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Review Article

The efficacy of resistance training for non-alcoholic fatty-liver disease: a meta-analysis of randomized controlled trials

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Abstract: Introduction: The efficacy of resistance training to treat non-alcoholic fatty-liver disease (NAFLD) remains controversial. In this study, a systematic review and meta-analysis was performed to explore the influence of resistance training on NAFLD. Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were search for dates through March 2018 for randomized controlled trials (RCTs) assessing the effect of resistance training on liver function of NAFLD. Meta-analysis was performed using the random-effect model. Results: Four RCTs involving 133 patients are included in the meta-analysis. Overall, compared with control group (i.e. usual activities or aerobic activities) for NAFLD, resistance training can significantly reduce alanine transferase (ALT) (mean difference (MD) = -6.63; 95% confidence interval (CI) = -12.87 to -0.40; P = 0.04), aspartate transferase (AST) (MD = -1.17; 95% CI = -1.82 to -0.52; P = 0.0004), gamma-glutamyl transferase (GGT) (MD = -2.87; 95% CI = -5.20 to -0.54; P = 0.02), cholesterol (MD = -8.76; 95% CI = -13.08 to -4.44; P < 0.0001), low-density lipoprotein (LDL) (MD = -5.06; 95% CI = -6.25 to -3.87; P < 0.00001), but has no remarkable influence on glycosylated hemoglobin (HbA1C) (MD = -0.01; 95% CI = -0.08 to 0.06; P = 0.81). Conclusions: Resistance exercise has an important ability to reduce ALT, AST, GGT, cholesterol, and LDL in patients with NAFLD, but shows no influence on HbA1C.

Keywords: Resistance training, non-alcoholic fatty-liver disease (NAFLD), liver function, randomized controlled trials, meta-analysis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as a wide spectrum of disorders ranging from simple steatosis to progressive nonalcoholic steatohepatitis, hepatic fibrosis, and cirrhosis [1-3]. NAFLD causes elevated liver enzymes including alanine amino transferase (ALT) and aspartate amino transferase (AST) and build-up of fat within liver cells [4-7]. The incidence of NAFLD is about 20%-35% in the Western population, 19%-32% in Asian population, and 70%-90% in obese individuals [8, 9]. The severity of fatty liver is positively related to anthropometric measurements including body mass index, waist and hip circumference, subcutaneous adipose tissue thickness and hypertriglyceridaemia [10, 11].

There is no specific drug therapy approved for the treatment of NAFLD and current methods are to treat "metabolic syndrome" rather than NAFLD as an individual entity [12-15]. Lifestyle change and physical activities are currently the main recommendation for people with NAFLD [16]. Exercise training is a major component of treatment for NAFLD as recommended by the American Gastroenterological Association [17, 18]. Exercise training is reported to reduce the risk of insulin resistance, aminotransferase levels, dyslipidemia, liver fat and impaired fasting glucose and benefits to glucose-lipid metabolism [19]. Twelve studies are involved in one meta-analysis regarding exercise therapy versus control in NAFLD, and the results reveals the the benefit of exercise therapy on liver fat but not alanine transferase (ALT) levels [20]. Moderate intensity progress resistance training is associated with significant improvement in hepatic fat, subcutaneous fat and insulin sensitivity for NAFLD [9].

One recent meta-analysis compared aerobic with resistance exercise for NAFLD, and the results found that both exercise programs are able to reduce hepatic steatosis in NAFLD with similar frequency, duration, and period of exercise, but significantly lower intensity and energy consumption are needed for resistance exercise than that for aerobic exercise. These data suggest that resistance exercise may be preferred over aerobic exercise for NAFLD patients with poor cardiorespiratory fitness [16]. The use of resistance exercise on NAFLD still has not been well established. Recently, several RCTs on the topic have been published, and the results have been conflicting [21-23]. With accumulating evidence, a systematic review and meta-analysis of RCTs was performed to investigate the efficacy of resistance exercise on NAFLD.

Materials and methods

Ethics approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24].

Search strategy and study selection

Two investigators independently searched the following databases (inception to March 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: resistance training or resistance exercise, and non-alcoholic, and liver disease. Reference lists of the screened full-text studies were also searched to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) population: patients with non-alcoholic fatty-liver disease; (ii) intervention: resistance exercise; (iii) comparison: usual activities or aerobic activities; (iv) study design: RCT.

