Format for Manuscript Submission: Randomized Clinical Trial

Name of Journal: *World Journal of Gastroenterology*

Manuscript Type: RANDOMIZED CLINICAL TRIAL

Effect of resistance training on non-alcoholic fatty-liver disease: A randomized-clinical trial

Shira Zelber-Sagi, Assaf Buch, Hanny Yeshua, Nahum Vaisman, Muriel Webb, Gil Harari, Ofer Kis, Naomi Fliss-Isakov, Elena Izkhakov, Zamir Halpern, Erwin Santo, Ran Oren, Oren Shibolet

Shira Zelber-Sagi, Assaf Buch, Hanny Yeshua, Nahum Vaisman, Muriel Webb, Naomi Fliss-Isakov, Elena Izkhakov, Zamir Halpern, Erwin Santo, Ran Oren, Oren Shibolet, Department of Gastroenterology, Tel Aviv Medical Center, 6423906 Tel-Aviv, Israel

Shira Zelber-Sagi, Gil Harari, School of Public Health, University of Haifa, 3498838 Haifa, Israel

Assaf Buch, **Hanny Yeshua, Nahum Vaisman, Naomi Fliss-Isakov, Zamir Halpern, Erwin Santo, Ran Oren, Oren Shibolet,** The Sackler Faculty of Medicine, Tel-Aviv University, 6997801 Tel Aviv, Israel

Ofer Kis, Wingate Institute for Physical Education and Sport, 4290200 Netanya, Israel

ORCID number: Shira Zelber-Sagi **( );** Assaf Buch, Hanny Yeshua **( );**

Nahum Vaisman **( );** Muriel Webb **( );** Gil Harari, Ofer Kis **( );** Naomi Fliss-Isakov **( );** Elena Izkhakov **( );** Zamir Halpern **( );** Erwin Santo, Ran Oren **( );** Oren Shibolet **( ).**

Author contributions: Zelber-Sagi S conceived the study; Zelber-Sagi S and Buch A designed the study; Zelber-Sagi S, Buch A and Harari G analyzed the data; Zelber-Sagi S, Buch A and Yeshua H performed the data collection; Vaisman N, Webb M, Kis O, Fliss-Isakov N, Izkhakov E helped in data collection; Halpern Z, Santo E, Oren R, and Shibolet O conducted on data collection; Zelber-Sagi S, Buch A and Shibolet O wrote the manuscript; All authors critically reviewed the manuscript and approved it.

Supported by

Institutional review board statement:

Clinical trial registration:

Informed consent statement:

Conflict-of-interest statement:

Data sharing statement:

CONSORT 2010 statement:

Corresponding author: Shira Zelber-Sagi, PhD, Department of Gastroenterology, Tel Aviv Medical Center, Yermiyahu 37, 6423906 Tel-Aviv, Israel. zelbersagi@bezeqint.net

Telephone: +972-3-6973984

Fax: +972-3-6974622

Abstract

BACKGROUND

AIM

To evaluate the effect of resistance training (RT) on non alcoholic liver disease (NAFLD) patients.

METHODS

A randomized clinical trial enrolling NAFLD patients without secondary liver disease (*e.g.,* without hepatitis B virus, hepatitis C virus or excessive alcohol consumption). Patients were randomly allocated either to RT, three times weekly, for 3 mo or a control arm consisting of home stretching. The RT included leg press, chest press, seated rowing, latissimus pull down *etc.* with 8-12 repetitions, 3 sets for each exercise, for a total duration of 40 min. Hepatic ultrasound, fasting blood tests, anthropometrics and body composition by dual energy X-ray absorptiometry were assessed. At baseline and follow-up, patients filled out a detailed semi-quantitative food frequency questionnaire reporting their habitual nutritional intake. Steatosis was quantified by the hepatorenal-ultrasound index (HRI) representing the ratio between the brightness level of the liver and the right kidney. The HRI has been previously demonstrated to be highly reproducible and was validated against liver biopsy and proton magnetic resonance spectroscopy.

RESULTS

Eighty two patients with primary NAFLD were randomized to receive 3 mo of either RT or stretching. After dropout or exclusion from analysis because of protocol violation (weight change > 3 kg), thirty three patients in the RT arm and 31 in the stretching arm completed the study per protocol. All baseline characteristics were similar for the two treatment groups with respect to demographics, anthropometrics and body composition, blood tests and liver steatosis on imaging. HRI score was reduced significantly in the RT arm as

compared to the stretching arm (-0.25 ± 0.37 *vs* -0.05 ± 0.28, $P = 0.017$). The RT arm had a significantly higher reduction in total, trunk and android fat with increase in lean body mass. There was no correlation between the reduction in HRI in the RT arm and weight change during the study, but it was positively correlated with the change in trunk fat ($r = 0.37$, $P = 0.048$). The RT arm had a significant reduction in serum ferritin and total cholesterol. There was no significant difference between arms in dietary changes and these did not correlate with HRI change.

CONCLUSION

Three months RT improves hepatic fat content accompanied by favorable changes in body composition and ferritin. RT may serve as a complement to treatment of NAFLD.

Key words: Resistance exercise; Obesity; Nutrition; Physical activity; Abdominal fat

Core tip: Resistance training is viewed as a complement to aerobic training. However, data on the effect of resistance training on non alcoholic liver disease (NAFLD) is scant. A three month resistance training in NAFLD patients exerted a significant reduction in liver fat as well as reduction in total body and trunk fat with increase in lean body mass. Furthermore, resistance training led to reduction in serum ferritin and cholesterol. In NAFLD patients, compliance to aerobic training may be low due to fatigue. Therefore, resistance training can serve as an easier alternative or a complement form of exercise in these patients.

Zelber-Sagi S, Buch A, Yeshua H, Vaisman N, Webb M, Harari G, Kis O, Fliss-Isakov N, Izkhakov E, Halpern Z, Santo E, Oren R, Shibolet O. Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial.

INTRODUCTION

Lifestyle modifications, including weight reduction and physical activity, improve many of the risk factors for non alcoholic liver disease (NAFLD)[1] and have become the primary treatment modalities for the disease[2]. The role of physical activity (PA) as a potential treatment for NAFLD has been tested in several observational studies and a few clinical trials, mostly testing the effect of aerobic training. Resistance training (strength training) is a means for developing and maintaining muscular strength, endurance, power, and muscle mass that has grown in popularity over the past two decades[3,4]. In a study of the general population, resistance training (RT) was inversely associated with NAFLD. This association remained significant after adjusting to multiple confounders including body mass index (BMI), homeostasis model assessment, nutritional factors, adiponectin, and resistin[5]. Two small trials found beneficial effects for RT as a single treatment in NAFLD patients, but results regarding reduction in steatosis were conflicting[6,7]. In a randomized clinical trial (RCT) in 19 sedentary adult NAFLD patients, 8 wk of RT, consisting of 45 min sessions trice weekly, led to a reduction in liver fat without weight loss[7]. In an uncontrolled clinical trial in 12 obese adolescents, a three-month RT program consisting of 1 h sessions twice weekly did not change hepatic fat content but improved hepatic insulin sensitivity [6]. In a recent RCT among type-2 diabetic patients, it was demonstrated that resistance training and aerobic training are equally effective in reducing hepatic fat content[8].

NAFLD patients report a poorer health-related quality of life compared with healthy United States population both on physical and mental health scores[9]. Furthermore, fatigue is a common symptom in NAFLD patients[10], and they report low scores for vitality[9]. Although NAFLD patients understand the benefits of exercise, they lack the confidence to perform it and express a fear of falling[11]. The potential benefits of RT are not only to cardiovascular health and to weight management but it also improves balance and reduces the risk of falls[12-14]. RT improves several components of physical

function, contributes to health-related quality of life[15,16], and is well tolerated even among patients with coronary heart disease or the elderly[15,17]. In recent years, increasing attention has been paid to RT as a useful adjunctive tool of exercise in various metabolic diseases including diabetes and heart disease[4,18,19]. Indeed, the American Heart association and American College of Sport Medicine (ACSM) recommend RT at least twice a week in addition to aerobic training[4]. For those patients who may have physical limitation or low motivation that prevents them from performing aerobic PA, RT can serve as an alternative option.

