ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-3323

Association between Sarcopenic Obesity and Nonalcoholic Fatty Liver Disease and Fibrosis detected by Fibroscan

Karn Wijarnpreecha[1], Elizabeth S. Aby[2], Aijaz Ahmed[3], Donghee Kim[3]

1) Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Jacksonville, Florida;
2) Department of Medicine, Division of Gastroenterology and Hepatology, University of Minnesota, Minneapolis, MN;
3) Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Address for correspondence:
Donghee Kim, M.D., Ph.D.
Division of Gastroenterology and Hepatology
Stanford University School of Medicine
300 Pasteur Drive, Stanford, CA 94304
messmd@chol.com, dhkimmd@stanford.edu

Received: 16.12.2020
Accepted: 30.03.2021

ABSTRACT

Background & Aims: Nonalcoholic fatty liver disease (NAFLD) and sarcopenic obesity share several pathophysiologic backgrounds. No prior studies have determined a plausible association between sarcopenic obesity and NAFLD and NAFLD-associated fibrosis. We aim to investigate the association between sarcopenic obesity and NAFLD, and NAFLD-associated fibrosis detected by transient elastography.
Methods: In a cross-sectional study from the 2017-2018 National Health and Nutrition Examination Survey, 1,925 participants were identified. NAFLD was defined by controlled attenuation parameter (CAP) scores and significant fibrosis (≥F2)/cirrhosis by liver stiffness measurements on transient elastography. Sarcopenic obesity was defined by appendicular lean mass and body fat.
Results: Individuals with sarcopenic obesity had a significantly higher odds of having NAFLD [CAP score ≥263 dB/m, odds ratio (OR): 2.88, 95% confidence interval (CI): 1.82-4.57, and CAP score ≥285, OR: 3.71, 95%CI: 2.24-6.14] after adjusting for age, gender, and race/ethnicity. The association remained statistically significant after adjustment for socioeconomic status, lifestyle and behavioral risk factors, and metabolic conditions (CAP score ≥263, OR: 2.61, 95%CI: 1.51-4.50, and CAP score ≥285, OR: 3.31, 95%CI: 1.85-5.96). Sarcopenic obesity was also associated with higher odds of having NAFLD-associated significant fibrosis (OR 2.22, 95% CI: 1.03-4.80) in the multivariate model. While those with sarcopenic obesity had a higher prevalence of NAFLD-associated cirrhosis, this association did not reach statistical significance.
Conclusions: Sarcopenic obesity was independently associated with an increased risk of NAFLD and NAFLD-associated significant fibrosis independent of well-defined risk factors. Targeted interventions to improve sarcopenic obesity may reduce the risk of NAFLD and NAFLD-associated siginificant fibrosis.

Key words: hepatic steatosis – sarcopenia – cirrhosis – NAFLD – NASH – NHANES.

Abbreviations: ALM: appendicular lean mass; AUROC: area under the receiver operating characteristic curve; BMI: body mass index; CAP: controlled attenuation parameter; CI: confidence interval; DEXA: dual-energy X-ray absorptiometry; NAFLD: nonalcoholic fatty liver disease; NAS: nonalcoholic fatty liver disease activity score; NASH: nonalcoholic steatohepatitis; NHANES: National Health and Nutrition Examination Survey; OR: odds ratio.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease worldwide, with a prevalence of 25% [1]. Nonalcoholic fatty liver disease represents a wide range of diseases, from simple hepatic steatosis to inflammation with hepatocyte degeneration [nonalcoholic steatohepatitis (NASH)], hepatic fibrosis, and more advanced disease, such as cirrhosis and hepatocellular carcinoma [2]. It is generally characterized by excess accumulation of fat in the liver without significant alcohol consumption or other causes of liver disease [2]. As the incidence of NAFLD rises, the estimated healthcare and economic burden from NAFLD is expected to rise in tandem. The annual direct medical cost in the United States related to NAFLD is projected to be $103 billion, along with $188 billion from societal costs [3]. Nonalcoholic fatty liver disease has been associated with multiple metabolic comorbidities, such as diabetes mellitus, insulin resistance, metabolic syndrome, dyslipidemia, and sarcopenia [4, 5]. At present there are no approved pharmacologic treatments

for NAFLD, thus efforts are needed to better understand modifiable risk factors for NAFLD and NAFLD-associated fibrosis.

