HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Relationship Between Sarcopenia and Nonalcoholic Fatty Liver Disease: The Korean Sarcopenic Obesity Study

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Previous studies have shown that nonalcoholic fatty liver disease (NAFLD) and sarcopenia may share pathophysiological mechanisms, such as insulin resistance, inflammation, vitamin D deficiency, and decreased physical activity. However, their direct relationship has not been investigated. The association between NAFLD and sarcopenia was examined in 452 apparently healthy adults enrolled in the Korean Sarcopenic Obesity Study (KSOS), an ongoing prospective observational cohort study. The liver attenuation index (LAI), which was measured using abdominal computed tomography (CT), was used as a parameter for the diagnosis of NAFLD. Sarcopenia was defined using a skeletal muscle mass index (SMI) [SMI (%) = total skeletal muscle mass (kg) / weight (kg) × 100] that was measured by dual energy X-ray absorptiometry (DXA). After adjusting for age and sex, both SMI and LAI were negatively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) ($P < 0.001$) and high sensitivity C-reactive protein (hsCRP) ($P < 0.001$) as well as brachial-ankle pulse wave velocity (baPWV), an indicator of arterial stiffness. Furthermore, SMI and LAI had positive relationships with high-density lipoprotein (HDL)-cholesterol, but both had a negative relationship with triglyceride, alanine aminotransferase (ALT), and total body fat. In a multiple logistic regression analysis, the odds ratio for NAFLD risk was 5.16 (95% confidence interval [CI] = 1.63-16.33) in the lowest quartile of SMI compared to the highest after adjusting for potential confounding factors. *Conclusion:* Individuals with lower muscle mass exhibited increased risk of NAFLD. This result may provide a novel insight into the mechanism linking between sarcopenia and NAFLD. (Clinical trial no. NCT01594710.) (HEPATOLOGY 2014;59:1772-1778)

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Industrial countries are facing the challenge of an aging society. According to the Korea National Statistical Office, 7.2% of the Korean population was aged 65 and older in 2000.[1] This percentage is expected to rise to 24.3% in 2030 and 40.1% in 2060.[1] The increasing proportion of an elderly population imposes a serious burden on society by escalating costs of healthcare. One of the typical changes in human body composition related to aging is a progressive loss of muscle mass and strength, called sarcopenia.[2] Sarcopenia leads to metabolic complications and mortality as well as physical disability and immobilization.[3,4]

Nonalcoholic fatty liver disease (NAFLD) is characterized by an accumulation of fat in the liver, which is one of the most common forms of chronic liver

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; ALT, alanine aminotransferase; ASM, appendicular skeletal muscle mass; baPWV, brachial-ankle pulse wave velocity; CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; IL-6, interleukin-6; KSOS, the Korean Sarcopenic Obesity Study; LAI, liver attenuation index; NAFLD, nonalcoholic fatty liver disease; NRF, National Research Foundation; SBP, systolic blood pressure; SMI, skeletal muscle mass index; SO, sarcopenic obesity; TNF-α, tumor necrosis factor-α.

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Received July 4, 2013; accepted August 25, 2013.

Supported by the Basic Science Research Program through the National Research Foundation of Korea, which is funded by the Ministry of Education, Science and Technology (2012006363) (K.M.C.), the Brain Korea 21 Project of the Ministry of Education and Human Resources Development, Republic of Korea (K.M.C. and S.H.B.) (HI10V-0007-010013), and by a grant from Korea University (K.M.C.).

disease in developed countries.[5] In Western countries, the prevalence of NAFLD in the general population is estimated to be 20%-30%; in obese populations, this increases to 57.5%-74%.[5,6] Each component of metabolic syndrome, such as central obesity, dyslipidemia, and hyperglycemia, is closely related to NAFLD.[7] Also, Hamaguchi et al.[8] reported that aging is a risk factor for NAFLD, independent of metabolic syndrome (MetS).

