Research Article

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Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver

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Background & Aims: Guidelines about recommendations for amounts of exercise/physical activity are variable in non-alcoholic fatty liver disease. Our aim was to determine the amount of exercise that was associated with two outcomes: a) development of incident liver fat and b) resolution of baseline liver fat, at five-year follow-up.

Methods: In an occupational health screening program, weekly frequency of exercise was assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF). Liver fat identified by ultrasonography (3.5 MHz probe) at baseline and at five-year follow-up. Fully adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs and 95% confidence intervals [CI]) for incident fatty liver and resolution of fatty liver at follow-up.

Results: 233,676 men and women were studied between 2002 and 2014. 126,811 individuals were identified without fatty liver, and of these subjects, 29,014 subjects developed incident fatty liver during follow-up. At baseline, there were 42,536 individuals with liver fat and of these individuals, fatty liver resolved in 14,514, during follow-up. After full adjustment, compared to no exercise, exercise was associated with benefit for both outcomes; for exercise $\geqslant$5 times per week for incident fatty liver: HR 0.86 (95% CI 0.80,0.92), p <0.001, and for resolution of fatty liver HR 1.40 (95% CI 1.25,1.55), p <0.001.

Conclusions: Moderate to vigorous exercise is beneficial in decreasing risk of development of new fatty liver or improving resolution of existing fatty liver during 5 years of follow-up.

Lay summary: The amount of exercise/physical activity to benefit fatty liver disease in non-alcoholic fatty liver disease is not known. In a large study of free-living people, our aim was to determine the amount of exercise that was linked with a decrease in new fatty liver and also improvement of existing fatty liver over 5 years of follow-up. Compared to no exercise, exercise $\geqslant$5 times per week (lasting at least 10 min on each occasion) was linked to a highly significantly benefit for both a decrease in new fatty liver and also improvement of existing fatty liver.

Introduction

It is now accepted that the clinical burden of non-alcoholic fatty liver disease (NAFLD) extends beyond liver-related morbidity and mortality, with the concept that NAFLD is a multisystem disease that also affects several extra-hepatic organs and regulatory pathways [1,2]. Incidence rates for NAFLD are uncertain (because of difficulties with establishing a precise diagnosis during sequential follow-up) but current incidence rates are approximately 20/10,000 person-years, peaking in the sixth decade of life with NAFLD being more common in men [3]. NAFLD comprises a complex spectrum of disease that begins with liver fat accumulation (non-alcoholic fatty liver or NAFL) and progress with inflammation and fibrosis (non-alcoholic steatohepatitis or NASH). There is now a wealth of evidence that NAFLD increases risk of type 2 diabetes (T2DM) (summarised in [1,4]) but there is limited evidence to date that treatment of NAFLD decreases risk of T2DM. We have shown previously that resolution of fatty liver (detected by ultrasound) over 5 years, was independently associated with marked attenuation of the risk of incident T2DM [5] and also incident hypertension [6], over five years of follow-up. Recently our findings for attenuation of the risk of T2DM has been verified in a Japanese population (that also confirmed the resolution of liver

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Abbreviations: IPAQ-SF, International Physical Activity Questionnaire Short Form; NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; BMI, body mass index.

fat by ultrasonography) [7]. In contrast to previous notions that NAFL did not cause serious chronic liver disease, increasing evidence is now showing that NAFL is not harmless. Recently it has been shown that NAFL is an important risk factor for the development of clinically relevant liver fibrosis [8–11] and consequently it is now being realized that it is important to understand what interventions and treatments are effective for decreasing liver fat [12] within the spectrum of liver disease in NAFLD.

In short duration studies, lifestyle changes that have focussed on diet and exercise modification have shown promise in decreasing liver fat as a manifestation of early disease in NAFLD [13–16]. However, guidelines from specialist societies regarding recommendations for amounts and intensity of exercise/physical activity in NAFLD are variable. For example, the American Association for the Study of Liver Diseases guideline does not make a specific recommendation about the amount or the desired intensity of exercise in NAFLD and states that 'exercise alone in adults (with NAFLD) may reduce hepatic steatosis, but its ability to improve other aspects of liver histology are unknown' [17]. The European Association for the Study of the Liver (EASL) recommends that in NAFLD guidelines for patients with type 2 diabetes are followed and recommends 150 min per week of moderate intensity exercise [18] and this recommendation is largely in keeping with guidelines for the general population [19]. Thus, at present it is unclear how much exercise is needed or how intense that exercise should be to prevent development of new fatty liver or to resolve existing fatty liver. We have utilized a retrospective study design of an occupational cohort in which there were measurements of exercise/physical activity at baseline and at follow-up (as key exposures) with measurements of fatty liver assessed by ultrasonography at baseline and at follow-up (as the key outcomes) to assess relationships between exercise and change in fatty liver status over time. Although ultrasonography has limited sensitivity to detect liver fat in NAFLD, liver ultrasonography is a good technique to assess whether liver fat is present, providing liver fat accumulation is approximately 30% [20,21]. Since it remains uncertain how much exercise is needed, or for how long that exercise is needed, (to treat liver fat and to decrease risk of developing new liver fat), we have studied relationships between numbers of weekly exercise sessions at baseline and change in numbers of weekly exercise sessions between baseline and follow-up, with both incident fatty liver at follow-up and resolution of baseline fatty liver at follow-up. Specifically, our aim was to determine the amount of baseline exercise that was associated with: a) decreased development of incident liver fat and b) resolution of baseline liver fat (as the outcomes of interest), at five-year follow-up. Additionally, we aimed to assess whether any increase in the number of exercise sessions between baseline and follow-up was associated with these fatty liver-related outcomes at five-year follow-up after adjusting for key confounders that also included change in body mass index (BMI) between baseline and follow-up.