Therefore we conducted a randomized controlled trial of RT *vs* stretching. Our main aim was to evaluate the effect of 3 mo RT on the presence of fatty liver measured by abdominal ultrasound and on the hepato-renal index (HRI) as a quantitative objective measurement of steatosis. We also evaluated the effect of the RT program on liver enzymes, metabolic parameters and body composition.

MATERIALS AND METHODS

We conducted a RCT (sealed envelopes randomization stratified by gender) in consecutive patients with ultrasound diagnosed fatty liver attending the liver clinic at the Tel-Aviv Medical center during 2010-2012 and community regional HMO's clinics. Inclusion criteria were age between 20-65 years and a diagnosis of fatty liver by US in the past 6 mo and on the baseline US examination. Exclusion criteria were any known secondary liver disease including the presence of hepatitis B surface antigen or anti-hepatitis C virus antibodies, excessive alcohol consumption defined as ≥ 30 g/d in men or 20 g/d in women, administration of medical treatment that may elevate alanine aminotransferase (ALT) or lead to hepatic steatosis, known diabetes, major chronic diseases including: renal, cardiovascular, lung, uncontrolled hypertension, inflammatory bowel disease, active cancer, autoimmune disorders and orthopedic contraindications for RT. Adults with diabetes were excluded to avoid a confounding effect, since it is unclear whether they would

have the same response to physical training and since changes in antidiabetic medications during the trial might occur. We also excluded patients regularly performing RT in the 3 mo or 6 mo prior to study enrolment for novice and progressive trainee respectively (novice-trained continuously less than 2 mo, progressive-trained continuously more than 2 mo). Patients performing vigorous aerobic PA in the 3 mo prior to the study, defined as aerobic exercise ≥ 5 d a week 30 min at moderate pace or 3 d a week 20 min at vigorous pace or 4 times a week with combination of both and patients with recent weight reduction (more than 3 kg in the last 3 mo) were also excluded.

A sample size of 32 patients in each group was calculated to be needed for a 90% power to detect a difference of 0.25 with a standard deviation of 0.30, based on previously published data on HRI change following weight change[20], with a 0.050 two-sided significance level. Additional 20% patients were recruited taking into consideration attrition or protocol violation.

The study was approved by the Tel-Aviv Medical center ethics committee and all patients signed an informed consent. The study was pre-registered in the NIH registration website (TRIAL no. NCT01264198).

Lifestyle and medical evaluation

Each patient underwent at baseline a face-to-face interview by the same trained interviewer. The questionnaire was assembled by the Israeli center for disease control and was used in the first Israeli National Health Survey. It consists of structured questions about alcohol consumption, medications and medical history. PA evaluation was performed by a questionnaire that was tailored and validated for the Israeli population[21], according to which a summarized index of all questions was calculated and used as an indicator of PA levels.

At baseline, patients filled out a detailed semi-quantitative food frequency questionnaire (FFQ) reporting their habitual nutritional intake in the past year. The FFQ was assembled by the Food and Nutrition Administration, Ministry of Health and was previously described in detail[5,22,23]. The FFQ is composed

of 120 food items with specified serving sizes or standard weight and volume measures of the servings commonly consumed in this study population. The nutrient components of each food item were taken from the Israeli National Nutrient Database. At the end of the trial patients filled out the same FFQ but reported their nutritional intake in the past 3 mo in order to evaluate changes in nutritional habits during the trial.

Blood pressure was measured by an experienced nurse following a uniform protocol. Each participant underwent biochemical testing, following a 12 h fast, for liver enzymes, serum lipid profile, and fasting serum glucose and insulin levels. The homeostasis model assessment (HOMA) was calculated as fasting serum insulin [(μU/mL) × fasting plasma glucose (mmol/L)]/22.5.

Ultrasonographic examination for determination of NAFLD and quantification of steatosis

Fatty liver was assessed by abdominal ultrasonography using standardized criteria[24]. Ultrasonography was performed in all subjects both at baseline and at follow up with the same equipment (EUB-8500 scanner Hitachi Medical Corporation, Tokyo, Japan) and by the same experienced radiologist (Webb M) as described previously[22,23,25]. The radiologist was blinded to patient allocation and to laboratory values and medical history of the participants. During the ultrasonography, a histogram of brightness levels, *i.e.*, a graphical representation of echo intensity within a region of interest (ROI) was obtained. In the liver, the ROI was measured in the 7th or 8th intercostal space in the mid or anterior axillary line in the superficial aspect of the liver. In the right kidney, the ROI was determined as the cortical area between the pyramids. The brightness level for each organ was recorded and the ratio between the median brightness level of the liver and the right kidney cortex was calculated to determine the HRI. The HRI has been previously demonstrated to be highly reproducible (r = 0.77, P < 0.001, kappa = 0.86) and was validated against liver biopsy[26]. HRI ≥ 1.5 indicates fatty liver.

Anthropometric and body composition evaluation

Height, weight and waist circumference were measured following a uniform protocol and BMI was calculated. Lean body mass (LBM) and fat mass (FM) were evaluated by the dual energy X-ray absorptiometry (DEXA) method [27,28] by a blinded technician at the Metabolic Nutrition Clinic.

All participants were instructed to maintain their pre-trial PA habits, regular nutritional intake, medications and nutritional supplements. A weight change during the study of more than 3 kg in either direction, which is clinically significant for NAFLD[20] and other metabolic parameters[29,30], was pre-defined as a protocol violation.

Intervention

RT training: The RT program was according to the ACSM 2009 position paper on "Progression Models in Resistance Training for Healthy Adults"[31]. Exercises included were: leg press, leg extension, leg curl, seated chest press, seated rowing, latissimus pull down, biceps curl and shoulder press with 8-12 repetitions, 3 sets for each exercise with 1-2 min rest between sets, for a total duration of about 40 min. Participants performed the training in a community setting in one of the hosting gyms closest to their house or place of work. On the first training meeting, the researchers performed a personal training session and provided explanation on the RT equipment using a comfortable load (determined by volitional fatigue reached with 10-12 repetitions). The load was gradually increased by 2%-10% in the following training sessions, according to the individual ability of the patient (when the patient felt he can perform 1-2 extra repetition) and with consultation of the professional trainers of the hosting gym. All changes were routinely documented. Standardization of the RT for all participants was ensured by the highly controlled environment at the gyms and a uniform protocol including: a uniform and meticulous familiarization with the training, all participants (treatment and control) received a comprehensive booklet graphically illustrating by pictures all exercises. Participating gyms (all belonging to a single regional chain) have

uniform standard equipment and all the gyms instructors, certified by the sports ministry, were given detailed and comprehensive instructions regarding the training protocol. Using equipment that was not included in the study protocol was not allowed. Every 2 wk phone calls were made to ensure adherence to the training protocol and participants were repeatedly instructed not to perform aerobic training (cycling, treadmill, etc.) during the sessions. All patients were observed for an entire exercise session at least twice during the trial by the researchers.

Active control arm: The home stretching routine followed the ACSM's guidelines for a general stretching program[32]. The program included 8 stretching exercises for the major muscle/tendon groups using the static stretching technique. The participants performed 4 repetitions of these static stretches each lasting 20 s. Each session was performed on 3 non-consecutive days a week[32]. Participants received a booklet with instructions on the stretching training illustrated by pictures.

Statistical analysis

Statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, United States) software and SAS ® version 9.1 (SAS Institute, Cary North Carolina).

Continuous variables are presented as mean ± SD. Paired *t*-tests were used to evaluate within group changes from baseline to end of treatment. To test baseline differences in continuous variables between the two groups the independent samples *t*-test was performed. The Wilcoxon signed ranks test or the Mann-Whitney test were used if non-parametric tests were required based on data distribution. Analysis of variance using repeated measurements model was applied for testing the group X time interactions and exact *F* statistics was performed.

