily), of which 4 days were spent above 3000-m elevation. Patients received a written training program 6 months prior to the expedition and were advised to perform two endurance and two resistance training sessions for a total 3.5-6 hours per week.

The aims of the program were to achieve a normal estimated workload capacity and to improve general physical fitness. Patients trained themselves without supervision, but they kept in contact with the expedition physicians. Patients recorded their food intake and energy expenditure for 1 week per month during the 6-month training program and continuously during the expedition by using a web-based dietary program and a physical activity monitor (SenseWear Pro 3 Armband; BodyMedia, Pittsburgh, Pa). At inclusion and after the training period, the maximum workload capacity was determined with a maximal exertion cycle ergometer test. Maximum oxygen uptake (oxygen uptake maximum) was calculated. Patients underwent MR examinations on two occasions: at 7 days before the start of training and 200 days after the start of training (Figure 1). At least 4 hours after the last meal, MR measurements were obtained, blood was drawn, and anthropometric measurements (i.e., body weight and blood pressure) were obtained.

**Figure 1.** Timeline of the study. Screening was performed 90 days before the start of the training program. The training program consisted of a 6-month individualized training program, followed by a 12-day trekking expedition to Mount Toubkal in Morocco. An MR examination was performed approximately 1 week before the start of the training and at least 1 week after the trekking expedition.
Subcutaneous and visceral abdominal fat

A 1.5 Tesla MR imager (Gyroscan ACS-NT 15; Philips Medical Systems, Best, the Netherlands) was used for all MR imaging. Patients were examined in a supine position. Abdominal fat was imaged by using a turbo spin-echo imaging sequence. Three 10-mm-thick transverse sections were imaged at the fifth lumbar vertebrae during breath holds (Figure 2). Imaging parameters were as follows: repetition time ms/echo time ms, 168/11; flip angle, 90°. Contours were drawn around the visceral and subcutaneous abdominal fat deposits by using software (MASS; Medis Medical Imaging Systems, Leiden, the Netherlands). The area of each section was multiplied by the section thickness to estimate the volume, and the volumes of all three sections were summed.

All MR imaging and MR spectroscopy acquisition at 1.5 T was performed by J.T.J., R.W.v.d.M., and S.H. (4, 8, and 8 years of respective experience in MR imaging and MR spectroscopy), and postprocessing was performed by J.T.J., who was supervised by H.J.L. (21 years of experience in MR imaging and MR spectroscopy).

Figure 2. Top: Quantification of (upper figures) epicardial (red) and paracardial fat (green) volume and (lower figures) visceral (red) and subcutaneous (green) abdominal fat. For the abdominal fat, only one transverse section is shown; three sections were imaged. The area of fat of each individual section was multiplied by the section thickness to estimate the volume, and the volumes of all three sections were summed. Bottom: Box and whisker plot of relative changes in epicardial and paracardial (11 patients) and visceral and subcutaneous (Subc.) abdominal fat volume (12 patients) after 6 months of exercise compared with before start of training (12 patients; seven men, five women; mean age, 46 years ± 2). * = P < 0.05 change after exercise compared with baseline.
Epicardial and paracardial fat quantification

The heart was examined by using gated ECG breath holds with a multi-shot turbo spin-echo sequence in a four-chamber view orientation (Figure 2). Water was suppressed by using spectral inversion recovery. Imaging parameters were ≥ 1000/8.6; flip angle, 90°; section thickness, 4 mm; 251 × 256 matrix. Contours were drawn around the epicardial and paracardial fat that surrounded the ventricles and atria by using software (MASS; Medis Medical Imaging Systems). The number of pixels was converted to square centimeters and multiplied by the section thickness to obtain volume.

Proton MR spectroscopy of myocardial and hepatic TG content

1.5 Tesla hydrogen-proton MR spectroscopy (Gyrosan ACS-NT 15; Philips Medical Systems, Best, the Netherlands) was used to quantify myocardial and hepatic TG content (Figures...
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Myocardial and hepatic hydrogen-proton single-voxel MR spectroscopic data were acquired by using a point-resolved spectroscopy sequence. One voxel was placed in the liver and myocardial interventricular septum. ECG triggering and respiratory pencil-beam navigators were used during acquisition. A water-suppressed spectrum for TG signal resonances and a spectrum without water suppression (for internal standard) were obtained. Repetition time (ms) and echo time (ms) were ≥ 3000 and 26. For the water-suppressed spectrum, 1024 data points were obtained and averaged over 128 acquisitions, with a 1000-Hz spectral width. For the nonsuppressed spectrum, repetition time was 10000 ms.
ms and only four signal averages were acquired. MR user interface software (jMRUI version 2.2; MRUI, Leuven, Belgium), with prior knowledge files, was used to fit the spectra as previously described. The TG content was calculated as (amplitude of TG signal / amplitude of water signal) × 100.