Patients and methods

Study population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea. More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health law requires annual or biennial health screening examinations of all employees, offered free of charge. The remaining participants were subjects voluntarily taking part in the screening examinations. The study population consisted of individuals who participated in a comprehensive health screening program, at least twice, at Kangbuk Samsung Hospital, Seoul, Korea from 2002 to 2014 (n = 233,676). To test relationships between exercise and incident fatty liver, and exercise and resolution of existing fatty liver, we excluded subjects in which there was missing data for smoking, exercise, fatty liver and cancer (n = 19,613). Subjects were also excluded if they were hepatitis B surface antigen (HBsAg) positive (n = 9,297), hepatitis C virus antibody positive (n = 307), and daily alcohol consumption was more than 20 g (men) and 10 g (women) (n = 38,296). Also, in order to test relationships with incident fatty liver at follow-up, subjects with baseline fatty liver (n = 60,522) were excluded. Thus 126,811 subjects were included in this analysis, and their mean ± standard deviation (SD) follow-up period was 4.95 ± 3.29 years. Relationships between exercise and resolution of fatty liver were examined in 42,536 individuals and subjects were included who had fatty liver at baseline. Mean (± SD) follow-up was 4.29 (± 3.26) years. The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital and any requirement for informed consent was waived by the Board, because de-identified information was retrieved retrospectively.

Measurements

As part of the health screening program, individuals completed self-administered questionnaires, related to their medical and social history and medication use. Individuals were asked about duration of education (years), smoking history (never, former, or current) and alcohol consumption (grams, g/week). From 2011, we assessed the weekly frequency of moderate- or vigorous-intensity physical activity using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) [22]. Prior to 2011, similar questionnaires were used, but at that time the IPAQ-SF had not been officially adopted. The IPAQ-SF measures the frequency and duration of moderate to vigorous physical activity undertaken for more than 10 continuous minutes across all usual activities at work, home or during leisure for middle aged individuals during a seven-day period. To assess the number of exercise sessions undertaken per week by each participant, the following specific questions were asked to gauge the number of times per week a participant engaged in exercise. "How many days did you undertake physical activity (enough to perspire)?" or "during the last seven days, on how many days did you do moderate intensity physical activity e.g., carrying light loads, bicycling at a steady pace, or playing tennis? Do not include walking in your response" If the answer was greater than zero, additional questions were asked such as "How much time did you usually spend doing moderate or vigorous physical activities on one of those days?" In our study, subjects were classified into four categories for analysis of exercise as the exposure with the outcomes of interest. No regular physical activity, exercise 1–2 times per week, exercise 3–4 times per week and exercise ⩾5 times per week. Additionally, we defined change in exercise between baseline and follow-up, according to a decrease, no change, or an increase in the number of weekly exercise sessions per week.

Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. BMI was calculated as weight in kilograms divided by height in meters squared. Blood samples were collected after at least 10-h of fasting and analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

Abdominal ultrasonography (Logic Q700 MR; GE, Milwaukee, WI, USA) was undertaken by clinical radiologists using a 3.5 MHz probe for all subjects at baseline and after five years. The following images were undertaken; i) sagittal view of the right lobe of the liver and right kidney, ii) transverse view of the left lateral segment of the liver and spleen and iii) transverse view of the liver for altered echo texture. Fatty infiltration of the liver (fatty liver) was identified if there was an increase in echogenicity of the liver compared with the echogenicity of the renal cortex where the diaphragm and intrahepatic vessels appeared normal [21].

Statistical analyses

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). Reported *p* values were two-tailed, and <0.05 were considered statistically significant. The distribution of continuous variables was evaluated and transformations were conducted for nonparametric variables. Cox