Simple Resistance Exercise helps Patients with Non-alcoholic Fatty Liver Disease

Authors
A. Takahashi[1], K. Abe[1], K. Usami[2], H. Imaizumi[1], M. Hayashi[1], K. Okai[1], Y. Kanno[1], N. Tanji[3], H. Watanabe[1], H. Ohira[1]

Affiliations
[1] Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan
[2] Internal Medicine, Usami Medical Clinic, Koriyama, Japan
[3] Gastroenterology, Watari Hospital, Fukushima, Japan

Key words
- push-ups
- squats
- NAFLD

Abstract

To date, only limited evidence has supported the notion that resistance exercise positively impacts non-alcoholic fatty liver disease. We evaluated the effects of resistance exercise on the metabolic parameters of non-alcoholic fatty liver disease (NAFLD) in 53 patients who were assigned to either a group that performed push-ups and squats 3 times weekly for 12 weeks (exercise group; $n=31$) or a group that did not (control; $n=22$). Patients in the control group proceeded with regular physical activities under a restricted diet throughout the study. The effects of the exercise were compared between the 2 groups after 12 weeks. Fat-free mass and muscle mass significantly increased, whereas hepatic steatosis grade, mean insulin and ferritin levels, and the homeostasis model assessment-estimated insulin resistance index were significantly decreased in the exercise group. Compliance with the resistance exercise program did not significantly correlate with patient background characteristics such as age, sex, BMI and metabolic complications. These findings show that resistance exercise comprising squats and push-ups helps to improve the characteristics of metabolic syndrome in patients with non-alcoholic fatty liver disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome that is prevalent in 20–30% of adults worldwide [3,9,31]. Non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD that can progress to cirrhosis or hepatocellular carcinoma. Therefore, early treatment is important to prevent progression from NAFLD to NASH.

Several treatments for NAFLD have been suggested [34], but regimens differ among individuals. For example, since increases in body weight and insulin resistance induce NAFLD, changes in lifestyle are important for treating this disease [18,26,28,30]. Both aerobic and resistance types of exercise comprise effective lifestyle intervention for NAFLD [19,21,33]. The effects of aerobic exercise have been investigated in patients with NAFLD [19,21,33], but less is known about those of resistance exercise on NAFLD [2,14,35]. Hallsworth et al. discovered that a resistance exercise program comprising biceps curls, calf raises, triceps press, chest press, seated hamstring curls, shoulder press, leg extension and lateral pull-down improves NAFLD independently of changes in body weight [14]. These findings were unique because NAFLD improved without a loss of body weight. In contrast, Bacchi et al. found that resistance and aerobic types of training are equally effective in reducing hepatic fat content among patients with type-2 diabetes and NAFLD [2]. Their resistance exercise program involving the major muscle groups required exercise equipment for chest press, shoulder press, vertical traction, leg press, leg extensions, leg curls and abdominal crunches; and free weights for biceps, and abdominals. Moreover, Lee et al. demonstrated that either aerobic or resistance exercise can reduce abdominal fat and intrahepatic lipid in obese adolescent boys [24]. Although both resistance training and aerobic exercise can reduce hepatic fat content and improve insulin sensitivity, defined training methods, specialized equipment and a specific environment, such as a gym, are usually required. The effects of both types of exercise are restricted by poor compliance, and thus a simple, convenient and safe exercise program is important for treating NAFLD. Therefore, we evaluated the effects of push-ups and squats in patients with NAFLD.

accepted after revision
March 25, 2015

Bibliography
DOI http://dx.doi.org/10.1055/s-0035-1549853
Published online: June 19, 2015
Int J Sports Med 2015; 36: 848–852 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0172-4622

Correspondence
Dr. Atsushi Takahashi, MD
Gastroenterology and Rheumatology
Fukushima Medical University School of Medicine
1 HikarigaokaFukushima
Fukushima
Japan 960-1295
Tel.: +81/24/547 1202
Fax: +81/24/547 2005
junior@fmu.ac.jp