Associations between nominal variables were performed with the Pearson $\div^2$ test. Pearson correlation was used to test the correlation between change in

HRI and change in other parameters. $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Trial participants and compliance

Eighty two patients with primary NAFLD were randomized to receive 3 mo of either RT or stretching. Forty four were randomized to the RT group of which 36 (82%) completed the 3 month follow up period. Thirty eight were randomized to the stretching arm and 33 (87%) completed the study. Two patients dropped out of the RT group due to adverse events (knee pain, shoulder pain), and one from the stretching arm (back pain). Five patients were excluded from analysis because of protocol violation reaching a weight change of more than the pre-defined 3 kg. Hence, thirty three patients in the RT arm and 31 in the stretching arm completed the study per protocol. A flow chart of trial participation is described in Figure 1. The average age was 46.47 ± 10.76 years, with 34 (53%) males. Average BMI was 31.02 ± 4.32 kg/m^2. The average fasting insulin levels were elevated, but in accordance with the exclusion criteria fasting glucose levels were within the normal range.

All baseline characteristics were similar for the two treatment groups with respect to demographics, anthropometrics and body composition, blood tests including liver enzymes and liver steatosis on imaging as assessed by the HRI (Table 1). Furthermore, no difference in dietary intake at baseline was observed between arms ($P \geq 0.40$ for all comparisons, data not shown).

The average number of training sessions at the gym, that was automatically recorded every time a patient entered the gym with his personal chip, was 2.2 ± 0.65 times a week, representing 73% ± 20.5% of the recommended number of sessions of 3 times a week during the 12 week trial. There was a significant increment in the weight lifted during the trial: leg press increased from 39.73 ± 31.83 to 63.87 ± 44.56 kg ($P < 0.001$), and chest press increased from 20.61 ± 22.34 to 32.09 ± 27.55 kg ($P < 0.001$).

Primary outcome

HRI score was significantly reduced in the RT arm as compared to the stretching arm (-0.25 ± 0.37 *vs* -0.05 ± 0.28, $P = 0.017$), representing an 11% *vs* 3.5% relative reduction from the baseline in the two groups respectively (Figure 2).

The RT arm had a significant but small reduction in weight (-0.39 ± 1.43 kg *vs* 0.33 ± 1.21 kg) and BMI (Table 2) compared to the stretching arm.

The RT arm had a significant reduction in total FM, trunk fat and android fat and increase in LBM compared to the stretching arm (Figure 3). There was no correlation between the reduction in HRI in the RT arm and weight change or BMI change during the study ($r = 0.25$, $P = 0.17$) nor with total FM change ($r = 0.29$, $P = 0.13$) as observed by DEXA. However, the change in HRI was positively correlated with the change in trunk fat ($r = 0.37$, $P = 0.048$). In contrast, in the stretching arm the change in HRI was positively correlated with weight change ($r = 0.35$, $P = 0.055$) and BMI change ($r = 0.36$, $P = 0.049$).

There was no significant difference between arms in dietary change during the study in of total calories, carbohydrates, protein, fat and different types of fat ($P \geq 0.114$ for all comparisons) (Table 2). Furthermore, there was no correlation between the reduction in HRI in the RT arm and change in dietary intake of total calories and different dietary components ($P \geq 0.42$ for all correlations).

Secondary outcomes

The RT arm had significantly higher reduction in serum ferritin and total cholesterol. There was no significant difference in reduction of liver enzymes between arms. ALT was significantly reduced only in the RT arm in within group comparison. RT had no significant impact on serum glucose, insulin, glycosylated hemoglobin and triglycerides (Table 2).

DISCUSSION

In this randomized controlled trial, NAFLD patients without diabetes

underwent either RT trice weekly or dynamic stretching. The results suggest that RT exerts beneficial effects on several clinical and biochemical parameters including liver fat and body composition.

The 2007 update of the American Heart Association dealing with resistance exercise concludes that RT should be viewed as a complement to aerobic exercise[14]. However, the beneficial effect of RT for patients with steatosis was so far not supported by strong evidence.

The present trial is one of the first to test this question on a large group of patients. We have demonstrated a significant reduction in steatosis as measured by an objective ultrasonographic tool, the HRI. The modest relative reduction of about 10% is similar to the 13% relative reduction in steatosis previously demonstrated[7]. Although the RT arm had a nonsignificant reduction in caloric intake and a small but significant weight reduction of less than half a kg, these changes did not correlate with HRI change. Our results suggest that the reduction in steatosis in the RT arm cannot be explained by weight loss or dietary change. RT also improved body composition, most importantly trunk fat mass that was positively correlated with the change in HRI.

The weight-reduction independent beneficial effect of aerobic exercise in NAFLD is supported by clinical trials demonstrating a relative reduction of hepatic triglyceride concentration by 21%-35%[33-35] following supervised training such as cycling. However, in a trial of a more modest activity that included brisk walk, there was a relative reduction of 10.3% in liver fat[36], similar to the one observed by the present study.

In previous published trials about the effect of RT in adult NAFLD patients, there was a significant improvement in glycemic control and no improvement in liver enzymes[7,8]. Our study did not demonstrate improved glucose metabolism, this discrepancy may stem from the exclusion of diabetic patients from our study. It was previously shown that RT improves hyperglycemia, only in patients with disturbed glucose metabolism or diabetes[37-41]. Our study showed significant improvement in the liver enzymes (ALT and

aspartate aminotransferase-AST) within group but with no difference between arms. Interestingly, there seems to be a limited correlation between exercise and liver enzyme reduction. Aerobic PA led to a significant reduction in liver enzymes in some trials[42] while no reduction was seen in other trials despite reduced steatosis[8,34,35]. With specific reference for resistance training, it has been shown that weightlifting exercise resulted in increases in liver enzymes; AST and ALT, though the underlying mechanisms are unknown[43]. Thus, it may be in our study that the reduction of liver enzymes in the RT arm was masked and is underestimated.

Serum ferritin was significantly reduced only in the RT group. This novel effect of RT in NAFLD patients, that has been previously demonstrated with aerobic training [42] and lifestyle intervention[44], is of importance due to the strong association of ferritin with fibrosis and inflammation[45,46] and with insulin resistance (IR)[23,47] in NAFLD patients. The mechanisms by which PA, and specifically RT, reduces serum ferrtin are unknown. Serum ferritin is associated with insulin resistance[23,48] and is an acute phase protein that can be induced in the setting of systemic or hepatic inflammation[49-52]. Serum ferririn was demonstrated to be a predictor of histologic severity including steatosis[46]. Thus, we can assume that a reduction in liver fat demonstrated in our study or improved hepatic insulin sensitivity by RT, that was demonstrated in another study[6], led to a reduction of serum ferritin. Furthermore, RT may have an anti-inflammatory effect, as demonstrated by increasing adiponectin levels[53], and serum ferritin was found to be inversely correlated with serum adiponectin[54]. However, it is unclear if hyperferritinemia in NAFLD is simply a consequence of disease severity or actively contributes to disease progression[46]. Ferritin was found to inhibit the secretion of apolipoprotein B and in this way may alter cholesterol and triglyceride transport in the liver[55]. Interestingly, some studies reported that PA plays an important role in reducing serum ferritin concentration[56,57] and this may be another explanation for the reduction in liver fat in our study.

Another beneficial effect of RT in our study was a significant reduction of

serum cholesterol. Although data regarding the effect of RT on lipid metabolism are equivocal, reduction of serum total cholesterol and LDL by resistance training has been previously demonstrated in a meta-analysis of randomized controlled trials[58]. It is well established that liver steatosis is associated with IR and lipid abnormalities including alteration in cholesterol metabolism[59-62]. Recent data show that increased IR contributes to the shift in cholesterol metabolism to increased synthesis and decreased absorption, independent of body weight[63-65]. Several studies have demonstrated that resistance training improves IR, including hepatic IR[6,66], and therefore may contribute to decreased synthesis of hepatic cholesterol. However, the precise mechanisms involved still need to be clarified[67].

