Aerobic Exercise Training Reduces Hepatic and Visceral Lipids in Obese Individuals Without Weight Loss

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Weight loss remains the most common therapy advocated for reducing hepatic lipid in obesity and nonalcoholic fatty liver disease. Yet, reduction of body weight by lifestyle intervention is often modest, and thus, therapies which effectively modulate the burden of fatty liver but are not contingent upon weight loss are of the highest practical significance. However, the effect of aerobic exercise on liver fat independent of weight loss has not been clarified. We assessed the effect of aerobic exercise training on hepatic, blood, abdominal and muscle lipids in 19 sedentary obese men and women using magnetic resonance imaging and proton magnetic resonance spectroscopy (^{1}H-MRS). Four weeks of aerobic cycling exercise, in accordance with current physical activity guidelines, significantly reduced visceral adipose tissue volume by 12% ($P < 0.01$) and hepatic triglyceride concentration by 21% ($P < 0.05$). This was associated with a significant (14%) reduction in plasma free fatty acids ($P < 0.05$). Exercise training did not alter body weight, vastus lateralis intramyocellular triglyceride concentration, abdominal subcutaneous adipose tissue volume, ^{1}H-MRS–measured hepatic lipid saturation, or HOMA-IR (homeostasis model assessment of insulin resistance; $P > 0.05$). *Conclusion:* These data provide the first direct experimental evidence demonstrating that regular aerobic exercise reduces hepatic lipids in obesity even in the absence of body weight reduction. Physical activity should be strongly promoted for the management of fatty liver, the benefits of which are not exclusively contingent upon weight loss. (HEPATOLOGY 2009;50:1105-1112.)

The health risks of obesity are well documented and the location of body fatness, particularly visceral adipose tissue (VAT), is now increasingly recognized as being of greater importance in determining the metabolic and cardiovascular consequences of excess adiposity.[1] Further, evidence is emerging that excessive storage of hepatocellular triglyceride is a common feature of obesity[2] and independently increases the risk of insulin resistance,[3] metabolic syndrome,[4] and cardiovascular disease.[5] Hepatic steatosis not attributable to excessive alcohol intake or nonalcoholic fatty liver disease (NAFLD) may affect 30% of the adult population[6,7] and the majority of obese individuals.[2]

Interventions which reduce hepatic triglyceride concentration (HTGC) are often accompanied by significant improvements in metabolic function, including restoration of euglycemia in type 2 diabetes.[8] Yet, owing partly to the invasive nature of traditional hepatic triglyceride measurement via liver biopsy and histological grading, there is a paucity of evidence regarding the effects of lifestyle (diet and exercise) interventions on HTGC and no definitive pharmacotherapy exists for reducing HTGC.[9] Although intervention aimed at weight loss is advocated,[10] reductions in weight by dietary restriction are typically modest and are increasingly viewed as an unsustainable outcome of lifestyle modification.[11-13] Therefore, appropriate therapeutic strategies for reducing HTGC, which are not contingent upon weight loss, are needed.

Abbreviations: ALT, alanine aminotransferase; FFA, free fatty acid; ^{1}H-MRS, proton magnetic resonance spectroscopy; HOMA-IR, homeostasis model assessment of insulin resistance; HTGC, hepatic triglyceride concentration; IMTG, intramyocellular triglyceride concentration; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; SAT, subcutaneous adipose tissue; SI, saturation index; VAT, visceral adipose tissue; VLDL, very low density lipoprotein; VO_{2peak}, peak oxygen uptake.

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Data from cross-sectional research show that poor physical fitness and inactivity are associated with an increased propensity for NAFLD.[14-17] Case studies employing dietary modulation in combination with exercise therapy have observed reductions in HTGC in obese individuals.[18,19] However, it is difficult to attribute this benefit to the exercise stimulus, given that it cannot be dissociated from the confounding effects of weight loss and/or dietary change. In rodents, habitual exercise lowers HTGC[20] and prevents diet-induced fatty liver.[21] We have also recently shown that in individuals who received lifestyle counseling, those who increased habitual physical activity and cardiorespiratory fitness exhibited the greatest improvement in liver enzymes.[22] However, the effect of exercise therapy on HTGC in humans, independent of weight loss, remains unclear.

