Both Resistance Training and Aerobic Training Reduce Hepatic Fat Content in Type 2 Diabetic Subjects With Nonalcoholic Fatty Liver Disease (the RAED2 Randomized Trial)

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Although lifestyle interventions are considered the first-line therapy for nonalcoholic fatty liver disease (NAFLD), which is extremely common in people with type 2 diabetes, no intervention studies have compared the effects of aerobic (AER) or resistance (RES) training on hepatic fat content in type 2 diabetic subjects with NAFLD. In this randomized controlled trial, we compared the 4-month effects of either AER or RES training on insulin sensitivity (by hyperinsulinemic euglycemic clamp), body composition (by dual-energy X-ray absorptiometry), as well as hepatic fat content and visceral (VAT), superficial (SSAT), and deep (DSAT) subcutaneous abdominal adipose tissue (all quantified by an in-opposed-phase magnetic resonance imaging technique) in 31 sedentary adults with type 2 diabetes and NAFLD. After training, hepatic fat content was markedly reduced ($P < 0.001$), to a similar extent, in both the AER and the RES training groups (mean relative reduction from baseline [95% confidence interval] $-32.8\% \text{ [} -58.20 \text{ to } -7.52\% \text{]}$ versus $-25.9\% \text{ [} -50.92 \text{ to } -0.94\% \text{]}$, respectively). Additionally, hepatic steatosis (defined as hepatic fat content $>5.56\%$) disappeared in about one-quarter of the patients in each intervention group (23.1% in the AER group and 23.5% in the RES group). Insulin sensitivity during euglycemic clamp was increased, whereas total body fat mass, VAT, SSAT, and hemoglobin A1c were reduced comparably in both intervention groups. **Conclusion**: This is the first randomized controlled study to demonstrate that resistance training and aerobic training are equally effective in reducing hepatic fat content among type 2 diabetic patients with NAFLD. (HEPATOL 2013;00:000-000)

Type 2 diabetes is typically characterized by abdominal overweight/obesity and ectopic fat accumulation in several tissues and organs. In this regard, nonalcoholic fatty liver disease (NAFLD) is a very common pathologic condition in people with type 2 diabetes.1 It has been estimated that $\sim 50\%$-70% of patients with type 2 diabetes have NAFLD, which is a spectrum of progressive liver disease encompassing simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. In the last decade, the role of NAFLD has raised considerable scientific interest, as liver fat infiltration plays an important role in the development of some metabolic disorders of diabetes (e.g., insulin resistance and atherogenic dyslipidemia) and is also linked to an increased risk of cardiovascular events.1

To date, weight loss is the only recognized therapy for the treatment of NAFLD and lifestyle interventions

**Abbreviations**: AER, aerobic training; ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; BP, blood pressure; DSAT, deep subcutaneous adipose tissue; FFM, fat-free mass; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; RES, resistance training; ROI, region of interest; SAD, sagittal abdominal diameter; SAT, subcutaneous adipose tissue; SI, signal intensity; SSAT, superficial subcutaneous adipose tissue; VAT, visceral abdominal adipose tissue.

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are considered the cornerstone of management. Interestingly, exercise training has been shown to improve body fat distribution, insulin sensitivity, glycemic control, and other cardiometabolic risk factors in patients with type 2 diabetes.²,³ Although these beneficial exercise-induced changes could also favorably affect hepatic fat content in these patients, currently the evidence still remains elusive.⁴,⁵

Most cross-sectional studies carried out in nondiabetic subjects showed an association between physical activity and the prevalence of NAFLD,⁴ suggesting that exercise is a useful tool to improve hepatic steatosis. However, data from intervention studies, which assessed the effects on hepatic fat of aerobic, resistance, or combined training, with or without diet, are scant and somewhat discordant. Whereas exercise combined with a hypocaloric diet generally induce significant reductions of hepatic fat content, the results are modest or inconsistent when exercise-only interventions are used.⁴

In particular, very few clinical trials have been conducted and their results have been inconclusive regarding the effect of exercise training on hepatic fat content, as evaluated by magnetic resonance imaging (MRI), in people with type 2 diabetes.⁶-⁹ Moreover, no randomized controlled trials have compared the effect of different types of exercise training on hepatic fat content in patients with type 2 diabetes and NAFLD, and there is uncertainty as to whether resistance training alone plays a role in improving hepatic fat content and other fat depots in such patients.

