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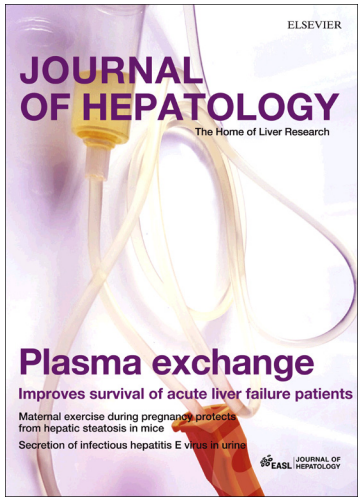

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Aerobic versus Resistance Exercise in Non-alcoholic Fatty Liver Disease: A Systematic Review

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Keywords: aerobic training, resistance training, exercise energy consumption, adipokine, myokine

Abbreviations: NAFLD, non-alcoholic fatty liver disease; MR, magnetic resonance; METs, metabolic equivalents; %VO_2max, percentage of maximum oxygen consumption; BMI, body mass index; ALT, alanine aminotransferase; HIIT, high-intensity interval training.

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Abstract

Background & aims: Exercise is a first-line therapy for patients with non-alcoholic fatty liver disease (NAFLD). We sought to 1) summarize effective aerobic and resistance exercise protocols for NAFLD and 2) compare the effects and energy consumption of aerobic and resistance exercises.

Methods: A literature search was performed using PubMed, Web of Science, and Scopas to January 28, 2016. From a total of 95 articles, 23 studies including 24 aerobic and 7 resistance exercise protocols were selected for the summary of exercise protocols. Twelve articles including 13 aerobic and 4 resistance exercise protocols were selected for the comparative analysis.

Results: For aerobic exercise, the median effective protocol was 4.8 metabolic equivalents (METs) for 40 min/session, 3 times/week for 12 weeks. For resistance exercise, the median effective protocol was 3.5 METs for 45 min/session, 3 times/week for 12 weeks. Aerobic and resistance exercise improved hepatic steatosis. No significant difference was seen in the duration, frequency, or period of exercise between the two exercise groups; however, %VO_2max and energy consumption were significantly lower in the resistance than in the aerobic group (50 [45-98] vs. 28 [28-28]%, P = 0.0034; 11,064 [6,394-21,087] vs. 6,470 [4,104-12,310] kcal/total period, P = 0.0475).

Conclusions: Resistance exercise improves NAFLD with less energy consumption. Thus, resistance exercise may be more feasible than aerobic exercise for NAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise. These data may indicate a possible link between resistance exercise and lipid metabolism in the liver.

Key Point Box

- ✓ Both aerobic and resistance exercise reduce hepatic steatosis in non-alcoholic fatty liver disease (NAFLD) with similar frequency, duration, and period of exercise (40-45 min/session 3 times/week for 12 weeks); however, the 2 forms of exercise have different characteristics.
- ✓ Intensity and energy consumption were significantly lower for resistance than for aerobic exercise.
- ✓ Resistance exercise may be more feasible than aerobic exercise for NAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise.

Introduction

Exercise is a first-line therapy for patients with various chronic diseases [1, 2]. It results not only in an increase in energy consumption and muscle strength, but also an improvement of arthritis and depression [2]. These pleiotropic effects are thought to be beneficial for patients with metabolic syndrome, including for non-alcoholic fatty liver disease (NAFLD), its hepatic manifestation. The latter is a risk factor for the development of diabetes mellitus, cardiovascular disease, cirrhosis, and hepatocellular carcinoma [3, 4]. Since there are no approved pharmacotherapies for NAFLD, exercise is a cornerstone for the management of patients with NAFLD [5, 6]. Both aerobic and resistance exercises improve several health outcomes in patients with NAFLD [5, 6]; however, they have different characteristics.

Aerobic exercise, such as walking and cycling is a low-cost non-pharmacological intervention, irrespective of place, and available to the vast majority of the general public. A feature of aerobic exercise is higher energy consumption during the exercise session. Aerobic exercise reduces body weight as well as other variables associated with NAFLD, such as hemoglobin A1c, resting blood pressure, and serum cholesterol levels [7]. On the other hand, aerobic exercise causes fatigue and discomfort, leading to poor long-term compliance. Since it requires high cardiorespiratory fitness, such exercise can itself be detrimental to those with cardiovascular disease [8].

Resistance exercise is any form of exercise that causes the muscles to contract against external resistance with the expectation of increasing muscular strength, mass and bone density. Resistance exercise also improves

dyslipidemia, hypertension, and insulin resistance [8-10]. One feature of resistance exercise is that it improvements metabolic parameters with less energy consumption [11]. Thus, resistance exercise may be more feasible for subgroups of patients with NAFLD, particularly those with poor cardiorespiratory fitness or those who are overweight and cannot tolerate or participate in aerobic fitness [4]. However, resistance exercise might be less accessible than aerobic exercise because of the requirement for specialized equipment and specific exercise methods.

Informative reviews regarding exercise prescription for NAFLD have been published, highlighting that both aerobic and resistance exercise can improve NAFLD [5, 6, 12-19]. However, the most effective exercise protocol, such as the required frequency, intensity, and duration of aerobic and resistance exercises for the improvement of NAFLD remains unclear. Moreover, given the high prevalence of cardiovascular diseases in NAFLD [20], the choice of exercise type in relation to exercise energy consumption has not been compared.

Hence, the aims of this systematic review were to first summarize the required frequency, intensity, and duration of aerobic and resistance exercise required for improvement of hepatic steatosis in NAFLD. Additionally, we compared the therapeutic effects on hepatic steatosis between aerobic and resistance exercise regimens with regard to energy consumption.

Materials and Methods

Data Sources

A search of the published literature was performed using the PubMed, Web of Science, and Scopas databases to January 28, 2016.

Search Terms

The following search terms were used to identify potential articles: non-alcoholic steatohepatitis OR nonalcoholic steatohepatitis OR fatty liver OR NAFLD OR NASH; aerobic exercise OR aerobic training OR walking OR jogging OR treadmill OR running OR swimming; resistance exercise OR resistance training OR muscle exercise OR muscle training; patients OR subjects in combination with the Boolean operators AND and OR by 2 study investigators (R.H. and T.K.). The title and abstract of studies identified in the search were independently reviewed by 2 authors (R.H. and T.K.) to exclude studies that did not answer the research questions of interest. References within each report that met the selection criteria were manually searched for other potentially relevant studies. All relevant abstracts and full text peer reviewed articles published in English were collected for analysis.

Inclusion and Exclusion Criteria

Articles were selected if they met the following inclusion criteria: (1) study design: randomized controlled trial, non-randomized controlled clinical trial, before and after clinical trial, or observational cohort study; (2) study issue: the effects of therapeutic exercise on hepatic steatosis in patients with NAFLD; (3)

exercise type: aerobic or resistance exercise; (4) study subjects: patients with NAFLD diagnosed by a combination of biochemical examinations and liver biopsy or abdominal imaging including ultrasonography, computed tomography, and magnetic resonance (MR) imaging. Studies were excluded if they (1) were not original research (systematic review, narrative review, commentary, or editorial), (2) were case reports or conference abstracts, (3) did not provide sufficient data for this study, (4) were animal studies, or (5) were non-English literature.

To identify factors associated with an improvement in NAFLD, we combined aerobic and resistance exercise protocols. The combined database was analyzed by multivariate stepwise analysis and also using a decision tree algorithm.

In a comparative analysis between aerobic and resistance exercise, studies that did not provide body weight before initiation of therapeutic exercise were excluded, because body weight data is required to estimate energy consumption. To match the duration and period between aerobic and resistance exercises, exercises with a duration of less than 20 min or a period of less than 1 week or more than 12 weeks were excluded.

Quality assessment of the included studies

The quality of included studies was independently assessed by two authors (R.H. and T.K.). Non-randomized and randomized controlled studies were assessed by the criteria formulated by the Cochran Effective Practice and Organization of Care group [21]. Before-after studies were assessed based on

the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group developed by National Institutes of Health [22]. Case-control studies were assessed by the Newcastle-Ottawa scale [23].

Estimation of Energy Consumption of Exercise

To compare the effects of exercise on hepatic steatosis among the studies, the energy consumption of exercise was estimated by the following formula: Energy consumption of exercise (kcal) = exercise intensity (metabolic equivalents; METs) × exercise time (hours) × body weight (kg) [24]. In this review, the mean body weight and mean exercise time of each study were used. Exercise intensity was converted to METs based on a previous report [24].

