Low Muscle Strength as Risk Factor for Non-Alcoholic Fatty Liver Disease in Different Metabolic Conditions

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Background: Non-alcoholic fatty liver disease (NAFLD) recently became a leading liver disease that threatens health worldwide. Low muscle strength, obesity, insulin resistance, and metabolic syndrome are recognized key factors for NAFLD. However, the impact of low muscle strength itself in different metabolic conditions has not been widely studied.

Methods: A cross-sectional analysis was performed of a sample of 5,427 participants from the 2019 Korea National Health and Nutrition Examination Survey. Relative handgrip strength (rHGS, defined as handgrip strength/body mass index) was used to assess muscle strength. The cut-off values for a low rHGS were 1.405 for men and 0.850 for women. NAFLD was diagnosed if the Hepatic Steatosis Index was >36. Participants were stratified according to insulin resistance, metabolic syndrome, and central obesity for the subgroup analyses.

Results: Complex sample multivariate logistic regression analysis revealed a significant association between low muscle strength and NAFLD after the adjustment for other confounders (odds ratio [OR], 1.92; P<0.001). In the insulin resistance, metabolic syndrome, and central obesity subgroups, a significant association between low muscle strength and NAFLD remained (OR, 1.66–4.19 depending on subgroup; all P<0.05), whereas it did not in the no central obesity group.

Conclusion: This study demonstrated that low muscle strength is correlated with a risk of NAFLD. This relationship was independent of insulin resistance and metabolic syndrome but was dependent on the presence of central obesity.

Keywords: Muscle Strength; Sarcopenia; Non-alcoholic Fatty Liver Disease; Insulin Resistance; Metabolic Syndrome

Received: July 31, 2023, Revised: September 21, 2023, Accepted: September 26, 2023
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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a liver disease characterized by the presence of excess fat deposits in the liver in the absence of other causes, such as heavy alcohol consumption, medication use, or viral hepatitis. Intrahepatic fatty deposits, as known as steatosis, is defined as fat deposition in 5% or more of hepatocytes on a liver histological examination. NAFLD is a spectrum of liver diseases that includes non-alcoholic fatty liver, non-alcoholic steatohepatitis (NASH), and NAFLD-associated cirrhosis depending on the presence of liver injury with inflammation or fibrosis.

NAFLD is closely associated with systemic metabolic disease and a variety of extrahepatic conditions. Key extrahepatic manifestations of NAFLD include cardiovascular disease, type 2 diabetes, metabolic syndrome, chronic kidney disease, and hypothyroidism. Metabolic syndrome in particular is both a risk factor for and a consequence of NAFLD. Recently, as aging and physical inactivity become major global concerns, sarcopenia was identified as a major cause of several diseases such as metabolic diseases, diabetes mellitus, obesity, and insulin resistance. Therefore, it is reasonable to assume that sarcopenia may be associated with NAFLD. There is growing evidence that sarcopenia increases the risk of NAFLD. Hong et al. reported a higher risk of NAFLD in individuals with lower muscle mass compared to a control group from the Korean Sarcopenic Obesity Study. Another Korean study reported that sarcopenic subjects with a low skeletal muscle index were at increased risk of NAFLD independent of obesity or metabolic syndrome. However, most studies focused only on muscle mass.

Muscle strength is a more convenient and accurate predictor of adverse health outcomes than muscle mass. For example, Newman et al. showed that both quadriceps and grip strength were strongly correlated with mortality, whereas lean muscle mass was not. Muscle strength in particular can be easily measured by handgrip strength (HGS) using a calibrated dynamometer. Clinically, HGS is a simple, inexpensive, and noninvasive measure of muscle strength that is widely performed in everyday life.

Few studies have evaluated the association between muscle strength and NAFLD. The single-institution cross-sectional study by Santos et al. found that a low HGS was associated with metabolic-associated fatty liver disease in patients with chronic hepatitis B. However, because many metabolic risk factors are correlated with muscle strength and NAFLD, it was difficult to properly exclude them.