Professional societies recommend ≥ 30 min of moderate-intensity aerobic PA on most, and preferably all, days of the week, or vigorous-intensity PA ≥ 3 times per week for ≥ 20 min each time. However, only 27.7% United States adults meet recommended levels of either moderate or vigorous physical activity, whereas 29.2% report no regular PA outside of their work [68,69]. Moreover, the prevalence of physically active adults among patients with diabetes is lower than in those without diabetes[70] and they are less likely to meet PA recommendations[71]. In NAFLD patients, compliance may be even lower because fatigue has been demonstrated to be markedly higher in NAFLD patients compared to controls, and is associated with inactivity and excessive daytime sleepiness[10]. Therefore, an alternative or a complement form of exercise that may be easier to perform or to adhere to, such as RT, may be helpful in the treatment of NAFLD patients.

The major limitation of this study is that due to ethical and practical considerations we were unable to perform repeated liver biopsies in our short term study preventing any inference regarding the effect of RT on inflammation and fibrosis. Ideally, quantification of liver fat is performed by liver biopsy or magnetic resonance spectroscopy (^{1}H-MRS) that is an accepted noninvasive method to reliably quantify steatosis[72,73].

HRI has been validated *vs* liver biopsy and provides a highly sensitive,

objective and quantitative tool for liver fat evaluation with a high correlation (r = 0.82, P < 0.001) and a kappa of 0.75 as compared with histological steatosis[26]. Another group compared HRI to ^{1}H-MRS as a reference standard, demonstrating high correlation (r^2 = 0.92, P < 0.0001) and therefore confirming that HRI can be a valuable analytic tool in clinical investigation[72]. It was also recently shown that HRI highly correlates with biochemical surrogate markers of liver steatosis: the fatty liver index (FLI) (r = 0.55, P < 0.001) and the SteatoTest (r = 0.52, P < 0.001)[74]. Furthermore, since a baseline biopsy wasn't performed, we were unable to distinguish between patients with simple steatosis or NASH. NASH is the NAFLD variant that needs to be treated more urgently due to a worse natural history of progression to cirrhosis, hepatocellular carcinoma[75] and increased liver related mortality [76]. Recently, ultrasonographic FLI, another semi-quantitative evaluation tool of hepatic steatosis, was demonstrated to successfully predict biopsy diagnosed NASH[77].

In conclusion, this relatively large randomized clinical trial demonstrated a significant reduction in steatosis, as assessed by HRI, during 3 mo RT accompanied by favorable changes in body composition and reduction of serum ferritin.

REFERENCES

1 **Duncan GE**, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care* 2003; **26**: 557-562 [PMID: 12610001]

2 **Bellentani S**, Dalle Grave R, Suppini A, Marchesini G. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. *Hepatology* 2008; **47**: 746-754 [PMID: 18098321]

3 **Kraemer WJ**, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. *Med Sci Sports Exerc* 2004; **36**: 674-688 [PMID: 15064596]

4 **Pollock ML**, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, Limacher M, Piña IL, Stein RA, Williams M, Bazzarre T. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000; **101**: 828-833 [PMID: 10683360]

5 **Zelber-Sagi S**, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, Blendis L, Halpern Z, Oren R. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. *Hepatology* 2008; **48**: 1791-1798 [PMID: 18972405 DOI: 10.1002/hep.22525]

6 **Van Der Heijden GJ**, Wang ZJ, Chu Z, Toffolo G, Manesso E, Sauer PJ, Sunehag AL. Strength exercise improves muscle mass and hepatic insulin sensitivity in obese youth. *Med Sci Sports Exerc* 2010; **42**: 1973-1980 [PMID: 20351587 DOI: 10.1249/MSS.0b013e3181df16d9]

7 **Hallsworth K**, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, Day CP, Trenell MI. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut* 2011; **60**: 1278-1283 [PMID: 21708823 DOI: 10.1136/gut.2011.242073]

8 **Bacchi E**, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, Zanolin E, Schena F, Bonora E, Moghetti P. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology* 2013; **58**: 1287-1295 [PMID: 23504926 DOI: 10.1002/hep.26393]

9 **David K**, Kowdley KV, Unalp A, Kanwal F, Brunt EM, Schwimmer JB. Quality of life in adults with nonalcoholic fatty liver disease: baseline data from the nonalcoholic steatohepatitis clinical research network. *Hepatology* 2009; **49**: 1904-1912 [PMID: 19434741 DOI: 10.1002/hep.22868]

10 **Newton JL**, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 2008; **57**: 807-813 [PMID: 18270241 DOI: gut.2007.139303]

11 **Frith J**, Day CP, Robinson L, Elliott C, Jones DE, Newton JL. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. *J Hepatol* 2010; **52**: 112-116 [PMID: 19897272 DOI: 10.1016/j.jhep.2009.10.010]

12 **Seguin R**, Nelson ME. The benefits of strength training for older adults. *Am J Prev Med* 2003; **25**: 141-149 [PMID: 14552938 DOI: S0749379703001776]

13 **Orr R**, de Vos NJ, Singh NA, Ross DA, Stavrinos TM, Fiatarone-Singh MA. Power training improves balance in healthy older adults. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 78-85 [PMID: 16456197]

14 **Williams MA**, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, Gulanick M, Laing ST, Stewart KJ. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2007; **116**: 572-584 [PMID: 17638929 DOI: 10.1161/CIRCULATIONAHA.107.185214]

15 **Beniamini Y**, Rubenstein JJ, Faigenbaum AD, Lichtenstein AH, Crim MC. High-intensity strength training of patients enrolled in an outpatient cardiac

rehabilitation program. *J Cardiopulm Rehabil* 1999; **19**: 8-17 [PMID: 10079415]
16 **Brovold T**, Skelton DA, Bergland A. The efficacy of counseling and progressive resistance home-exercises on adherence, health-related quality of life and function after discharge from a geriatric day-hospital. *Arch Gerontol Geriatr* 2012; **55**: 453-459 [PMID: 22503654 DOI: 10.1016/j.archger.2012.01.015]
17 **Nichols JF**, Omizo DK, Peterson KK, Nelson KP. Efficacy of heavy-resistance training for active women over sixty: muscular strength, body composition, and program adherence. *J Am Geriatr Soc* 1993; **41**: 205-210 [PMID: 8440838]
18 **Albright A**, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, Verity LS. American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med Sci Sports Exerc* 2000; **32**: 1345-1360 [PMID: 10912903]
19 **Arena R**, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007; **116**: 329-343 [PMID: 17576872]
20 **Zelber-Sagi S**, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, Nitzan Kaluski D, Halpern Z, Oren R. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. *J Hepatol* 2012; **56**: 1145-1151 [PMID: 22245895 DOI: 10.1016/j.jhep.2011.12.011]
21 **Ken-Dror G**, Lerman Y, Segev S, Dankner R. [Measurement and assessment of habitual physical activity in epidemiological studies]. *Harefuah* 2005; **144**: 200-25, 230, 229 [PMID: 15844461]
22 **Zelber-Sagi S**, Nitzan-Kaluski D, Goldsmith R, Webb M, Blendis L, Halpern Z, Oren R. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. *J Hepatol* 2007; **47**: 711-717 [PMID: 17850914 DOI: S0168-8278(07)00427-8]
23 **Zelber-Sagi S**, Nitzan-Kaluski D, Halpern Z, Oren R. NAFLD and hyperinsulinemia are major determinants of serum ferritin levels. *J Hepatol*

2007; **46**: 700-707 [PMID: 17150278]

24 **Gore R**. Diffuse liver disease. In: Gore R, Levine M, Laufer I. editor Textbook of Gastrointestinal Radiology: Philadelphia: Saunders, 1994: 1968-2017

25 **Zelber-Sagi S**, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. *Liver Int* 2006; **26**: 856-863 [PMID: 16911469 DOI: LIV1311]