We therefore undertook a randomized placebo-controlled study to determine whether aerobic exercise training that is currently prescribed for public health[23] influences blood, intramyocellular, abdominal, and hepatic lipids in sedentary obese adults, independent of weight loss. HTGC was measured using reliable[7,24,25] noninvasive proton magnetic resonance spectroscopy (^{1}H-MRS) which is now regarded as the most accurate method available for quantification of HTGC.[4] A short-term aerobic exercise training program was employed to mitigate the possible confounding effects of weight loss.

Patients and Methods

Protocol. Twenty-three obese adults (15 male, 8 female) volunteered for this study. All had a body mass index $\geq$30 kg/m^2 and reported a sedentary lifestyle and low alcohol intake (0-20 g/day). Volunteers had no known acute or chronic disease other than obesity and hypertension and were not eligible for participation if taking lipid-lowering medications or they had a fasting plasma glucose $\geq$7.0 mmol/L. Five subjects were receiving antihypertensive medications. Medication dose was not altered throughout the study; subjects refrained from medication for 72 hours prior to measurements. This study was approved by the Human Research Ethics Committee of The University of Sydney, and subjects provided written informed consent.

The effect of aerobic exercise training on lipid partitioning was investigated using a randomized placebo-controlled design. Baseline measurements were performed to determine HTGC and saturation index (SI),[25] abdominal VAT and subcutaneous adipose tissue (SAT) area and volume, intramyocellular triglyceride concentration (IMTG), cardiorespiratory fitness, anthropometry, and blood biochemistry. Subjects were then randomly allocated (by computer-generated sequence) to receive 4 weeks of aerobic exercise training (Exercise) or a sham intervention involving regular stretching (Placebo). Measurements were repeated at completion.

All magnetic resonance imaging (MRI), ^{1}H-MRS, and biochemical measurements were performed after a 10-hour overnight fast. For 3 days before baseline and after intervention, subjects were provided a standard diet comprising 60% of energy as carbohydrate, 20% as fat (12% as saturated, 5% as monounsaturated, and 3% as polyunsaturated), and 20% as protein. Subjects were instructed to refrain from all forms of exercise during these periods.

Assessment of Cardiorespiratory Fitness. Cardiorespiratory fitness was assessed by means of the Physical Work Capacity test undertaken on a cycle ergometer (Lode, Groningen, Netherlands), involving three 5-minute stages at heart rates of 110-120 beats per minute (bpm), 130-140 bpm, and 150-160 bpm, respectively. External power output and mean heart rate were obtained from an electrocardiogram attained during the final 60 seconds of each workload, and this was used to derive peak oxygen uptake (VO_{2peak}) and training power outputs for the Exercise group.

Exercise Training. Participants allocated to the Exercise group undertook a supervised, progressive aerobic exercise program for 4 weeks which met current adult guidelines for exercise participation.[23] Training comprised three cycle ergometer sessions (30-45 minutes each) per week, with intensity increased such that subjects exercised at a power output designed to elicit 50% of pretraining VO_{2peak} for week 1, 60% for week 2, and 70% for weeks 3 and 4. Sessions were undertaken as 15-minute bouts with intervening 5-minute rests. Heart rate and blood pressure were monitored.

The Placebo group was given a 30-minute home-based whole-body stretching routine to perform three times per week. Subjects received one supervised stretching session at treatment initiation, a booklet detailing the stretches, and were unsupervised thereafter. All individuals were informed that the research hypothesis was that regular stretching could reduce inflammation and assist in the preferential reduction of adiposity from the liver and viscera.

All subjects were free-living and were instructed to consume their habitual diet during the training phase. Twenty-four-hour food records were maintained throughout, with total energy intake and macronutrient composition for all listed foods summed for the initial (week 1) and final (week 4) three training days and averaged to produce a mean intake at early-intervention and late-intervention. Diet composition was quantified by

FoodWorks, version 5.0 (Xyris Software, Melbourne, Australia).

Magnetic Resonance Data Acquisition. All MRI and ^{1}H-MRS measurements were acquired using a 1.5-T Intera whole-body system (Philips Medical Systems, Best, The Netherlands). Abdominal lipids were measured by MRI with the patient supine. A sagittal localizing image was used to position five transverse slices, such that the middle (3rd) slice was at the level of the L4-L5 intervertebral space. Axial T1-weighted fast-field echo images were acquired (TR = 11 ms, TE = 4.5 ms, flip angle = 40 degrees) with slice thickness of 10 mm and interslice gap of 10 mm. Images were acquired during suspended end-expiration.