Methods

Participants

All protocols were approved by the Ethics Committee of Watari Hospital and Fukushima Medical University School of Medicine (Fukushima, Japan). All patients provided written informed consent to participate in the study, which conformed to the ethical standards of Sports and Exercise Science Research [15]. The diagnosis of NAFLD was based on the Asia-Pacific Working Party guidelines for NAFLD [8]. The exclusion criteria comprised evidence of other liver diseases such as chronic hepatitis C, chronic hepatitis B, autoimmune hepatitis, primary biliary cirrhosis and alcoholic liver disease (>20 g of alcohol/day), consumption of weight-loss agents, corticosteroids, tamoxifen, herbal medicines and anti-diabetic agents (patients with type-2 diabetes mellitus who were stable for >6 months without additional drugs included), heart or kidney disease and other preexisting medical conditions that might prevent participation in the exercise program. Among 60 patients who agreed to participate in this study, 5 and 2 were excluded due to protocol violations and missing data, respectively. The remaining 53 patients were assigned to a group that performed resistance exercise or a control group.

Procedure

Resistance exercise

The patients were educated about resistance exercise comprising push-ups and squats at the beginning of the study (**Fig. 1a, b**). The exercise group performed 3 sets of 10 push-ups and 3 sets of 10 squats at 1-min intervals per set over a period of 20–30 min and recorded their compliance with the regimen.

Controls

The control group was educated about dietary restrictions and encouraged to participate in regular physical activities according to the American Gastroenterological Association for NAFLD [1] and the Physical Activity of Health Promotion guidelines recommended by the Ministry of Health, Labor and Welfare of Japan [26].

Outcome measurements

Total body weight and composition were measured using a DC-320 bioelectrical impedance analyzer (Tanita Corporation, Tokyo, Japan). Body mass index (BMI) was calculated by dividing body weight (kg) by height (m^2). Venous blood samples were collected in the morning after an overnight fast. Levels of aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), gamma-glutamyl transpeptidase (γ-GTP, IU/L), high-density lipoprotein cholesterol (HDL-C, mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), triglyceride (TG, mg/dL), fasting plasma glucose (FPG, mg/dL) and plasma insulin (μU/mL) were determined using standard methods. Insulin resistance was calculated according to the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index using the following formula: HOMA-IR = FPG (mg/dL) × fasting plasma insulin (μU/mL)/405

Hepatic steatosis was assessed according to Saadeh et al. using LOGIQ 7 (GE Health Care, Piscataway, NJ, USA) and Pro Sound alpha-7 ultrasonographs (Hitachi-Aloka Medical Ltd., Tokyo, Japan) [29] and graded according to the severity of echogenicity. Grade 1 included a slight diffuse increase in fine echoes in liver parenchyma, with normal visualization of the diaphragm and intrahepatic vessel borders; Grade 2 a moderate diffuse increase