This cross-sectional study of the Korean general population stratified participants by insulin resistance, metabolic syndrome, and central obesity and then correlated muscle strength with NAFLD. This study aimed to investigate how the association between muscle strength and NAFLD changes among these three major metabolic conditions and determine the confounding effects of each. Clinically, this study is expected to encourage primary care physicians to measure muscle strength as part of an NAFLD risk assessment in various patients. Furthermore, it will help them identify which patients may benefit from strength training to prevent NAFLD.

METHODS

1. Study Subjects

The Korea National Health and Nutrition Examination Survey (KNHANES) is a nationally representative cross-sectional health examination and survey that aimed to assess the health and nutritional status of the Korean population. It was conducted every 3 years from 1998 to 2005 and annually since 2007 by the Chronic Disease Surveillance Division of the Korea Centers for Disease Control and Prevention in the Ministry of Health and Welfare. Each KNHANES adopted a two-stage stratified cluster sampling method regarding survey districts and households as the primary and secondary sampling units, respectively. First, 192 primary sampling units (PSUs) were selected from all regions of the country. Next, 20 households were selected for each PSU using systematic sampling. Within the sample households, individuals aged ≥1 year were targeted.

In this study, among the 8,110 individuals from the KNHANES 2019, we initially selected 6,606 subjects aged ≥19 years (2,956 men, 3,650 women). Subjects for whom data were missing for HGS and body mass index (BMI) were excluded (n=535). Subjects who met the following criteria based on our protocol were also excluded (n=644): (1) positive serologic markers for hepatitis B virus or hepatitis C virus or (2) excessive alcohol consumption (>210 g/wk for men, >140 g/wk for women). The remaining 5,427 participants (2,278 men, 3,149 women) were eligible for inclusion. As the KNHANES was a weighted survey, 5,427 participants were considered representative of the entire cohort of 36,978,442. All participants in the KNHANES survey signed an informed consent before the survey began. The KNHANES was reviewed and approved by the Ethics Committee of the Korea Centers for Disease Control and Prevention. This study was approved by the Institutional Review Board of St. Mary’s Hospital, Seoul, Korea (no., KC16RISB0592).

2. Anthropometric and Clinical Parameters and Biochemical Analysis

The KNHANES was conducted thorough health examinations and health interviews and included body measurements, blood pressure, smoking, alcohol use, physical activity, and personal medical conditions. Subjects were considered as having central obesity with a waist circumference (WC) ≥90 cm in men and ≥80 cm in women.

Smoking status was classified into three groups by self-reported questionnaires as current, past, or never smoker. Current smokers were defined as having smoked >100 cigarettes in their lifetime and currently smoking. Past smoker was defined as having smoked >100 cigarettes in their lifetime and not currently smoking. Never smoker was defined as having smoked <100 cigarettes in their lifetime. Alcohol consumption was defined as drinking at least one drink per month in the past year.
Aerobic exercise was defined as engaging in ≥2 hours, 30 minutes of moderate-intensity aerobic physical activity, ≥1 hour, 15 minutes of vigorous-intensity aerobic physical activity, or a combination of moderate- and vigorous-intensity physical activity (1 minute of vigorous-intensity activity equals 2 minutes of moderate-intensity activity) per week. Resistance exercise was defined as at least 2 days of strength training, such as push-ups, sit-ups, dumbbells, weights, or barbells, in the past week.10

Diabetes mellitus was diagnosed if an individual’s fasting blood glucose was ≥126 mg/dL, glycated hemoglobin level was ≥6.5%, or the participant was taking oral hypoglycemic agents or insulin. Hypertension was diagnosed in participants with a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or use of oral antihypertensive agents.

Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) method as follows: fasting insulin (μU/mL)×fasting glucose (mg/dL)/405. Insulin resistance is diagnosed at a HOMA-IR ≥2.5.11

3. Measurement of Muscle Strength

Handgrip tests were performed using a digital HGS dynamometer (T.K.K 5401; Takei, Tokyo, Japan). The maximum value of bilateral hand force from three measurements was counted as the absolute HGS. As HGS is correlated with body size, relative HGS (rHGS), which is calculated as the absolute HGS divided by BMI, was used. The rHGS was previously used as an indicator of muscle strength.12 The rHGS values were divided into sex-specific quartiles, and the low rHGS group was defined as those with the lowest quartile of sex-specific rHGS.

4. Definition of Non-alcoholic Fatty Liver Disease and Metabolic Syndrome

To measure the risk of NAFLD, the following two previously validated predictive models were used: (1) Hepatic Steatosis Index (HSI) and (2) NAFLD liver fat score (NLFS). First, HSI was calculated as 8×alanine aminotransferase (ALT)/aspartate aminotransferase (AST)+BMI (+2 if diabetes; +2 if female). NAFLD was diagnosed at an HSI >36. The sensitivity and specificity of HSI for predicting NAFLD in the Korean population are 86% and 66%, respectively.13 Second, NLFS was calculated as -2.89+1.18×metabolic syndrome (yes=1 or no=0)+0.45×diabetes (yes=2 or no=0)+0.15×(fasting insulin, μIU/mL)+0.04×AST-0.94×ALT ratio. NAFLD was diagnosed at an NLFS ≥-0.640.14

Metabolic syndrome was defined according to the harmonized criteria, which state that an individual has metabolic syndrome if they exhibit any three of five components.15 These five components are as follows: (1) WC ≥90 cm in men and ≥80 cm in women; (2) blood pressure ≥130/85 mm Hg or a history of hypertension; (3) fasting blood glucose ≥100 mg/dL or a history of diabetes mellitus; (4) triglyceride level ≥150 mg/dL or a history of hyperlipidemia; and (5) high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women.

5. Statistical Analysis

The KNHANES survey follows a multistage sampling method, and the sample weights were constructed for sample participants to improve the representativeness of the Korean population and the precision of the estimates.10 Therefore, all analyses were conducted using a weighted sample.

The characteristics of the study subjects were analyzed using a complex samples descriptive analysis for continuous variables and a frequency analysis for categorical variables, including the prevalence of NAFLD. To compare the characteristics between the low muscle strength group and NAFLD by subgroup, a complex samples cross-tabulation analysis and a complex samples general linear model (CSGLM) were used for categorical variables and continuous variables, respectively. To determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) of NAFLD for low muscle strength, a complex samples multivariate logistic regression analysis was used with the adjustment for age and sex. To control for the effects of insulin resistance, metabolic syndrome, and central obesity, the study participants were stratified into two groups based on the presence of each of these conditions.

The CSGLM was used to compare the weighted mean HSI between those in the lowest sex-specific rHGS quartile and those in the second to fourth sex-specific rHGS quartiles by subgroup after the adjustment for age and sex. Additionally, ORs were compared among subgroups using the complex samples multivariate logistic regression analysis. Continuous and categorical variables are expressed as mean±standard error and %±standard error, respectively. Values of P<0.05 were considered statistically significant. The statistical analyses were performed using IBM SPSS ver. 26.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