26 **Webb M**, Yeshua H, Zelber-Sagi S, Santo E, Brazowski E, Halpern Z, Oren R. Diagnostic value of a computerized hepatorenal index for sonographic quantification of liver steatosis. *AJR Am J Roentgenol* 2009; **192**: 909-914 [PMID: 19304694]

27 **Going SB**, Massett MP, Hall MC, Bare LA, Root PA, Williams DP, Lohman TG. Detection of small changes in body composition by dual-energy x-ray absorptiometry. *Am J Clin Nutr* 1993; **57**: 845-850 [PMID: 8503351]

28 **Haarbo J**, Gotfredsen A, Hassager C, Christiansen C. Validation of body composition by dual energy X-ray absorptiometry (DEXA). *Clin Physiol* 1991; **11**: 331-341 [PMID: 1914437]

29 **Katan MB**. Weight-loss diets for the prevention and treatment of obesity. *N Engl J Med* 2009; **360**: 923-925 [PMID: 19246365 DOI: 360/9/923]

30 **Kataja-Tuomola M**, Sundell J, Männistö S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers. *Eur J Epidemiol* 2010; **25**: 333-339 [PMID: 20352298 DOI: 10.1007/s10654-010-9444-6]

31 . American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; **41**: 687-708 [PMID: 19204579 DOI: 10.1249/MSS.0b013e3181915670]

32 . American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 1998; **30**: 975-991 [PMID: 9624661]

33 **Finucane FM**, Sharp SJ, Purslow LR, Horton K, Horton J, Savage DB, Brage S, Besson H, De Lucia Rolfe E, Sleigh A, Martin HJ, Aihie Sayer A, Cooper C, Ekelund U, Griffin SJ, Wareham NJ. The effects of aerobic exercise on metabolic risk, insulin sensitivity and intrahepatic lipid in healthy older people from the Hertfordshire Cohort Study: a randomised controlled trial. *Diabetologia* 2010; **53**: 624-631 [PMID: 20052455 DOI: 10.1007/s00125-009-1641-z]

34 **van der Heijden GJ**, Wang ZJ, Chu ZD, Sauer PJ, Haymond MW, Rodriguez LM, Sunehag AL. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. *Obesity (Silver Spring)* 2010; **18**: 384-390 [PMID: 19696755 DOI: 10.1038/oby.2009.274]

35 **Johnson NA**, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, George J. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology* 2009; **50**: 1105-1112 [PMID: 19637289 DOI: 10.1002/hep.23129]

36 **Sullivan S**, Kirk EP, Mittendorfer B, Patterson BW, Klein S. Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty liver disease. *Hepatology* 2012; **55**: 1738-1745 [PMID: 22213436 DOI: 10.1002/hep.25548]

37 **Fenicchia LM**, Kanaley JA, Azevedo JL, Miller CS, Weinstock RS, Carhart RL, Ploutz-Snyder LL. Influence of resistance exercise training on glucose control in women with type 2 diabetes. *Metabolism* 2004; **53**: 284-289 [PMID: 15015138 DOI: S0026049503004992]

38 **Banz WJ**, Maher MA, Thompson WG, Bassett DR, Moore W, Ashraf M, Keefer DJ, Zemel MB. Effects of resistance versus aerobic training on coronary artery disease risk factors. *Exp Biol Med (Maywood)* 2003; **228**: 434-440 [PMID: 12671188]

39 **Fluckey JD**, Hickey MS, Brambrink JK, Hart KK, Alexander K, Craig BW. Effects of resistance exercise on glucose tolerance in normal and glucose-intolerant subjects. *J Appl Physiol (1985)* 1994; **77**: 1087-1092 [PMID:

7836108]

40 **Castaneda C**, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 2002; **25**: 2335-2341 [PMID: 12453982]

41 **Hameed UA**, Manzar D, Raza S, Shareef MY, Hussain ME. Resistance Training Leads to Clinically Meaningful Improvements in Control of Glycemia and Muscular Strength in Untrained Middle-aged Patients with type 2 Diabetes Mellitus. *N Am J Med Sci* 2012; **4**: 336-343 [PMID: 22912941 DOI: 10.4103/1947-2714.99507]

42 **St George A**, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. *Hepatology* 2009; **50**: 68-76 [PMID: 19444870 DOI: 10.1002/hep.22940]

43 **Pettersson J**, Hindorf U, Persson P, Bengtsson T, Malmqvist U, Werkström V, Ekelund M. Muscular exercise can cause highly pathological liver function tests in healthy men. *Br J Clin Pharmacol* 2008; **65**: 253-259 [PMID: 17764474 DOI: 10.1111/j.1365-2125.2007.03001.x]

44 **St George A**, Bauman A, Johnston A, Farrell G, Chey T, George J. Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. *J Gastroenterol Hepatol* 2009; **24**: 399-407 [PMID: 19067776 DOI: JGH5694]

45 **Manousou P**, Kalambokis G, Grillo F, Watkins J, Xirouchakis E, Pleguezuelo M, Leandro G, Arvaniti V, Germani G, Patch D, Calvaruso V, Mikhailidis DP, Dhillon AP, Burroughs AK. Serum ferritin is a discriminant marker for both fibrosis and inflammation in histologically proven non-alcoholic fatty liver disease patients. *Liver Int* 2011; **31**: 730-739 [PMID: 21457446 DOI: 10.1111/j.1478-3231.2011.02488.x]

46 **Kowdley KV**, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, Sanyal AJ, Nelson JE. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty

liver disease. *Hepatology* 2012; **55**: 77-85 [PMID: 21953442 DOI: 10.1002/hep.24706]

47 **Brudevold R**, Hole T, Hammerstrøm J. Hyperferritinemia is associated with insulin resistance and fatty liver in patients without iron overload. *PLoS One* 2008; **3**: e3547 [PMID: 18958176 DOI: 10.1371/journal.pone.0003547]

48 **Fernández-Real JM**, Ricart-Engel W, Arroyo E, Balançá R, Casamitjana-Abella R, Cabrero D, Fernández-Castañer M, Soler J. Serum ferritin as a component of the insulin resistance syndrome. *Diabetes Care* 1998; **21**: 62-68 [PMID: 9580307]

49 **Kalantar-Zadeh K**, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. *Nephrol Dial Transplant* 2004; **19**: 141-149 [PMID: 14671049]

50 **Valenti L**, Dongiovanni P, Fargion S. Diagnostic and therapeutic implications of the association between ferritin level and severity of nonalcoholic fatty liver disease. *World J Gastroenterol* 2012; **18**: 3782-3786 [PMID: 22876027 DOI: 10.3748/wjg.v18.i29.3782]

51 **Miller LL**, Miller SC, Torti SV, Tsuji Y, Torti FM. Iron-independent induction of ferritin H chain by tumor necrosis factor. *Proc Natl Acad Sci U S A* 1991; **88**: 4946-4950 [PMID: 2052577]

52 **Pham CG**, Bubici C, Zazzeroni F, Papa S, Jones J, Alvarez K, Jayawardena S, De Smaele E, Cong R, Beaumont C, Torti FM, Torti SV, Franzoso G. Ferritin heavy chain upregulation by NF-kappaB inhibits TNFalpha-induced apoptosis by suppressing reactive oxygen species. *Cell* 2004; **119**: 529-542 [PMID: 15537542 DOI: 10.1016/j.cell.2004.10.017]

53 **de Piano A**, de Mello MT, Sanches Pde L, da Silva PL, Campos RM, Carnier J, Corgosinho F, Foschini D, Masquio DL, Tock L, Oyama LM, do Nascimento CM, Tufik S, Dâmaso AR. Long-term effects of aerobic plus resistance training on the adipokines and neuropeptides in nonalcoholic fatty liver disease obese adolescents. *Eur J Gastroenterol Hepatol* 2012; **24**: 1313-1324 [PMID: 22932160 DOI: 10.1097/MEG.0b013e32835793ac]

54 **Ku BJ**, Kim SY, Lee TY, Park KS. Serum ferritin is inversely correlated with serum adiponectin level: population-based cross-sectional study. *Dis Markers* 2009; **27**: 303-310 [PMID: 20075513 DOI: 10.3233/DMA-2009-0676]