To address these issues, in this randomized clinical trial we compared the effects of 4 months of either aerobic or resistance exercise training on hepatic fat content and other fat depots among sedentary type 2 diabetic subjects with NAFLD.

**Participants and Methods**

**Participants and Study Design**

This is a subproject of the RAED2 Study, a single-center, randomized controlled trial primarily aimed at comparing the effects of 4 months of either aerobic (AER) or resistance (RES) training on metabolic control in sedentary subjects with type 2 diabetes.¹⁰ This prespecified subproject focuses on the differential effects of AER or RES training on hepatic fat content and other fat depots in diabetic patients with NAFLD.

Details on the inclusion and exclusion criteria and the randomization schedule of the RAED2 study have been described extensively elsewhere.¹¹ Briefly, the inclusion criteria comprised Caucasian race, age between 40-70 years, hemoglobin A1c (HbA1c) between 6.5%-9.0%, and body mass index (BMI) between 24-36 kg/m². Subjects had to be untrained, and oral hypoglycemic agents were the only diabetes medications allowed. We excluded patients who had advanced diabetic complications. Body weight had to remain stable in the 2 months prior to the intervention study. All subjects had no evidence of viral and autoimmune hepatitis, hemochromatosis, or drug-induced liver diseases and drank <20 g of alcohol per day.

As detailed in Fig. 1, of the 40 type 2 diabetic patients who were initially recruited in the RAED2 study, 31 patients with NAFLD were included in this subproject. Six patients were excluded as their compliance to MRI scans was inadequate for reliable measurements of all ectopic fat depots, one patient abandoned the study before completing the baseline procedures, and the remaining two patients did not have steatosis on MRI at baseline.

Overall, the 31 participants of this subproject did not differ significantly from the whole sample of the RAED2 study in terms of baseline demographics, anthropometric variables, HbA1c, serum liver enzymes, and insulin sensitivity (data not shown).

The trial (#NCT01182948, clinicaltrials.gov) was approved by the Ethics Committee of the Azienda Ospedaliera Universitaria Integrata of Verona, and written informed consent was obtained from all participants.

**Intervention**

Aerobic and resistance experimental groups exercised in the Fitness Centre of the Exercise and Sport Science School of Verona University three times a week for 4 months. All training sessions were carried out under the supervision of exercise specialists.

**Aerobic Exercise Training.** Participants exercised for 60 minutes per session at 60%-65% of heart rate.
Aerobic activities were performed on treadmill, cycle, or elliptical machines and participants were free to change the cardiovascular equipment used from one session to the next. Heart rate monitors were used to standardize exercise intensity.

**Resistance Exercise Training.** Participants performed nine different exercises involving the major muscle groups on weight machines (chest press, shoulder press, vertical traction, leg press, leg extension, leg curl, abdominal crunch) and free weight (biceps, abdominal). After a learning phase, participants performed 3 series of 10 repetitions at 70%-80% 1-RM, with 1 minute of recovery between series.

**Diet.** All participants met a single nutritionist for nutritional counseling at least 2 months before the study. Participants were encouraged to follow a healthy diet, according to standard recommendations for people with type 2 diabetes. Thereafter, participants were instructed to maintain their baseline calorie intake by consuming self-selected foods. The same nutritionist met the participants of both groups on two occasions, just before and at the end of the intervention, to record and analyze their 3-day food recalls.