**Proton MR spectroscopy of intramyocellular lipid content**

Localized hydrogen-proton MR spectroscopy was performed in the left tibialis anterior muscle with a 7 Tesla whole-body imaging system (Philips Achieva; Philips Healthcare, Best, the Netherlands) to ensure optimal separation of intramyocellular lipid (IMCL) and extramyocellular lipid signals by using a stimulated echo acquisition mode sequence with variable pulse power and optimized relaxation delays water suppression with the following parameters: 2000/22; mixing time, 28 ms; voxel size, 10 × 10 × 10 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 by avoiding vascular structures, tendon plates, and visible fat (Figure 4). Software (jMRUI version 2.2; MRUI) was used for postprocessing. Signals were fitted for creatine, trimethylammonium, lipids at 2.4 ppm, and six resonances for IMCL and extramyocellular lipid (around 2.2 ppm, 2 ppm, 1.45 ppm, 1.3 ppm, 1.1 ppm, and 0.8 ppm). The average separation between CH2 of IMCL and extramyocellular lipid was 0.22 ppm ± 0.03. All values were corrected for T2 relaxation times (IMCL, 80 ms; water, 30 ms). Ratios of the CH2 resonance of IMCL at 1.3 ppm were calculated relative to the water peak. Acquisition and postprocessing of the spectra at 7 Tesla were performed by R.L.W., H.E.K., and A.G.W. (4, 12, and 12 years of experience, respectively, in spectroscopy).

**Left ventricular cardiac function**

The heart was imaged from apex to base during breath holds in short-axis view with a sensitivity-encoded balanced steady-state free precession sequence. Imaging parameters were 3.4/1.7; flip angle, 35°; field of view, 400 mm²; section thickness, 10 mm with a 0-mm gap; 256 × 256 matrix. To assess systolic function, epicardial and endocardial contours were manually drawn with software (MASS; Medis Medical Systems). 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 by using ECG-gated gradient-echo sequence with a velocity sensitivity of 100 cm/s. Imaging parameters were 14/4.8; flip angle, 20°; field of view, 350 mm²; section thickness, 8 mm; 256 × 256 matrix. Analytic software (FLOW; Medis Medical Systems) was used to create velocity versus time curves and to assess the peak velocity of the early diastole and atrial contraction. The peak deceleration gradient of early diastole, the early diastole-atrial contraction peak ratio, and LV filling pressures were determined.
**Assays**

Serum C-peptide was measured with an automated immunoluminometric assay on an analyzer (Immuliite 2500; Siemens Diagnostics, Breda, the Netherlands). Glycated hemoglobin values were measured with a semiautomated high-performance liquid chromatography machine (Primus Ultra 2; Ordia, Leiden, the Netherlands). Serum aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, cholesterol, and TGs were measured by using a chemistry analyzer (Modular P800; Roche Diagnostics, Mannheim, Germany).

**Statistical analysis**

All statistical analyses were performed by using statistical software (SPSS 17.0; SPSS, Chicago, Ill). Nonnormally 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 P value of 0.05 or less indicated statistical significance. Data are mean values ± standard error.