Conversion of different measures of relative exercise intensity into percentage maximum oxygen consumption (%VO_2max)

The equation used to determine the energy consumption of exercise can bias the results of studies designed to evaluate the effects of frequency, duration, and intensity of physical activity on specific health outcomes in clinical studies. Therefore, different measures of relative exercise intensity such as percentage of heart rate reserve were converted into %VO_2max based on The American College of Sports Medicine's Guidelines for Exercise Testing and Prescription [25] and %VO_2max was used a comparator across studies.

Statistical Analysis

Data are expressed as the number, median (range), or mean ± standard

deviation. Nonparametric comparisons were made using the Wilcoxon signed-rank test (JMP Pro12, SAS Institute Inc., Cary, NC, USA). To identify factors associated with the improvement of NAFLD, multivariate stepwise analysis and a decision tree algorithm were employed as previously described [26, 27]. The level of statistical significance was set at $P < 0.05$.

Search Results

We identified 84 articles using the pres-specified search criteria. Eleven additional reports were identified from the article references (Figure 1). There was no duplication in the reports; therefore a total of 95 articles were screened. We removed 72 articles for the following 6 reasons: different topic (n = 25), no hepatic imaging assessment (n = 20), review article (n = 11), non-interventional study (n = 9), basic study (n = 6), and a mixture of aerobic and resistance exercise (n = 1). As a result, 23 reports including 24 aerobic and 7 resistance exercise protocols were employed for Review 1, which summarized the required frequency, intensity, and duration of aerobic and resistance exercises for the improvement of hepatic steatosis in NAFLD (Figure 1). In addition, factors or profiles associated with an improvement in NAFLD were investigated. In the next phase, a further 12 articles were removed because of insufficient information regarding the estimation of exercise energy consumption (n = 8) and the duration and period of exercise (n = 4). Thus, 12 articles including 13 aerobic and 4 resistance exercise protocols were employed for Review 2, comparing the %VO_2max, energy consumption and therapeutic effects of aerobic versus resistance exercise for NAFLD (Figure 1).

Quality of the included studies

The quality of the included studies are summarized in Supplementary Tables 1 - 3. The quality of non-randomized and randomized controlled trials was moderate to high. The most common reason for high risk was that participants in the intervention group could not be blinded (Supplementary Table 1). The quality

of before-after studies was fair to good. The common reasons for high risk were the following two issues: 1) outcome measures were not taken multiple times before and after the intervention, and 2) the intervention was not conducted at a whole hospital or community level (Supplementary Table 2). The quality of the case-control studies was 5/9. The most common reasons for high risk were lack of community controls and non-blinded interview to cases and controls (Supplementary Table 3).

Systematic Review 1; Frequency, intensity, and duration of exercise for improvement of hepatic steatosis in NAFLD

1. Aerobic Exercise

There were 24 exercise protocols in 18 articles that assessed the effect of aerobic exercise on hepatic steatosis by abdominal imaging including abdominal ultrasonography or MR spectroscopy. The patients' characteristics, exercise protocols, and results are summarized in Table 1 and 2. A decrease in hepatic steatosis was seen in 91.7% (22/24) of the protocols from 17 studies (total number of patients; n = 582). In the 22 exercise protocols, the median age was 48 years and median body mass index (BMI) 30.9 kg/m^2. The frequency of exercise was 3 times per week in all studies. Median METs, duration, and exercise period were 4.8 METs, 40 min, and 12 weeks, respectively. The median protocol was consistent with the 2008 US Physical Activity Guidelines for Adults, which recommends the accumulation of 120 minutes of moderate intensity activity accumulated most days of the week [28].

With aerobic exercise, changes in BMI and serum alanine

aminotransferase (ALT) levels were -0.7 kg/m^2 and -10 IU/L (Table 2). Nine of 22 protocols (40.9%) showed an improvement in hepatic steatosis without significant weight loss. MR spectroscopy was performed in 10 protocols (n=169) and demonstrated a median decrease in intrahepatic lipid of 2.65%.

Most of the 22 exercise protocols investigated the effect of conventional aerobic exercise, such as walking or cycling with a constant intensity. However, Hallsworth et al. [29] recently examined a new type of aerobic exercise, high-intensity interval training (HIIT), in patients with NAFLD. HIIT is an aerobic exercise consisting of high-intensity bouts of exercise and recovery periods as follows: a 5-min warm up at a very light intensity followed by 5 intervals of cycling at a very hard intensity interspersed with 3-min recovery periods and followed by a 3-min cool down after the last interval. HIIT can provide comparable or greater benefits to cardiorespiratory fitness than continuous moderate-intensity exercise of a longer duration. In the study, 12 patients enrolled in a cycle ergometer-based HIIT protocol for 30-40 min sessions 3 times per week for 12 weeks [29]. HIIT reduced 2 kg of whole body fat mass, 10 IU/L of serum ALT and 2.8% of hepatic lipids by MR spectroscopy. Although HIIT is not suitable for NAFLD patients with cardiovascular complications, it may be suitable for patients who have insufficient time for exercise.

Although the majority of studies showed an improvement in hepatic steatosis by aerobic exercise, 2 protocols showed no significant change. In the study by Fealy et al., 13 participants performed 60 min of supervised aerobic exercise (treadmill walking) at 80-85% of maximum heart rate (approximately 5.5 METs) [30]. The median MET and duration of exercise in this study was higher

and longer than that in the other 23 protocols. However, the period of exercise was only 7 consecutive days, shorter than that in the other 23 protocols. In another study by Keatng et al, the “placebo group” performing 5-minute low intensity (approximately 3.5 METs) cycling exercise demonstrated no improvement in hepatic steatosis. However, the other 3 active intervention groups expending 4.8-5.5 METs reduced hepatic steatosis. Oh et al. reported a significant correlation between the volume of aerobic exercise and the degree of decrease in steatosis [31]. Thus, very short or low intensity exercise may be insufficient for improving hepatic steatosis. In fact, estimated exercise energy consumption was 3,861.6 kcal/total period and 634.9 kcal/total period in the studies by Fealy et al. [30] and Keating et al. [32], respectively (data not shown). In contrast, the median estimated exercise energy consumption was 11,064 (range: 6,394-2,1087) kcal/total period in an effective aerobic exercise protocol (Figure 3F). Although the minimum requirement of exercise energy consumption for improvement of NAFLD remains unclear, 6,394 kcal/total period of aerobic exercise is the lowest reported exercise energy consumption for improvement of NAFLD [32].

2. Resistance Exercise

There were 7 protocols in 7 studies that assessed the effect of resistance exercise on hepatic steatosis by abdominal imaging including ultrasound or MR spectroscopy. The protocols and the results are summarized in Table 3 and 4. A reduction of hepatic steatosis was seen in 85.7% (6/7) of the protocols including 5 randomized controlled trials (total number of patients; n =

116). Among the 7 protocols, the median age was 49.2 years and median BMI was 30.6 kg/m^2. The frequency of exercise was 3 times per week in all studies. Median METs, duration, and period of exercise were 3.5 METs, 45 min, and 12 weeks, respectively.

With resistance exercise, changes in BMI and serum ALT levels were -0.35 kg/m^2 and -5.3 IU/L (Table 4). Among the 7 protocols, 3 (50%) demonstrated an improvement in hepatic steatosis without significant weight loss. MR spectroscopy was performed in 3 studies and showed a decrease in levels of intrahepatic lipids by 13%, 2%, and 12%, respectively.

Most of the studies used weight machines with specialized environment and equipment. However, Takahashi et al. evaluated the effect of a simple, convenient and safe resistance exercise program [33]. Squats and push-ups that use body weight as a load are simple resistance exercises that affect muscle strength. The authors evaluated the effects of push-ups and squats with a protocol of 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 3 times per week for 12 weeks. They found a significant interaction with increased muscle mass and a decrease in ALT level and a decrease in hepatic steatosis as evaluated by ultrasonography [33]. These findings imply that specific equipment is not necessarily required to improve hepatic steatosis by resistance exercise.

One study by Slentz et al. [34] demonstrated no improvement in hepatic steatosis by resistance exercise. There was no marked difference in age, exercise duration, frequency of exercise, and energy consumption per exercise between that study and the other 6 others. Although it remains unclear why

resistance exercise failed to improve hepatic steatosis, the resistance exercise program by Slentz et al. lasted 32 weeks and subjects showed a significant increase in body weight. On the other hand, the median exercise period for the other 6 studies was 12 weeks. Although the effects of long-term resistance exercise remain unclear, it is evident that 12-week resistance exercise improves steatosis in patients with NAFLD.