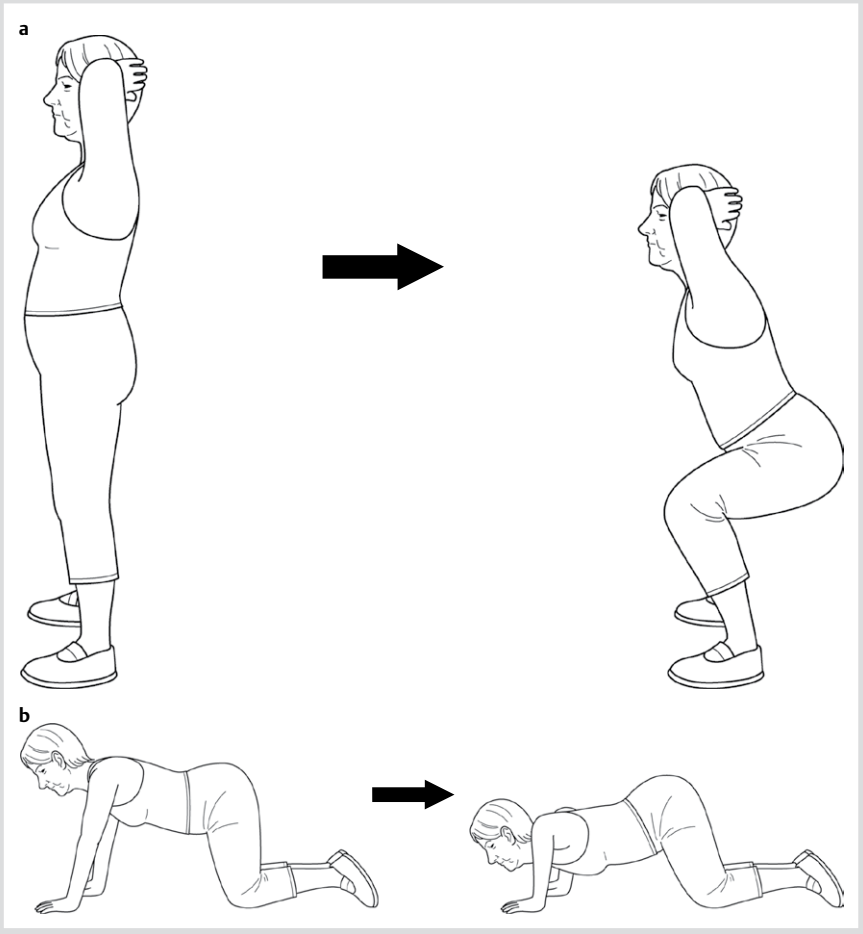

Fig. 1 Resistance exercise program. **a** Squats. The patient stands with feet positioned about 2 fists wider than the shoulders with the toes turned slightly outward. The patient will slowly sit down over a period of 9–10 s until the posterior surface of the thigh is parallel to the floor and maintain this position for 1–2 s. Immediately thereafter, the patients will rapidly stand upright. The back should be kept straight to prevent lumbago. This series of movements should proceed under natural breathing rhythms. **b** Push-ups. The knees and the palms of splayed hands are placed on the floor. The elbows will slowly bend for 9–10 s to bring the chest close to the floor. This position should be maintained for 1–2 s and then the patient will straighten the elbows by pushing against the floor and immediately return to the original position while breathing naturally. The back should remain flat during this exercise.

in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; and Grade 3 an obvious increase in fine echoes with poor or obscured visualization of intrahepatic vessel borders, diaphragm and posterior right liver lobe.

Table 1 Patient characteristics.

Characteristic	Control (n=22)	Resistance exercise (n=31)	*P*
sex (male/female)	10/12	9/22	0.348
age (y)	51.4±14.8	55.5±13.2	0.343
body weight (kg)	72.8±13.1	72.0±12.2	0.787
body mass index	28.2±4.2	28.5±3.1	0.454
diabetes mellitus (n)	8	9	0.791
dyslipidemia (n)	18	21	0.407
hypertension (n)	5	14	0.165

Values are expressed as means±SD. Data were statistically analyzed using Mann-Whitney *U* test and χ^2 tests

Table 2 Exercise program compliance rate and patient factors.

Patient factors			Rate of compliance (r)	*P*
age			0.2288	0.208
body mass index			−0.2429	0.180
		n	Rate of compliance (%)	*P* *
male		9	61.3±27.5	0.519
female		22	71.8±29.0	
diabetes mellitus	Yes	9	61.1±28.3	0.520
	No	22	71.4±28.7	
dyslipidemia	Yes	21	68.2±28.4	0.729
	No	10	68.9±29.7	
hypertension	Yes	15	64.2±28.5	0.763
	No	16	72.3±28.8	

Values are expressed as means±SD; r, correlations between variables measured using Pearson's correlation coefficient. * Mann-Whitney *U* test

Statistical analyses

Results are expressed as means±standard deviation (SDs). Differences between the 2 groups were analyzed using Mann-Whitney *U* tests. After tests for normal distribution, significant within-group differences between before and after 12 weeks were determined using paired Student's *t*-tests. Treatment group×time interactions were assessed using two-way (group×time) repeated measures ANOVA. Dichotomous variables were compared using the χ^2 test. Correlations between variables were measured using Pearson's correlation coefficient. $P<0.05$ was considered to indicate statistically significant differences.

