Research Article

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Exercise and non-alcoholic fatty liver disease: A systematic review and meta-analysis

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Background & Aims: Exercise is an integral component of lifestyle intervention aimed at weight loss, but an independent benefit of exercise in NAFLD has also been suggested.

Methods: We aimed to evaluate the efficacy of aerobic exercise and/or progressive resistance training for the modulation of liver fat and alanine aminotransferase (ALT) levels in adults. Relevant databases were searched up to August 2011 for controlled trials, which compared regular exercise *vs.* a non-exercise control on change in liver fat and/or ALT.

Results: Of the 16,822 studies from the initial search, 12 were included. There was a significant pooled effect size (ES) for the comparison between exercise therapy *vs.* control (ES = −0.37, 95% CI: −0.06 to −0.69; $p = 0.02$), but only when interventions which compared combined exercise and diet *vs.* diet-alone and achieved substantial weight loss, were omitted. The benefit of exercise on liver fat occurred with minimal or no weight loss. There was no effect of exercise alone *vs.* control on ALT (ES = −0.15, 95% CI: 0.14 to −0.45; $p = 0.32$).

Conclusions: Individual reports of exercise interventions often have low sample sizes and insufficient power to detect clinically meaningful hepatic benefits. By pooling current research, we show clear evidence for a benefit of exercise therapy on liver fat but not ALT levels. This benefit is apparent with minimal or no weight loss and at exercise levels below current exercise recommendations for obesity management. Given the paucity of current treatment options, exercise provides a valid, low-cost therapy for disorders characterised by fatty liver.

Keywords: NAFLD; Physical activity; Aerobic; Resistance training; Obesity, Weight loss.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase; BMI, body mass index; NASH, non-alcoholic steatohepatitis; ^{1}H-MRS, proton magnetic resonance spectroscopy; AST, aspartate aminotransferase; AEx, aerobic exercise training; PRT, progressive resistance exercise training; ES, effect size; CI, confidence interval; RCT, randomized controlled trial; CT, computed tomography; MRI, magnetic resonance imaging; DXA, duel energy X-ray absorptiometry; VO_{2peak}, peak rate of oxygen consumption; RPE, rating of perceived exertion; METs, metabolic equivalents; 1RM, one repetition maximum.

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects up to one third of the adult population in affluent nations [1], and most obese individuals [2]. While bland steatosis is considered to have a relatively benign prognosis as far as liver-related outcomes are concerned [3], those with steatohepatitis can progress to cirrhosis and its complications, including liver cancer [4]. NAFLD is recognised as an independent predictor of insulin resistance [5], the metabolic syndrome [6], and cardiovascular disease [7]. As a consequence, research examining the efficacy of therapies targeting improvements in liver fat and serum aminotransferase levels has risen exponentially.

Pharmacological and neutraceutical agents have been trialed, but their use in clinical practice is limited by concerns regarding their effectiveness, the small study cohort sizes, the relatively small number of high quality studies, issues with compliance [8], and side-effects [9]. Only thiazolidinediones are widely recognised to reduce liver fat [10,11], but concerns regarding the safety of this class of compounds and weight gain are limiting factors. In light of this, and the fact that NAFLD is often co-morbid with obesity and linked to cardio-metabolic risk [12], there has been increasing interest in diet and exercise strategies to manage fatty liver disorders. Serial quantification of serum aminotransferases and liver fat by proton magnetic resonance spectroscopy (^{1}H-MRS), computed tomography (CT), ultrasonography or direct histological evaluation has shown that the synergy of aerobic exercise training and dietary restriction positively affects NAFLD when weight loss approximating 4–9% of body weight is achieved [13].

It is not possible to conclude a benefit of exercise *per se* on NAFLD on the basis of findings from combined diet/exercise interventions [13]. Yet, cross-sectional studies have strengthened the argument of a direct hepatic benefit of exercise by demonstrating an inverse correlation between NAFLD and physical activity [14] or fitness levels [15,16]. More recently, a number of laboratories have sought to delineate the effect of exercise from that of dietary modification by examining the impact of exercise *per se* on liver fat and/or serum aminotransferases via longitudinal investigation. The results of individual studies nonetheless, have been variable.

The aim of this study, therefore, was to conduct a systematic review with meta-analysis of the pooled data from controlled adult human trials to assess the efficacy of exercise interventions for modifying liver fat and serum alanine aminotransferase (ALT) levels. Such an analysis is ideal for objectively evaluating exercise therapies as the individual reports in this area tend to have low sample sizes and may lack sufficient power to detect small, but clinically meaningful changes. We hypothesised that, when compared with a non-exercise control condition, interventions involving exercise therapy would significantly reduce liver fat and ALT.

Materials and methods

A systematic literature search was conducted by one researcher (SK) to identify and appraise studies of exercise in non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Databases searched from inception to August 2011 were: Medline (Ovid), Cinahl (EBSCO Host), AMED (Ovid), Web of Science (ISI Web of Knowledge), Scopus, CAM, Embase, ProQuest 5000, Science Direct, and PubMed.

The database searches were performed using the keywords: (aerobic exercise, endurance exercise, aerobic training, endurance training, cardio training, exercise, physical endurance, physical exertion) or (strength training, weight training, resistance training, progressive training, progressive resistance, weight lifting) and (NAFLD, non-alcoholic fatty liver disease, fatty liver, hepatic steatosis, hepatic, liver, steatohepatitis, NASH, aminotransferase, AST, ALT). Reference lists of all retrieved papers were manually searched for potentially eligible papers. Controlled trials were reviewed while uncontrolled trials and cross-sectional studies were excluded from analysis. Manuscripts published in all languages were included. Studies were excluded based on file type: book sections, theses, film/broadcast, opinion articles, observational studies, and abstracts without adequate data or reviews (Fig. 1).