According to previous reports, general resistance exercise consists of 3 sets of 8-12 repetitions, 3 times per week. In order to increase exercise energy consumption, it is recommended to use 7 to 8 different types of weight training exercises targeting the major muscles, including the pectoralis major, latissimus dorsi, gluteus maximus, quadriceps femoris, and hamstring muscles (e.g. chest press, shoulder press, vertical traction, leg press, leg extension, leg curl, abdominal crunch, and bicep curl). Moreover, we noticed that changes in BMI after resistance exercise were only -0.35 kg/m^2 (versus -0.7 kg/m^2 for aerobic regimens), and 50% (3/6) of reports demonstrated an improvement in steatosis independent of body weight reduction. These findings indicate that the therapeutic characteristics of resistance exercise may be different from that of aerobic exercise in patients with NAFLD.

3. Factors and profiles associated with the improvement of NAFLD

To identify factors associated with the improvement of NAFLD, we combined the 24 aerobic protocols and the7 resistance exercise protocols. Patient characteristics are summarized in Table 5. In a multivariate stepwise analysis, there was a tendency towards an improvement in NAFLD with sex

(male ratio; Odds ratio -8.2, 95% CI -28.3 to 0.33, P=0.06); however, none of the factors were significantly associated with improvement of NAFLD. Since complex interactions of these risk factors may underlie the improvement in NAFLD, we also performed a decision tree analysis to identify profiles associated with an improvement in NAFLD.

The decision-tree algorithm is an exploratory technique of data-mining that represents a series of rules for classification by identifying priorities based on automated analysis [26, 27]. The decision-tree algorithm was created with two variables: sex and type of exercise. Male ratio was selected as the variable for the initial split with a cut-off value of 42%. Type of exercise (aerobic exercise or resistance exercise) was selected as the second split. In studies with a male ratio ≥ 42%, 95% (19/20) of protocols showed an improvement of NAFLD. In contrast, 81.8% (9/11) of protocols showed an improvement of NAFLD in studies with a male ratio < 42%. In addition, in protocols with a male ratio ≥ 42%, all protocols showed an improvement of NAFLD by aerobic exercise (Group1 in Figure 2). On the other hand, in protocols with a male ratio < 42%, all protocols showed an improvement of NAFLD by resistance exercise (Group4 in Figure 2). These data suggest that there is a sex difference in the effectiveness of exercise on the improvement of NAFLD. Furthermore, to improve NAFLD, aerobic and resistance exercise may be recommended for male and female patients, respectively. Moreover, age was not detected as a factor associated with the improvement of NAFLD, suggesting that exercise is effective regardless of age.

Review 2; Comparison of the therapeutic effects on hepatic steatosis and

exercise energy consumption between aerobic and resistance exercise

Several studies investigated the difference between aerobic and resistance exercises with respect to the improvement in hepatic steatosis. However, which exercise is suitable for patients with NAFLD remains controversial. A standard measurement of exercise is energy consumption (kcal) estimated by exercise intensity (METs), exercise time (hours), and body weight (kg) [24]. Therefore, we next compared the therapeutic effects on hepatic steatosis and exercise energy consumption of aerobic and resistance exercise.

There was no significant difference between the aerobic and resistance exercise groups in age, sex, baseline body weight, baseline BMI, or the number of studies that included diet consultation (Table 6). There was no significant difference in changes in BMI, serum ALT levels or intrahepatic lipids between the aerobic and resistance exercise groups (Table 6), indicating that both regimens improved NAFLD equally. For exercise-related variables, there was no significant difference in duration, frequency, or period of exercise between the aerobic and resistance exercise groups (Figure 3 A-C). However, in the resistance exercise group, the $\%VO_2max$ and METs of exercise were significantly lower (Figure 3 D and E), and energy consumption (kcal/exercise) tended to be lower than in the aerobic exercise group (Figure 3 F). Similarly, total energy consumption (kcal/total period) was significantly lower in the resistance exercise group than that in the aerobic exercise group (Figure 3 G). We also performed a comparative analysis between aerobic and resistance exercise by using studies that employed ^{1}HMR spectroscopy as an outcome measurement. As shown in Supplementary Table 4, no significant difference was seen for

changes in intrahepatic lipid, exercise duration, exercise frequency, and exercise period. However, %VO_2max and METs were significantly lower in the resistance exercise group compared to that in the aerobic exercise group (Supplementary Table 4). These data indicate that aerobic and resistance training improves NAFLD through different mechanisms.

Moderate aerobic exercise is exceptionally difficult in a subset of NAFLD patients such as those who are morbidly obese, incapacitated or bedridden individuals, elderly patients, or those with other mobility-limiting comorbidities. Resistance exercise also has risks for such NAFLD patients; however, low intensity exercise may offer a therapeutic option to patients with NAFLD who are debilitated by comorbid illnesses. There are advantages and disadvantages of resistance exercise, and physicians should consider the aspects that may limit a person's ability to participate in lifestyle modification such as motivation, access to gym facilities, and physical limitations.

Mechanisms by which aerobic and resistance exercise may improve hepatic steatosis

It is well documented that aerobic exercise causes lipolysis in various tissues including adipose tissues [35, 36], leading to acetyl-CoA production through up-regulation of β-oxidation. Acetyl-CoA is metabolized to protons in the tricarboxylic acid cycle, resulting in adenosine triphosphate production in the electron transport system of mitochondria [36]. Aerobic exercise also up-regulates uncoupling protein-1 and peroxisome proliferator-activated

receptor γ, leading to lipolysis in adipose tissues [37-41]. In addition, Aghapour et al. have demonstrated that aerobic exercise decreases serum levels of resistin in postmenopausal women with hypertension [42]. Moreover, Haus et al. have reported that aerobic exercise increases serum levels of high molecular weight adiponectin in patients with NAFLD [43]. Nikseresht et al. also showed that aerobic exercise increases serum adiponectin levels [44]. Taken together, aerobic exercise may improve NAFLD thorough activation of lipolysis, up-regulation of uncoupling protein-1 and peroxisome proliferator-activated receptor γ, and alteration of adipocytokines (Figure 4).

Resistance exercise in contrast improves hepatic steatosis with less energy consumption. Why resistance exercise improves hepatic steatosis remains unclear; however, a possible explanation is a muscle fiber type-specific alteration by resistance exercise. Muscle fibers are classified into 2 major types (type I and type II) based on their energy metabolism [45]. A feature of type I fibers is slow oxidative, while type II fibers have fast glycolytic metabolism [45]. Verdijk et al. reported resistance exercise causes hypertrophy of type II but not type I fibers in elderly men [46]. Moreover,a Gallagher et al. reported that resistance exercise increases glucose transporter 4 expression in type II fibers in healthy men, a change not seen in type I fibers [47]. In addition, Oh et al. demonstrated that resistance but not aerobic exercise, up-regulates key molecules of intracellular insulin sensitivity including AMP-activated protein kinase and caveolins in type II muscle fibers of 50 week-old rats [48]. Thus, resistance exercise may change muscle characteristics, leading to an

improvement of hepatic steatosis through up-regulation of glycolysis and amelioration of insulin resistance (Figure 4).

Another possible mechanism for resistance exercise-induced improvement of NAFLD is organ-to-organ interaction. Skeletal muscles are able to interact with other organs by secreting cytokines or peptides called “myokines” [49, 50]. Irisin is an exercise-induced myokine that increases thermogenesis-related energy consumption through the browning of subcutaneous adipocytes [51]. In addition, irisin has been reported to modulate lipid metabolism in hepatocytes. Recombinant irisin inhibits the palmitic acid-induced increase in master regulators of lipogenesis, including sterol regulatory element-binding protein-1c and lipogenic enzymes such as fatty acid synthase in hepatocytes [52]. Overexpression of irisin improves hepatic steatosis in obese mice [53]. In patients with NAFLD, serum irisin levels are reported to be lower than that in healthy individuals [54]. Recently, Kim et al. investigated the effects of aerobic and resistance exercises on circulating irisin levels and demonstrated that the circulating irisin level was significantly increased in the resistance exercise but not in the aerobic exercise group [55], indicating that the former is specifically linked to lipid metabolism in the liver. Thus, a possible reason why resistance exercise improves NAFLD despite lower energy consumption may be a muscle-liver crosstalk through which irisin inhibits lipogenesis in hepatocytes (Figure 4).