1. Subjects’ Characteristics

Of the 8,110 subjects in the 2019 KNHANES, we ultimately analyzed data for 5,427 (2,278 men, 3,149 women). The mean age of the study population was 47.88±0.46 years. The prevalence of NAFLD diagnosed by HSI and NLFS was 24.0%±0.8% and 28.5%±0.9%, respectively. Individuals in the lowest sex-specific rHGS quartile were older and had a higher weight, BMI, WC, systolic blood pressure, fasting blood glucose, fasting insulin, HOMA-IR, triglycerides, AST, ALT, and HSI. However, there were no significant differences in sex, diastolic blood pressure, or total cholesterol. The proportions of diabetes mellitus, hypertension, insulin resistance, metabolic syndrome, central obesity, and NAFLD were higher in the lowest sex-specific rHGS quartile than in the other quartiles. The ratios of never smoking and a rural residence were higher as well. However, the proportions of alcohol consumption, aerobic exercise, and resistance exercise were higher in the second to fourth sex-specific rHGS quartiles (Table 1).
Multivariate logistic regression analyses were performed to determine the association between low muscle strength and NAFLD as assessed by the two prediction models. The unadjusted ORs for NAFLD in the lowest sex-specific rHGS quartile were 3.49 and 3.40 as assessed by the HSI and NLFS, respectively. After adjustment for other confounders, the adjusted OR for NAFLD assessed by the HSI was attenuated to 1.92,
which remained statistically significant. However, in the case of NAFLD assessed by the NLFS, the adjusted ORs were not statistically significant after the adjustment for covariates (Table 2).

### 3. Subgroup Analyses

To determine the confounding effect of insulin resistance, metabolic syndrome, and obesity, the study population was stratified according to the following criteria: (1) subgroup 1, presence of insulin resistance with a HOMA-IR cut-off value of 2.5; (2) subgroup 2, presence of metabolic syndrome; and (3) subgroup 3, presence of central obesity. The insulin resistance, metabolic syndrome, and central obesity groups had higher weighted mean HSI values than the non-insulin resistance (mean 37.32 versus 30.89), no metabolic syndrome (mean 37.11 versus 30.57), and no central obesity (mean 37.17 versus 29.50) groups after adjustment for age and sex (all P<0.001). The weighted mean of the HSI was then compared between the lowest sex-specific rHGS quartile and the second to fourth sex-specific rHGS quartiles according to each subgroup. The weighted mean HSI was higher among subjects in the lowest sex-specific rHGS quartile regardless of insulin resistance, metabolic syndrome, and central obesity (all P<0.001) (Table 3).

Multivariate logistic regression analyses of the association between a low rHGS and NAFLD were conducted for each subgroup. First, after adjustment for age and sex (model 1), NAFLD assessed by HSI was positively associated with a low rHGS, with ORs of 2.94 and 3.04 in subjects with and without insulin resistance, respectively. The ORs were attenuated to 2.11 and 1.77 after further adjustment for weight, HOMA-IR, total cholesterol, and hypertension (model 2) but remained statistically significant. After further adjustment for aerobic exercise, resistant exercise, alcohol status, and place of residence (model 3), those with a low rHGS were 1.66–1.98 times more likely to be diagnosed with NAFLD than others independent of insulin resistance. Similarly, the risk of NAFLD assessed by HSI was positively associated with a low rHGS, with multivariate-adjusted ORs of 1.76–2.29 regardless of metabolic syndrome. In individuals with central obesity,
NAFLD was positively associated with a low rHGS, with multivariate-adjusted ORs of 1.89–2.76, but there was no significant association in individuals without central obesity (Table 4).

**DISCUSSION**

This nationally representative study of Korean adults investigated the association between a low HGS and the risk of NAFLD. Our results indicated that a low HGS normalized by BMI was inversely associated with NAFLD as assessed by the HSI in Korean adults regardless of insulin resistance and metabolic syndrome status. Given previous concerns that NAFLD is strongly associated with insulin resistance, metabolic syndrome, and obesity, we minimized the effect of these metabolic profiles using two methods: multivariate logistic regression analysis and subgroup analysis.

The inverse association between muscle strength and NAFLD is in line with findings of previous studies. The Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort Study reported that HGS per body weight was inversely associated with NAFLD diagnosed by ultrasonography. In Korea, Lee et al. found that HGS per body weight was also inversely associated with NAFLD assessed by blood-based biomarkers in older adults. Park et al. also reported that rHGS was inversely associated with NAFLD in children. On the other hand, in the present study, there was no significant association between low muscle strength and NLFS after the further adjustment for cardiometabolic factors, which were not included in the previous study.

