The role of exercise in limiting progression from liver inflammation to carcinoma: meta-analysis of human and animal studies

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INTRODUCTION

Liver disease is a global concern, with increasing incidence across all demographics[1]. Non-alcoholic fatty liver disease (NAFLD) affects approximately 20-30% of adults[2], and about 20% of these cases progress to non-alcoholic steatohepatitis (NASH)[3]. NAFLD covers a spectrum from benign non-alcoholic fatty liver (NAFL) to severe conditions like cirrhosis and hepatocellular carcinoma (HCC). NAFL has a low risk of progression compared to NASH with active inflammation. Once liver fibrosis is present, the risk of disease progression and complications rises significantly, with a sevenfold greater chance of developing HCC compared to those without liver disease[4]. Given that HCC is the third leading cause of cancer-related deaths worldwide[6] and approximately 90-95% of people with HCC have underlying liver cirrhosis[7], the progression from liver cirrhosis to HCC is a matter of great concern.

The liver is one of only a few organs that can regenerate. Its regeneration capacity, however, is finite. Lifestyle modification, such as increasing physical activity, may help improve liver disease outcomes. Emerging evidence suggests that increasing physical activity may enhance liver repair, reduce the risk of liver diseases, such as NAFLD and liver cancer, and slow the progression from HBV, HCV, NAFLD, and alcohol-related liver disease to liver cirrhosis and HCC[5,6]. While epidemiological data indicates that higher physical activity levels may offer protection against liver cancer, the experimental evidence remains inconclusive; largely due to factors such as heterogeneity in the assessment of 'exposure'. Consequently, these challenges limit the endorsement of exercise interventions for treating liver disease.

Examining the evidence for the biological plausibility of exercise reducing the risk of liver disease can provide support for causal inference. Preclinical studies indicate that, if hepatic steatosis can be reversed through exercise intervention, then liver inflammation and fibrosis can be resolved.

Due to the invasive nature of liver biopsy, much of the mechanistic evidence for the effects of exercise on liver disease comes from animal studies. However, in vivo animal studies suggest liver fibrosis is more susceptible to regeneration in animals compared to humans. Therefore, to ensure translation, human mechanistic studies must also be examined.

Developing a better understanding of how exercise affects intermediate biological processes may provide insight into the best ways to alter exposures for disease prevention. The overarching objective of this review is to improve the understanding of whether exercise has the capacity to:

1. promote regression of early fibrosis,
2. decrease or delay progression to cirrhosis,
3. decrease or delay progression to carcinoma.

METHODS

Relevant publications were identified using tailored search strategies of MEDLINE (via Ovid) from 1946 - June 27, 2021, EMBASE (via Ovid) from 1974 - June 27, 2021, and SportDiscus (via EBSCO) from 1985 - July 4, 2021. A version of the search strategy for MEDLINE is presented in the supplementary files.

Eligibility criteria

Study design: Parallel group randomized controlled trials (RCTs) and randomized crossover trials (RXTs) designs.

Population: Human: Adults (>18 years old) with liver inflammation (including NAFL and NASH) or fibrosis. Populations with other clinically relevant health conditions (e.g., metabolic syndrome, type II diabetes) were also considered.
Animal: Genetic and induced models of liver disease; induction methods included, but were not limited to, exposure to diet and alcohol.

Intervention: Any exercise intervention that disturbed the bodies homeostasis through muscular activity, whether exclusively concentric, eccentric, or isometric, or a combination thereof. We excluded studies if the effects of exercise could not be isolated and if the period of exercise was less than seven days.

Outcome: Invasive; liver biopsy
Non-Invasive: FibroScan (Transient Elastography), blood tests, magnetic resonance elastography (MSE), shear wave elastography (SWE), fibrosis blood panels and other imaging modalities (i.e., CT and MRI)

Extracted data were summarised and presented descriptively. For outcomes that were consistently defined and reported in at least three studies, random effects meta-analysis was used to estimate the effects of exercise on liver outcomes. Meta-analysis compared post-intervention means and standard deviation between intervention and control groups. When studies had more than one intervention group that met the criteria for inclusion, post-intervention means, and standard deviations were combined as per the Cochrane Collaboration manual.

Meta-analysis effect estimates are presented as standardised mean difference (SMD) and 95% confidence interval (95%CI). Heterogeneity was assessed using the I2 statistic. Publication bias was assessed via visual inspection of funnel plots (Supplementary file).

For animal studies, meta-regression was used to assess the influence of study year, study location (i.e., region), animal type, disease, and disease inducement method on effect estimates (Supplementary file).

For human studies, meta-regression was used to assess the influence of study year, study region, and disease type on effect estimates (Supplementary file).

Results of studies not included in the meta-analyses were presented descriptively.