Both liver and muscle are target organs for insulin action, and insulin resistance is known as a key factor in the pathophysiology for both NAFLD and sarcopenia.[9,10] NAFLD is now regarded as a cause and consequence of insulin resistance.[10] Moreover, insulin resistance is involved in age-related muscle protein loss, progressively leading to sarcopenia.[11] In addition to insulin resistance, NAFLD and sarcopenia seem to have similar pathophysiological backgrounds, such as chronic inflammation, vitamin D deficiency, oxidative stress, and decreased physical activity. Cesari et al.[12] reported that C-reactive protein (CRP) and interleukin-6 (IL-6) are negatively associated with fat-adjusted appendicular lean mass and positively associated with total fat mass. Accumulation of visceral fat leads to increased secretion of proinflammatory cytokines that may promote a catabolic effect on muscles as well as the development of NAFLD.[13,14] On the other hand, Visser et al.[15] reported that lower serum 25-hydroxyvitamin D (25[OH]D) levels increase the risk of sarcopenia in older men and women. Recently, Barchetta et al.[16] found a strong association between NAFLD and low 25[OH]D levels in an adult population with normal serum liver enzymes. Furthermore, it is presumed that decreased physical activity, induced by sarcopenia, can cause a reduction of energy expenditure, which may result in obesity and hepatic steatosis in sarcopenic patients. However, to the best of our knowledge no previous studies have explored whether individuals with sarcopenia have a higher risk of NAFLD than those without sarcopenia.

In the present study we examined the relationship between sarcopenia and NAFLD in a Korean population. For this purpose we compared cardiometabolic parameters that are known to be risk factors for NAFLD between individuals with and without sarcopenia. Additionally, risk of NAFLD by quartiles of muscle mass index was calculated after adjusting for potential confounding factors.

Subjects and Methods

Subjects and Data Collection. We analyzed baseline cross-sectional data from the Korean Sarcopenic Obesity Study (KSOS), which is an ongoing epidemiologic study supported by the National Research Foundation of Korea (NRF). This prospective observational cohort study was designed to examine the prevalence of sarcopenic obesity (SO) in Korean adults and to evaluate its effects on metabolic disorders and health outcomes. Details of the KSOS have been published in our previous studies.[17,18] The KSOS cohort of adults aged $\geq$20 years during the period of September 2007 through August 2008 consisted of 526 subjects (198 men and 328 women). Eligible participants had no history of any type of diabetes, CVD (myocardial infarction, unstable angina, stroke or cardiovascular revascularization), stage 2 hypertension (resting blood pressure, $\geq$160/100 mmHg), malignant disease, or severe renal or hepatic disease. Subjects taking medications that could affect body weight or body composition were excluded. The following exclusion criteria were also applied: alcohol consumption (>140 g/week), a previous positive test for hepatitis B surface antigen or hepatitis C antibody, and use of herbal medications within the past 6 months. After excluding ineligible cases, analyses were performed on 452 participants (167 men and 285 women) who had complete clinical laboratory data and body compositional data. Among them, young healthy study subjects (125 subjects; aged 20-40; 47 men, 78 women) were regarded as a sex-specific young reference group. All participants provided written informed consent, and the Korea University Institutional Review Board, in accordance with the Declaration of Helsinki by the World Medical Association, approved the study protocol.

Clinical and Laboratory Measurements. All blood samples were obtained in the morning after a 12-hour overnight fast and were immediately stored at -80°C for subsequent assays. Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL)-

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DOI 10.1002/hep.26716

Potential conflict of interest: Nothing to report.

cholesterol levels were determined enzymatically using a chemistry analyzer (Hitachi 747; Tokyo, Japan). A glucose oxidase method was used to measure fasting plasma glucose (FPG), and an immunoradiometric assay (DIAsource Diagnostics, Nivelles, Belgium) was used to measure insulin levels. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR). High-sensitivity CRP (hsCRP) levels were measured using a latex-enhanced turbidimetric immunoassay (HiSens hsCRP LTIA; HBI, Anyang, Korea) with an interassay coefficient of variation of 7.2%. Serum 25[OH]D levels were measured using radioimmunoassay kits (DIAsource Diagnostics) with quality control materials provided by the manufacturer. MetS was defined according to the criteria established by the National Cholesterol Education Program Adult Treatment Panel III using the adjusted waist circumference for Asians.[19,20]

Dual-Energy X-ray Absorptiometry (DXA). A whole-body DXA scan was performed on each patient to measure total and regional lean mass (kg), total body fat (kg), and total body fat percentage (%) using fan-beam technology (Discovery A; Hologic, Bedford, MA). Appendicular skeletal muscle mass [ASM (kg)] and skeletal muscle mass index [SMI (%) = total skeletal muscle mass (kg) / weight (kg) $\times$ 100] were obtained as previously described.[17,18]

Brachial-Ankle Pulse Wave Velocity (baPWV). baPWV was measured using a Colin waveform analyzer (BP-203RPE II; Colin, Komaki, Japan). After each subject had rested in the supine position for 5 minutes, baPWV was measured. baPWV was calculated as the mean of the left (left upper arm to left ankle) and right (right upper arm to right ankle) baPWV values.