Data extraction and outcome measures

The following information was extracted: author, number of patients, age, body mass index, female, body fat and detail methods in each group etc. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. The corresponding author was also contacted to obtain the data when necessary. No simplifications and assumptions are made. The primary outcomes are ALT and aspartate transferase (AST) change. Secondary outcomes include the change of gamma-glutamyl transferase (GGT), cholesterol, low-density lipoprotein (LDL), and glycosylated hemoglobin (HbA1C).

Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale [25]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [26].

Statistical analysis

The mean difference (MD) was estimated with 95% confidence interval (CI) for continuous outcomes (ALT, AST, GGT, cholesterol, LDL, and HbA1C). A random-effects model was used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [27]. Whenever significant heterogeneity is present, potential sources of heterogeneity were searched via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (< 10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. 556 potentially relevant articles are identified initially. Finally, four RCTs that meet the inclusion criteria are included in the meta-analysis [21-23, 28].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in **Table 1**. The four studies are published between

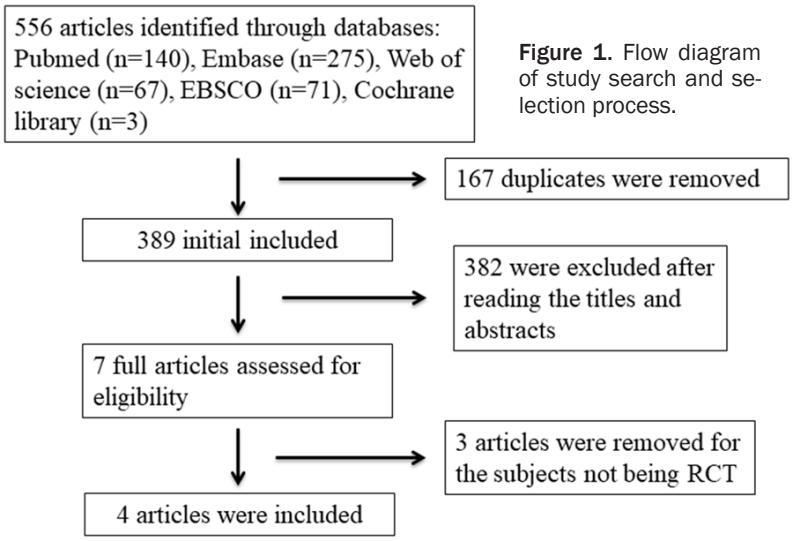

Figure 1. Flow diagram of study search and selection process.

2011 and 2015, and sample sizes range from 19 to 64 with a total of 133. The detailed intensity of resistance exercise were different in each RCT. The intervention treatments in control group included usual activities [21, 22, 28] and aerobic activities [23].

Among the four studies included here, three studies report ALT and AST [21-23], and two studies report GGT, cholesterol, LDL, and HbA1C [22, 23]. Jadad scores of the four included studies vary from 3 to 5, and all four studies are considered to be high-quality ones according to quality assessment.

Primary outcomes: ALT and AST change

These outcome data are analyzed with the random-effects model, and the pooled estimate of the three included RCTs suggested that compared to control group for non-alcoholic fatty-liver disease, resistance exercise can significantly reduce ALT (MD = -6.63; 95% CI = -12.87 to -0.40; P = 0.04), with significant heterogeneity among the studies (I^2 = 79%, heterogeneity P = 0.008) (**Figure 2**).

Consistently, resistance exercise was associated with substantially decreased AST for non-alcoholic fatty-liver disease (MD = -1.17; 95% CI = -1.82 to -0.52; P = 0.0004), with low heterogeneity among the studies (I^2 = 4%, heterogeneity P = 0.35) (**Figure 3**).

Sensitivity analysis

Low heterogeneity was observed among the included studies for AST analysis, but ALT analysis results in significant heterogeneity. When performing sensitivity analysis via omitting one study in turn, there was still significant heterogeneity.

Secondary outcomes

Compared to the control group for non-alcoholic fatty-liver disease, resistance exercise was able to substantially reduce GGT (MD = -2.87; 95% CI = -5.20 to -0.54; P = 0.02; **Figure 4**), cholesterol (MD = -8.76; 95% CI = -13.08 to -4.44; P < 0.0001; **Figure 5**), LDL (MD = -5.06; 95% CI = -6.25 to -3.87; P < 0.00001; **Figure 6**), but showed no significant influence on HbA1C (MD = -0.01; 95% CI = -0.08 to 0.06; P = 0.81; **Figure 7**).