Inclusion and exclusion criteria

Inclusion and exclusion criteria were determined *a priori* by two researchers (SK and NJ). Included studies employed exercise trials of three sessions or more. This cut-off was established to differentiate studies examining the acute effects of exercise from those examining training adaptations. Trials involving aerobic exercise and/or progressive resistance exercise training (PRT) in male and/or female adults ($\geqslant$18 years) were included. Trials with either NAFLD or NASH cohorts (where this was specified) were considered for inclusion. Studies involving dietary control/intervention were included only if the diet was the same between the exercise and control groups thus allowing the independent effect of exercise to be delineated. Studies were excluded if they addressed alcoholic, drug-induced, total parenteral nutrition-induced, viral or genetic causes of liver injury.

Data extraction

Outcome measures used in this review were: liver fat quantified by histological assessment or proton magnetic resonance spectroscopy (^{1}H-MRS), or inferred by computed tomography (CT) or ultrasonography; and plasma alanine aminotransferase (ALT) level. Data on participant characteristics, exercise and control interventions (mode of exercise, nutritional intervention, exercise frequency, intensity, session duration and intervention duration), and NAFLD measurements were extracted independently by two researchers (SK and DH) with disagreements resolved by a third researcher (NJ). In cases where journal articles contained insufficient information, attempts were made to contact authors to obtain missing details. In some papers, data for liver parameters were not represented in numerical form; but rather in graphical format. In this instance, the graph was enlarged, and the data estimated manually. Where required, means and standard deviations were calculated using appropriate equations [17].

Analyses and meta-analyses

The between-trial standardised mean difference, or effect size (ES), and 95% confidence intervals (CI) were calculated. The ES was used to standardise changes of liver fat and ALT. Pooled estimates of the effect of exercise on liver fat and ALT, using ES, were obtained using a random-effects model. We presumed a correlation of 0.5 between outcomes measured within each comparison group.

We performed two analyses to compare the effect of exercise *vs.* control on (i) liver fat change and (ii) ALT change. Sub-analyses were also performed *a priori* for studies which used only exercise intervention, as opposed to those which employed a dietary intervention in both the exercise and control groups. All analyses were conducted using Comprehensive Meta-analysis Version 2, Biostat, Englewood, NJ (2005).

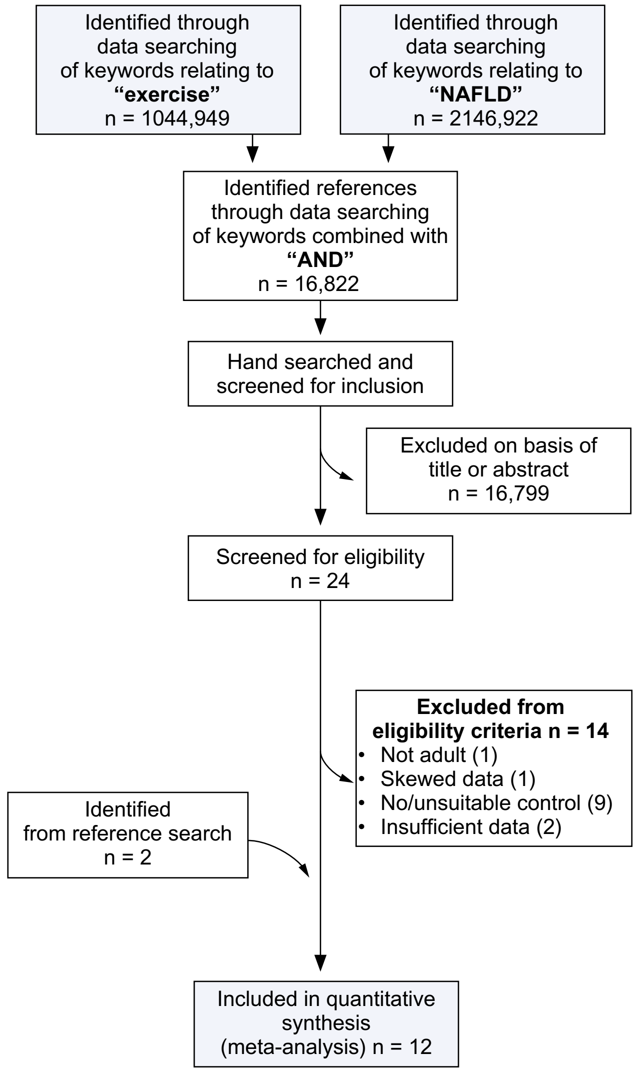

Fig. 1. Flowchart showing the process for the inclusion of studies.

Study quality assessment

Study quality was assessed by two researchers (SK and DH) using a modified Downs and Black checklist [18]. Representative participants for checklist item 11 were defined as any adult with NAFLD or NASH. The scale was modified to include criteria for adequate description of control, whether the exercise sessions were supervised, and whether ^{1}H-MRS (the most valid method to quantify changes in intrahepatic lipid [13]) was used for liver fat measurement. Where reviewers disagreed, specific criteria were discussed with a third reviewer (NJ) until consensus was reached. If an item was unable to be determined a 'no' was given.

Results

Identification and selection of studies

The original search netted 16,822 studies. Two more studies were found from the reference lists of the manuscripts retrieved. One