**RESULTS**

**Clinical and biochemical characteristics**

Table 1 shows the baseline characteristics. Mean energy expenditure increased from 2965 kCal/day ± 111 at day 0 to 3439 kCal/day ± 152 at day 192 (P < 0.01). Maximum oxygen uptake increased from 33.0 mL/kg/min ± 2.2 at beginning of training to 36.1 mL/kg/min ± 2.3 at 180 days after start of training (P < 0.01) (Figure 1). Exercise intensity did not differ significantly during the study period (P = 0.96); however, mean daily exercise duration increased substantially during the trekking expedition compared with the training period (138 min/day ± 43 vs. 291 min/day ± 63; P < 0.001). At the start of training, seven patients used metformin, three patients used a sulfonyl urea derivate, three patients used insulin, and one patient used a dipeptidyl peptidase IV inhibitor. During the training period and before the expedition, one patient stopped using the sulfonyl urea derivate. Self-reported caloric intake did not change during the exercise period (P = 0.22), nor did the composition of the diet over the exercise period. Body mass index decreased from 28.7 kg/m² ± 1.2 at the start of training to 27.3 kg/m² ± 1.1 at 200 days after the start of training (P < 0.001). No significant changes in plasma γ-glutamyltransferase (P = 0.8), aspartate aminotransferase (P = 0.2), glycated hemoglobin (P = 0.5), or C-peptide levels (P = 0.8) occurred (Table 1). Cholesterol (P = 0.3), high-density lipoprotein (HDL; P = 0.4), and TG concentrations (P = 0.8) did not change during the training period, but there was a decrease in the cholesterol-to-HDL ratio (3.9 ± 0.4 at the start of training to 3.3 ± 0.3 at 200 days after the start of training (P = 0.01) (Table 1). There was a significant decrease in alanine aminotransferase from 32.8 U/L ± 2.5 at the start of training to 25.6 U/L ± 3.1 at 200 days after the start of training (P = 0.04).
Fat compartments

Visceral abdominal fat volume significantly decreased from 348 mL ± 57 at the start of training to 219 mL ± 33 at 200 days after the start of training (P < 0.01) (Table 2). Subcutaneous abdominal fat volume (Table 2) remained unchanged in terms of statistical significance (P = 0.9). Accordingly, the ratio between visceral and subcutaneous fat decreased significantly.
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from 0.53 ± 0.11 at the start of training to 0.34 ± 0.06 at 200 days after the start of training (P < 0.01). Due to motion artifacts, the epicardial and paracardial fat of one patient could not be measured. Exercise reduced the paracardial fat volume from 4.6 mL ± 0.9 to 3.7 mL ± 0.8 in 11 patients (P = 0.02), and the hepatic TG content was reduced from 6.8% ± 2.3 at baseline to 4.6% ± 1.6 after the expedition (P < 0.01). Exercise did not affect myocardial TG content (P = 0.9), IMCL (P = 0.3), or epicardial fat volume (P = 0.9, 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), or hepatic TG content (P = 0.9).

The relative changes in the previously mentioned fat compartments are depicted in Figures 2, 3, and 4.

Myocardial function

Systolic and diastolic blood pressure, heart rate, LV mass, and diastolic function (early diastole- atrial contraction peak flow and early diastole deceleration peak) remained unchanged (Table 3). Ejection fraction (56% ± 1 at the start of training to 58% ± 1 at 200 days after the start of training; P = .06), cardiac output, and cardiac index did not change.

Table 3. Hemodynamics and cardiac function at baseline and after 6 months of exercise in 12 patients with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (start of training)</th>
<th>After exercise (200 days after start of training)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142 ± 7</td>
<td>142 ± 7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>87 ± 4</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>71 ± 2</td>
<td>68 ± 2</td>
</tr>
<tr>
<td><strong>Cardiac dimensions and function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>103 ± 8</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>50 ± 3</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>176 ± 9</td>
<td>179 ± 9</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>77 ± 4</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>LV stroke volume (mL)</td>
<td>99 ± 5</td>
<td>103 ± 5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56 ± 1</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td>E/A peak flow</td>
<td>1.45 ± 0.16</td>
<td>1.31 ± 0.11</td>
</tr>
<tr>
<td>E deceleration peak (mL/s² x 10⁻³)</td>
<td>3.9 ± 4.3</td>
<td>3.9 ± 3.4</td>
</tr>
<tr>
<td>E/Ea</td>
<td>10.8 ± 0.64</td>
<td>11.4 ± 0.71</td>
</tr>
</tbody>
</table>

Data are mean ± standard error. A = diastolic atrial contraction, E = early diastolic filling phase, E/Ea = estimate of LV filling pressure.

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DISCUSSION

Our study took place in a real-life setting and was composed of a 6-month training period of moderate-intensity exercise followed by a trekking expedition with prolonged moderate-intensity exercise. This caused a greater than 20% decrease in visceral fat, hepatic TG content, and paracardial fat in patients with type 2 diabetes mellitus, but we did not observe changes in subcutaneous abdominal fat, myocardial or intramyocellular TG content, epicardial fat volume, or cardiac function.