Limitations

Validity of the outcome measurement

This systematic review included 10 protocols that used ultrasonographic steatosis as the outcome. Other studies employed ^{1}HMR spectroscopy or CT for the evaluation of steatosis, and, therefore, the outcome measurement was heterogenous across the reports. Although comparisons of changes in hepatic steatosis between aerobic and resistance exercise by using studies that only utilised ^{1}HMR spectroscopy showed similar results as for the whole analysis, the number of studies were small and further validation is required.

The impact of exercise on hepatic fibrosis

Changes in hepatic fibrosis, rather than steatosis, is an important outcome prognostically for patients with NAFLD. There were 3 studies which evaluated the effects of exercise on hepatic fibrosis by repeated biopsy. Two studies, by Ueno et al. [56] and Bhat et al. [57] showed no significant improvement of hepatic fibrosis. However, the third study by Vilar Gomez E et al. [58] showed a significant improvement of hepatic fibrosis after a lifestyle intervention that combined both diet and exercise components. The patients' characteristics and exercise protocols were similar among the 3 studies. Thus, it is still unclear if exercise is able to improve hepatic fibrosis.

Head-to-head comparisons between aerobic and resistance exercise

There were only 3 studies which undertook a head-to-head comparison between aerobic and resistance exercise for hepatic steatosis. Although Slentz

et al. [34] demonstrated that aerobic exercise is more effective than resistance exercise for improving hepatic steatosis, Bacchi et al. [59] and Shamsoddini et al. [60] demonstrated that both were equally effective. Thus, it remains controversial as to which type of exercise is more beneficial for patients with NAFLD and caution needs to be exercised in interpreting the current data.

The impact of high- vs. Low-volume resistance training programs on hepatic steatosis.

The median protocol for resistance exercise was based on a small number of protocols, and the duration and intensity were largely fixed. Further, no study has investigated changes in hepatic steatosis by different intensities of resistance exercise, nor how to effectively and safely deliver resistance exercise programs to patients with NAFLD. These aspects therefore represent an unmet research need.

Conclusion

Based on this systematic review, resistance exercise improves NAFLD with less energy consumption and, therefore, may be more feasible than aerobic exercise for NAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise. In addition, these data suggest a possible link between resistance exercise and lipid metabolism in the liver. The muscle-liver axis may be important in elucidating the pathogenesis of NAFLD

and for drug development.

References

[1] Curfman GD. The health benefits of exercise. A critical reappraisal. N Engl J Med 1993;328:574-576.

[2] Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;25 Suppl 3:1-72.

[3] Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010;51:1820-1832.

[4] Whitsett M, VanWagner LB. Physical activity as a treatment of non-alcoholic fatty liver disease: A systematic review. World J Hepatol 2015;7:2041-2052.

[5] 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.

[6] Berzigotti A, Saran U, Dufour JF. Physical activity and liver diseases. Hepatology 2016;63:1026-1040.

[7] Kelley GA, Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. Prev Cardiol 2008;11:71-75.

[8] Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut 2011;60:1278-1283.

[9] Lemes IR, Ferreira PH, Linares SN, Machado AF, Pastre CM, Netto JJ. Resistance training reduces systolic blood pressure in metabolic syndrome: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med 2016.

[10] Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. 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.

[11] Chatzinikolaou A, Fatouros I, Petridou A, Jamurtas A, Avloniti A, Douroudos I, et al. Adipose tissue lipolysis is upregulated in lean and obese men during acute resistance exercise. Diabetes Care 2008;31:1397-1399.

[12] Johnson NA, Keating SE, George J. Exercise and the liver: implications for therapy in fatty liver disorders. Semin Liver Dis 2012;32:65-79.

[13] Hannah WN, Jr., Harrison SA. Lifestyle and Dietary Interventions in the

Management of Nonalcoholic Fatty Liver Disease. Dig Dis Sci 2016;61:1365-1374.

[14] Mahady SE, George J. Exercise and diet in the management of nonalcoholic fatty liver disease. Metabolism: clinical and experimental 2015.

[15] Oliveira CP, de Lima Sanches P, de Abreu-Silva EO, Marcadenti A. Nutrition and Physical Activity in Nonalcoholic Fatty Liver Disease. J Diabetes Res 2016;2016:4597246.

[16] Marchesini G, Petta S, Dalle Grave R. Diet, weight loss, and liver health in nonalcoholic fatty liver disease: Pathophysiology, evidence, and practice. Hepatology 2015.

[17] Bellentani S, Dalle Grave R, Suppini A, Marchesini G, Fatty Liver Italian N. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008;47:746-754.

[18] Rodriguez B, Torres DM, Harrison SA. Physical activity: an essential component of lifestyle modification in NAFLD. Nat Rev Gastroenterol Hepatol 2012;9:726-731.

[19] Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. Nat Rev Gastroenterol Hepatol 2016;13:196-205.

[20] Ghouri N, Preiss D, Sattar N. Liver enzymes, nonalcoholic fatty liver disease, and incident cardiovascular disease: a narrative review and clinical perspective of prospective data. Hepatology 2010;52:1156-1161.

[21] Effective Practice and Organisation of Care (EPOC). EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2015. . Available at: http://epoccochraneorg/epoc-specific-resources-review-authors.

[22] National Institutes of Health. Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group Available at: http://wwwnhlbinihgov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after.

[23] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://wwwohrica/programs/clinical_epidemiology/oxfordasp.

[24] Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr.,

Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575-1581.

[25] American Colllege of Sports Medicine; Linda S. Pescatello RA, Deborah Riebe, Paul D. Thompson, editor. ACSM's Guidelines for Exercise Testing and Prescription, ninth ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2014.

[26] Yamada S, Kawaguchi A, Kawaguchi T, Fukushima N, Kuromatsu R, Sumie S, et al. Serum albumin level is a notable profiling factor for non-B, non-C hepatitis virus-related hepatocellular carcinoma: A data-mining analysis. Hepatol Res 2014;44:837-845.

[27] Kawaguchi T, Kohjima M, Ichikawa T, Seike M, Ide Y, Mizuta T, et al. The morbidity and associated risk factors of cancer in chronic liver disease patients with diabetes mellitus: a multicenter field survey. J Gastroenterol 2015;50:333-341.

[28] U.S. Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. 2008:http://health.gov/paguidelines/pdf/paguide.pdf.

[29] Hallsworth K, Thoma C, Hollingsworth KG, Cassidy S, Anstee QM, Day CP, et al. Modified high-intensity interval training reduces liver fat and improves cardiac function in non-alcoholic fatty liver disease: a randomized controlled trial. Clin Sci (Lond) 2015;129:1097-1105.

[30] Fealy CE, Haus JM, Solomon TP, Pagadala M, Flask CA, McCullough AJ, et al. Short-term exercise reduces markers of hepatocyte apoptosis in nonalcoholic fatty liver disease. Journal of applied physiology 2012;113:1-6.

[31] Oh S, Shida T, Yamagishi K, Tanaka K, So R, Tsujimoto T, et al. Moderate to vigorous physical activity volume is an important factor for managing nonalcoholic fatty liver disease: a retrospective study. Hepatology 2015;61:1205-1215.

[32] Keating SE, Hackett DA, Parker HM, O'Connor HT, Gerofi JA, Sainsbury A, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. Journal of hepatology 2015;63:174-182.

[33] Takahashi A, Abe K, Usami K, Imaizumi H, Hayashi M, Okai K, et al. Simple Resistance Exercise helps Patients with Non-alcoholic Fatty Liver Disease. Int J Sports Med 2015;36:848-852.

[34] Slentz CA, Bateman LA, Willis LH, Shields AT, Tanner CJ, Piner LW, et al. Effects of aerobic vs. resistance training on visceral and liver fat stores, liver enzymes, and insulin resistance by HOMA in overweight adults from STRRIDE AT/RT. Am J Physiol Endocrinol Metab 2011;301:E1033-1039.

[35] Stich V, de Glisezinski I, Berlan M, Bulow J, Galitzky J, Harant I, et al. Adipose tissue lipolysis is increased during a repeated bout of aerobic exercise. Journal of applied physiology 2000;88:1277-1283.

[36] Sertie RA, Andreotti S, Proenca AR, Campana AB, Lima-Salgado TM, Batista ML, Jr., et al. Cessation of physical exercise changes metabolism and modifies the adipocyte cellularity of the periepididymal white adipose tissue in rats. Journal of applied physiology 2013;115:394-402.

[37] Ricquier D. Respiration uncoupling and metabolism in the control of energy expenditure. The Proceedings of the Nutrition Society 2005;64:47-52.