Results

Between January 2012 and September 2013, 53 patients (female, n=34) with NAFLD were assigned to 12 weeks of resistance exercise (n=31) or lifestyle counseling (n=22; controls). **Table 1** summarizes the clinical characteristics of the patients. The 2 groups were matched for baseline values and metabolic complications (**Table 1**, **3**).

None of the patients in the exercise group developed severe adverse events during the study period.

Compliance with the resistance exercise program was 67.2%, and it did not significantly correlate with patient age and BMI. However, age and compliance were positively correlated. A weak negative correlation was also observed between BMI and compliance. There was no significant difference in compliance by patient sex. Compliance rates between patients with and without metabolic complications also did not significantly differ (**Table 2**).

There was a significant time-by-treatment interaction in fat-free mass ($p=0.014$) and muscle ($p=0.024$). Fat-free mass (45.1±10.2 vs. 45.4±10.1 kg, p=0.018) significantly increased in the exer-

Table 3 Changes in physical and clinical parameters after 12 weeks of resistance exercise.

	Control			Resistance exercise			Time×treatment interaction (*p*)
	Baseline	12 weeks	*p*	Baseline	12 weeks	*p*	
body weight (kg)	72.8±13.1	72.5±12.6	0.309	72.0±12.2	71.7±11.5	0.323	0.855
body mass index (kg/m^2)	28.2±4.2	28.1±3.9	0.406	28.5±3.1	28.4±2.9	0.254	0.921
body fat (kg)	25.3±6.9	25.2±6.4	0.800	26.9±6.1	26.3±5.6	0.013	0.186
fat free mass (kg)	47.6±11.2	47.3±10.8	0.212	45.1±10.2	45.4±10.1	0.018 *	0.014†
muscle (kg)	45.0±10.7	44.7±10.3	0.192	42.6±9.8	42.8±9.6	0.055	0.024†
muscle/body weight (%)	61.5±7.2	61.4±6.9	0.803	58.9±6.9	59.5±6.5	0.024	0.108
AST (IU/L)	48.0±25.4	42.5±14.9	0.216	45.2±25.1	38.1±18.4	0.042	0.077
ALT (IU/L)	78.5±47.6	71.0±38.4	0.243	75.1±61.3	56.3±49.7	<0.001	0.158
ALP (IU/L)	236.1±71.8	234.0±78.0	0.776	274.5±91.9	256.1±91.1	0.222	0.257
γGTP (IU/L)	67.0±40.6	59.1±28.4	0.137	48.7±32.6	43.9±34.1	0.099	0.470
LDL-C (mg/dL)	158.1±32.2	145.2±34.8	0.026 *	125.3±29.2	126.4±27.4	0.691	0.016†
HDL-C (mg/dL)	53.1±14.0	52.0±13.9	0.521	55.8±18.0	57.7±25.5	0.608	0.455
triglyceride (mg/dL)	175.9±86.6	169.3±85.9	0.748	139.3±84.9	145.1±88.4	0.565	0.125
ferritin (ng/dL)	182.5±193.0	164.6±110.0	0.503	206.0±202.9	174.8±202.5	0.036	0.632
blood glucose (mg/dL)	113.2±25.4	112.3±25.0	0.737	111.6±17.2	108.7±15.5	0.090	0.503
insulin (μU/mL)	11.8±5.4	11.3±5.6	0.616	13.4±8.1	11.3±4.6	0.041	0.128
HOMA-IR	3.1±1.4	3.1±1.7	0.888	3.8±2.8	3.1±1.5	0.042	0.163
HbA1c (%)	6.1±0.9	6.1±1.0	0.392	6.0±0.6	6.0±0.7	0.224	0.713
hepatic steatosis	2.00±0.60	2.05±0.58	0.427	1.77±0.80	1.53±0.64	0.004 *	0.007†