Definitions of Sarcopenia and NAFLD. Sarcopenia was defined as an SMI of 1 SD below the sex-specific mean value for the young reference group.[3,21] The cutoff point for sarcopenia was 39.8% in men and 34.1% in women. NAFLD was diagnosed using unenhanced computed tomography (CT) (Brilliance 64; Philips Medical Systems, Cleveland, OH) by a single experienced radiologist who was blinded to the anthropometric and laboratory data. The liver attenuation index (LAI), derived from the difference between mean hepatic and splenic attenuation, was used as a parameter for the diagnosis of NAFLD.[22] Details of measuring LAI have been explained in our previous study.[23] The hepatic attenuation was measured by means of a random selection of three circular regions of interest (ROIs) on five transverse sections. To provide an internal control, the mean splenic attenuation was also calculated by averaging two random ROI values of splenic attenuation measurement on transverse section levels. Hubscher[24] reported that histological confirmation of NAFLD requires a minimum of 5% steatosis. Limanond et al.[22] documented that the degree of steatosis correlated very well with the LAI (r = 0.92), and an LAI <5 HU correctly predicted >5% steatosis. Therefore, NAFLD in the present study was defined when the value of LAI was <5 HU.

Statistical Analysis. Data are expressed as mean $\pm$ SD, median and interquartile range (25%-75%), or percentage. Differences between groups were tested using Student t test or the Mann-Whitney U test, and the χ^2-test was used to test for differences in the distribution of categorical variables. Each variable was examined for normal distribution and any positively skewed variable was log-transformed. A correlation analysis of SMI and LAI was conducted with other metabolic variables. Odds ratios (ORs) and 95% confidence intervals (CIs), predicting NAFLD based on LAI, were obtained from logistic regression models after controlling for potential covariates similar to age and sex. $P < 0.05$ was considered statistically significant in all analyses. All statistical results were based on two-sided tests. Data were analyzed using SAS for Windows (v. 9.20, SAS Institute, Cary, NC).

Results

Characteristics of Study Subjects. The characteristics of all study subjects are presented in Table 1. The subjects in the sarcopenia group had greater body mass index (BMI), waist circumference, and total body fat mass (percentage) as well as higher systolic blood pressure (SBP) and worse lipid profiles compared with the normal group. Moreover, as the markers for insulin resistance, chronic inflammation, and vitamin D deficiency, there were significant differences in HOMA-IR, hsCRP, and 25[OH]D levels between the two groups. One of the reliable noninvasive markers for arterial stiffness, baPWV, was also higher in the group with sarcopenia.

Correlation of SMI and LAI With Cardiometabolic Risk Factors. Table 2 shows the correlation analysis of SMI and LAI with other major metabolic variables in the study populations. After adjusting for age and sex, SMI and LAI were negatively correlated with most of the cardiometabolic risk factors, including HOMA-IR, hsCRP, baPWV values, and the number of MetS components. Additionally, SMI and LAI were also negatively correlated with triglyceride, alanine aminotransferase (ALT), and total body fat mass.