[38] Slocum N, Durrant JR, Bailey D, Yoon L, Jordan H, Barton J, et al. Responses of brown adipose tissue to diet-induced obesity, exercise, dietary restriction and ephedrine treatment. Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie 2013;65:549-557.

[39] Guo R, Liong EC, So KF, Fung ML, Tipoe GL. Beneficial mechanisms of aerobic exercise on hepatic lipid metabolism in non-alcoholic fatty liver disease. Hepatobiliary & pancreatic diseases international : HBPD INT 2015;14:139-144.

[40] Petridou A, Tsalouhidou S, Tsalis G, Schulz T, Michna H, Mougios V. Long-term exercise increases the DNA binding activity of peroxisome proliferator-activated receptor gamma in rat adipose tissue. Metabolism: clinical and experimental 2007;56:1029-1036.

[41] Ogasawara J, Sakurai T, Kizaki T, Ishibashi Y, Izawa T, Sumitani Y, et al. Higher levels of ATGL are associated with exercise-induced enhancement of lipolysis in rat epididymal adipocytes. PloS one 2012;7:e40876.

[42] Aghapour A, Farzanegi P. Effect of six-week aerobic exercise on Chemerin and Resistin concentration in hypertensive postmenopausal women. Electronic physician 2013;5:623-630.

[43] Haus JM, Solomon TP, Kelly KR, Fealy CE, Kullman EL, Scelsi AR, et al. Improved

hepatic lipid composition following short-term exercise in nonalcoholic fatty liver disease. The Journal of clinical endocrinology and metabolism 2013;98:E1181-1188.

[44] Nikseresht M, Sadeghifard N, Agha-Alinejad H, Ebrahim K. Inflammatory markers and adipocytokine responses to exercise training and detraining in men who are obese. Journal of strength and conditioning research / National Strength & Conditioning Association 2014;28:3399-3410.

[45] Lillioja S, Young AA, Culter CL, Ivy JL, Abbott WG, Zawadzki JK, et al. Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. The Journal of clinical investigation 1987;80:415-424.

[46] Verdijk LB, Gleeson BG, Jonkers RA, Meijer K, Savelberg HH, Dendale P, et al. Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men. The journals of gerontology Series A, Biological sciences and medical sciences 2009;64:332-339.

[47] Gallagher PM, Touchberry CD, Teson K, McCabe E, Tehel M, Wacker MJ. Effects of an acute bout of resistance exercise on fiber-type specific to GLUT4 and IGF-1R expression. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2013;38:581-586.

[48] Oh YS, Kim HJ, Ryu SJ, Cho KA, Park YS, Park H, et al. Exercise type and muscle fiber specific induction of caveolin-1 expression for insulin sensitivity of skeletal muscle. Experimental & molecular medicine 2007;39:395-401.

[49] Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nat Rev Rheumatol 2015;11:86-97.

[50] Karstoft K, Pedersen BK. Skeletal muscle as a gene regulatory endocrine organ. Curr Opin Clin Nutr Metab Care 2016.

[51] Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481:463-468.

[52] Park MJ, Kim DI, Choi JH, Heo YR, Park SH. New role of irisin in hepatocytes: The protective effect of hepatic steatosis in vitro. Cell Signal 2015;27:1831-1839.

[53] Mo L, Shen J, Liu Q, Zhang Y, Kuang J, Pu S, et al. Irisin Is Regulated by CAR in

Liver and Is a Mediator of Hepatic Glucose and Lipid Metabolism. Mol Endocrinol 2016;30:533-542.

[54] Polyzos SA, Kountouras J, Anastasilakis AD, Geladari EV, Mantzoros CS. Irisin in patients with nonalcoholic fatty liver disease. Metabolism: clinical and experimental 2014;63:207-217.

[55] Kim H, Lee HJ, So B, Son JS, Yoon D, Song W. Effect of aerobic training and resistance training on circulating irisin level and their association with change of body composition in overweight/obese adults: a pilot study. Physiol Res 2015.

[56] Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol 1997;27:103-107.

[57] Bhat G, Baba CS, Pandey A, Kumari N, Choudhuri G. Life style modification improves insulin resistance and liver histology in patients with non-alcoholic fatty liver disease. World J Hepatol 2012;4:209-217.

[58] Vilar Gomez E, Rodriguez De Miranda A, Gra Oramas B, Arus Soler E, Llanio Navarro R, Calzadilla Bertot L, et al. Clinical trial: a nutritional supplement Viusid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2009;30:999-1009.

[59] Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, et al. 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.

[60] Shamsoddini A, Sobhani V, Ghamar Chehreh ME, Alavian SM, Zaree A. Effect of Aerobic and Resistance Exercise Training on Liver Enzymes and Hepatic Fat in Iranian Men With Nonalcoholic Fatty Liver Disease. Hepat Mon 2015;15:e31434.

[61] Chen SM, Liu CY, Li SR, Huang HT, Tsai CY, Jou HJ. Effects of therapeutic lifestyle program on ultrasound-diagnosed nonalcoholic fatty liver disease. J Chin Med Assoc 2008;71:551-558.

[62] Kantartzis K, Thamer C, Peter A, Machann J, Schick F, Schraml C, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. Gut

2009;58:1281-1288.

[63] Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology 2009;50:1105-1112.

[64] 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.

[65] Khaoshbaten M, Gholami N, Sokhtehzari S, Monazami AH, Nejad MR. The effect of an aerobic exercise on serum level of liver enzymes and liver echogenicity in patients with non alcoholic fatty liver disease. Gastroenterol Hepatol Bed Bench 2013;6:S112-116.

[66] Yoshimura E, Kumahara H, Tobina T, Matsuda T, Ayabe M, Kiyonaga A, et al. Lifestyle intervention involving calorie restriction with or without aerobic exercise training improves liver fat in adults with visceral adiposity. J Obes 2014;2014:197216.

[67] 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.

[68] Zelber-Sagi S, Buch A, Yeshua H, Vaisman N, Webb M, Harari G, et al. Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial. World J Gastroenterol 2014;20:4382-4392.

Figure legends

Figure 1. A flow chart summarizing article identification and selection for the systematic review. Abbreviation: NAFLD, Non-alcoholic fatty liver disease

Figure 2. Decision-tree algorithm for improvement of NAFLD. The exercise protocols were classified according to the indicated cut-off value for male ratio or type of exercise. The pie graphs indicate the proportion of exercise protocols with improvement of NAFLD (white) or protocols with no improvement (black). Abbreviation: NAFLD, non-alcoholic fatty liver disease

Figure 3. Comparisons of exercise protocol and energy consumption between aerobic and resistance exercise. (A) Exercise duration, (B) Frequency of exercise, (C) Exercise period, (D) METs, (E) Energy consumption/exercise, and (F) Energy consumption/total period. Data are expressed as median (range). Nonparametric comparisons were made using the Wilcoxon signed-rank test. The level of statistical significance was set at $P < 0.05$. Abbreviation: METs, metabolic equivalents.

Figure 4. A scheme of different mechanisms for the improvement of NAFLD between aerobic and resistance exercises. Abbreviations: NAFLD, non-alcoholic fatty liver disease; UCP-1, uncoupling protein-1; PPARγ, peroxisome proliferator-activated receptor γ; GLUT4, glucose transporter 4; AMPK, AMP-activated protein kinase.