RESULTS

Of the 1,535 records identified via database search, 1,352 titles and abstracts were screened, and 174 full texts were assessed for eligibility, with 60 full texts meeting all criteria for inclusion. Of these, there were 29 interventions in animals and 18 interventions conducted in humans. Study characteristics of human and animal studies are presented in the Supplementary files.

Only one study directly reported the number of NAFLD participants who experienced disease regression, reduction, or progression. In most studies, liver function and/or damage were used as surrogate markers for remission and progression, and included tests for 1. liver enzymes: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), 2. liver triglyceride content: hepatic triglyceride content (HTGC), intrahepatic triglyceride content (IHTG), HTGC/IHTG, liver fat percentage, intra-hepatocellular lipid (IHCL), liver lipid percentage, intrahepatic lipid content (IHL), liver triacylglycerol (TAG), and hepatic fat content (HFC), 3. liver steatosis and other related measures, the fatty liver index, ferritin, fetuin A, hepatic steatosis, NAFLD, NAFLD activity score (NAS), fibrosis score, and steatosis score.

Only one study[8] directly investigated the impact of exercise on the remission or progression of NAFLD.

The findings revealed that 14% (n = 3/22) of participants assigned to the exercise group achieved a decrease in HFC to less than 5.6% (normal levels), while this was observed in only 11% (n = 2/18) of those who received no intervention. Additionally, the exercise group demonstrated a 54% reduction in HFC (n = 12/22), whereas only 17% (n = 3/18) in the no intervention group improved, and elevated HFC was seen in just 32% (n = 7/22) of exercise group participants, in contrast to 72% (n = 13/18) in the no intervention arm. These findings suggest a positive association between exercise intervention and the regression of early fibrosis, as well as a delay in the progression to cirrhosis. We found no studies that directly evaluated the progression to HCC.

Meta-analysis of human studies identified decreases in liver enzymes; ALT (SMD = -0.28, 95%CI = -0.53, -0.03), AST (SMD = -0.12, 95%CI = -0.32, 0.07), GGT (SMD = -0.23, 95%CI = -0.36, -0.10), as well as a small increase in ALP (SMD = 0.23, 95%CI = -0.13, 0.59), and liver triglycerides (SMD = -0.24, 95%CI = -0.66, 0.18) (Figure 1).

Meta-analysis of animal studies identified decreases in liver enzymes; ALT (SMD = -2.85, 95%CI = -4.55, -1.14), AST (SMD = -2.85, 95%CI = -4.55, -1.14), and liver triglycerides (SMD = -1.36, 95%CI = -2.08, -0.65), liver weight (SMD = -1.94, 95%CI = -2.78, -1.10), and the NAFLD activity score (SMD = -1.36, 95%CI = -2.08, -0.65) (Figure 2).