Table 1. Clinical, Anthropometric, and Metabolic Characteristics of Study Subjects

	Normal (n = 324)	Sarcopenia (n = 128)	*P*
Age (years)	51 (38, 61)	60 (52, 67)	<0.001
Sex, female (%)	189 (58.0)	96 (75.0)	0.001
Weight (kg)	61.4 (53.9, 71.0)	63.5 (58.4, 73.2)	0.003
BMI (kg/m^2)	23.5 (21.6, 25.2)	25.9 (23.5, 28.2)	<0.001
Waist circumference (cm)	83.0 (77.0, 89.0)	88.0 (83.8, 94.0)	<0.001
SBP (mmHg)	121.0 (113.0, 130.0)	124.5 (116.0, 134.0)	0.007
DBP (mmHg)	80.0 (72.0, 86.0)	80.0 (74.0, 87.3)	0.481
Total cholesterol (mmol/L)	4.7 (4.1, 5.3)	5.0 (4.5, 5.4)	0.014
Triglyceride (mmol/L)	1.2 (0.8, 1.7)	1.4 (1.0, 1.9)	0.007
HDL-cholesterol (mmol/L)	1.4 (1.2, 1.7)	1.3 (1.1, 1.6)	0.033
LDL-cholesterol (mmol/L)	2.6 (2.1, 3.0)	2.8 (2.4, 3.3)	<0.001
Glucose (mmol/L)	5.1 (4.8, 5.6)	5.2 (5.0, 5.7)	0.093
AST (IU/L)	20.0 (16.0, 24.0)	20.0 (17.0, 23.0)	0.597
ALT (IU/L)	17.0 (13.0, 22.0)	18.0 (15.0, 24.0)	0.030
Number of MetS components	1 (0, 2)	2 (1, 3)	<0.001
Total body fat percentage (%)	24.2 (19.1, 28.7)	32.3 (28.8, 35.1)	<0.001
Total body fat mass (kg)	15.2 (12.4, 18.3)	20.0 (17.7, 23.7)	<0.001
Total lean body mass (kg)	58.5 (48.9, 68.1)	61.3 (51.7, 70.3)	0.137
ASM (kg)	21.1 (18.0, 26.4)	18.4 (17.0, 21.9)	<0.001
ASM/height^2 (kg/m^2)	8.3 (7.4, 9.2)	7.7 (7.0, 8.5)	<0.001
SMI (%)	40.3 (36.7, 43.0)	33.2 (31.7, 34.0)	<0.001
HOMA-IR	1.9 (1.3, 2.5)	2.2 (1.7, 2.9)	<0.001
hsCRP (mg/L)	0.3 (0.1, 0.9)	0.6 (0.3, 1.3)	<0.001
25[OH]D (nmol/L)	76.3 (53.1, 107.8)	65.9 (47.9, 89.4)	0.008
baPWV (cm/sec)	1303.5 (1135.9, 1436.6)	1372.3 (1236.4, 1554.6)	<0.001

Data are presented as the median (interquartile range). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MetS, metabolic syndrome; ASM, appendicular skeletal muscle mass; SMI, skeletal muscle mass index; HOMA-IR, homeostasis model assessment insulin resistance; hsCRP, high sensitivity C-reactive protein; 25[OH]D, 25-hydroxyvitamin D; baPWV, brachial-ankle pulse wave velocity. Sarcopenia was defined as a SMI of one standard deviation below the sex-specific mean value for the young reference group.

On the other hand, HDL-cholesterol was positively correlated with both SMI and LAI.

Multiple Logistic Regression Analysis for NAFLD. Multiple logistic regression analysis was performed with NAFLD as a dependent variable, ORs and 95% CIs were calculated for each quartile of SMI (Table 3). In an unadjusted model, subjects in the third quartile for SMI value (OR = 3.42, 95% CI = 1.30-8.96), the second (OR = 4.03, 95% CI = 1.56-10.40), and the first (OR = 5.88, 95% CI = 2.33-14.84) had a significantly higher risk for NAFLD compared to those in the fourth quartile (*P* for trend = 0.002). This relationship persisted even after adjusting for potential confounding factors including insulin resistance and inflammation, although the strength of association was attenuated (*P* for trend = 0.041).

Discussion

The present study demonstrates a higher risk of NAFLD in individuals with lower muscle mass compared to a control group. Furthermore, individuals with sarcopenia had more body fat mass, more components of MetS, higher hsCRP levels, and higher arterial stiffness compared to those without sarcopenia. Considering that resistance exercise is a potent, nonpharmacological therapy that improves sarcopenia as well as components of MetS,[25] these results suggest that resistance training may have potential effects on sarcopenia in patients with NAFLD.