Moreover, the association between muscle strength and NAFLD was independent of insulin resistance and metabolic syndrome. However, low muscle strength was not related to NAFLD among individuals without central obesity, but it was in the central obesity group. This finding is inconsistent with that of the previous study. Lee linked poor muscle strength to NAFLD independent of obesity and metabolic syndrome. In this study, although individuals in the lowest sex-specific rHGS quartile had a higher HSI than those in the second to fourth sex-specific rHGS quartiles in the no central obesity group, there was no significant association between low HGS and NAFLD in the no central obesity group. Several factors may have contributed to this finding. The difference is that the study by Lee used BMI as a measure of obesity, while this study used WC as a measure of central obesity. Because most of the non-obese people did not have NAFLD, we would have had a selection bias with too low a prevalence of NAFLD in the non-obese group. On the other hand, the presence of central obesity would be an indispensable factor compared to insulin resistance or metabolic syndrome for the development of NAFLD.

The pathogenesis of skeletal muscle dysfunction in NAFLD is very complex and not fully understood. Recently, several mechanisms have been discussed to explain the interplay between muscle and the liver. First, insulin resistance is one of the most important risk factors for both sarcopenia and NAFLD, as it increases lipolysis in adipose tissue, inducing excessive delivery of free fatty acids to the liver. It also suppresses insulin growth factor-1 signaling, which is associated with reduced muscle size and strength. Moreover, adipose tissue and muscle tissue have been identified as endocrine organs that are responsible for energy expenditure in other tissues along with insulin. For example, adiponectin secreted from adipose tissue binds to a receptor expressed in skeletal muscle and liver to facilitate cellular uptake and processing of glucose and fatty acids. Myostatin secreted from skeletal muscle cells also binds to a receptor found in hepatic cells, inhibiting hepatic glucose uptake and reducing insulin sensitivity. The physiological mechanisms underlying the adipose-liver-muscle axis remain under investigation.

Second, chronic inflammation has been implicated as a risk factor for sarcopenia and NAFLD. Inflammatory cytokines such as nuclear factor kappa B, interleukin-6, and tumor necrosis factor-α are frequently elevated in NAFLD and cause liver injury. Additionally, their catabolic effects lead to a loss of muscle mass. In the present study, a low muscle strength was related to NAFLD regardless of insulin resistance or metabolic syndrome. This suggests that muscle weakness itself is related to the risk of NAFLD not mediated by systemic insulin resistance. Further studies are needed to investigate the insulin-independent pathways that mediate the interactions between muscle and liver.

There are some limitations to this study. First, only blood-based parameters were used to diagnose NAFLD. Radiological studies like ultrasonography and liver biopsy could not be used because they are expensive and invasive, making them unsuitable for a large-scale study. Second, the 2019 KNHANES did not measure muscle mass. Although some studies reported that HGS is strongly correlated with muscle mass in patients with liver cirrhosis, muscle strength as well as muscle mass and the degree of physical performance were necessary to precisely evaluate sarcopenia. Therefore, further studies must measure all such variables simultaneously. Third, because this was an observational cross-sectional study, the causal relationship between HGS and NAFLD was not clear. Fourth, this study did not adjust for confounders other than metabolic covariates, such as the individuals’ degrees of inflammation or dietary patterns.

Despite these limitations, this study had several strengths. First, its large population-based analysis with multi-cluster stratification strengthened the statistical power of its results. Second, it is the first study to exclude the effects of metabolic covariates in NAFLD by stratifying the population into insulin resistance, metabolic syndrome, and central obesity subgroups.

In conclusion, low muscle strength is correlated with a high risk of NAFLD in Korean adults regardless of insulin resistance and metabolic syndrome status. However, this association was dependent on the presence of central obesity. This study’s findings may stimulate further research on complex muscle-liver interactions.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.
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