**Anthropometry and Biochemical Measurements**

Weight was recorded on an electronic scale (Tanita BWB-800, MA, USA), height was measured with a Harpenden stadiometer, and BMI was calculated as weight (kg)/height² (m). Total body fat mass was evaluated by dual-energy x-ray absorptiometry (DXA) using a total body scanner (QDR Explorer W, Hologic, Waltham, MA).

HbA1c was measured by a Diabetes Control Complications Trial (DCCT)-aligned method, with an automated high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy). Serum lipids and transaminase levels were determined by standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald equation.

**Magnetic Resonance Imaging**

MRI was used to measure the amount of fat at the level of the liver and abdomen. A single radiologist, who was blinded to participants’ clinical details, performed all MRI examinations by using a 1.5-T magnet (Magnetom Vision; Siemens Medical, Erlangen, Germany). Liver fat accumulation was measured by...
comparing the in- and out-of-phase images of tissues according to Dixon’s two-point method.\textsuperscript{13-15} To obtain these data, patients were positioned supine using a phased array coil. Axial T1-weighted gradient echo images and in-phase and out-of-phase images were obtained from the upper abdomen and the thighs. Scan parameters were the following: TR/TE 160/2.1 msec (out-of-phase) and 4.2 msec (in-phase), flip angle 80°, slice thickness 8 mm with 1 mm interslice gap. Image postprocessing was performed using a workstation (MV-1000; Siemens Medical). For each pair of images a region of interest (ROI) was drawn in the liver using an adjustable round cursor. The ROI selected in each image measured at least 1 cm\textsuperscript{2} and was placed in the liver parenchyma to exclude contamination from blood vessels, motion artifacts, or partial volume effects. The mean pixel signal intensity (SI) levels for each ROI were recorded; five separate in-phase and out-of-phase ROIs were obtained from each patient and the average values were calculated. Fat fraction was subsequently calculated from the mean pixel SI data using the following formula: $\text{SI}_{\text{in-phase}} - \text{SI}_{\text{out-of-phase}}$. A hepatic fat fraction cutoff of 5.56\% was chosen as the threshold to define hepatic steatosis.\textsuperscript{15,16} This threshold is commonly used and is based on a large MR spectroscopy study performed on participants in the Dallas Heart Study, in which the 95th percentile cutoff of 5.56\% fat fraction (which corresponds to a hepatic triglyceride level of 55.6 mg/g) was determined from a subset of 345 subjects with no identifiable risk factors for hepatic steatosis.\textsuperscript{16} Using this threshold, both MR spectroscopy and MRI have accuracy close to 100\% for the detection of steatosis and can potentially be used to classify patients as having clinically significant steatosis.\textsuperscript{16-19} In particular, it is known that the in-opposed-phase MRI technique is widely used to quantify the hepatic fat content.\textsuperscript{17-19} The Dixon method (\textsuperscript{1}H chemical shift technique) is most commonly used to measure fatty infiltration by MRI. In essence, the protons in fat and water produce different signals, which means the fat signal intensity of a given region relative to its water signal intensity can be used as a marker of lipid infiltration. Using this method, the in-opposed-phase MRI cannot quantify the lipid signal specifically attributed to the intra- and extracellular lipid compartments (as purported in MR spectroscopy). This is not, however, a concern in the liver as lipid exists only within the cell (hepatocyte). Overall, the in-opposed-phase MRI technique provides accurate, noninvasive measures of hepatic fat accumulation that correlate very well with hepatic intracellular lipid measures obtained by using either proton MR spectroscopy or biopsy.\textsuperscript{17-19} The intra- and intercoefficients of variation for MR techniques in quantifying hepatic fat accumulation was below 6\%.\textsuperscript{15,16}