Hepatic lipid content and composition were measured by ^{1}H-MRS according to the methods previously outlined.[25] Briefly, image-guided, localized (3.0 cm × 2.0 cm × 2.0 cm voxel) ^{1}H-MRS scans were acquired using the whole-body (Q body) (transmit) coil and a circular polarized surface (receive) coil, with volumes of interest centered within the right lobe of the liver. Subjects lay in a right decubitus position on the surface coil to minimize abdominal movement caused by breathing. For determination of IMTG content, a 5 cm × 1.5 cm × 1.5 cm voxel was centered within the vastus lateralis at the level of the mid-femur. Hepatic and muscle spectra were acquired using the point-resolved spectroscopy (PRESS) technique (TR = 5000 ms, TE = 30 ms, 64 measurements, 1024 sample points). Fully automated high-order shimming was performed on the volume of interest to ensure maximum field homogeneity. Excitation water suppression was used to suppress the water signal during data acquisition. Unsuppressed water spectra were acquired *in vivo* for use as the internal standard.

Cross-sectional areas of both VAT and SAT depots were computed by automated software (Hippo Fat)[26] with manual editing of contour lines and Gaussian curve as necessary. This automated technique reduces the considerable time required for manual tagging of these depots. Repeated-measures investigation by Hippo Fat can be applied reliably with minimal supervision[26,27] and has superior inter-rater reliability for VAT determination than can be achieved with less-automated software.[28] Volumes of VAT and SAT from approximately the L3-S1 space were calculated by summation of VAT and SAT area from the five abdominal slices, adjusted for slice thickness and interslice gap. The slice at the level of the L4-L5 intervertebral space was used for measurement of abdominal SAT and VAT area, which is the most commonly used single-image location for MRI studies of visceral adiposity.[27]

Spectral data were post-processed by magnetic resonance user interface software (jMRUI version 3.0, EU Project). For hepatic lipid concentration and composition, a six-resonance model was employed as previously described in detail.[25] IMTG concentration was determined according to our method described previously.[25] Hepatic and muscle water signal amplitudes were measured from the non–water suppressed spectrum using HLSVD (Hankel Lanczos Squares Singular Values Decomposition). MRI and ^{1}H-MRS processing was performed by an experimenter blinded to treatment allocation.

Blood Sampling and Analysis. After an overnight fast, venous blood (~6 mL) was collected. Plasma glucose was determined on an EML 105 analyzer (Radiometer A/S, Copenhagen, Denmark). Plasma free fatty acid (FFA) concentration was measured enzymatically using a Wako NEFA C (nonesterified fatty acid) test kit (Wako Pure Chemicals, Osaka, Japan). Serum insulin concentration was measured using a commercial enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX). Triglycerides were analyzed enzymatically (ThermoElectron, Melbourne, Australia). Alanine aminotransferase (ALT) and cholesterol were measured using a conventional automated analyzer at Westmead Hospital. All measurements were made in duplicate. The basal insulin sensitivity index was measured by the homeostasis model assessment for insulin resistance (HOMA-IR).[25]

Calculations. Volumetric units (cm^3) were used for SAT and VAT throughout, with mass estimated using the conversion equation of 1 L adipose tissue = 0.923 kg. *In vivo* HTGC and IMTG concentrations were determined as the percentage of the methylene resonance to water corrected for T_2 effects[7,29] and hepatic lipid saturation index (SI) was measured as: $SI = 1 - [(I_{allylic})/(I_{allylic} + I_{methylene} + I_{methyl})]$, where $I_{allylic}$, $I_{methylene}$, and I_{methyl} are the signal amplitudes of the fatty acid allylic methylene, bulk methylene, and terminal methyl peaks, respectively. This index is based on that which we have described previously.[25]

Statistics. One-way analysis of variance (ANOVA) was performed to examine differences between groups at baseline. The effect of exercise training on anthropometric, biochemistry, *in vivo* ^{1}H-MRS, and MRI measures were compared by two-way repeated measures ANOVA for investigation of treatment group × time interactions. Relationships between change in HTGC with intervention and change in other metabolic variables (expressed as percentages) during treatment were determined by Pearson correlation coefficients. Statistical significance was accepted at $P < 0.05$. Calculations were performed using