Figure 1. Meta analysis of human studies

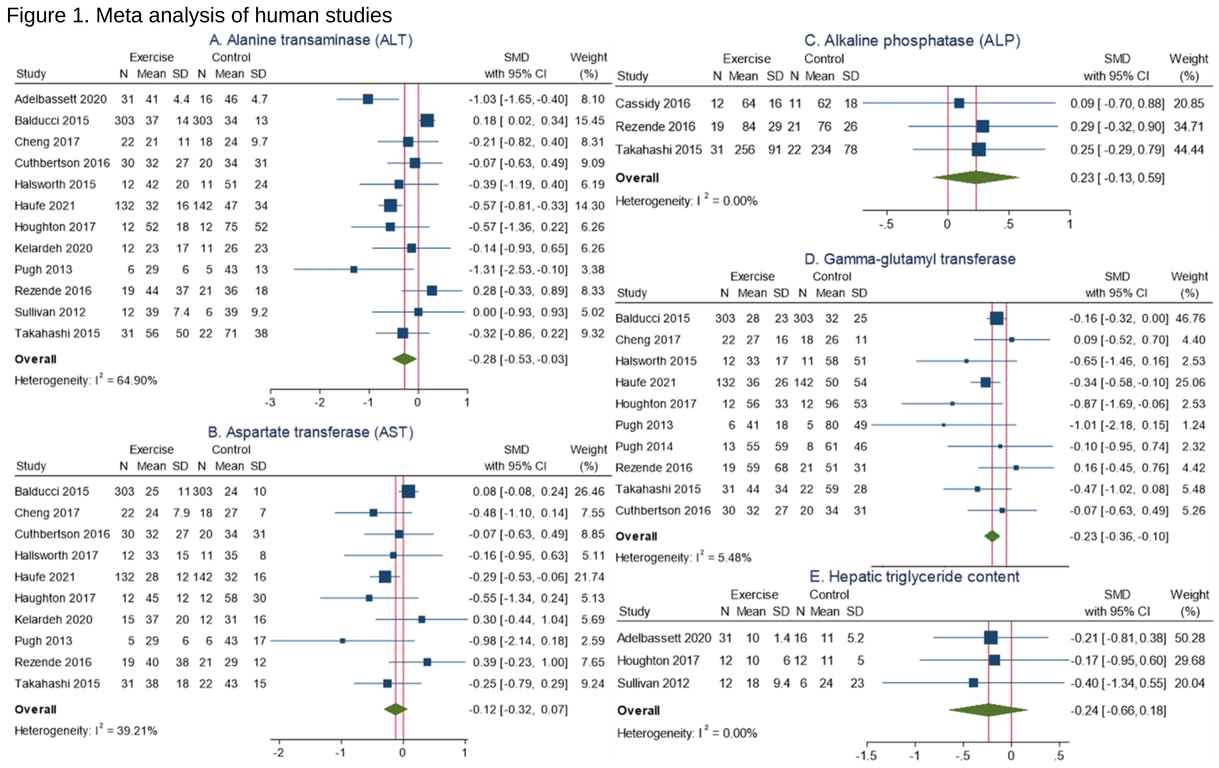
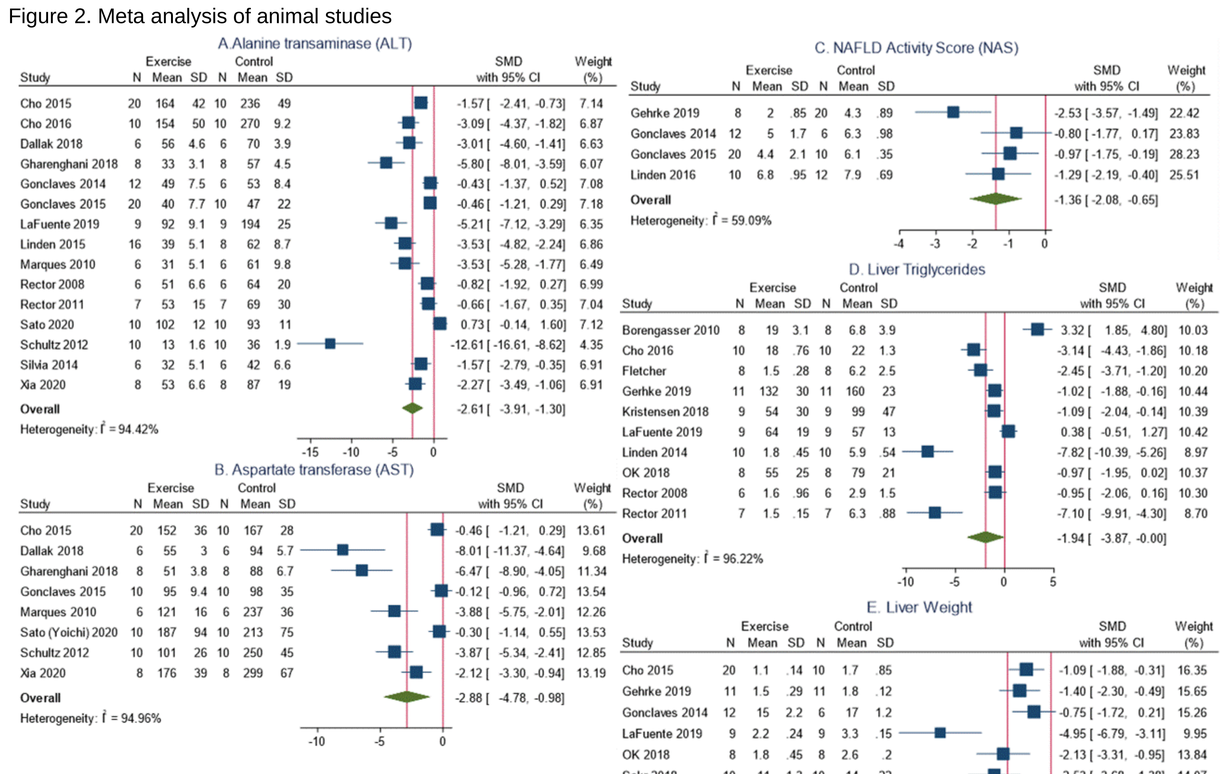


Figure 2. Meta analysis of animal studies



CONCLUSION

1. A single investigation focusing on the effect of exercise on the progression and remission of NAFLD revealed a significant association between exercise intervention and the regression of initial fibrosis, as well as a delay in the progression of cirrhosis.
2. A comprehensive review of existing literature reveals consistent indications of exercise's positive impact on liver function and reduction of liver damage in both human subjects and animal models with established liver disease.
3. These results substantiate the biological plausibility of exercise as a beneficial therapeutic strategy for enhancing liver function and combatting liver disease.
4. Further research and clinical trials are warranted to fully elucidate the mechanisms underlying these observed effects and to establish more robust guidelines for exercise-based interventions in liver disease management

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