A single slice at the L4 to L5 level was used to measure abdominal visceral and subcutaneous adipose tissue.\textsuperscript{15} The abdominal adipose tissue compartments were defined according to the classification of Shen et al.\textsuperscript{20} The visceral adipose tissue (VAT) compartment is bounded by the internal margin of the abdominal muscle walls and includes intraperitoneal, preperitoneal, and retroperitoneal adipose tissues. The subcutaneous adipose tissue (SAT) compartment includes the adipose tissues outside of the VAT boundary. This compartment is predominately composed of subcutaneous fat, but also includes the small intermuscular and paravertebral components.\textsuperscript{21} Within the SAT, a superficial fascial plane separates this fat depot into a superficial SAT layer (SSAT) with compact fascial septa (Camper’s fascia) and a deep SAT layer (DSAT) with more loosely organized fascial septa (Scarpa’s fascia). With the use of a cursor, a free-hand ROI was drawn around DSAT and SSAT. The mean SI ± standard deviation (SD) of the adipose tissue was obtained from these ROIs. The threshold for adipose tissue was defined as the mean SI ± 2 SD. Sagittal abdominal diameter (SAD) was measured as the anterior-to-posterior distance at the middle part of the vertebral body.

Participants were instructed not to exercise for 24 hours before each MRI evaluation.

**Statistical Analysis**

Data are expressed as mean ± SE or 95\% confidence interval (CI). Power and sample size calculations have been reported in detail elsewhere.\textsuperscript{10} Normality of the distribution of the studied variables was assessed by the Shapiro-Wilks test. Skewed variables were log- or square root-transformed before analysis.

Repeated measures analysis of variance (ANOVA) was used to compare changes over the 4 months of intervention, with the parameters assessed in the study as the dependent variable and time, study group, and time-by-group interaction as the independent variables. Relative changes from baseline in hepatic fat content were compared in both intervention groups by the Mann-Whitney test. Fisher’s exact test was used to check for differences between groups in hypoglycemic therapy changes and in the number of patients free of hepatic steatosis after training. Bivariate associations between variables of interest were assessed by Pearson’s correlation coefficients or Spearman’s rank correlations when variables were not normally distributed. Multiple
Table 1. Main Baseline Characteristics of the Subjects Enrolled in the Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Aerobic Training (n = 14)</th>
<th>Resistance Training (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.6 (2.0)</td>
<td>56.0 (1.9)</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>9.5 (1.7)</td>
<td>9.8 (2.0)</td>
</tr>
<tr>
<td>Men/women, n/n</td>
<td>10/4</td>
<td>12/5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.5 (1.0)</td>
<td>28.6 (1.1)</td>
</tr>
<tr>
<td>Fat mass, %</td>
<td>31.8 (1.4)</td>
<td>29.8 (1.9)</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>220.2 (27.3)</td>
<td>200.5 (25.0)</td>
</tr>
<tr>
<td>SAT, cm²</td>
<td>190.6 (25.0)</td>
<td>182.0 (19.6)</td>
</tr>
<tr>
<td>SSAT, cm²</td>
<td>101.6 (12.5)</td>
<td>95.3 (15.7)</td>
</tr>
<tr>
<td>DSAT, cm²</td>
<td>88.9 (12.8)</td>
<td>86.7 (7.1)</td>
</tr>
<tr>
<td>SAD, cm</td>
<td>26.1 (1.2)</td>
<td>24.6 (0.8)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>137.1 (3.2)</td>
<td>129.3 (3.7)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>83.6 (1.3)</td>
<td>78.9 (2.0)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.26 (0.19)</td>
<td>7.31 (0.17)</td>
</tr>
<tr>
<td>Glucose disposal rate, mg kg FFM⁻¹ min⁻¹</td>
<td>3.72 (0.61)</td>
<td>4.64 (0.56)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>125.9 (20.9)</td>
<td>148.5 (25.3)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>165.8 (9.8)</td>
<td>165.7 (6.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51.5 (2.9)</td>
<td>46.7 (2.9)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>24.7 (3.1)</td>
<td>32.4 (6.2)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>17.7 (1.1)</td>
<td>20.5 (2.5)</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>35.7 (7.8)</td>
<td>39.4 (9.3)</td>
</tr>
<tr>
<td>Hepatic fat content, %</td>
<td>25.7 (3.7)</td>
<td>31.3 (4.8)</td>
</tr>
<tr>
<td>Caloric intake, kcal/day</td>
<td>1700 (101)</td>
<td>1476 (64)</td>
</tr>
</tbody>
</table>