Sarcopenia is characterized by the progressive loss of skeletal muscle mass, strength, and function [6, 7]. Several assessment tools have been developed to better diagnose sarcopenia, such as dual-energy X-ray absorptiometry (DEXA), which measures body fat, fat-free mass, and bone mineral content, or cross-sectional computed tomography scan, which assesses anatomic sarcopenia [8]. Previous studies have shown an association between sarcopenia and NAFLD, mainly in Asian cohorts [9-15]. Moreover, the only population-based study that showed an association between sarcopenia and NAFLD used the third National Health and Nutrition Examination Survey (NHANES), which was performed 30 years ago [15]. Therefore, the reported prevalence of NAFLD, sarcopenia, and obesity may underestimate the current state. Baumgartner et al. [16] first described the impact of obesity on skeletal muscle mass; sarcopenic obesity was independent associated with disability in the elderly. A recent article discussed the association between sarcopenic obesity and insulin resistance and cardiometabolic diseases, including cardiovascular disease and type 2 diabetes, which were closely associated with NAFLD [17]. Further understanding of the relationship between sarcopenic obesity and NAFLD may help develop preventative strategies to mitigate cardiometabolic diseases [17]. This population-based study aimed to investigate the association between sarcopenic obesity and NAFLD and NAFLD-associated liver fibrosis measured by transient elastography in the United States.

METHODS

We analyzed data from the 2017-2018 NHANES database. According to the NHANES DEXA protocol, participants aged 8-59 years were eligible for DEXA examination for this survey [18]. Pregnant females were excluded from undergoing DEXA [18]. A total of 2,353 adults (≥18 years) had eligible DEXA examination and available body mass index (BMI). Subjects with viral hepatitis (n=32), exposure to steatogenic medications (n=22), significant alcohol consumption (n=224) and incomplete transient elastography data (n=150) were excluded. A total of 1,925 subjects were enrolled.

The Fibroscan model 502 V2 Touch (Echosens, Waltham, MA) was equipped with medium or extra-large probes, which were used to assess the controlled attenuation parameter (CAP) score and liver stiffness [19, 20]. Elastography results were considered as incomplete and excluded if any of the following were present: <10 complete stiffness measurements, liver stiffness interquartile range/median ≥30%, or <3 hours of fasting prior to the exam [19, 20]. The quality control procedures ensure the collection and documentation of accurate and reliable CAP and liver stiffness measurement data [19]. The NHANES health technician were trained by survey staff and expert FibroScan technicians from Echosens with didactic presentations and sufficient practical sessions with several volunteer subjects. A retraining session was arranged when significant protocol changes or lack of standardization was observed among the technologists [19]. The interobserver reliability was 0.94 for CAP and 0.86 for liver stiffness [19, 20]. This model has an automatic built-in probe recommendation tool based on the skin-to-capsule distance measurement by the probe which detects ultrasound signals [21, 22]. As this tool operates in real-time, the examiners can confirm the type of probe according to the Fibroscan's recommendation [21, 22]. According to the automatic recommendation, among 1,925 participants, 403 (20.9%) were evaluated using the XL probe. A recent study has been validated the use of CAP score for diagnosis of NAFLD with the area under the receiver operating characteristic curve (AUROC) of 0.823 (0.809-0.837) [21]. In addition, liver stiffness measurement has been validated in patients with NAFLD with advanced fibrosis (AUROC: 0.83, 95%CI: 0.79-0.87) and cirrhosis (AUROC: 0.93 95%CI: 0.90-0.97) [22]. This study showed that the diagnostic performance of liver stiffness measurement for assessing advanced fibrosis and CAP for assessing steatosis did not vary by BMI category [22]. We defined suspected NAFLD (≥S1) as CAP scores ≥263 dB/m (cut-off of sensitivity fixed at 90%) [20, 22]. For the sensitivity analysis, CAP scores ≥285 dB/m (cut-off optimizing sensitivity and specificity) were defined as suspected NAFLD [20, 22]. Among individuals with NAFLD, liver stiffness of ≥8 kPa (≥F2) [23-25] and ≥13.1 kPa (≥F4) [22, 23] were used to define significant fibrosis and cirrhosis, respectively.

Appendicular lean mass (ALM), the sum of the muscle mass of both legs and arms, was used to assess for sarcopenia. Sarcopenia was defined as ALM adjusted for BMI using the ratio of ALM and BMI (men<0.789 and women<0.512) [8, 26, 27]. Sarcopenic obesity was defined if individuals met the criteria for sarcopenia and obesity by having a significant body fat using DEXA (≥25% and ≥35% for men and women, respectively) [8, 26].