Table 1. Subject Characteristics

Parameter	Placebo		Exercise		*P* Value
	Baseline	Posttreatment	Baseline	Posttreatment	Treatment × time interaction
Anthropometry					
Age, years	47.3 (3.6)	–	49.1 (2.3)		–
Weight, kg	98.8 (6.0)	98.6 (6.3)	94.4 (3.8)	94.1 (4.0)	0.938
BMI, kg m^{-2}	31.1 (1.1)	31.0 (1.2)	32.2 (0.8)	32.1 (0.8)	0.962
Metabolic					
VO_{2peak}, mL · kg^{-1} · min^{-1}	25.0 (1.6)	26.1 (1.7)	25.9 (1.4)	29.2 (1.5)*	0.017
Plasma glucose, mmol L^{-1}	6.11 (0.40)	6.01 (0.29)	5.62 (0.29)	5.63 (0.33)	0.553
Plasma insulin, pmol L^{-1}	16.69 (2.63)	17.49 (2.61)	18.59 (2.80)	17.39 (2.91)	0.438
Plasma FFAs, μmol L^{-1}	554 (65)	531 (53)	500 (42)	429 (39)*	0.047
Plasma TG, mmol L^{-1}	1.68 (0.22)	1.59 (0.20)	1.26 (0.14)	1.26 (0.14)	0.498
HOMA-IR	4.75 (1.09)	4.81 (0.93)	4.59 (0.69)	4.40 (0.76)	0.733
ALT (U L^{-1})	37.7 (4.6)	38.4 (3.0)	35.7 (6.5)	32.9 (5.9)	0.158
Cholesterol (mmol L^{-1})	5.7 (0.2)	5.5 (0.2)	5.5 (0.4)	5.1 (0.4)	0.455
Diet record analysis					
Energy intake (kJ day^{-1})	9821 (1083)	9703 (1089)	10093 (667)	10196 (751)	0.503
% carbohydrate	52 (2)	54 (3)	54 (2)	55 (2)	0.878
% fat	31 (2)	30 (3)	32 (2)	31 (2)	0.921
% protein	17 (1)	16 (1)	15 (1)	14 (1)	0.906

ALT, alanine aminotransferase; FFAs, free fatty acids; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; VO_2peak, aerobic capacity. Values are means (SE); n = 19. *Significant treatment × time interaction Exercise versus Placebo ($P < 0.05$).

SPSS for Windows, version 16 (SPSS Inc., Chicago, IL). All values are expressed as means ± standard error (SE).

Results

Two subjects withdrew during the trial: one was dissatisfied with treatment allocation (Placebo), and another had a change in work circumstances. One subject (Placebo) was removed after baseline measures due to hyperglycemia. Data for another subject (Placebo) was excluded from analysis because this individual had very low HTGC (<0.5%) and VAT (< 80 cm^2) values accompanied by normal blood glucose and lipids. Thus, data was analyzed for 19 subjects (seven from the Placebo group; 12 from the Exercise group). There was no significant difference between groups for all baseline measurements (Table 1), although baseline plasma triglyceride concentration tended to be higher in Placebo versus Exercise ($P = 0.110$; Table 1). All subjects allocated to the Exercise group completed 12 sessions of supervised exercise training.

Anthropometry and Cardiorespiratory Fitness. Cardiorespiratory fitness significantly improved in the Exercise group versus Placebo ($P < 0.05$; Table 1). Body weight ($P = 0.938$) and body mass index ($P = 0.962$) were not altered (Table 1).

Blood Metabolites/Hormones and Food Record Analysis. There was no treatment × time interaction for basal plasma glucose, insulin, HOMA-IR, ALT, or cholesterol ($P > 0.05$; Table 1). Basal plasma FFAs were significantly reduced with Exercise ($P = 0.047$; Table 1). Energy intake was not significantly different between Exercise and Placebo during early-intervention ($P = 0.820$). There was no significant difference in reported dietary carbohydrate ($P = 0.715$), fat ($P = 0.802$), and protein ($P = 0.147$) composition during early-intervention in Exercise versus Placebo. There was no significant change in reported energy intake ($P = 0.503$) or macronutrient composition ($P > 0.05$ for all) over the intervention schedule (Table 1).

