Research Article

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Relationship of sitting time and physical activity with non-alcoholic fatty liver disease

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Abstract

Background & Aims: The goal of this study was to examine the association of sitting time and physical activity level with non-alcoholic fatty liver disease (NAFLD) in Korean men and women and to explore whether any observed associations were mediated by adiposity.

Methods: A cross-sectional study was performed on 139,056 Koreans, who underwent a health examination between March 2011 and December 2013. Physical activity level and sitting time were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form. The presence of fatty liver was determined using ultrasonographic findings. Poisson regression models with robust variance were used to evaluate the association of sitting time and physical activity level with NAFLD.

Results: Of the 139,056 subjects, 39,257 had NAFLD. In a multivariable-adjusted model, both prolonged sitting time and decreased physical activity level were independently associated with increasing prevalence of NAFLD. The prevalence ratios (95% CIs) for NAFLD comparing 5–9 and $\geqslant$10 h/day sitting time to <5 h/day were 1.04 (1.02–1.07) and 1.09 (1.06–1.11), respectively (*p* for trend <0.001). These associations were still observed in subjects with BMI <23 kg/m^2. The prevalence ratios (95% CIs) for NAFLD comparing minimally active and health-enhancing physically active groups to the inactive group were 0.94 (0.92–0.95) and 0.80 (0.78–0.82), respectively (*p* for trend <0.001).

Conclusions: Prolonged sitting time and decreased physical activity level were positively associated with the prevalence of NAFLD in a large sample of middle-aged Koreans, supporting the importance of reducing time spent sitting in addition to promoting physical activity.

Introduction

Physical activity is well-recognized to reduce the incidence and mortality of various chronic diseases, including cardiovascular disease, diabetes, stroke and several types of cancer [1–3]. More than one half of the average person's waking day involves sedentary activities associated with prolonged sitting such as watching TV and using the computer [4]. Recently, the deleterious effects of sedentary behavior regardless of additional physical activity have received a great deal of attention [5–8]. Indeed, a growing number of epidemiologic studies have suggested an association between sedentary behavior and adverse outcomes including obesity, diabetes, insulin resistance, metabolic syndrome, cardiovascular disease, cancer and mortality that is distinct from those related to a lack of physical activity [7–10]. Notably, this association was still observed among those participating in high levels of moderate to

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Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FLI, fatty liver index; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NAFLD, non-alcoholic fatty liver disease; SMI, skeletal muscle mass.

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vigorous physical activity, indicating that regular participation in high levels of physical activity does not fully protect against the risks associated with prolonged bouts of sedentary behaviors [11].

Non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of liver disease from simple steatosis to non-alcoholic steatohepatitis [12,13]. In addition to its potential to progress to cirrhosis or hepatocellular carcinoma [14], NAFLD has been linked to a substantial increase in risk for metabolic complications such as diabetes and cardiovascular disease [15,16]. NAFLD is closely related to obesity, insulin resistance, and metabolic syndrome [17,18], all of which have been associated with insufficient physical activity and prolonged sitting. Experimental studies show that prolonged sitting and lack of contraction of lower limb muscles leads to metabolic abnormalities via suppressed action of skeletal muscle lipoprotein lipase and insulin, supporting a unique "inactivity physiology" paradigm, and impairing lipoprotein lipase in skeletal muscle was associated with insulin resistance in liver and other tissues [7,19–21]. Therefore, it can be hypothesized that prolonged sitting could play a potential role in the development of NAFLD, independent of physical activity level. In addition, the association between prolonged sitting and NAFLD has implications for public health due to evidence showing that time in sedentary behavior has increased in recent years, coinciding with an increasing prevalence of obesity and NAFLD [22–24].

Until now, the association between sitting time and NAFLD independent of physical activity has remained largely unexplored. The only study reporting a positive association between sitting time and NAFLD was limited by small sample size (74 British people) as well as the absence of liver fat and blood sample measurements for control subjects [25]. Therefore, the goal of this study was to examine the association of sitting time and physical activity level with NAFLD in a large sample of Korean men and women, and to explore whether any observed associations were due to adiposity or insulin resistance.

Methods

Study population

The Kangbuk Samsung Health Study was a cohort study of Korean men and women who underwent a comprehensive annual or biennial examination at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [26,27]. The study population consisted of 178,906 men and women who completed a physical activity questionnaire and underwent a comprehensive health examination between March, 2011 and December, 2013.

We excluded 39,850 participants for the following reasons: missing abdominal ultrasonography data (N = 101); alcohol intake of $\geqslant$30 g/day for men and $\geqslant$20 g/day for women (N = 28,286) [28]; positive serologic markers for hepatitis B or C virus (N = 6509); and use of medications associated with NAFLD within the past year such as valproate, amiodarone, methotrexate, tamoxifen, or corticosteroids (N = 1398) [28]. We also excluded participants with known liver disease or use of medications for liver disease (N = 6394) or a past history of a malignancy (N = 4324). Because some individuals met more than one exclusion criterion, the total number of patients eligible for the study was 139,056. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, and the requirement for informed consent was waived because we used de-identified retrospective data routinely collected during the health screening process.