Because of the complex sample design employed by NHANES, appropriate sample weights were used to reconstitute United States representative population-level data. Baseline characteristics were compared using the χ^2-test for categorical variables or Student's t-test or linear regression for continuous variables. We used multivariate logistic regression models to identify predictors of NAFLD and NAFLD-associated significant fibrosis and cirrhosis after adjusting for multiple confounders, including age, gender, race/ethnicity, high school education attainment, marriage status, diabetes, smoking status, hypertension, total cholesterol, physical activity, total calorie intake (per day), and alcohol consumption. Analyses were carried out using STATA 15.1 (StataCorp., College Station, Texas, USA) using Taylor series linearization.

RESULTS

Of 1,925 participants, 194 (weighted proportion: 7.8%, 95%CI: 5.6-10.7) individuals met the criteria for sarcopenic obesity. The prevalence of NAFLD was 41.8% (95%CI: 38.7-45.1) and 31% (95%CI: 27.4-34.9) based on CAP scores of ≥263 dB/m and ≥285 dB/m, respectively. Individuals with sarcopenic obesity are significantly more likely to have NAFLD, using both CAP score cut-offs (69.7% versus 39.5% in CAP ≥263 dB/m, and 62.5% versus 28.4% in CAP ≥285 dB/m), compared to those without (Table I). Individuals with sarcopenic obesity tend to be older, male, Hispanic, and are more likely to have

hypertension and diabetes (Table I). As expected, individuals with sarcopenic obesity have a significantly higher BMI, waist circumference, alanine aminotransferase, and glycated hemoglobin compared to those without (Table I).

Individuals with sarcopenic obesity had significantly higher odds of having NAFLD (CAP score ≥263 dB/m, odds ratio (OR): 2.88, 95%CI: 1.82-4.57, and CAP score ≥285, OR: 3.71, 95%CI: 2.24-6.14) after adjusting for age, gender, and race/ethnicity (Table II). Sarcopenic obesity was associated with an increased risk of having NAFLD (CAP score ≥263 dB/m, OR: 2.61, 95%CI: 1.51-4.50, and CAP score ≥285 dB/m, OR: 3.31, 95%CI: 1.85-5.96), after additionally adjusting for socioeconomic status, lifestyle factors (smoking, physical activity, total calorie intake, and alcohol consumption), and metabolic risk factors (hypertension, diabetes, and total cholesterol).

Among individuals with NAFLD, the prevalence of significant fibrosis (≥F2) and cirrhosis (≥F4) was 10.8% (95%CI: 8.1-14.4) and 3.2% (95%CI: 1.6-6.4), respectively. Individuals with sarcopenic obesity had a higher prevalence of significant fibrosis (20.9%, 95%CI: 12.8-32.1) than those without (9.4%, 95%CI: 6.4-13.5). Individuals with sarcopenic obesity had significantly higher odds of having NAFLD-associated significant fibrosis in the age, gender, and race/ethnicity-adjusted model (OR: 2.60, 95%CI: 1.24-5.46). After adjusting for socioeconomic status, lifestyle factors, and metabolic risk factors, this association remained significant (OR: 2.22, 95%CI: 1.03-4.80) (Table III). In terms of NAFLD-associated cirrhosis, individuals with sarcopenic obesity had a higher prevalence of cirrhosis (7.5%, 95%CI: 2.6-20.2) than those without (2.6%, 95%CI: 1.0-6.7). Individuals with sarcopenic obesity have approximately 3 times higher odds of having NAFLD-associated cirrhosis, but this association did not reach statistical significance (Table III).