Lipid Partitioning and Hepatic Lipid Concentration and Composition. Mean HTGC was significantly reduced in the Exercise group versus the Placebo group ($P = 0.042$; Fig. 1A; Table 2). Ten of 12 individuals in the Exercise group demonstrated a lowering of HTGC, compared with only one in the Placebo group. Mean reduction in HTGC in the Exercise group was 21%. Hepatic lipid composition as determined by the SI was not altered by exercise training ($P = 0.891$; Fig. 1B). Average VAT was significantly reduced in Exercise versus Placebo ($P < 0.01$; Fig. 2A), but SAT was not affected by treatment ($P = 0.884$; Fig. 2C). SAT and VAT areas at L4-L5 correlated strongly with average SAT and VAT volumes ($r = 0.978$ and $r = 0.935$, respectively, $P < 0.01$ for both). Mean VAT area was significantly reduced in Exercise versus Placebo ($P < 0.01$; Fig. 2B). Due to inadequate differentiation of intramyocellular lipid from extramyocellular lipid in four samples (one from the Placebo group; three from the Exercise group), IMTG concentration was not analyzed for these individuals. Statistical analysis was therefore performed on 15 subjects

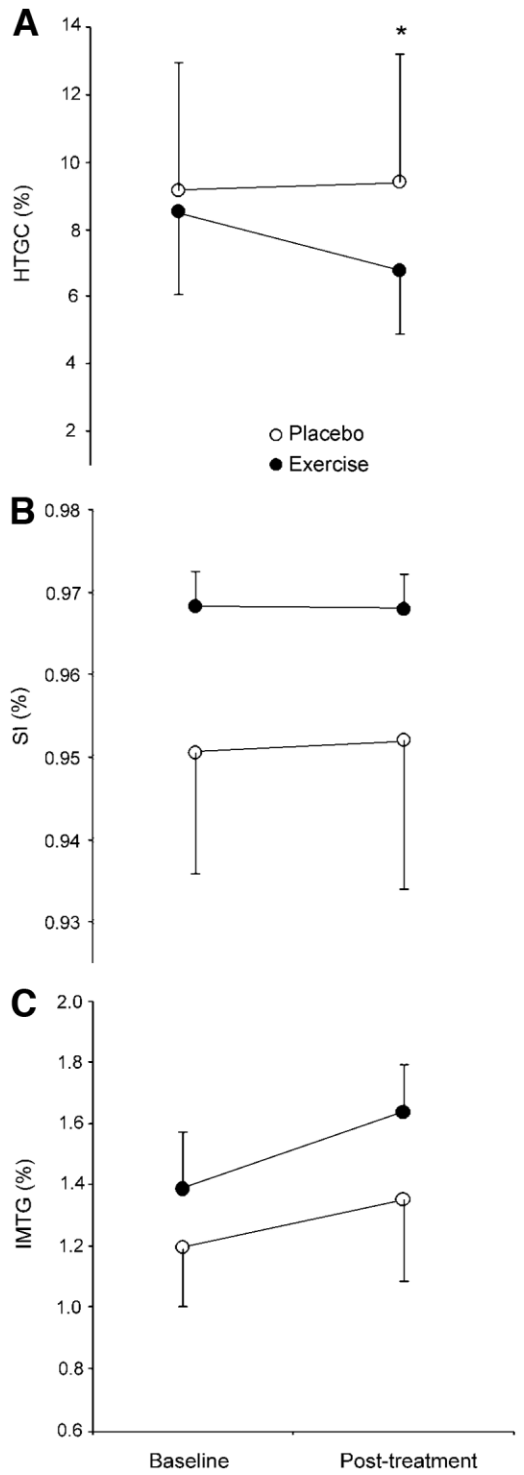

Fig. 1. Effect of 4 weeks of exercise training (Exercise) or control (Placebo) on (A) hepatic triglyceride concentration (HTGC), (B) ^{1}H-MRS measured hepatic lipid saturation index (SI), and (C) vastus lateralis intramyocellular triglyceride concentration (IMTG). Values are means ± SE; n = 7 for Placebo; n = 12 for Exercise. *Significant treatment × time interaction ($P < 0.05$).

(six Placebo; nine Exercise). There was no significant interaction between treatment and time for IMTG ($P = 0.685$; Fig. 1C).