Discussion

The American Heart Association has recommended resistance exercise as a complement to aerobic exercise [29]. Resistance exercise is reported to significantly reduce steatosis as measured by an objective ultrasonographic tool [28]. The meta-analysis reported here suggests that resistance exercise is able to substantially reduce ALT, AST, and GGT for patients with NAFLD, but has no important influence on HbA1C.

It is important to understand whether resistance or aerobic training is superior in inducing changes in hepatic fat liver enzymes and body composition in NAFLD. The mechanisms underlying the change in hepatic fat by exercise training have some association with changes in insulin sensitivity, circulatory lipids and energy balance [28]. Insulin sensitivity is very important for internal hepatic lipid homeostasis. Exercise training can increase body glucose disposal partly due to increased expression of GLUT4 in skeletal muscles, insulin receptor and glycogen storage [30]. An 8-week resistance exercise program reveals reduction in liver lipid and HOMA-IR for NAFLD independent of any change in body weight [28]. Another RCT reports that resistance exercise and aerobic exercise are equally effective to decrease hepatic fat content and liver enzyme levels for NAFLD. In addition, aerobic exercise results in

Table 1. Characteristics of included studies

NO.	Author	Resistance exercise group						Control group						Jada scores
		Number	Age (years)	Female (n)	Body mass index (kg/m^2)	Body fat (%)	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m^2)	Body fat (%)	Methods	
1	Shamsoddini 2015, Iran	10	45.9 ± 7.3	-	30.6 ± 2.6	25.6 ± 4.4	Seven resistance exercises at intensity of 50%-70% of 1 repetition maximum	10	45.8 ± 7.3	-	28.2 ± 3.7	23.3 ± 6	No exercise training program	4
2	Zelber-Sagi 2014, Israel	33	46.32 ± 10.32	17	30.75 ± 4.52	-	Resistance exercises, three times weekly, for 3 months	31	46.64 ± 11.4	13	31.30 ± 4.14	-	Home stretching	5
3	Bacchi 2013, Italy	17	56.0 ± 1.9	5	28.8 ±1.1	29.8 ± 1.9	3 series of 10 repetitions at 70%-80% 1- repetition maximum, with 1 minute of recovery between series	13	55.6 ± 2.0	4	30.5 ± 1.0	29.8 ± 1.9	Aerobic activities	4
4	Hallsworth 2011, UK	11	-	-	32.3 ± 4.9	-	Three times per week on non-consecutive days for 8 weeks	8	-	-	32.3 ± 4.8	-	Continued normal treatment	3

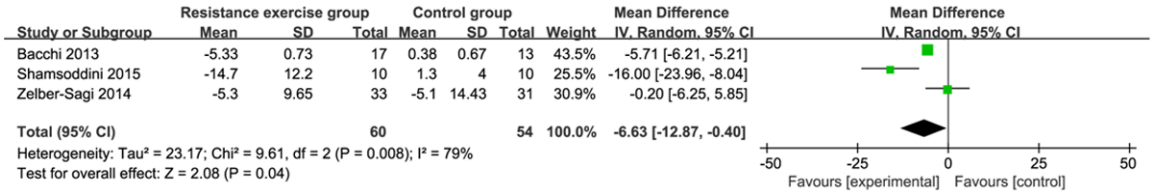

Figure 2. Forest plot for the meta-analysis of ALT change (U/L).

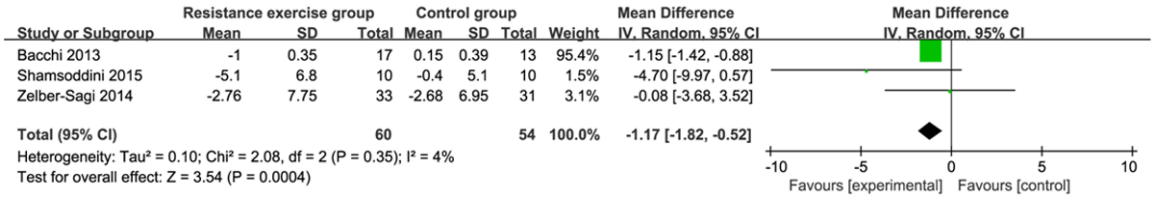

Figure 3. Forest plot for the meta-analysis of AST change (U/L).