Sarcopenia has become a key concept for understanding the impact of aging on health outcomes. In 1989, Rosenberg first introduced the term "sarcopenia" to refer to age-related loss of skeletal muscle mass and volume.[26] Muscle mass accounts for ~75% of body cell mass and 45% of body mass.[27] Once people reach 50 years of age, they lose ~1-2% of their muscle mass per year.[28] Sarcopenia is a common disorder in elderly populations that contributes to functional decline, disability, frailty, and falls.[29] Furthermore, several studies reported the increased risk of chronic metabolic disorders and mortality in individuals with low muscle mass.[28]

The pathophysiological mechanisms that result in sarcopenia are multifactorial, but still not fully understood. The impact of insulin resistance on sarcopenia has recently been suggested. Increase in intramyocellular fat mass with aging is a well-known factor related

Table 2. Spearman Partial Correlation Analysis of Skeletal Muscle Mass Index (SMI) and Liver Attenuation Index (LAI) With Cardiometabolic Parameters after Adjusting For Age and Sex

	SMI	LAI
Systolic blood pressure	$r = -0.11$	$r = -0.18$
	$P = 0.021$	$P < 0.001$
Diastolic blood pressure	$r = -0.07$	$r = -0.12$
	$P = 0.161$	$P = 0.009$
Total cholesterol	$r = -0.07$	$r = -0.07$
	$P = 0.141$	$P = 0.134$
Triglyceride	$r = -0.22$	$r = -0.23$
	$P < 0.001$	$P < 0.001$
HDL-cholesterol	$r = 0.21$	$r = 0.22$
	$P < 0.001$	$P < 0.001$
LDL-cholesterol	$r = -0.12$	$r = -0.07$
	$P = 0.011$	$P = 0.156$
Glucose	$r = -0.06$	$r = -0.09$
	$P = 0.198$	$P = 0.059$
AST	$r = -0.05$	$r = -0.16$
	$P = 0.252$	$P < 0.001$
ALT	$r = -0.18$	$r = -0.31$
	$P < 0.001$	$P < 0.001$
Number of MetS components	$r = -0.26$	$r = -0.29$
	$P < 0.001$	$P < 0.001$
Total body fat mass	$r = -0.66$	$r = -0.38$
	$P < 0.001$	$P < 0.001$
Total lean body mass	$r = -0.24$	$r = -0.18$
	$P < 0.001$	$P < 0.001$
HOMA-IR	$r = -0.33$	$r = -0.29$
	$P < 0.001$	$P < 0.001$
hsCRP	$r = -0.28$	$r = -0.24$
	$P < 0.001$	$P < 0.001$
25[OH]D	$r = 0.07$	$r = 0.06$
	$P = 0.126$	$P = 0.223$
baPWV	$r = -0.16$	$r = -0.15$
	$P < 0.001$	$P = 0.001$

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; MetS, metabolic syndrome; HOMA-IR, homeostasis model assessment insulin resistance; hsCRP, high sensitivity C-reactive protein; 25[OH]D, 25-hydroxyvitamin D; baPWV, brachial-ankle pulse wave velocity.

to risk of insulin resistance.[28] Recent studies found that insulin resistance and mitochondrial dysfunction has an important role on loss of muscle mass.[30] Moreover, Srikanthan et al.[31] have shown that sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia using the data from the National Health and Nutrition Examination Survey III (NHANES III). On the other hand, ectopic fat accumulation in the liver is closely associated with systemic insulin resistance,[10] which may enhance hepatic steatosis by increasing free fatty acid delivery.[32] Treatment aimed at improving insulin resistance, such as weight loss, metformin, and thiazolidinediones, have shown some benefit in patients with NAFLD.[32] The present study revealed an increased insulin resistance index in subjects with sarcopenia compared to those without sarcopenia. Insulin resistance and SMI (an index of muscle mass) showed a significant negative correlation. Additionally, a significant relationship between insulin resistance and LAI, which reflects fat accumulation in the liver, was found.

Age-related, chronic, low-grade inflammation has been recognized as an important causative factor for sarcopenia.[14] Cross-sectional and longitudinal studies support the hypothesis that there is an association between inflammation and sarcopenia.[14] Tumor necrosis factor-α (TNF-α) and IL-6 are the most reported inflammatory markers.[14] Insulin resistance is often associated with chronic low-grade inflammation, and various kinds of inflammatory adipokines released from visceral adipocytes with aging contribute to the development of insulin resistance.[33] In this study, individuals with sarcopenia had increased levels of hsCRP compared to those without sarcopenia. Moreover, hsCRP concentrations were closely correlated with both SMI and LAI ($P < 0.001$), which suggests that inflammation may be an important underlying factor associated with both sarcopenia and NAFLD.