Current therapies

- Antidiabetic therapy, n
  - Only diet: 1
  - Metformin: 11
  - Thiazolidinediones: 3
  - Sulfonylureas: 3
  - Incretins: 0
  - Meglitinides: 0
- Lipid-lowering therapy, n
  - Statins: 8
  - Fibrates: 2

Values are mean (SE) unless otherwise specified.

linear regression analyses were performed, using changes in hepatic fat content as the dependent variable. In these analyses, baseline values of the dependent variable, and changes in VAT, SSAT, and DSAT, sex, and age were tested in the regression models as independent variables. \( P < 0.05 \) was considered statistically significant. Analyses were carried out using STATA v. 12.0 (StataCorp, College Station, TX).

Results

Table 1 summarizes the baseline characteristics of the two groups of patients with NAFLD, who were randomly assigned to 4 months of either AER or RES training. One patient, assigned to the AER training, dropped out early during the intervention period. Therefore, the final analysis was carried out in 30 subjects, 13 in the AER group and 17 in the RES group.

Median attendance to supervised training sessions was similar in the two groups: 91% (interquartile range [IQR] 78%-96%) and 93% (IQR 87%-98%) in the AER and the RES groups, respectively (\( P = 0.34 \)).

As shown in Table 1, the two groups were similar for baseline clinical features and use of medications. During the 4 months of training, no changes in lipolytic and only minimal changes in hypoglycemic drugs were recorded in these subjects. The three subjects in the AER group treated with thiazolidinediones were all taking pioglitazone for a long time before recruitment (>12 months) and the medication dose did not change during the intervention period. No participants were taking vitamin E.

As shown in Table 2, HDL-cholesterol, triglycerides, HbA1c, and clamp-measured insulin sensitivity significantly improved, to a similar extent, in both groups. Neither intervention was associated with significant changes in serum transaminase levels and total daily caloric intake.

As shown in Table 3, BMI, total body fat mass, SAD, VAT, SAT, and SSAT were significantly reduced after training, to a similar extent in both groups.

Notably, as shown in Fig. 2, both exercise regimens elicited a marked absolute and relative reduction in hepatic fat content, which was comparable in the two

Table 2. Metabolic Changes Observed After 4 Months of Training in the Aerobic and Resistance Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Aerobic Group</th>
<th>Resistance Group</th>
<th>( P ) Value Time</th>
<th>( P ) Value Time-by-Group Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>-0.34 (−0.61 to −0.08)</td>
<td>-0.32 (−0.60 to −0.05)</td>
<td>&lt;0.001</td>
<td>0.969</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>8.7 (−10.8 to 28.3)</td>
<td>0.76 (−7.8 to 9.23)</td>
<td>0.385</td>
<td>0.510</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>8.4 (−6.0 to 22.9)</td>
<td>3.4 (−4.3 to 11.1)</td>
<td>0.327</td>
<td>0.718</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-13.7 (−47.5 to 19.9)</td>
<td>-21.0 (−49.6 to 7.5)</td>
<td>0.036</td>
<td>0.543</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>0.38 (−4.35 to 5.12)</td>
<td>-5.33 (−10.77 to 0.10)</td>
<td>0.721</td>
<td>0.449</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>0.15 (−2.61 to 2.92)</td>
<td>-1 (−3.82 to 1.82)</td>
<td>0.612</td>
<td>0.970</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>0.69 (−8.61 to 9.99)</td>
<td>-1.8 (−4.73 to 1.13)</td>
<td>0.913</td>
<td>0.651</td>
</tr>
<tr>
<td>Glucose disposal rate, mg kg FFM⁻¹ min⁻¹</td>
<td>0.97 (−0.11 to 2.06)</td>
<td>0.52 (−0.33 to 1.38)</td>
<td>0.025</td>
<td>0.488</td>
</tr>
<tr>
<td>Caloric intake, kcal/day</td>
<td>-77.4 (−313 to 158)</td>
<td>-91.9 (−200 to 16)</td>
<td>0.119</td>
<td>0.890</td>
</tr>
</tbody>
</table>