55 **Hevi S**, Chuck SL. Ferritins can regulate the secretion of apolipoprotein B. *J Biol Chem* 2003; **278**: 31924-31929 [PMID: 12813058 DOI: 10.1074/jbc.M303081200]

56 **Liu JM**, Hankinson SE, Stampfer MJ, Rifai N, Willett WC, Ma J. Body iron stores and their determinants in healthy postmenopausal US women. *Am J Clin Nutr* 2003; **78**: 1160-1167 [PMID: 14668279]

57 **Lakka TA**, Nyyssönen K, Salonen JT. Higher levels of conditioning leisure time physical activity are associated with reduced levels of stored iron in Finnish men. *Am J Epidemiol* 1994; **140**: 148-160 [PMID: 8023803]

58 **Kelley GA**, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Prev Med* 2009; **48**: 9-19 [PMID: 19013187 DOI: 10.1016/j.ypmed.2008.10.010]

59 **Wasada T**, Kasahara T, Wada J, Jimba S, Fujimaki R, Nakagami T, Iwamoto Y. Hepatic steatosis rather than visceral adiposity is more closely associated with insulin resistance in the early stage of obesity. *Metabolism* 2008; **57**: 980-985 [PMID: 18555841 DOI: 10.1016/j.metabol.2008.02.015]

60 **Speliotes EK**, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, Hirschhorn JN, O'Donnell CJ, Fox CS. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. *Hepatology* 2010; **51**: 1979-1987 [PMID: 20336705 DOI: 10.1002/hep.23593]

61 **Kim LJ**, Nalls MA, Eiriksdottir G, Sigurdsson S, Launer LJ, Koster A, Chaves PH, Jonsdottir B, Garcia M, Gudnason V, Harris TB. Associations of visceral and liver fat with the metabolic syndrome across the spectrum of obesity: the AGES-Reykjavik study. *Obesity (Silver Spring)* 2011; **19**: 1265-1271 [PMID: 21183935 DOI: 10.1038/oby.2010.291]

62 **Bugianesi E**, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. *Curr Pharm Des* 2010; **16**: 1941-1951 [PMID:

20370677]

63 **Simonen P**, Kotronen A, Hallikainen M, Sevastianova K, Makkonen J, Hakkarainen A, Lundbom N, Miettinen TA, Gylling H, Yki-Järvinen H. Cholesterol synthesis is increased and absorption decreased in non-alcoholic fatty liver disease independent of obesity. *J Hepatol* 2011; **54**: 153-159 [PMID: 20947198 DOI: 10.1016/j.jhep.2010.05.037]

64 **Hoenig MR**, Sellke FW. Insulin resistance is associated with increased cholesterol synthesis, decreased cholesterol absorption and enhanced lipid response to statin therapy. *Atherosclerosis* 2010; **211**: 260-265 [PMID: 20356594 DOI: 10.1016/j.atherosclerosis.2010.02.029]

65 **Flannery C**, Dufour S, Rabøl R, Shulman GI, Petersen KF. Skeletal muscle insulin resistance promotes increased hepatic de novo lipogenesis, hyperlipidemia, and hepatic steatosis in the elderly. *Diabetes* 2012; **61**: 2711-2717 [PMID: 22829450 DOI: 10.2337/db12-0206]

66 **Brooks N**, Layne JE, Gordon PL, Roubenoff R, Nelson ME, Castaneda-Sceppa C. Strength training improves muscle quality and insulin sensitivity in Hispanic older adults with type 2 diabetes. *Int J Med Sci* 2007; **4**: 19-27 [PMID: 17211497]

67 **Mann S**, Beedie C, Jimenez A. Differential Effects of Aerobic Exercise, Resistance Training and Combined Exercise Modalities on Cholesterol and the Lipid Profile: Review, Synthesis and Recommendations. *Sports Med* 2013; : [PMID: 24174305 DOI: 10.1007/s40279-013-0110-5]

68 **Pratt M**, Macera CA, Blanton C. Levels of physical activity and inactivity in children and adults in the United States: current evidence and research issues. *Med Sci Sports Exerc* 1999; **31**: S526-S533 [PMID: 10593523]

69 **Peterson JA**. Get moving! Physical activity counseling in primary care. *J Am Acad Nurse Pract* 2007; **19**: 349-357 [PMID: 17680900]

70 **Morrato EH**, Hill JO, Wyatt HR, Ghushchyan V, Sullivan PW. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care* 2007; **30**: 203-209 [PMID: 17259482 DOI: 30/2/203]

71 **Zhao G**, Ford ES, Li C, Mokdad AH. Compliance with physical activity

recommendations in US adults with diabetes. *Diabet Med* 2008; **25**: 221-227 [PMID: 18201213]

72 **Mancini M**, Prinster A, Annuzzi G, Liuzzi R, Giacco R, Medagli C, Cremone M, Clemente G, Maurea S, Riccardi G, Rivellese AA, Salvatore M. Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with (1)H magnetic resonance spectroscopy. *Metabolism* 2009; **58**: 1724-1730 [PMID: 19716568 DOI: 10.1016/j.metabol.2009.05.032]

73 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384 [PMID: 20494470 DOI: 10.1016/j.jhep.2010.04.008]

74 **Zelber-Sagi S**, Webb M, Assy N, Blendis L, Yeshua H, Leshno M, Ratziu V, Halpern Z, Oren R, Santo E. Comparison of fatty liver index with noninvasive methods for steatosis detection and quantification. *World J Gastroenterol* 2013; **19**: 57-64 [PMID: 23326163 DOI: 10.3748/wjg.v19.i1.57]

75 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

76 **Angulo P**. Diagnosing steatohepatitis and predicting liver-related mortality in patients with NAFLD: two distinct concepts. *Hepatology* 2011; **53**: 1792-1794 [PMID: 21557278 DOI: 10.1002/hep.24403]

77 **Ballestri S**, Lonardo A, Romagnoli D, Carulli L, Losi L, Day CP, Loria P. Ultrasonographic fatty liver indicator, a novel score which rules out NASH and is correlated with metabolic parameters in NAFLD. *Liver Int* 2012; **32**: 1242-1252 [PMID: 22520641 DOI: 10.1111/j.1478-3231.2012.02804.x]