Epicardial and paracardial fat

Because epicardial fat and visceral abdominal fat were cross-sectionally correlated\textsuperscript{10,11}, we hypothesized that both fat compartments would be similarly affected by exercise. Interestingly, our 6-month exercise program decreased visceral abdominal fat and paracardial fat but did not change epicardial fat volume in patients with type 2 diabetes mellitus. Recent studies\textsuperscript{18,19} have shown that paracardial fat volume is a better predictor of cardiovascular risk than epicardial fat, and therefore a decrease in paracardial fat might indicate a decreased cardiovascular risk. Kim et al\textsuperscript{20} found a significant reduction in epicardial fat in obese men after a 12-week exercise program, and the change in epicardial fat correlated with the change in visceral fat. One study\textsuperscript{21} in pigs 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.

Therefore, epicardial fat may show regional differences in its response to exercise. Interestingly, Sicari et al\textsuperscript{18} found a cross-sectional correlation between visceral and paracardial fat but not epicardial fat volumes. Apparently, exercise in patients with type 2 diabetes mellitus has a disparate effect on visceral and epicardial adipose tissue, which resulted in a decrease in visceral and paracardial fat without a change in epicardial fat in our study.

Hepatic TG content

At baseline, patients had a mean hepatic TG content of 6.8%. Hepatic steatosis is defined as TG content greater than 5.6% measured with hydrogen-proton MR spectroscopy\textsuperscript{22}. We found that exercise decreased hepatic TG content by 26% in patients with type 2 diabetes mellitus, thereby reducing their hepatic TG content to normal values. This decrease was accompanied by a decrease in alanine aminotransferase. Previous studies reported on the effects of exercise on hepatic TG content, but only in patients without diabetes\textsuperscript{21}.

To our knowledge, the exact mechanism behind the exercise-induced reduction in hepatic TG content is not clear. Although patients in our study lost some weight, we found no significant correlation between changes in body weight and changes in hepatic TG content. The decrease in hepatic TG content may be due to a diminished flow of free fatty acids from
the visceral adipose tissue, in accordance with the portal hypothesis\textsuperscript{24}. However, reduction in hepatic TG content has also been described without a reduction in visceral fat\textsuperscript{25}.

Our results indicated that the liver is not a passive bystander that adapts to changes in fatty acid metabolism. Rector et al\textsuperscript{26} showed that sudden cessation of daily physical activity in hyperphagic or 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 levels of hepatic malonyl-coenzyme A.

**IMCLs and myocardial TG content**

Data regarding the effects of exercise on IMCL content in insulin-resistant patients are inconsistent. A 16-week moderate-intensity exercise program in obese insulin-resistant patients increased IMCL\textsuperscript{27}; however, two studies of 10-12 weeks of exercise in overweight men and patients with type 2 diabetes mellitus found no change in IMCL\textsuperscript{28, 29}. We found no effect of a 6-month exercise program on IMCL.

To our knowledge, only two studies have examined the effects of exercise on myocardial TG content. Twelve weeks of exercise decreased myocardial TG content in healthy obese patients\textsuperscript{30}, but it did not decrease myocardial TG content in patients with type 2 diabetes mellitus\textsuperscript{31}. Our study confirms and extends the latter result.

Previously, an association was found between myocardial TG content and diastolic cardiac function\textsuperscript{8, 32}. In our study, exercise did not change myocardial TG content, and we found no change in systolic or diastolic function. Similarly, 1 year of training in patients with type 2 diabetes mellitus\textsuperscript{33} and 12 weeks of training in patients who were overweight\textsuperscript{30} showed no significant changes in myocardial function; however, in the latter study, ejection fraction increased by 2%.

The major limitation of our study is the small number of patients. Patients acted as their own control. Despite this small patient number, our data show statistically significant changes in fat distribution with exercise. Secondly, diet could have varied between patients; we did not control for this. Finally, there were interindividual differences in the exercise duration and intensity during the training and trekking expedition.

Though exercise intensity did not differ during the study, mean exercise duration increased substantially during the trekking expedition compared with the training period. Furthermore, factors related to altitude, such as hypoxia, may have influenced the results. Many studies that examine the 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 without specifically attempting to diet. Therefore, we assume that their weight loss was achieved only by training.

In conclusion, a 6-month exercise training regimen, without changes in diet, decreased hepatic TG content and visceral abdominal and paracardial fat volume in patients with type
2 diabetes mellitus. These fat compartments are all associated with increased cardiovascular risk. Subcutaneous fat, epicardial fat, and intramyocellular and myocardial TG content did not change. Therefore, our study demonstrated tissue-specific exercise-induced changes in body fat distribution in patients with type 2 diabetes mellitus.
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