Figure 1

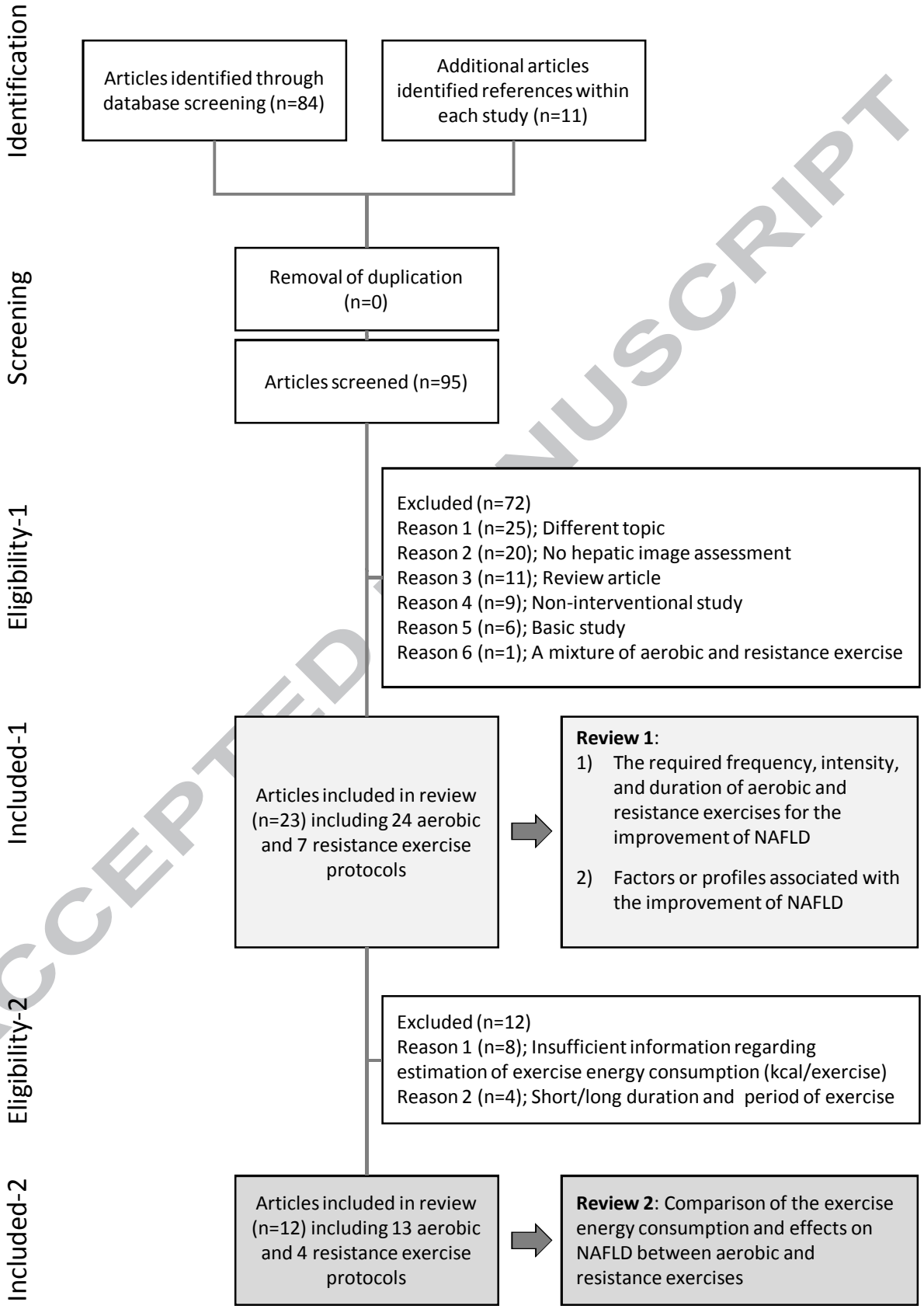

Figure 2

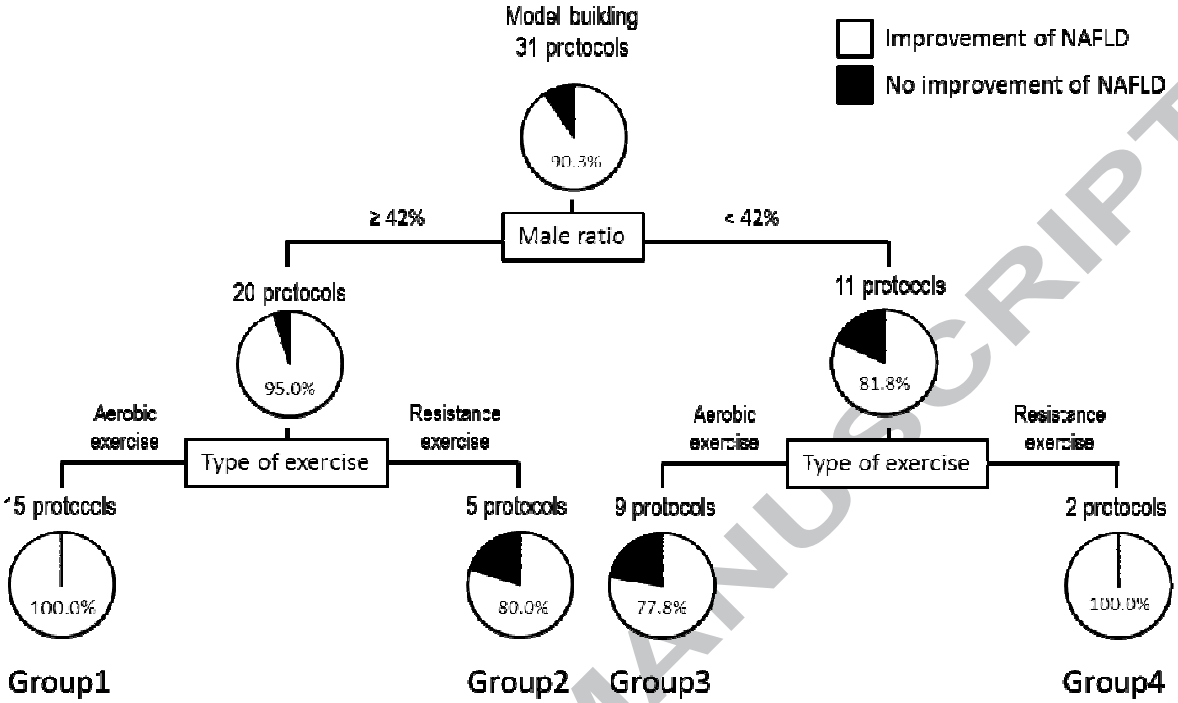

Figure 3

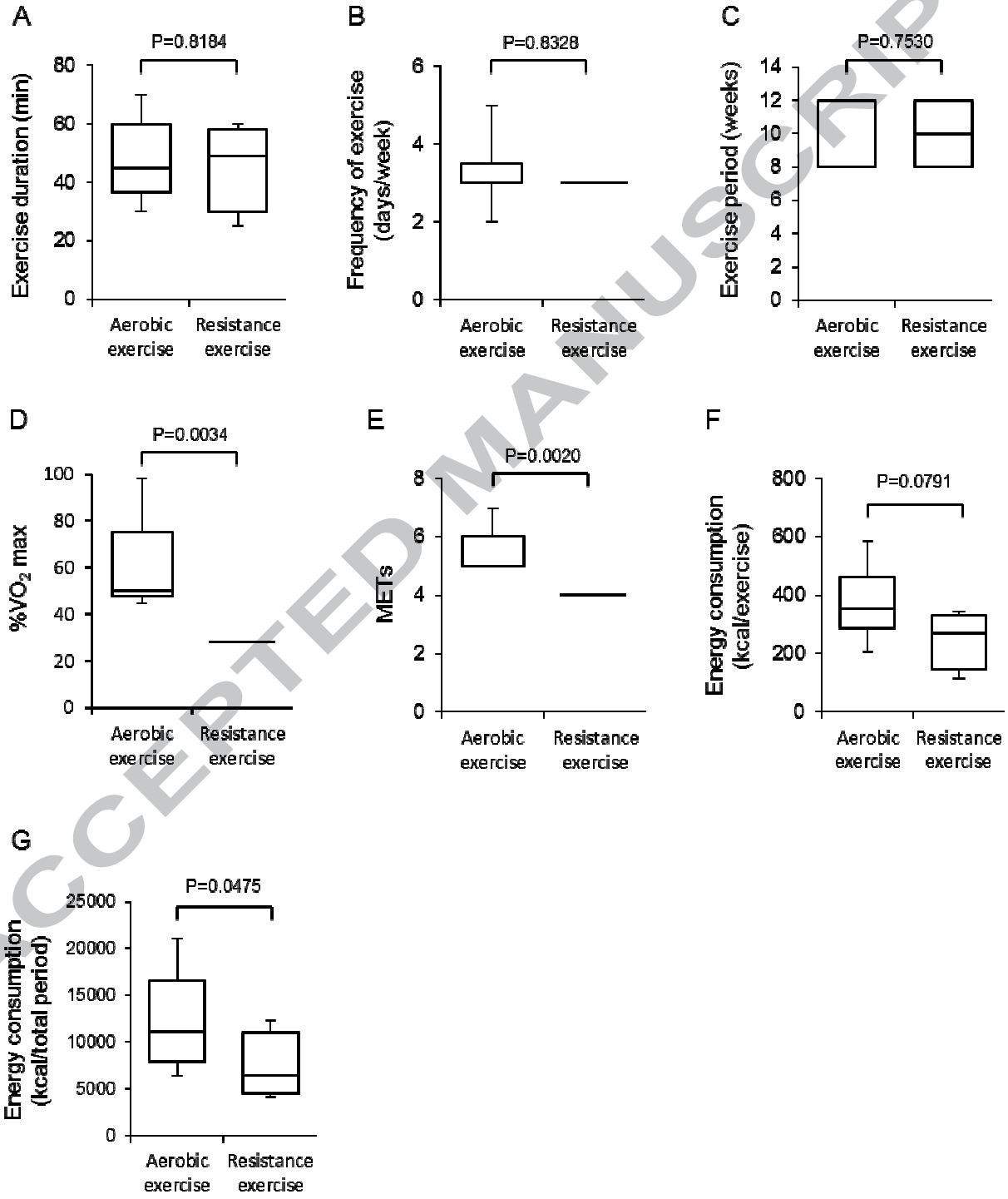

Figure 4

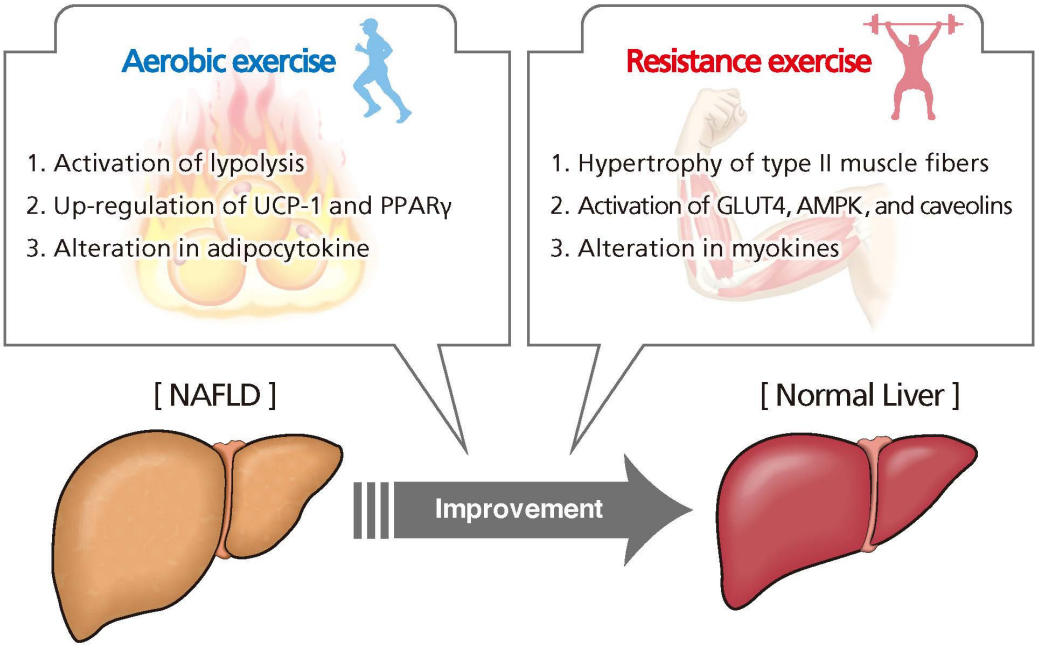

Table 1. Characteristics of aerobic exercise protocols

Protocol number	Author name	Study design	n	Age (year)	Female/male	BMI	Body weight (kg)	Dietary counseling
1	Ueno T et al.	Non-randomized controlled trial	15	39.0	7/8	31.0	83.0	Yes
2	Chen SM et al.	Non-randomized controlled trial	16	40.1	6/10	30.2	83.3	Yes
3		Non-randomized controlled trial	23	36.0	7/16	30.7	85.3	No
4	Kantartzis K et al.	Before-after study	50	47.4	22/28	31.5	N/A	Yes
5	Johnson NA et al.	Randomized controlled trial	12	49.1	N/A	32.2	94.4	No
6	Vilar Gomez E et al.	Randomized controlled trial	30	49.0	14/16	31.5	82.4	Yes
7	Slentz CA et al.	Randomized controlled trial	48	49.5	26/22	30.4	88.5	No
8	Sullivan S et al.	Randomized controlled trial	12	48.6	8/4	37.1	N/A	No
9	Bhat G et al.	Non-randomized controlled trial	45	40.1	8/37	26.7	N/A	Yes
10	Bacchi E et al.	Randomized controlled trial	14	55.6	10/4	30.5	N/A	Yes
11	Haus JM et al.	Before-after study	17	54	N/A	34.4	100.2	No
12	Khaoshbaten M et al.	Non-randomized controlled trial	45	35.6	16/29	28.9	84.2	No
13	Yoshimura E et al.	Randomized controlled trial	12	61.0	11/4	27.3	68.6	Yes
14	Oh S et al.	Case-control study	40	52.6	0/40	29.4	86.1	Yes
15		Case-control study	42	49	0/42	28.8	82.9	Yes
16		Case-control study	87	51.9	0/87	29.2	84.3	Yes
17	Keating SE et al.	Non-randomized controlled trial	12	44.2	6/6	36.3	103.0	No
18		Non-randomized controlled trial	12	45.5	7/5	33.9	96.1	No
19		Non-randomized controlled trial	12	45.6	9/3	31.3	88.8	No
20	Hallsworth K et al.	Randomized controlled trial	12	54.0	N/A	31.0	90.0	No
21	Shamsoddini A et al.	Randomized controlled trial	10	39.7	0/10	28.1	85.7	No
22	Lee S et al	Randomized controlled trial	16	15.2	0/16	33.6	106.5	Yes
Median (ranges) or sum of the effective protocols			582	48 (15.2-61.0)	157/387	30.9 (26.7-37.1)	85.9 (68.6-106.5)	11
23	Fealy CE et al.	Before-after study	13	58.0	N/A	35.2	100.3	No
24	Keating SE et al.	Randomized controlled trial	12	39.1	9/3	32.2	90.7	No