Table I. Baseline characteristics of the study participants

	Sarcopenic obesity (n=194)	No sarcopenic obesity (n=1,731)	p
Age (years)	42.2 ± 1.06	37.5 ± 0.52	0.003
Male gender (%)	55.2 ± 4.52	47.8 ± 1.09	0.127
Body mass index (kg/m^2)	35.6 ± 0.75	28.0 ± 0.33	<0.001
Waist circumference (cm)	112.3 ± 1.63	94.8 ± 0.88	<0.001
Race-ethnicity (%)			<0.001
Non-Hispanic White	41.4 ± 6.13	57.3 ± 3.31	<0.001
Non-Hispanic Black	2.6 ± 1.46	11.0 ± 1.58	<0.001
Hispanic	43.1 ± 5.75	19.3 ± 2.79	<0.001
Non-Hispanic Asian	6.7 ± 1.36	7.9 ± 1.49	<0.001
Others	6.2 ± 2.63	4.4 ± 0.62	<0.001
Smoking (%)			0.630
Never smoker	65.1 ± 2.70	65.4 ± 2.16	0.630
Previous smoker	16.8 ± 2.87	18.7 ± 1.55	0.630
Current smoker	18.2 ± 2.68	15.9 ± 1.56	0.630
High Education (%)	72.9 ± 3.73	85.0 ± 1.24	<0.001
Married (%)	61.7 ± 5.24	60.9 ± 1.92	0.894
Hypertension (%)	32.3 ± 6.03	16.7 ± 1.70	0.002
Diabetes (%)	14.9 ± 2.80	5.6 ± 0.97	0.003
Total cholesterol (mg/dL)	192.3 ± 3.88	187.1 ± 1.88	0.238
ALT (IU/L)	26.6 ± 1.31	22.7 ± 0.34	0.034
AST (IU/L)	21.3 ± 0.89	21.4 ± 0. 29	0.958
GGT (IU/L)	41.9 ± 2.67	26.0 ± 0.85	0.125
Glucose (mg/dL)	125.8 ± 5.07	105.4 ± 1.54	0.042
HbA1c (%)	5.89 ± 0.09	5.48 ± 0.03	0.007
ALM_BMI	0.62 ± 0.01	0.82 ± 0.01	<0.001
NAFLD (CAP ≥263 dB/m)	69.7 ± 3.49	39.5 ± 1.57	<0.001
NAFLD (CAP ≥285 dB/m)	62.5 ± 4.51	28.4 ± 1.84	<0.001

Data were presented as weighed mean ± SE or weighted proportion ± SE. ALT: alanine aminotransferase. AST: aspartate aminotransferase; ALM_BMI: the ratio of appendicular lean mass and body mass index; CAP: controlled attenuation parameter; GGT: gamma-glutamyl transferase; HbA1c: glycated hemoglobin; NAFLD: nonalcoholic fatty liver disease.

DISCUSSION

This is the first population-based study to investigate the association between sarcopenic obesity measured by DEXA and NAFLD and NAFLD-associated significant fibrosis measured by transient elastography. The current study demonstrates that individuals with sarcopenic obesity had a two-fold higher prevalence of NAFLD and NAFLD-associated significant fibrosis than those without sarcopenic obesity. We found that sarcopenic obesity was associated with an increased risk of NAFLD and NAFLD-associated significant fibrosis independent of demographic factors, socioeconomic status as well as behavioral and metabolic risk factors. Fibrosis stage (not NASH) has been shown to predict mortality and the time to develop advanced liver disease in NAFLD [28]. A randomized study showed that physical activity with exercise program enhances muscle mass, functional capacity, and health-related quality of life in patients with cirrhosis [29].

Table II. Univariate and multivariate odds ratio of risk factors for NAFLD based on the prevalence of sarcopenic obesity

	Sarcopenic obesity OR (95% CI)	p	Sarcopenic obesity OR (95% CI)	p
	NAFLD (CAP ≥263 dB/m)		NAFLD (CAP ≥285 dB/m)	
Age, sex, ethnicity-adjusted	2.88 (1.82-4.57)	<0.001	3.71 (2.24-6.14)	<0.001
Multivariate model 1	2.69 (1.57-4.60)	0.001	3.37 (1.88-6.01)	<0.001
Multivariate model 2	2.61 (1.51-4.50)	0.002	3.31 (1.85-5.96)	0.001

The multivariate model 1 included age, gender, race/ethnicity, education status, marriage status, diabetes, smoking status, hypertension, and total cholesterol. The multivariate model 2 included physical activity, total calorie intake, and alcohol consumption in addition to the variables addressed in model 1. CAP: controlled attenuation parameter; CI: confidence interval; OR: odds ratio; NAFLD: nonalcoholic fatty liver disease.