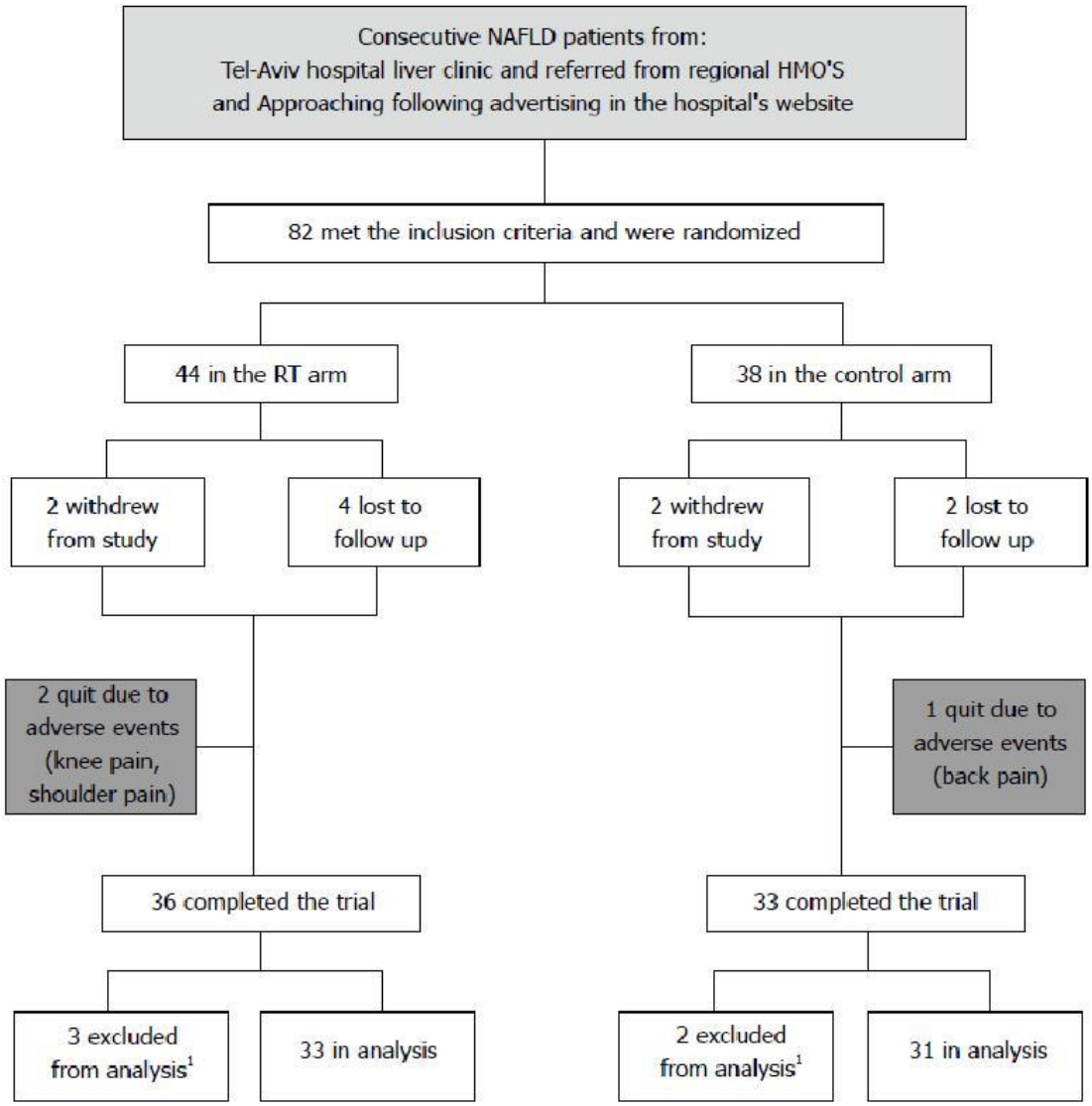

Figure 1 Flow chart of trial participants. RT: Resistance training; NAFLD: Non alcoholic liver disease.

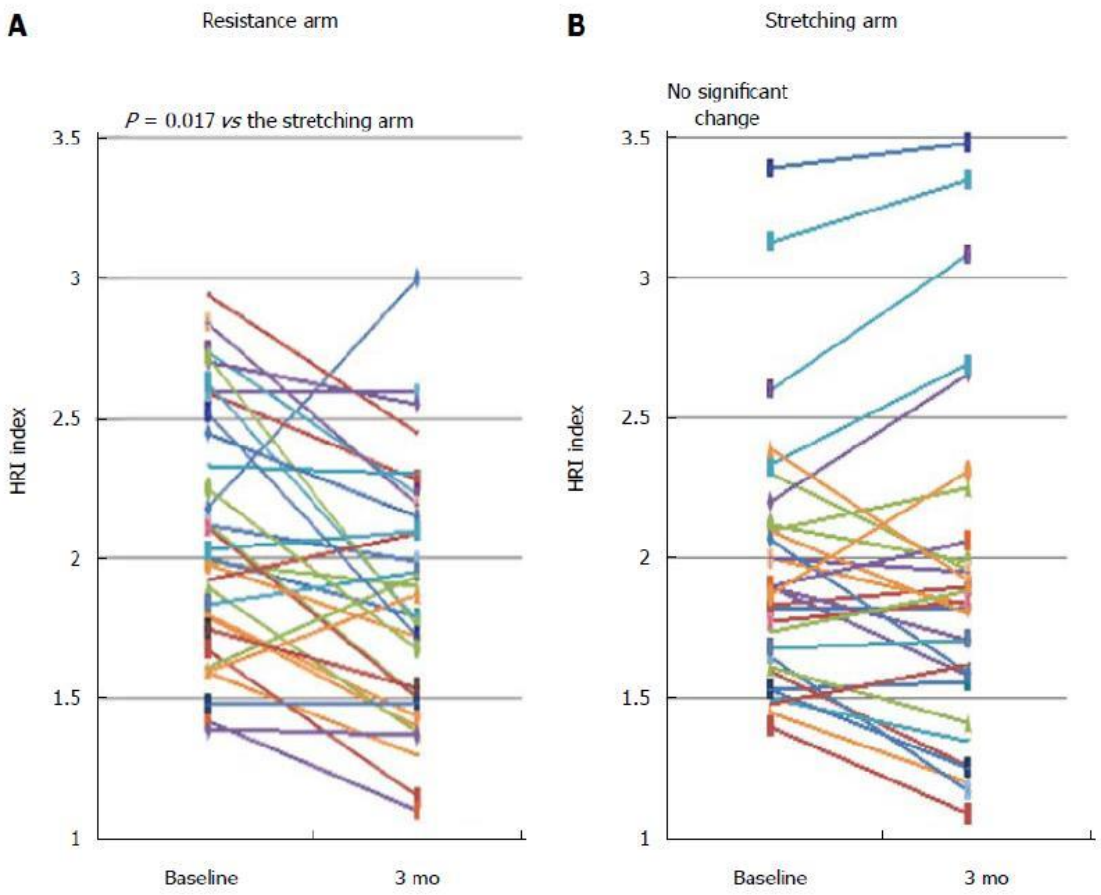

Figure 2 Change (absolute) in hepatorenal-ultrasound index values between baseline and end of trial by treatment arm. A: Resistance arm; B: Stretching arm. Each line represents a single patient. HRI: Hepatorenal-ultrasound index.