Table 1. Continue

Exercise duration (min)	Frequency of exercise (days/week)	METs	Exercise Period (week)	Reference
40	5	4.8	12	[56]
60	2	5.5	10	[61]
60	2	5.5	10	[61]
N/A	N/A	4.8	35	[62]
37.5	3	5.5	4	[63]
40	5	4.8	24	[58]
39	3	5.5	32	[34]
44.8	5	4.8	16	[64]
30	5	5.5	24	[57]
60	3	4.8	16	[59]
55	7	5.5	1	[43]
30	3	7.3	12	[65]
60	5	4.8	12	[66]
14.5	3	4.8	12	[31]
30.9	3	4.8	12	[31]
58.5	3	4.8	12	[31]
37.5	3	5.5	8	[32]
70	4	4.8	8	[32]
37.5	3	4.8	8	[32]
35	3	7	12	[29]
45	3	4.8	8	[60]
60	3	5.5	12	[67]
40 (14.5－70)	3 (2-7)	4.8 (4.8-7.3)	12 (1-35)	
60	7	5.5	1	[30]
5	3	3.5	8	[32]

Note. Data are expressed as median or number. Abbreviations, BMI, body mass index; METs, metabolic equivalents; N/A, not applicable.

Table 2. Results of aerobic exercise protocols

Protocol number	Improvement of hepatic steatosis	Assessment modality for hepatic steatosis	Main finding for improvement of hepatic steatosis	Changes in BMI	Changes in body weight (kg)	Significant Weight loss	Changes in ALT	Changes in intrahepatic lipid (%) evaluated by ^{1}HMR spectroscopy	Reference
1	Yes	Liver biopsy	About 20% reduction of hepatic steatosis	-3.0	N/A	Yes	-56.0	N/A	[56]
2	Yes	Ultrasonography	0.44 point reduction of ultrasound score (scale of 0 [none] to 3 [severe])	-1.6	-5.2	No	-15.4	N/A	[61]
3	Yes	Ultrasonography	0.61 point reduction of ultrasound score (scale of 0 [none] to 3 [severe])	-0.4	-1.41	No	-3.3	N/A	[61]
4	Yes	^{1}HMR spectroscopy	About 5% reduction of hepatic steatosis	-1.6	N/A	Yes	-12.9	-4.6	[62]
5	Yes	^{1}HMR spectroscopy	21% reduction of hepatic steatosis	-0.1	-0.3	No	-2.8	-21.0	[63]
6	Yes	Liver biopsy	2.25 point reduction in NAFLD activity score	-3.5	-8.7	Yes	-19.0	N/A	[58]
7	Yes	Computed tomography	-1.5 HU reduction in hepatic attenuation	N/A	-2	Yes	-4.3	N/A	[34]
8	Yes	^{1}HMR spectroscopy	10.3% reduction of hepatic steatosis	0.0	-0.2	No	-6.3	-10.3	[64]
9	Yes	Liver biopsy	2.0 point reduction in NAFLD activity score	-1.3	N/A	Yes	-46.5	N/A	[57]
10	Yes	^{1}HMR spectroscopy	10% reduction of hepatic steatosis	-0.7	N/A	Yes	0.4	-10.0	[59]
11	Yes	^{1}HMR spectroscopy	0.7% reduction of hepatic steatosis	0.1	0.2	No	N/A	-0.7	[43]