Values are expressed as means±SD. Severity of hepatic steatosis graded according to criteria of Saadeh et al. [15]. Significant within-group differences between before and after 12 weeks were determined using paired Student's *t*-tests. Treatment group×time interaction were assessed using two-way (group×time) repeated measures ANOVA. * Significant differences between baseline and after 12 weeks ($p<0.05$). † Significant differences time×treatment interaction ($p<0.05$). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol

Table 4 Induced changes after 12 weeks of resistance exercise.

Δ	Control	Resistance exercise	*p*
body fat (kg)	−0.08±1.49	−0.58±1.23	0.263
fat free mass (kg)	−0.24±0.88	0.30±0.67	0.011 *
muscle (kg)	−0.24±0.82	0.25±0.70	0.024 *
muscle/body weight (%)	−0.08±1.45	0.53±1.23	0.056
AST (IU/L)	−5.6±20.6	−7.1±18.6	0.371
ALT (IU/L)	−7.5±29.1	−18.8±28.0	0.108
LDL-C (mg/dL)	−13.0±24.7	1.1±14.8	0.047 *
ferritin (ng/dL)	−18.0±117.6	−31.2±77.8	0.004 *
insulin (μU/mL)	−0.46±3.80	−2.03±5.28	<0.001 *
HOMA-IR	−0.03±1.07	−0.70±1.81	<0.001 *
hepatic steatosis	0.05±0.26	−0.24±0.43	0.012 *

Δ, change in variable between baseline and 12 weeks later. Differences between groups analyzed using Mann-Whitney *U* test. * Significant differences between control vs. resistance exercise ($p<0.05$)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance

cise group after 12 weeks. We also found a significant time by treatment interaction in hepatic steatosis grade ($p=0.007$). Moreover, hepatic steatosis grade (1.77±0.80 vs. 1.53±0.64, $p=0.004$) significantly decreased in the exercise but not in the control group (**Table 3**). Mean levels of fat-free mass (−0.24±0.88 vs. 0.30±0.67 kg, p=0.011) and muscle (−0.24±0.82 vs. 0.25±0.70 kg, p=0.024) significantly increased in the exercise, compared with the control group. The grade of hepatic steatosis (0.05±0.26 vs. −0.24±0.43 p=0.012) significantly decreased in the exercise compared with the control group (**Table 4**). The grade of hepatic steatosis also significantly decreased in patients with diabetes (n=9) in the exercise (0.13±0.44 vs. −0.50±0.50 p=0.023) compared with the control (n=8) group. Changes in the ratio of muscle to body weight correlated with exercise compliance (r=0.336, p=0.060).

There was a significant time-by-treatment interaction in levels of low-density lipoprotein cholesterol (LDL-C) ($p=0.016$). The levels of LDL-C significantly decreased in the control (158.1±32.2 vs. 145.2±34.8 mg/dL, $P=0.026$) (**Table 3**). Mean values for ferritin (−18.0±117.6 vs. −31.2±77.8 ng/mL, $P=0.004$), insulin (−0.46±3.80 vs. −2.03±5.28 μU/mL, $P<0.001$) and the HOMA-IR index (−0.03±1.07 vs. −0.70±1.81, $P<0.001$) were significantly decreased in the exercise compared with the control group (**Table 4**).

Mean levels of AST, ALT and LDL-C did not significantly change in patients with diabetes in the control (n=8) and exercise (n=9) groups at 12 weeks. Changes in ALT levels (r=−0.258, $p=0.155$) and the HOMA-IR index (r=−0.236, $p=0.193$) weakly and negatively correlated with changes in the muscle: body weight ratio in the exercise group.