In addition to insulin resistance and inflammation in this study, both SMI and LAI were negatively associated with SBP, triglyceride, ALT, total body fat mass, and number of MetS components, but were positively correlated with HDL-cholesterol. These parameters are

Table 3. Unadjusted and Adjusted Odds Ratios (ORs) With 95% Confidence Intervals (CIs) of Having Nonalcoholic Fatty Liver Disease (NAFLD) by Quartiles of SMI After Adjusting for Potential Compounding Factors

	Quartiles of SMI (%)				
	Q4	Q3	Q2	Q1	*P* for trend
Unadjusted	1	3.42 (1.30, 8.96)	4.03 (1.56, 10.40)	5.88 (2.33, 14.84)	0.002
Model 1	1	3.99 (1.49, 10.64)	5.22 (1.96, 13.88)	8.25 (3.12, 21.82)	<0.001
Model 2	1	3.93 (1.45, 10.66)	5.27 (1.96, 14.22)	7.38 (2.71, 20.12)	0.001
Model 3	1	3.39 (1.10, 10.39)	4.13 (1.38, 12.32)	5.16 (1.63, 16.33)	0.041

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, smoking status, and physical activity.

Model 3: adjusted for age, sex, smoking status, physical activity, homeostasis model of insulin resistance (HOMA-IR), high sensitivity C-reactive protein (hsCRP), and 25[OH]D levels.

well-known risk factors for atherosclerosis and cardiovascular disease. Recently, Sanada et al.[34] demonstrated the interaction of sarcopenia and MetS, and the coexistence of sarcopenia and MetS increases the risk of cardiovascular disease in Japanese women. Interestingly, the present study exhibited that both SMI and LAI had a significant negative relationship with baPWV, which indicates arterial stiffness and atherosclerosis.

Recently, low vitamin D levels have been suggested to be associated with both sarcopenia and low physical activity. Scott et al.[35] reported that 25[OH]D may be important for the maintenance of muscle function, and higher skeletal muscle mass and physical activity levels may also be beneficial for 25[OH]D status in community-dwelling older adults. In the Longitudinal Aging Study Amsterdam, lower 25[OH]D levels increased the risk of sarcopenia in older men and women.[15] In the Ansan Geriatric Study, greater visceral fat and lower muscle mass were associated with lower 25[OH]D levels in elderly Korean men, but not women.[36] On the other hand, Roth et al.[37] recently have shown that vitamin D deficiency exacerbate NAFLD through Toll-like receptors (TLR) activation in obese rats, which causes insulin resistance and upregulation of hepatic inflammatory and oxidative stress. In a study including 262 Italian subjects, low 25[OH]D concentrations were associated with NAFLD independently from MetS and insulin resistance.[16] However, another study of a Chinese population reported that serum 25[OH]D levels were not significantly different between subjects with and without NAFLD.[38] In the present study, age- and gender-adjusted correlation analysis showed that both SMI and LAI were not significantly associated with 25[OH]D levels in Korean men and women.

There are several limitations to this study. First, the cross-sectional nature of this study did not allow us to identify causal relationships. Second, in diagnosing sarcopenia, muscle quality, such as muscle strength and muscle fiber types, were not considered. Finally, information on smoking status, alcohol consumption, and physical activity was self-reported, which may allow for a recall bias.

In conclusion, individuals with low muscle mass had an increased risk of NAFLD after adjusting for confounding factors, including insulin resistance and inflammation. This study may be a stimulant to provoke further research about the novel relationship between sarcopenia and NAFLD.

Author Contributions: K.M. Choi designed this study. H.C. Hong and K.M. Choi wrote the article. S.Y. Hwang analyzed the dataset. H.Y. Choi, H.J. Yoo, J.A. Seo, S.G. Kim, and N.H. Kim collected the data. S.H. Baik, D.S. Choi, and K.M. Choi reviewed and edited the article.

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