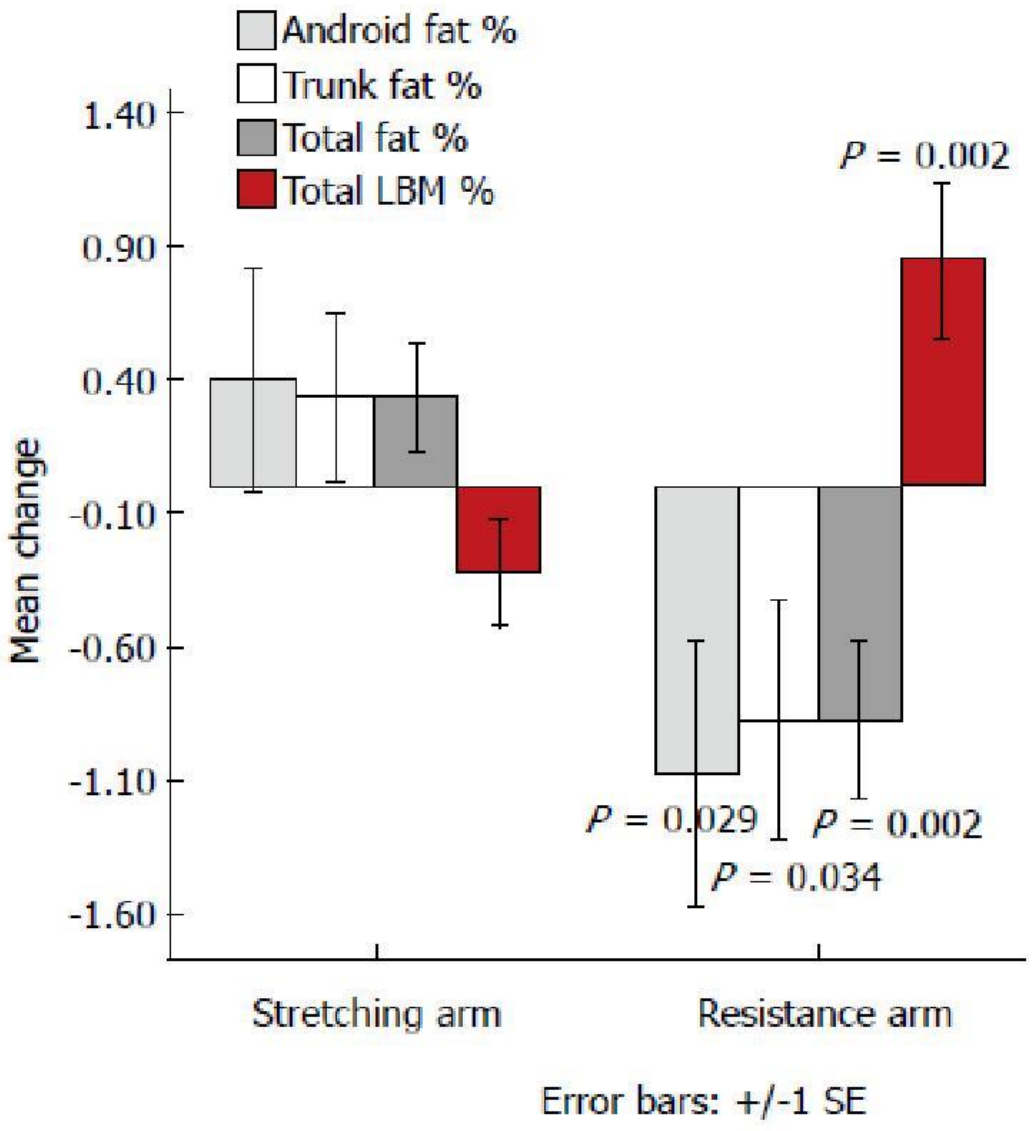

Figure 3 Change (absolute) in body composition parameters between baseline and end of trial by treatment arm. *P* represents the significance of difference between resistance and stretching arm for each parameter (n = 55). LBM: Lean body mass.

Table 1 Comparison between the two treatment arms (mean ± SD)

Parameter	Normal range	Total population (*n* = 64)	Resistance training (*n* = 33)	Stretching (*n* = 31)	*P*
Gender (males)		53.1%	48.5%	58.1%	0.443
Age (yr)		46.47 ± 10.76	46.32 ± 10.32	46.64 ± 11.4	0.909
HRI (score)		2.04 ± 0.45	2.11 ± 0.44	1.96 ± 0.46	0.203
BMI (kg/m^2)	20-25	31.02 ± 4.32	30.75 ± 4.52	31.30 ± 4.14	0.617
Waist circumference (cm)		105.85 ± 10.43	105.05 ± 10.77	106.71 ± 10.16	0.527
Systolic BP(mmHg)		120.79 ± 11.94	119.24 ± 11.74	122.44 ± 12.13	0.288
Diastolic BP (mmHg)		76.52 ± 7.49	75.89 ± 7.40	77.19 ± 7.64	0.492
Trunk fat		43.45% ± 6.21%	44.28% ± 5.99%	42.55% ± 6.42%	0.268
Android fat		47.49% ± 6.41%	48.10% ± 6.30%	46.88% ± 6.57%	0.47
Total fat		39.81% ± 7.89%	40.64% ± 7.29%	38.92% ± 8.52%	0.390
Lean body mass		58.20% ± 7.50%	57.34% ± 6.89%	59.11% ± 8.12%	0.349
Physical activity (index)		5.18 ± 1.84	5.23 ± 1.80	5.13 ± 1.92	0.82
Glucose (mg/dL)	70-110	84.44 ± 9.28	83.82 ± 8.50	85.10 ± 10.15	0.586
Insulin (mcu/mL)	5-25	27.40 ± 10.34	26.75 ± 9.69	28.10 ± 11.11	0.605
HOMA (score)		5.80 ± 2.55	5.65 ± 2.41	5.97 ± 2.72	0.616
HbA1C		5.59 ± 0.47	5.59 ± 0.49	5.59 ± 0.46	0.976
Cholesterol (mg/dL)	150-200	186.94 ± 41.07	192.18 ±	181.35 ±	0.288

			50.81	26.92	
Triglycerides (mg/dL)	50-175	143.80 ± 66.03	144.88 ± 75.69	142.65 ± 55.15	0.894
HDL (mg/dL)		47.51 ± 11.17	48.32 ± 12.29	46.65 ± 9.96	0.553
LDL (mg/dL)		110.72 ± 33.56	114.94 ± 40.37	106.23 ± 24.22	0.296
ALT (U/L)	5-39	51.61 ± 36.13	53.00 ± 35.61	50.13 ± 37.20	0.753
AST (U/L)	5-40	33.19 ± 16.14	34.30 ± 17.49	32.00 ± 14.76	0.572
GGT (U/L)	5-50	50.74 ± 56.6	55.69 ± 73.88	45.65 ± 30.44	0.486
Ferritin (ng/mL)	7.1-151	152.89 ± 135.81	162.15 ± 128.24	142.64 ± 145.39	0.586

BP: Blood pressure; HRI: Hepatorenal-ultrasound index; BMI: Body mass index; HOMA: Homeostasis model assessment; HbA1C: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase.

Table 2 Between group comparisons of changes from baseline to end of treatment and within group comparisons (mean ± SD)

Parameter	Normal range	Resistance training (*n* = 33)	Stretching (*n* = 31)	*P* between groups
HRI (score)		-0.25 ± 0.37[b]	-0.05 ± 0.28	0.017
Weight (kg)		-0.39 ± 1.43	0.33 ± 1.21	0.036
BMI (kg/m^2)	20-25	-0.13 ± 0.49	0.12 ± 0.41	0.036
Waist circumference (cm)		-0.79 ± 2.00[a]	0.70 ± 2.62	0.012
Systolic BP(mmHg)		1.27 ± 11.54	-1.19 ± 7.44	0.328
Diastolic BP (mmHg)		-2.53 ± 5.61[a]	-0.11 ± 4.43	0.066
Glucose (mg/dL)	70-110	2.24 ± 10.30	-0.23 ± 6.59	0.262
Insulin (mcu/mL)	5-25	0.82 ± 7.04	-0.62 ± 7.97	0.447
HOMA (score)		0.37 ± 2.04	-0.24 ± 1.75	0.209
HbA1C	3.9-6	-0.01% ± 0.13%	0.04% ± 0.14%	0.186
Cholesterol (mg/dL)	150-200	-8.61 ± 29.2	6.1 ± 17.25	0.018
Triglycerides (mg/dL)	50-175	-13.48 ± 62.30	11.55 ± 51.65	0.086
HDL (mg/dL)		0.13 ± 6.43	0.16 ± 5.64	0.984
LDL (mg/dL)		-6.09 ± 26.38	3.61 ± 14.57	0.076
ALT (U/L)	5-39	-5.30 ± 9.65[b]	-5.10 ± 14.43	0.946
AST (U/L)	5-40	-2.76 ± 7.75[a]	-2.68 ± 6.95[a]	0.965
GGT (U/L)	5-50	-4.25 ± 13.03	2.35 ± 16.48	0.082
Ferritin (ng/mL)		-18.29 ± 48.63[a]	8.25 ± 51.09	0.046

Total calories (kcal)	-527.55 ± 786.37[b]	-274.29 ± 871.19	0.230
Total fat (g)	-15.09 ± 35.24[b]	-5.87 ± 47.82[b]	0.386
Carbohydrates (g)	-84.08 ± 121.11[b]	-39.38 ± 98.72[a]	0.114
Protein (g)	-21.58 ± 41.54[b]	-19.30 ± 34.38[b]	0.813
Saturated fat (g)	-6.13 ± 10.39[b]	-3.07 ± 11.66	0.276
MUFA (g)	-4.00 ± 15.23	-2.44 ± 18.29	0.713
PUFA (g)	-3.45 ± 13.55	0.19 ± 16.64	0.344

For paired samples *t*-test, [a]$P < 0.05$, [b]$P < 0.01$ within group comparisons. BP: Blood pressure; HRI: Hepatorenal-ultrasound index; BMI: Body mass index; HOMA: Homeostasis model assessment; HbA1C: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; MUFA: Monounsaturated fat, PUFA: Polyunsaturated fat.