Table III. Univariate and multivariate odds ratio of risk factors for NAFLD-associated Fibrosis and cirrhosis according to the prevalence of sarcopenic obesity

	Sarcopenic obesity OR (95% CI)	p	Sarcopenic obesity OR (95% CI)	p
	Significant fibrosis (≥F2)		Cirrhosis (≥F4)	
Age, gender, ethnicity-adjusted	2.60 (1.24-5.46)	<0.001	3.15 (0.56-17.75)	0.178
Multivariate model 1	2.28 (1.09-4.75)	0.030	3.31 (0.63-17.28)	0.144
Multivariate model 2	2.22 (1.03-4.80)	0.043	3.89 (0.69-21.94)	0.115

The multivariate model 1 included age, gender, race/ethnicity, education status, marriage status, diabetes, smoking status, hypertension, and total cholesterol. The multivariate model 2 included physical activity, total calorie intake, and alcohol consumption in addition to the variables addressed in model 1. CAP: controlled attenuation parameter; CI: confidence interval; OR: odds ratio; NAFLD: nonalcoholic fatty liver disease.

Thus, physical activity may be beneficial in both sarcopenic obesity and NAFLD and/or advanced fibrosis.

Both obesity and sarcopenia have been shown to be associated with increased risk of cardiometabolic diseases, morbidity, and mortality [30, 31]. It has been proposed that sarcopenic obesity may have a higher impact on cardiometabolic disease associated with morbidity and mortality than obesity or sarcopenia alone [32-34]. There are several plausible mechanisms that may explain the increased risk of NAFLD and NAFLD-associated liver fibrosis in individuals with sarcopenic obesity. First, sarcopenic obesity and NAFLD share several pathophysiological processes, including decreased physical activity, increased insulin resistance, chronic inflammation, and reduced protein intake [35]. Second, a reduction of specific adiponectin, a protein hormone and adipokine, in obesity leads to insulin resistance and glucose intolerance, which are associated with NAFLD [36]. An increased leptin level in obesity can also induce insulin resistance, glucose intolerance, and activate the hepatic stellate cells and transforming growth factor β in Kupffer cells, which contributes to the progression of liver fibrosis [37]. In addition, low adiponectin levels in obesity can lead to fatty liver and liver fibrosis [36, 38]. Third, loss of skeletal muscle mass in sarcopenia leads to the reduction of insulin signaling, insulin resistance, increased adipose tissue lipolysis, and increased in hepatic steatosis [39]. In summary, the mechanism that is involved in the sarcopenia-NAFLD relationship is mainly from insulin resistance, chronic inflammation, oxidative stress, and interlink between organs by secretion of cytokines (hepatokines, myokines, and adipokines) [40].

The current study has several strengths. First, we used CAP score, which is a parameter with high accuracy for mild hepatic steatosis (>5% of hepatocytes) and has a higher sensitivity to identify NAFLD compared to ultrasonography [21]. Ultrasonography has a relatively lower sensitivity in identifying hepatic steatosis below 30% [41]. Thus, we believe a higher prevalence of NAFLD, measured by CAP score, versus the previous study based on ultrasonographic diagnosis [1] was mainly derived from the CAP score's accuracy. In addition, we defined significant fibrosis/cirrhosis using transient elastography, not non-invasive serum panels. To date, there is no data on the prevalence of NAFLD and significant fibrosis/cirrhosis based on sarcopenic obesity measured by DEXA, which is an accurate method compared to bioimpedance analysis in the general population. Second, this is the first population-based study representative of the general United States population.

The current study also has several limitations. First, the cross-sectional nature of this study could not allow us to draw a causal relationship. Second, we could not assess skeletal muscle function, such as handgrip strength, and we lack liver histology data due to study design. Third, we were unable to adjust for inflammation and insulin resistance due to the unavailability of these factors in the current NHANES dataset. Although we tried to adjust known risk factors between two conditions, we also could not eliminate the possibility of unadjusted residual confounders in this study, such as the presence of chronic obstructive pulmonary disease that may affect the risk of two conditions [42]. Fourth, there are known tendencies of difference between liver stiffness or CAP measurement and probe types of transient elastography, and it is possible that the NAFLD and significant fibrosis may have been misclassified. In addition, the NHANES database does not have liver biopsy data available. Thus, there is a possibility of misclassification in significant fibrosis. Liver biopsy data is crucial in future studies to minimize the risk of misclassification. Fifth, the current study focused on the association between sarcopenic obesity and NAFLD and fibrosis compared with those without sarcopenic obesity. Thus, further studies are warranted to investigate whether there are any different prevalence of NAFLD and fibrosis between individuals with sarcopenic obesity and nonobese individuals with sarcopenia. Finally, there is no universal cut-off to determine NAFLD using the CAP score or determine significant fibrosis or cirrhosis in individuals with NAFLD using liver stiffness. However, we used various validated cut-off points for CAP score and liver stiffness from previous studies [23-25].