Data are mean (95% CI). \( P \) values refer to comparisons between groups by repeated measures ANOVA.
groups. At the end of the study intervention, hepatic steatosis (defined as hepatic fat content >5.56%) disappeared in 3 out of 13 subjects (23.1%) in the AER group and in 4 out of 17 subjects (23.5%) in the RES group (P = 0.99 by Fisher’s exact test).

In univariate correlation analysis, in the whole sample of participants, the absolute reduction after training in hepatic fat content was inversely associated with changes in SSAT (r = −0.41; P = 0.02). Changes in total body fat mass (r = 0.01; P = 0.92), SAT (r = −0.33; P = 0.07), VAT (r = −0.27; P = 0.15), HbA1c (r = −0.04; P = 0.79), or insulin sensitivity (r = 0.11; P = 0.52) were not significantly associated with the absolute reduction in hepatic fat content.

In multiple regression analysis, adjusting for age and sex, the absolute reduction in hepatic fat content after training was positively predicted by baseline hepatic fat content and changes in DSAT, but negatively by SSAT changes (R² model = 0.63, P = 0.001).

**Discussion**

This is the first randomized controlled trial comparing the effects of aerobic or resistance training on hepatic fat content and abdominal visceral and subcutaneous adipose tissue in sedentary type 2 diabetic individuals with NAFLD. Although BMI and total body fat were slightly reduced, hepatic fat content showed a striking reduction in these patients after 4 months of either aerobic or resistance exercise. Interestingly, hepatic steatosis disappeared in about one-quarter of the patients in both intervention groups. This was also accompanied by significant improvements in insulin sensitivity, HbA1c, triglycerides, VAT, and SAT, which were similar in both intervention groups. Given that in our study daily calorie intake and the use of hypoglycemic and lipid-lowering medications remained essentially unchanged during the trial in both groups, it is possible to assume that the reduction in hepatic fat content was likely a consequence of exercise training per se. These findings are in line with the recent results of a short-term intervention study showing that a 1-month aerobic exercise training period significantly reduced hepatic fat content by 21% and VAT volume by 12% in a small sample of 19 nondiabetic obese individuals, even in the absence of significant body weight reduction.22

Until now, few randomized controlled trials have assessed the effect of exercise on hepatic fat content in subjects with type 2 diabetes.6-9,23 However, the

**Table 3. Total Body Fat Mass and Abdominal Fat Depots Changes Observed After 4 Months of Training in the Aerobic and Resistance Groups**

<table>
<thead>
<tr>
<th></th>
<th>Aerobic Group (n = 13)</th>
<th>Resistance Group (n = 17)</th>
<th>P Value Time</th>
<th>P Value Time-by-Group Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>−0.70 (−1.11 to −0.28)</td>
<td>−0.55 (−0.90 to −0.19)</td>
<td>&lt;0.001</td>
<td>0.554</td>
</tr>
<tr>
<td><strong>Fat mass, kg</strong></td>
<td>−1.90 (−2.85 to −0.95)</td>
<td>−1.76 (−2.49 to −1.02)</td>
<td>&lt;0.001</td>
<td>0.795</td>
</tr>
<tr>
<td><strong>VAT, cm²</strong></td>
<td>−66.8 (−117 to −16.3)</td>
<td>−38 (−56.1 to −19.8)</td>
<td>&lt;0.001</td>
<td>0.443</td>
</tr>
<tr>
<td><strong>SAT, cm²</strong></td>
<td>−17.5 (−28.5 to −6.6)</td>
<td>−22.5 (−38.1 to −6.8)</td>
<td>&lt;0.001</td>
<td>0.662</td>
</tr>
<tr>
<td><strong>SSAT, cm²</strong></td>
<td>−13.3 (−22.0 to −4.7)</td>
<td>−16.3 (−22.7 to −9.9)</td>
<td>&lt;0.001</td>
<td>0.162</td>
</tr>
<tr>
<td><strong>DSAT, cm²</strong></td>
<td>−4.2 (−10.6 to 2.2)</td>
<td>−6.1 (−19 to 6.7)</td>
<td>0.248</td>
<td>0.818</td>
</tr>
<tr>
<td><strong>SAD, cm²</strong></td>
<td>−1.53 (−2.33 to −0.73)</td>
<td>−0.94 (−1.46 to −0.43)</td>
<td>&lt;0.001</td>
<td>0.170</td>
</tr>
</tbody>
</table>