Time-Course of VAT and HTGC Changes. The longer-term effect of exercise training on VAT and HTGC was determined by studying six subjects (five women and one man) who continued supervised aerobic exercise training (Exercise) for a further 4 weeks. Average VAT in this subset was 1077 cm^3 ± 180 cm^3, 963 cm^3 ± 169 cm^3, and 928 cm^3 ± 131 cm^3 at baseline and follow-

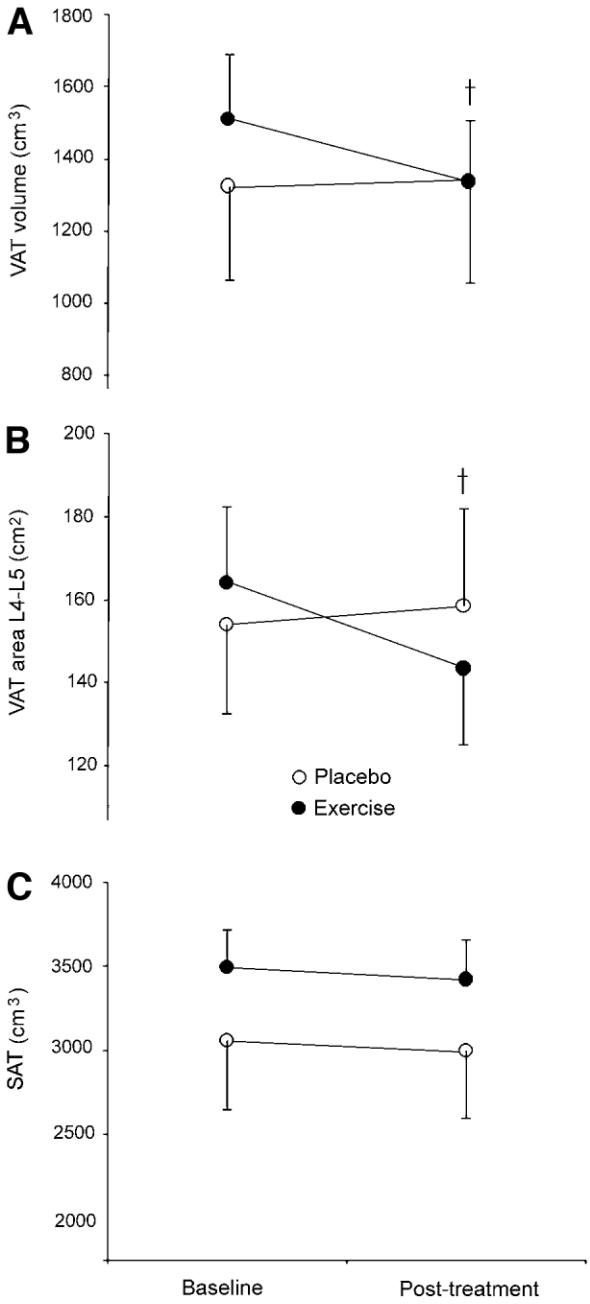

Fig. 2. Effect of 4 weeks of exercise training (Exercise) or control (Placebo) on (A) visceral adipose tissue (VAT) volume, (B) visceral adipose tissue (VAT) area (L4-L5 intervertebral space), and (C) abdominal subcutaneous adipose tissue (SAT) volume. Values are means ± SE; n = 7 for Placebo; n = 12 for Exercise. †Significant treatment × time interaction ($P < 0.01$).

Table 2. Hepatic Lipid Content and Composition and Abdominal and Muscle Triglyceride Content

Parameter	Placebo		Exercise		*P* Value
	Baseline	Posttreatment	Baseline	Posttreatment	Treatment × time interaction
HTGC, %	9.18 (3.80)	9.44 (3.89)	8.55 (2.49)	6.79 (1.90)*	0.042
Hepatic SI	0.951 (0.015)	0.952 (0.018)	0.968 (0.004)	0.968 (0.004)	0.891
SAT area, cm^2	364.6 (46.7)	355.8 (46.3)	403.4 (24.5)	397.1 (26.1)	0.793
Average SAT, cm^3	3057 (411)	2996 (405)	3490 (230)	3420 (235)	0.884
VAT area, cm^2	154.3 (21.2)	158.6 (23.9)	164.3 (18.3)	143.6 (18.7)**	<0.01
Average VAT, cm^3	1326 (262)	1340 (282)	1512 (182)	1337 (173)**	<0.01
IMTG, %	1.20 (0.19)	1.36 (0.27)	1.39 (0.19)	1.64 (0.16)	0.685

HTGC, hepatic triglyceride concentration; IMTG, vastus lateralis intramyocellular triglyceride concentration; SAT, subcutaneous adipose tissue area (L4-L5); SI, hepatic lipid saturation index; VAT, visceral adipose tissue area (L4-L5).