CONCLUSIONS

Sarcopenic obesity was associated with an increased risk of NAFLD and NAFLD-associated significant fibrosis independent of known risk factors. Given the significant association between sarcopenic obesity and NAFLD-associated significant fibrosis, increasing muscle mass and controlling body fat might be a target for the prevention and management of NAFLD-associated significant fibrosis. This study suggests the need for future prospective longitudinal studies to assess the impact of sarcopenic obesity on NAFLD and NAFLD-associated significant fibrosis and to assess the efficacy of

interventions for sarcopenic obesity on NAFLD associated outcomes.

Conflicts of interest: None to declare.

Authors' contributions: K.W., E.S.A., A.A., D.K. conceived and designed the study. K.W., E.S.A., collected the data. D.K. analyzed and interpreted the data. K.W., E.S.A., D.K. drafted the manuscript. K.W., A.A., D.K. critically revised the paper. A.A., D.K. supervised the study.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84. doi:10.1002/hep.28431
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357. doi:10.1002/hep.29367
3. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577-1586. doi:10.1002/hep.28785
4. Wijarnpreecha K, Panjawatanan P, Thongprayoon C, Jaruvongvanich V, Ungprasert P. Sarcopenia and risk of nonalcoholic fatty liver disease: A meta-analysis. Saudi J Gastroenterol 2018;24:12-17. doi:10.4103/sjg.SJG_237_17
5. Yang KC, Hung HF, Lu CW, Chang HH, Lee LT, Huang KC. Association of Non-alcoholic Fatty Liver Disease with Metabolic Syndrome Independently of Central Obesity and Insulin Resistance. Sci Rep 2016;6:27034. doi:10.1038/srep27034
6. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011;12:249-256. doi:10.1016/j.jamda.2011.01.003
7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412-423. doi:10.1093/ageing/afq034
8. Batsis JA, Mackenzie TA, Jones JD, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and inflammation: Results from the 1999-2004 National Health and Nutrition Examination Survey. Clin Nutr 2016;35:1472-1483. doi: 10.1016/j.clnu.2016.03.028
9. Issa D, Alkhouri N, Tsien C, et al. Presence of sarcopenia (muscle wasting) in patients with nonalcoholic steatohepatitis. Hepatology 2014;60:428-429. doi:10.1002/hep.26908
10. Kim G, Lee SE, Lee YB, et al. Relationship Between Relative Skeletal Muscle Mass and Nonalcoholic Fatty Liver Disease: A 7-Year Longitudinal Study. Hepatology 2018;68:1755-1768. doi:10.1002/hep.30049
11. Koo BK, Kim D, Joo SK, et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. J Hepatol 2017;66:123-131. doi:10.1016/j.jhep.2016.08.019
12. Lee SW, Youm Y, Lee WJ, et al. Appendicular skeletal muscle mass and insulin resistance in an elderly korean population: the korean social life, health and aging project-health examination cohort. Diabetes Metab J 2015;39:37-45. doi:10.4093/dmj.2015.39.1.37
13. Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The Association between Phase Angle of Bioelectrical Impedance Analysis and Survival Time in Advanced Cancer Patients: Preliminary Study. Korean J Fam Med 2014;35:251-256. doi:10.4082/kjfm.2014.35.5.251
14. Petta S, Ciminnisi S, Di Marco V, et al. Sarcopenia is associated with severe liver fibrosis in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2017;45:510-518. doi:10.1111/apt.13889
15. Wijarnpreecha K, Kim D, Raymond P, Scribani M, Ahmed A. Associations between sarcopenia and nonalcoholic fatty liver disease and advanced fibrosis in the USA. Eur J Gastroenterol Hepatol 2019;31:1121-1128. doi:10.1097/MEG.0000000000001397
16. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res 2004;12:1995-2004. doi:10.1038/oby.2004.250
17. Hong SH, Choi KM. Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences. Int J Mol Sci 2020;21:494. doi:10.3390/ijms21020494
18. National Health and Nutrition Examination Survey. Dual-Energy X-ray Absorptiometry - Whole Body (DXX_J). Available at:https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/DXX_J.htm. Accessed at: Sep 2020.
19. National Health and Nutrition Examination Survey. Liver Ultrasound Transient Elastography (LUX_J). Available at:https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/LUX_J.htm. Accessed at: Sep 2020.
20. Kim D, Cholankeril G, Loomba R, Ahmed A. Prevalence of Fatty Liver Disease and Fibrosis detected by Fibroscan in Adults in the United States, 2017-2018. Clin Gastroenterol Hepatol 2020 Aug 12. doi:10.1016/j.cgh.2020.08.017
21. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66:1022-1030. doi:10.1016/j.jhep.2016.12.022
22. Siddiqui MS, Vuppalanchi R, Van Natta ML, et al. Vibration-Controlled Transient Elastography to Assess Fibrosis and Steatosis in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2019;17:156-163.e2. doi:10.1016/j.cgh.2018.04.043
23. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1717-1730. doi:10.1053/j.gastro.2019.01.042
24. Abeysekera KWM, Fernandes GS, Hammerton G, et al. Prevalence of steatosis and fibrosis in young adults in the UK: a population-based study. Lancet Gastroenterol Hepatol 2020;5:295-305. doi:10.1016/S2468-1253(19)30419-4
25. Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1264-1281.e4. doi:10.1053/j.gastro.2018.12.036
26. Batsis JA, Barre LK, Mackenzie TA, Pratt SI, Lopez-Jimenez F, Bartels SJ. Variation in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with different research definitions: dual-energy X-ray absorptiometry data from the National Health and Nutrition Examination Survey 1999-2004. J Am Geriatr Soc 2013;61:974-980. doi:10.1111/jgs.12260
27. Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69:547-558. doi:10.1093/gerona/glu010
28. Hagstrom H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265-1273. doi:10.1016/j.jhep.2017.07.027