Data are mean (95% CI). P values refer to comparisons between groups by repeated measures ANOVA.

![Fig. 2. Absolute and relative reductions in hepatic fat content after 4 months of either aerobic or resistance exercise training. Data are means and SE. (A) Absolute values in hepatic fat content before and after training. (B) Percent changes in hepatic fat content after training. *Significant time effect by repeated measures ANOVA (P < 0.005), with no significant interaction by group. Percent changes were not significantly different between the two groups (by the Mann-Whitney test).](image-url)
experimental design of these studies makes it difficult to establish the effect of exercise per se, as some of them have compared intensive lifestyle interventions (including aerobic or combined exercise) versus standard care, whereas others were short-term or used a low volume of exercise. For example, the investigators of the Look AHEAD Study, a prospective study comparing intensive lifestyle intervention (hypocaloric diet and aerobic physical activity) versus standard care reported a significant decrease in hepatic fat content, as detected by MR spectroscopy, and a reduced incidence of NAFLD in type 2 diabetic subjects randomized to the intensive lifestyle group.7,8 Preliminary data by Bonekamp et al.6 suggested that combined exercise training, based on moderate aerobic exercise and weight lifting, without diet restrictions, reduced hepatic fat content independently of changes in body composition, HbA1c, and serum lipids. Conversely, two short-term intervention trials failed to find an additive effect of moderate aerobic training beyond that of either hypocaloric diet alone9 or isocaloric high monounsaturated fatty acid diet alone23 in patients with type 2 diabetes. Differences in the experimental design of these studies might largely account for these inconsistent results.

As previously mentioned, a novel finding of our study is that resistance training, similar to aerobic training, markedly reduced hepatic fat content in type 2 diabetic patients with NAFLD. Until now, no randomized controlled trials have reported direct measures of the effect of resistance training alone on hepatic fat content in patients with type 2 diabetes and NAFLD. In addition, the published data in nondiabetic subjects are scarce. In a recent short-term intervention study carried out in 18 sedentary adults with NAFLD (some of them with type 2 diabetes), who were randomly assigned to 8 weeks of either resistance training or standard care, Hallsworth et al.24 reported that resistance exercise was associated with a 13% relative reduction in hepatic fat content, without any changes in body weight, whole body fat mass, or VAT. Interestingly, in our study the mean relative reduction in hepatic fat content was ~2-fold greater than that reported in the Hallsworth et al. study.24 This difference might be explained by the higher exercise volume and the longer duration of intervention, which in our study was also accompanied by significant improvements in total body fat mass, VAT, SAT, HbA1c, and whole-body insulin sensitivity.

Consistent results for an independent role of physical exercise in NAFLD also came from several epidemiological studies (reviewed25,26). Interestingly, in a recent population-based study, which examined the relationship between NAFLD and different types of physical activity, Zelber-Sagi et al.27 found that resistance exercise activity, at least once a week, was associated with a lower proportion of subjects with NAFLD, independently of BMI, nutritional factors, insulin resistance, and some circulating adipokines, such as adiponectin and resistin.