Values are means (SE); n = 19 for HTGC, SAT, VAT; n = 15 for IMTG. *Significant treatment × time interaction Exercise versus Placebo ($P < 0.05$). **Significant treatment × time interaction Exercise versus Placebo ($P < 0.01$).

ing 4 and 8 weeks of Exercise, respectively. HTGC was 4.6% ± 1.7%, 4.1% ± 1.4%, and 4.0% ± 1.9% at 0, 4, and 8 weeks, respectively.

Relationship Between Change in HTGC and Other Variables. Percentage change in HTGC was significantly correlated with the percentage change in basal plasma FFAs ($r = 0.591$, $P < 0.05$) and tended toward being correlated with percentage change in VAT volume ($r = 0.31$, $P = 0.190$) and area ($r = 0.37$, $P = 0.122$), although this did not reach statistical significance. There was no significant correlation between the percentage change in HTGC and change in body weight ($r = -0.026$, $P = 0.917$), body mass index ($r = -0.05$, $P = 0.833$), or ALT ($r = -0.08$, $P = 0.744$). Change in HTGC was not related to HTGC at baseline ($r = -0.07$, $P = 0.777$).

Discussion

Cross-sectional investigations have previously shown an independent association between physical fitness and HTGC,[14-17] and case-studies have suggested a role for exercise in reducing HTGC.[18,19] Using a short-term aerobic cycling training intervention in previously sedentary obese adults, we provide the first direct experimental evidence demonstrating that regular aerobic exercise training reduces hepatic lipids without concurrent changes in body weight or abdominal SAT content. Although the short-term intervention employed did not alter IMTG, plasma triglycerides, insulin or HOMA-IR, exercise reduced VAT and was associated with a significant reduction in plasma FFAs.

The current study provides strong evidence for emphasizing the importance of physical activity in patients with excess hepatic triglyceride. Although dietary restriction with the aim of weight loss remains the most common therapy for obesity and fatty liver,[10] reductions of body weight through dietary restriction are often modest and typically return to baseline with time.[11-13] As evident from the Diabetes Prevention Program Research Group, exercise adherence appears to be more sustainable over time than weight loss.[30] As a result, our observation of a beneficial effect of regular exercise itself on hepatic and visceral lipids, independent of detectable changes in body weight or SAT, should refocus the debate, and hence policy, on the role of physical activity in the prevention and management of obesity and NAFLD.

Despite growing evidence of the metabolic and cardiovascular impact of NAFLD, there are relatively few studies examining the effects of lifestyle intervention. Much of the existing research, including our own,[22] has assessed the efficacy of therapeutic strategies for NAFLD via surrogate measurements of liver enzyme concentrations, which often show only a moderate correlation ($r = \sim 0.2\text{-}0.5$) with HTGC.[6] We used ^{1}H-MRS to measure HTGC, because the noninvasive nature of this technique makes it ideal for human intervention studies. Furthermore, liver ^{1}H-MRS is highly reproducible[7,25] and MRS-measured HTGC correlates well ($r = 0.89\text{-}0.93$) with that determined by biopsy and histology.[7,24] The ^{1}H-MRS method is now regarded as the most accurate method to quantify HTGC.[4] Our observation of a mean 21% reduction in HTGC with exercise training is significantly outside the coefficient of variation (~4%-7%) for this technique,[7,25] and occurred without a significant reduction in ALT ($P = 0.16$). We recently validated a measurement of hepatic lipid saturation using MRS,[25] but failed to find any change in hepatic SI in this study, which would be expected given the reliance of lipid composition on long-term dietary intake.

Using MRI, we also observed a significant reduction in VAT with exercise training. Automated VAT and SAT areas/volumes are comparable to those derived with biomedical image analysis software packages which require free-hand methods of area quantification, and the method has good reliability (coefficient of variation = 2% and 7% for SAT and VAT, respectively[27]). Some systematic underestimation of VAT is reported with Hippo Fat (although this is minimal in obese subjects[27,28]) and it should be noted that our partial

abdominal scanning (from approximately L3-S1) underestimates total abdominal VAT and SAT. Because our primary focus was to examine relative changes in abdominal adiposity with treatment, the automated nature and high reliability of this technique coupled with blinding of the experimenter made it the most appropriate tool for this study. The significant reduction in VAT without changes in SAT in the Exercise versus Placebo groups was also apparent on the basis of single-slice SAT and VAT areas at L4-L5. Such representation of abdominal adiposity correlates well with total abdominal adiposity[31] and reduces systematic error associated with Hippo Fat assessment.[27] In this study, we have provided further support for this simpler method by showing a strong correlation between SAT and VAT areas at L4-L5 and abdominal SAT and VAT volumes.