12	Yes	Ultrasonography	An improvement of liver echogenicity	-0.9	-2.1	Yes	-17.6	N/A	[65]
13	Yes	Computed tomography	0.13 increase in liver-to-spleen ratio	-2.0	-5	Yes	N/A	N/A	[66]
14	Yes	Ultrasonography	23.2% reduction of CAP	-1.9	-5.5	Yes	-8.2	N/A	[31]
15	Yes	Ultrasonography	23.2% reduction of CAP	-3.4	-9.9	Yes	-13.5	N/A	[31]
16	Yes	Ultrasonography	31.8% reduction of CAP	-3.7	-10.9	Yes	-11.7	N/A	[31]
17	Yes	^{1}HMR spectroscopy	2.4% reduction of hepatic steatosis	-0.5	-1.3	No	1.0	-2.4	[32]
18	Yes	^{1}HMR spectroscopy	2.6% reduction of hepatic steatosis	-0.5	-1.4	No	3.5	-2.5	[32]
19	Yes	^{1}HMR spectroscopy	0.8% reduction of hepatic steatosis	0.2	0.1	No	-0.3	-0.8	[32]
20	Yes	^{1}HMR spectroscopy	2.8% reduction of hepatic steatosis	-0.5	-1.4	Yes	-10.0	-2.8	[29]
21	Yes	Ultrasonography	0.9 point reduction of ultrasound score (scale of 0 [none] to 3 [severe])	0.6	-1.8	No	-12.5	N/A	[60]
22	Yes	^{1}HMR spectroscopy	1.9% reduction of hepatic steatosis	-0.3	-0.04	Yes	N/A	-1.9	[67]
Median (ranges) or sum of the effective protocols				-0.7 (-3.7-0.6)	-1.6 (-10.9- 0.2)	59.1% (13/22)	-10 (-56-4)	-2.65 (-21--0.7)	
24	No	^{1}HMR spectroscopy	0.7% reduction of hepatic steatosis	0.1	+0.1	No	-5.9	-0.7	[30]
25	No	^{1}HMR spectroscopy	1.1% increase of hepatic steatosis	0.7	+0.1	No	-8.0	1.1	[32]

Note. Data are expressed as median or number. Abbreviations, BMI, body mass index; ALT, alanine aminotransferase; HMR, hydrogen In vivo magnetic resonance; CAP, controlled attenuation parameter, N/A, not applicable.

Table 3. Characteristics of resistance exercise protocols

Protocol number	Author name	Study design	n	Age (year)	Female/male	BMI	Body weight (kg)	Dietary counseling
1	Hallsworth K et al.	Randomized controlled trial	11	52.0	N/A	32.3	96.1	No
2	Lee S et al	Randomized controlled trial	16	14.6	0/16	34.5	97.7	yes
3	Bacchi E et al.	Randomized controlled trial	17	56.0	5/12	28.8	N/A	yes
4	Zelber-Sagi S et al.	Randomized controlled trial	31	46.3	15/16	30.8	N/A	No
5	Takahashi A et al.	Non-randomized controlled trial	31	55.5	22/9	28.5	72	No
6	Shamsoddini A et al.	Randomized controlled trial	10	45.9	0/10	30.6	92.2	No
Median (ranges) or sum of the effective protocols			116	49.2(14.6-56)	42/63	30.6 (28.5-34.5)	94 (72-98)	2
7	Slentz CA et al.	Randomized controlled trial	52	49.7	30/22	30.5	88.6	No

Note. Data are expressed as median or number. Abbreviations: BMI, body mass index; METs, metabolic equivalents; N/A, not applicable.

Table 3. Continue

Exercise duration (min)	Frequency of exercise (days/week)	METs	Exercise Period (week)	Reference
53	3	3.5	8	[8]
60	3	3.5	12	[67]
N/A	3	3.5	16	[59]
40	3	3.5	12	[68]
25	3	3.8	12	[33]
45	3	3.5	8	[60]
45 (25-60)	3	3.5 (3.5-3.8)	12 (8-16)	
53	3	3.5	32	[34]

Table 4. Results of resistance exercise protocols

Protocol number	Improvement of hepatic steatosis	Assessment modality for hepatic steatosis	Main finding for improvement of hepatic steatosis	Changes in BMI	Changes in body weight (kg)	Significant Weight loss	Changes in ALT	Changes in intrahepatic lipid (%) evaluated by ^{1}HMR spectroscopy	Reference
1	Yes	^{1}HMR spectroscopy	1.8% reduction of hepatic steatosis	0	0	No	0	-1.8%	[8]
2	Yes	^{1}HMR spectroscopy	2.0% reduction of hepatic steatosis	-0.6	-0.6	Yes	N/A	-2%	[67]
3	Yes	^{1}HMR spectroscopy	12.0% reduction of hepatic steatosis	-0.6	N/A	Yes	-5.33	-12%	[59]
4	Yes	Ultrasonography	0.25 reduction of hepato-renal index	-0.1	N/A	No	-5.3	N/A	[68]
5	Yes	Ultrasonography	0.24 point reduction of ultrasound score (scale of 0 [none] to 3 [severe])	-0.1	N/A	No	-18.8	N/A	[33]
6	Yes	Ultrasonography	0.6 point reduction of ultrasound score (scale of 0 [none] to 3 [severe])	-0.7	-2.1	Yes	-14.7	N/A	[60]
Median (ranges) or sum of the effective protocols				-0.35 (-0.7-0)	-1.35 (-0.6- -2.1)	50% (3/6)	-5.3 (-18.8-0)	-12% (-2 - -13%)	
7	No	Computed tomography	-0.4 HU reduction in hepatic attenuation (not significant)	0.7	0.7	Yes	-2.8	-0.4	[34]

Note. Data are expressed as median (range) or number. Abbreviations: BMI, body mass index; ALT, alanine aminotransferase; HMR, hydrogen In vivo magnetic resonance; N/A, not applicable.

Table 5. Patients' characteristics combined aerobic and resistance exercise

	Variable
Number of protocols (number of articles)	31 (24)
Number of enrolled subjects	775
Age (years old)	48.6 (14.6-61)
Sex (Male; %)	54.5 (25-100)
BMI	31 (27-37)
Body weight (kg)	88.6 (69-107)
Dietary counseling (Yes)	43.8% (13/31)
Type of exercise (aerobic exercise/resistance exercise)	25/7
Exercise duration (min)	41.2 (5-70)
Frequency of exercise (days/week)	3 (2-7)
VO_2max	48 (28-98)
METs	4.8 (3.5-7.3)
Exercise period (week)	12 (1-35)
Changes in BMI	-0.5 (-3.7-0.7)
Changes in body weight (kg)	-1.4 (-10.9-0.7)
Changes in ALT level	-8 (-56-4)
Changes in Intrahepatic lipids (%)	-2 (-21-1.1)

Note. Data are expressed as median (range) or number. Abbreviations: VO_2 max, maximal oxygen consumption; METs, metabolic equivalents; BMI, body mass index; ALT, alanine aminotransferase.

Table 6. Comparisons of patients' characteristics and changes in hepatic steatosis between aerobic and resistance exercise

	Aerobic exercise	Resistance exercise	P
Number of protocols (number of articles)	13 (9)	4 (4)	
Number of enrolled subjects	314	68	
Age (years old)	44.2 (15.2-61)	52.0 (45.9-55.5)	0.1064
Sex (Male; %)	63.45	100	0.6018
BMI	31 (27-36)	32 (29-25)	0.4190
Body weight (kg)	85 (69-107)	94 (72-98)	0.4953
Dietary counseling (Yes)	46.2% (6/13)	25.0% (1/4)	0.4522
Changes in BMI	-1 (-4-1)	-0.5 (-1-0)	0.4106
Changes in ALT level	-12 (-56-4)	-15 (-19-0)	0.5325
Changes in Intrahepatic lipids (%)	-2 (-3-0)	-7.5 (-13- -2)	0.3150

Note. Data are expressed as median (range) or number. Abbreviations: BMI, body mass index, ALT, alanine aminotransferase.