The underlying mechanisms by which exercise, particularly resistance training, may reduce hepatic fat content are not entirely understood. They probably include changes in energy balance, circulatory lipids, fat oxidation, and insulin sensitivity.24 In our study, we were careful to avoid a hypocaloric diet or dietary changes during the exercise intervention. Thus, the mild weight loss we observed in both groups is attributable to the effects of exercise and is actually a proof of patients’ compliance with the training protocol.

Although transferring the results of randomized clinical trials, like ours, to “real-world” settings is not always easy, we believe that our data are clinically important, as they support a beneficial effect of exercise per se for the treatment of NAFLD in type 2 diabetic patients, which can be an adjunct to caloric restriction.

Moreover, the finding that resistance exercise is as effective as aerobic exercise in improving hepatic steatosis provides a useful alternative in patients in whom aerobic training may not be accessible, as the high cardiorespiratory demand characteristic of this type of exercise is associated with fatigue and discomfort.

Another interesting and novel finding of our study is the close association between changes in hepatic fat content and changes in SSAT and DSAT. In multivariate regression analysis, the absolute reduction in hepatic fat content was best predicted by baseline hepatic fat content and changes in SSAT and DSAT. Whereas the relation between baseline hepatic fat content and its change after exercise intervention could be an expected finding, the independent and opposite associations between the absolute reduction in hepatic fat content and changes in SSAT and DSAT are intriguing. Evidence indicates that these two subcutaneous fat depots differ in terms of structure and pathophysiology.28 Interestingly, whereas VAT and DSAT correlate negatively with whole-body insulin sensitivity, SSAT does not.29 Moreover, SSAT correlates with a more favorable cardiometabolic risk profile in type 2 diabetic patients, whereas DSAT behaves as a VAT depot.30 Based on these findings, it was hypothesized that higher energy storage in SSAT might exert protective effects by decreasing fat deposition in the liver as well.
as in other ectopic fat depots. Our data further support this hypothesis, showing that the lower the reduction in SSAT following exercise-induced energy burning, the higher the reduction in hepatic fat content. We can, therefore, speculate that there are factors regulating energy storage in SSAT versus DSAT and the liver. However, further research is needed to address this intriguing hypothesis.

Our study has some limitations. First, we do not have a sedentary control group. However, the care we adopted in designing the experimental protocol and the stability of body weight of participants in the 2 months preceding the intervention period makes it unlikely that our findings can be attributed to factors other than the exercise training per se. Second, we quantified hepatic fat content using an in-opposed-phase MRI technique instead of proton MR spectroscopy, which is thought to be the gold standard, noninvasive technique for quantifying hepatic fat content. However, the in-opposed-phase MRI technique provides accurate, noninvasive data on hepatic fat content that correlate very well with those obtained by proton MR spectroscopy as well as with the histopathologic findings on liver biopsy. Finally, we did not perform a liver biopsy in these patients and cannot, therefore, examine the potential beneficial effects of exercise training on some pathologic features of NAFLD (i.e., necroinflammation and fibrosis). However, we believe that it would be unacceptable to perform a liver biopsy on our subjects, who had normal or only mildly elevated serum aminotransferase levels.

Notwithstanding these limitations, the main strengths of this study are its randomized controlled trial design, the well-matched characteristics of subjects included in the two groups, the complete nature of the dataset, the relatively long duration of the trial, the assessment of several features (e.g., insulin sensitivity, body composition, hepatic fat content, and visceral adipose tissue) by state-of-the-art techniques, the diet monitoring, and the direct supervision of physical exercise sessions. This latter approach is of paramount importance to guarantee that all potential benefits of exercise training are reached, particularly in resistance exercise programs.

In conclusion, the results of this randomized controlled trial demonstrate for the first time that 4 months of resistance training or aerobic training are equally effective in reducing hepatic fat content in sedentary type 2 diabetic patients with NAFLD. Our data indicate that exercise alone can provide benefit for the management of NAFLD in patients with type 2 diabetes. However, the long-term impact of exercise training in the clinical management of such patients will depend on long-term maintenance and sustainability of exercise; this now needs to be investigated in longer randomized controlled trials.

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