29. Roman E, Torrades MT, Nadal MJ, et al. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. Dig Dis Sci 2014;59:1966-1975. doi:10.1007/s10620-014-3086-6
30. Androga L, Sharma D, Amodu A, Abramowitz MK. Sarcopenia, obesity, and mortality in US adults with and without chronic kidney disease. Kidney Int Rep 2017;2:201-211. doi:10.1016/j.ekir.2016.10.008
31. Tian S, Xu Y. Association of sarcopenic obesity with the risk of all-cause mortality: A meta-analysis of prospective cohort studies. Geriatr Gerontol Int 2016;16:155-166. doi:10.1111/ggi.12579
32. Kohara K. Sarcopenic obesity in aging population: current status and future directions for research. Endocrine 2014;45:15-25. doi:10.1007/s12020-013-9992-0
33. Choi KM. Sarcopenia and sarcopenic obesity. Korean J Intern Med 2016;31:1054-1060. doi:10.3904/kjim.2016.193
34. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc 2015;74:405-412. doi:10.1017/S002966511500169X
35. Merli M, Lattanzi B, Aprile F. Sarcopenic obesity in fatty liver. Curr Opin Clin Nutr Metab Care 2019;22:185-190. doi:10.1097/MCO.0000000000000558
36. Buechler C, Wanninger J, Neumeier M. Adiponectin, a key adipokine in obesity related liver diseases. World J Gastroenterol 2011;17:2801-2811.
37. Duan XF, Tang P, Li Q, Yu ZT. Obesity, adipokines and hepatocellular carcinoma. I Int J Cancer 2013;133:1776-1783. doi:10.1002/ijc.28105
38. Buechler C, Haberl EM, Rein-Fischboeck L, Aslanidis C. Adipokines in Liver Cirrhosis. Int J Mol Sci 2017;18:1392. doi:10.3390/ijms18071392
39. Pacifico L, Perla FM, Chiesa C. Sarcopenia and nonalcoholic fatty liver disease: a causal relationship. Hepatobiliary Surg Nutr 2019;8:144-147. doi:10.21037/hbsn.2018.11.11
40. Mikolasevic I, Pavic T, Kanizaj TF, Bender DV, Domislovic V, Krznaric Z. Nonalcoholic Fatty Liver Disease and Sarcopenia: Where Do We Stand? Can J Gastroenterol Hepatol2020;2020:8859719. doi:10.1155/2020/8859719
41. Sanyal AJ, American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-1725. doi:10.1053/gast.2002.36572
42. Hong KS, Kim MC, Ahn JH. Sarcopenia Is an Independent Risk Factor for NAFLD in COPD: A Nationwide Survey (KNHANES 2008-2011). Int J Chron Obstruct Pulmon Dis 2020;15:1005-1014. doi:10.2147/COPD.S249534