Although significant reductions in HTGC and abdominal visceral adiposity were observed with exercise training, the absolute reduction by weight was small: mean reduction of ~30 g for HTGC assuming an average liver weight of 1500 g and mean reduction of ~160 g for VAT based on partial abdominal volumes. This preferential fat loss did not appear to translate to a change in body weight, a finding previously observed for VAT in studies employing exercise interventions across a range of exercise regimens, with ad libitum or controlled food intake.[32] It is possible that the Exercise group increased energy intake to maintain energy balance, however, this was not reflected in the 24-hour food recording. The adaptive response to exercise training also involves an increase in plasma volume and accretion of muscle glycogen, which may account for this small offset in fat loss. Exercise-induced VAT reduction may result from preferential shunting of SAT-derived FFAs away from the viscera to the active muscle, and enhanced adipose lipolysis via lipoprotein lipase activation.[33,34]

We acknowledge the need to confirm the long-term efficacy of aerobic exercise on HTGC, but our short-term approach importantly allowed us to eliminate the confounding effects of weight change. Using a 6-week exercise training regime in overweight men and women, Shojaee-Moradie and colleagues observed significant lowering of VAT but not HTGC with exercise.[35] Based on data from our subset of obese volunteers who continued to exercise for 8 weeks, we found no evidence to suggest that the HTGC-lowering effect of exercise is reversed after 4 weeks, but we cannot exclude the possibility that differences in factors such as cardiorespiratory fitness at baseline or exercise regimen may explain the discrepant outcomes between these studies. Furthermore, these studies are characterized by differences in subject populations (our subjects were obese with significantly higher HTGC) which may contribute to this disparity, although it is noteworthy that we observed no relationship between the change in HTGC with treatment and baseline HTGC. The lack of associated improvement in secondary metabolic parameters, including HOMA-IR and plasma triglycerides, is not unexpected given the short duration of our intervention, the insensitivity of HOMA-IR to changes in dynamic insulin sensitivity,[36] and the relative normality of these in our cohort.

Our data suggest that when compared with subcutaneous adiposity, HTGC, like VAT, is labile. The mechanism behind the reduction in HTGC with exercise remains unclear, and available evidence suggests several physiological control points. Exercise increases fatty acid oxidation from adipose, intramyocellular, and possibly hepatic sources. Specifically, there is a significant increase during and after exercise in both very low density lipoprotein (VLDL) secretion and VLDL clearance by skeletal muscle,[37] which may accelerate the removal of HTGC-derived fatty acids. The capacity for VLDL clearance is also known to improve with regular exercise training.[38] Rodent studies demonstrating increases in adenosine monophosphate–activated protein kinase activity and subsequent attenuation of malonyl coenzyme A with exercise suggest a direct effect of exercise in increasing hepatic mitochondrial fatty acid transport and oxidation, which may persist after exercise cessation.[39]

The locus of control of HTGC has traditionally centered on VAT. Yet, our data support emerging evidence which suggests that SAT may be of greater importance than VAT in this relationship. The portal hypothesis that VAT-derived fatty acids are primarily responsible for fatty liver has been questioned with the observation that the bulk of portal vein FFAs originate from SAT in overnight-fasted obese individuals,[40] and that insulin resistance in adipose tissue (which promotes elevated FFAs) is positively correlated with HTGC.[41] Thus, we suggest that HTGC-lowering with exercise training is partly a function of adipose insulin sensitization, particularly in the bulk SAT component, which results in lower lipolysis-derived FFAs and subsequent hepatic fatty acid uptake. The finding of lower circulating FFAs concomitant with a reduction in HTGC in exercise-trained individuals in this study, and a tighter correlation between change in HTGC and FFAs than VAT, is consistent with this. Demonstration of a protective effect of exercise training on hepatic steatosis in rodents fed high-fat diets has also been shown to be accompanied by lower FFAs,[21] and a study in monozygotic twins showed that those with higher aerobic capacity had a lower uptake of FFAs into the liver.[42]

In conclusion, we have shown that aerobic exercise training itself reduces hepatic and visceral lipids in previously sedentary obese individuals. Thus, regular exercise may mitigate the metabolic and cardiovascular consequences of obesity, including fatty liver, and this is not contingent upon weight loss.

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