Discussion

Lifestyle changes are basic management tools for NAFLD [18,26,28,30,33]. Furthermore, weight loss is a confirmed therapy for NAFLD [30]. Exercise is a lifestyle therapy, and its effects on weight loss, liver fat reduction and insulin sensitivity in patients with NAFLD have been described in detail [19,21,33]. However, aerobic exercise might be a difficult therapeutic modality for NAFLD because of poor patient compliance and the longer duration required for aerobic exercise to decrease hepatic steatosis [6,12]. Resistance exercise requires low cardiorespiratory demand, is sustainable, and is acceptable to patients [13,23]. However, only a few studies have found that resistance exercise has value as a treatment for NAFLD [2,14,35]. Resistance exercise has no side effects in such patients and the reported compliance is also good [2,14]. However, resistance exercise might be less accessible than aerobic exercise because of a requirement for specialized equipment and specific exercise methods. In fact, others have reported the value of various types of resistance exercise using weight machines for patients with NAFLD [2,14]. Squats and push-ups that use body weight as a load are simple resistance exercises that affect muscle strength [7,22,25]. Therefore, we selected these simple exercises and confirmed their value as NAFLD therapy. This is the first study to show that resistance exercise can improve NAFLD equally well when applied using either body weight alone or various machines. This finding implied that specific equipment is not required to improve NAFLD. Moreover, our patients exercised at home and at will. These situations are more advantageous for exercise compliance than previous resistance training programs. Compliance did not significantly differ between individuals with and without metabolic complications in the present study, although compliance among obese patients remained low. Therefore, the exercise resistance program described herein should prove useful for patients with NAFLD regardless of circumstance.

Resistance exercise upregulates the expression of glucose transporter type 4 (GLUT4), glycogen synthase (GS), and total GS activity in skeletal muscle. Consequently, whole-body glucose metabolism increases [10,17]. Resistance exercise decreases liver fat and its mediators without decreasing body weight or fat mass in patients with NAFLD [2,14]. Moreover, hybrid training (muscle stimulated by electrical means and by voluntary contraction) decreases steatosis and insulin resistance in patients with NAFLD in concert with a decrease in body weight or fat mass [20]. The effects of resistance exercise in the present study were at least partially due to an increase in muscle mass. In fact, mean muscle mass significantly increased in the exercise compared with the control group. Moreover, changes in HOMA-IR weakly and negatively correlated with changes in the ratio of muscle to body weight.

Contracting skeletal muscle functions as an endocrine organ that produces and releases myokines, which influence metabolism in other tissues and organs [27]. Hybrid training decreases hepatic steatosis and insulin resistance independently of increases in muscle mass [20]. Therefore, myokine signaling can be a mediator of resistance exercise effectiveness in patients with NAFLD [11]. Kawaguchi et al. reported a decrease in serum levels of interleukin-6 (IL-6), which is the first myokine to appear in serum after hybrid training [20]. Thus, the effects of resistance exercise might be explained by these 2 mechanisms, although serum IL-6 levels did not significantly differ before and after resistance exercise in the present study (6.2±12.1 vs. 7.5±17.1 pg/mL, $P=0.519$). Plasma levels of IL-6 are directly related not only to exercise intensity but also to other factors [32]. Hence, the amount of resistance exercise might not have been sufficient to induce significant changes in IL-6 levels in the present study.

This study had limitations. Firstly, body composition and liver fat were respectively analyzed using bioelectrical impedance and ultrasonography (US), which is the most popular and minimally invasive method of detecting fatty liver disease. The sensitivity of US to detect fat infiltration is low when fatty changes

are <30% [5,16]. Saadeh et al. and Celle et al. independently reported a positive association between fat content determined by liver histology and US findings [4,29]. However, US has several issues such as technical difficulties with scanning obese patients and the subjective judgments of operators [29]. Therefore evaluation using magnetic resonance imaging, computed tomography, or liver biopsy is required to precisely measure body composition and liver fat. Secondly, this preliminary study sampled a small patient cohort and neither diet nor physical activities were evaluated. Therefore, with the exception of fat-free mass, muscle, hepatic steatosis grade, ferritin levels, insulin levels, and the HOMA-IR index, significant differences were not identified between the exercise and control groups. Moreover, we could not confirm a significant improvement in patients with diabetes mellitus, although this might be associated with low compliance or the effects of anti-diabetic drugs. In the future, a randomized large-scale study is required to confirm the value of simple resistance exercise as a treatment for NAFLD.