Measurements

All examinations were conducted at Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon. Data on demographic characteristics, smoking status, alcohol consumption, education level, medical history, and medication use were also collected by standardized, self-administered questionnaires as previously described [26,27].

Physical activity levels and sitting time were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) [29,30]. IPAQ-SF measures the frequency and duration of any walking and other moderate to vigorous physical activity undertaken for more than 10 continuous minutes across all contexts (i.e., work, home and leisure) during a seven-day period. IPAQ-SF enables the calculation of metabolic equivalents (MET-minutes per week), derived by assigning standardized MET values of 3.3, 4, and 8 for walking, moderate intensity and vigorous intensity, respectively. Physical activity levels were classified into three categories, inactive, minimally active, and health-enhancing physically active (HEPA). These categories are derived from the following established criteria, inactive, which meets neither minimally active nor HEPA; minimally active, which meets any of the following three criteria; (i) three or more days of vigorous activity for $\geqslant$20 min/day; (ii) five or more days of moderate intensity activity or walking for $\geqslant$30 min/day; or (iii) five days or more of any combination of walking and moderate intensity or vigorous intensity activities achieving $\geqslant$600 MET min/week; and HEPA, which meets either of two criteria; (i) vigorous intensity activity on three or more days per week accumulating $\geqslant$1500 MET min/week; or (ii) seven days of any combination of walking, moderate intensity, or vigorous intensity activities achieving at least 3000 MET min/week [29]. Total weekday sitting time was measured by the single question, "During the last 7 days, how much time did you usually spend sitting on a weekday?" which has shown acceptable validity and reliability [29]. This estimate included time spent sitting in a variety of domains (i.e., leisure, work, and recreation). To date, there are no well accepted thresholds for data presented as categorical levels. In our study, sitting time was categorized into the following groups using cut-points commonly found in previous studies, <5, 5–9, and $\geqslant$10 hours/day [31].

Usual dietary intake was assessed using a 103-item, self-administered food frequency questionnaire (FFQ) designed and validated for use in Korea [32]. The validity and reproducibility of our FFQ were evaluated previously by comparing nutrient and food intake derived from twelve 24-hour dietary recalls during four seasons and with a second FFQ administered one year later [32]. Total calorie intake was calculated using a standardized food composition database from the Korean Nutrition Society (Can Pro 4.0) [33]. We used the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality [34]. Component 3, regarding the number of hours of actual nighttime sleep during the past month, was used to assess sleep duration. Height, weight, and body composition were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. Body mass index (BMI) was calculated as height (m) divided by weight (kg) squared (m/kg^2). We classified BMI according to the criteria proposed for Asian populations [35]. Percentage of body fat and skeletal muscle mass were estimated using a multi-frequency bioimpedance analyzer with eight-point tactile electrodes (InBody 720, Biospace Co., Seoul Korea), which was validated with respect to reproducibility and accuracy for body composition [36]. Information on skeletal muscle mass was available in 81,952 participants who underwent a comprehensive health examination in 2012 or later. The skeletal muscle mass index (SMI) was calculated as SMI = skeletal muscle mass [kg]/weight [kg] $\times$ 100. Measurements for serum biochemical parameters, including glucose, uric acid, hemoglobin A1c, insulin, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) are described in detail elsewhere [26,27]. Insulin resistance was assessed with the homeostatic model assessment – insulin resistance (HOMA-IR) equation, fasting blood insulin (μIU/ml) $\times$ fasting blood glucose (mmol/l)/22.5. The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul, Korea is accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL), the laboratory participates in CAP (College of American Pathologists) Survey Proficiency Testing. Blood pressure was measured using an automated oscillometric device (53000, Welch Allyn, New York, USA) while subjects were in a sitting position with the arm supported at heart level. Hypertension was defined as a systolic blood pressure $\geqslant$140 mmHg, diastolic blood pressure $\geqslant$90 mmHg, or current use of antihypertensive medication. Diabetes was defined as a fasting serum glucose $\geqslant$126 mg/dl, hemoglobin A1c $\geqslant$6.5%, or current use of insulin or antidiabetic medications.

Abdominal ultrasounds were performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI, USA) by eleven experienced radiologists, all of whom were unaware of the aims of this study. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma [37]. The inter-observer reliability and intra-observer reliability for fatty liver diagnosis were substantial (kappa statistic of 0.74) and excellent (kappa statistic of 0.94), respectively [38].