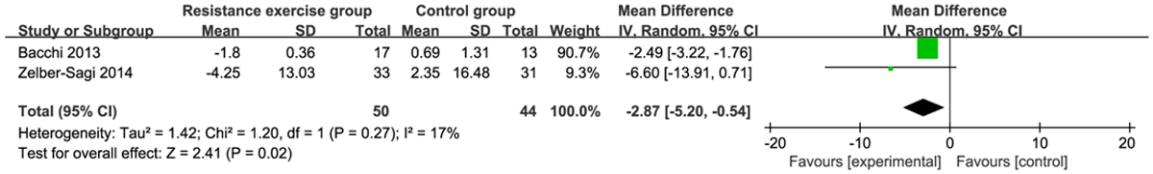

Figure 4. Forest plot for the meta-analysis of GGT change (U/L).

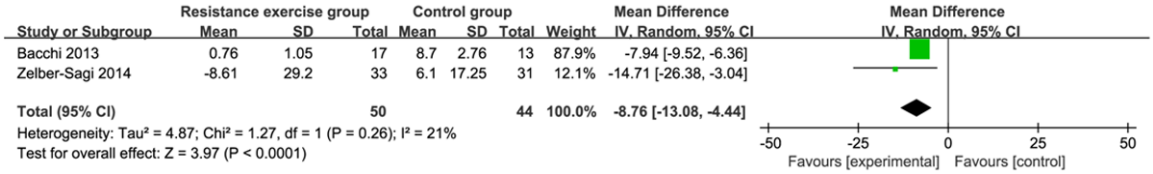

Figure 5. Forest plot for the meta-analysis of cholesterol change (mg/dL).

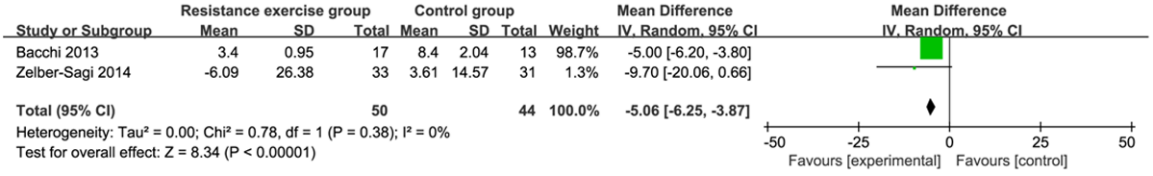

Figure 6. Forest plot for the meta-analysis of LDL change (mg/dL).

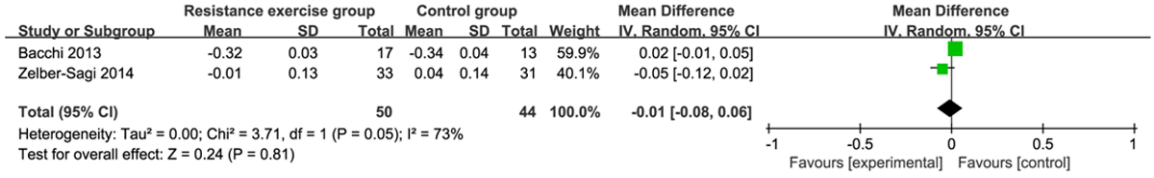

Figure 7. Forest plot for the meta-analysis of HbA1C change (%).

special improvement for NAFLD independent of any change in body weight [21].

Liver steatosis is associated with insulin resistance and lipid abnormalities [31, 32]. Increased insulin resistance contributes to the shift in cholesterol metabolism independent of body weight [33, 34]. Resistance training is found to improve insulin resistance including hepatic insulin resistance, and results in decreased synthesis of hepatic cholesterol [35, 36]. The precise mechanisms involving these processes remain elusive [37]. Lipid markers (i.e. cholesterol and LDL) is significantly decreased by resistance training in patients with NAFLD based on the results of our meta-analysis. There was still significant heterogeneity after performing sensitivity analysis via omitting one study in turn, and the possible explanations include the different methods and duration of resistance exercise, methods of control group and patients with various body mass index.

This meta-analysis has several potential limitations that should be taken into account. First, analysis is based on only four RCTs and all of them have a relatively small sample size ($n < 100$). More RCTs with large samples should be conducted to confirm this issue. Next, there is significant heterogeneity when performing sensitivity analysis, different methods and duration of resistance exercise and patient populations may have an influence on the pooling results. Finally, the diagnosis of is not based on histology in included RCTs, and the fat content is not measured by biopsy.

Conclusions

Resistance exercise can provide important benefits to patients with NAFLD, and should be recommended in clinical work.

Disclosure of conflict of interest

None.

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