We concluded that resistance exercise comprising push-ups and squats is simple, safe, and effective for patients with NAFLD. Therefore, this exercise program might complement NAFLD treatment regimens for patients who find aerobics or other types of resistance exercises challenging.

Acknowledgements

This study was supported by a fellowship from Fukushima Medical University.

References

1 *American Gastroenterological Association*. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 1702–1704
2 *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 NAFLD (The RAED2 randomized trial). Hepatology 2013; 58: 1287–1295
3 *Browning JD*, *Szczepaniak LS*, *Dobbins R*, *Nuremberg P*, *Horton JD*, *Cohen JC*, *Grundy SM*, *Hobbs HH*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40: 1387–1395
4 *Celle G*, *Savarino V*, *Picciotto A*, *Magnolia MR*, *Scalabrini P*, *Dodero M*. Is hepatic ultrasonography a valid alternative tool to liver biopsy? Report on 507 cases studied with both techniques. Dig Dis Sci 1988; 33: 467–471
5 *Dasarathy S*, *Dasarathy J*, *Khiyami A*, *Joseph R*, *Lopez R*, *McCullough AJ*. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009; 51: 1061–1067
6 *Devries MC*, *Samjoo IA*, *Hamadeh MJ*, *Tarnopolsky MA*. Effect of endurance exercise on hepatic lipid content, enzymes, and adiposity in men and women. Obesity (Silver Spring) 2008; 16: 2281–2288
7 *Durak EP*, *Jovanovic-Peterson L*, *Peterson CM*. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type I diabetic men. Diabetes Care 1990; 13: 1039–1043
8 *Farrell GC*, *Chitturi S*, *Lau GK*, *Sollano JD.Asia-Pacific Working Party on NAFLD*. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol 2007; 22: 775–777
9 *Farrell GC*, *Wong VW*, *Chitturi S*. NAFLD in Asia – as common and important as in the West. Nat Rev Gastroenterol Hepatol 2013; 10: 307–318
10 *Ferrara CM*, *Goldberg AP*, *Ortmeyer HK*. Effects of aerobic and resistive exercise training on glucose disposal and skeletal muscle metabolism in older men. J Gerontol A Biol Sci Med Sci 2006; 61: 480–487
11 *Finelli C*, *Tarantino G*. Have guidelines addressing physical activity been established in nonalcoholic fatty liver disease? World J Gastroenterol 2012; 18: 6790–6800
12 *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
13 *Gordon BA*, *Benson AC*, *Bird SR*, *Fraser SF*. Resistance training improves metabolic health in type 2 diabetes: a systematic review. Diabetes Res Clin Pract 2009; 83: 157–175
14 *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
15 *Harriss DJ*, *Atkinson G*. Ethical standards in sport and exercise science research: 2014 update. Int J Sports Med 2013; 34: 1025–1028
16 *Hernaez R*, *Lazo M*, *Bonekamp S*, *Kamel I*, *Brancati FL*, *Guallar E*, *Clark JM*. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011; 54: 1082–1090
17 *Holten MK*, *Zacho M*, *Gaster M*, *Juel C*, *Wojtaszewski JF*, *Dela F*. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes 2004; 53: 294–305
18 *Johnson NA*, *George J*. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. Hepatology 2010; 52: 370–381
19 *Johnson NA*, *Keating SE*, *George J*. Exercise and the liver: Implication for therapy in fatty liver disorders. Semin Liver Dis. 2012; 32: 65–79
20 *Kawaguchi T*, *Shiba N*, *Maeda T*, *Matsugaki T*, *Takano Y*, *Itou M*, *Sakata M*, *Taniguchi E*, *Nagata K*, *Sata M*. Hybrid training of voluntary and electrical muscle contractions reduces steatosis, insulin resistance, and IL-6 levels in patients with NAFLD: a pilot study. J Gastroenterol 2011; 46: 746–757
21 *Keating SE*, *Hackett DA*, *George J*, *Johnson NA*. Exercise and non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Hepatol 2012; 57: 157–166
22 *Kraemer WJ*, *Mazzetti SA*, *Nindl BC*, *Gotshalk LA*, *Volek JS*, *Bush JA*, *Marx JO*, *Dohi K*, *Gómez AL*, *Miles M*, *Fleck SJ*, *Newton RU*, *Häkkinen K*. Effect of resistance training on women's strength/power and occupational performances. Med Sci Sports Exerc 2001; 33: 1011–1025
23 *Larose J*, *Sigal RJ*, *Boule NG*, *Wells GA*, *Prud'homme D*, *Fortier MS*, *Reid RD*, *Tulloch H*, *Coyle D*, *Phillips P*, *Jennings A*, *Khandwala F*, *Kenny GP*. Effect of exercise training on physical fitness in type II diabetes mellitus. Med Sci Sports Exerc 2012; 42: 1439–1447
24 *Lee S*, *Bacha F*, *Hannon T*, *Kuk JL*, *Boesch C*, *Arslanian S*. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. Diabetes 2012; 61: 2787–2795
25 *McGuigan MR*, *Tatasciore M*, *Newton RU*, *Pettigrew S*. Eight weeks of resistance training can significantly alter body composition in children who are overweight or obese. J Strength Cond Res 2009; 23: 80–85
26 *Oza N*, *Eguchi Y*, *Mizuta T*, *Ishibashi E*, *Kitagima Y*, *Horie H*, *Ushirogawa M*, *Tsuzura T*, *Nakashita S*, *Takahashi H*, *Kawaguchi Y*, *Oda Y*, *Iwakiri R*, *Ozaki I*, *Eguchi T*, *Ono N*, *Fujimoto K*. A pilot trial of body weight reduction for nonalcoholic fatty liver disease with a home-based lifestyle modification intervention delivered in collaboration with interdisciplinary medical staff. J Gastroenterol 2009; 44: 1203–1208
27 *Pedersen BK*, *Akerström TC*, *Nielsen AR*, *Fischer CP*. Role of myokines in exercise and metabolism. J Appl Physiol 2007; 103: 1093–1098
28 *Promrat K*, *Kleiner DE*, *Niemeier HM*, *Jackvony E*, *Kearns M*, *Wands JR*, *Fava JL*, *Wing RR*. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010; 51: 121–129
29 *Saadeh S*, *Younossi ZM*, *Remer EM*, *Gramlich T*, *Ong JP*, *Hurley M*, *Mullen KD*, *Cooper JN*, *Sheridan MJ*. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745–750
30 *Thoma C*, *Day CP*, *Trenell MI*. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: A systematic review. J Hepatol 2012; 56: 255–266
31 *Torres DM*, *Harrison SA*. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008; 134: 1682–1698
32 *Tsochatzis EA*, *Papatheodoridis GV*, *Archimandritis AJ*. Adipokines in nonalcoholic steatohepatitis: from pathogenesis to implications in diagnosis and therapy. Mediators Inflamm 2009; 2009: 831670
33 *Ueno T*, *Sugawara H*, *Sujaku K*, *Hashimoto O*, *Tsuji R*, *Tamaki S*, *Torimura T*, *Inuzuka S*, *Sata M*, *Tanikawa K*. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol 1997; 27: 103–107
34 *Vuppalanchi R*, *Chalasani N*. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology 2009; 49: 306–317
35 *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