Original Article

Malnutrition and chronic inflammation as risk factors for sarcopenia in elderly patients with hip fracture

Jun-Il Yoo MD[1], Yong-Chan Ha MD[2], Hana Choi MD[3], Kyu-Hwang Kim MD[2], Young-Kyun Lee MD[4], Kyung-Hoi Koo MD[4], Ki-Soo Park PhD, MD[5]

[1]*Department of Orthopaedic Surgery Gyeongsang National University Hospital, Jinju, Korea*
[2]*Department of Orthopaedic Surgery, Chung-Ang University College of Medicine, Seoul, Korea*
[3]*Department of Rehabilitation, Dankook University College of Medicine, Cheonan, Korea*
[4]*Department of Orthopaedic Surgery, Seoul National University Bundang Hospital, Bundang, Korea*
[5]*Department of Preventive Medicine and Institute of Health Sciences, Gyeongsang National University Hospital, Jinju, Korea*

Background and Objectives: To evaluate malnutrition and chronic inflammation as risk factors for sarcopenia in elderly patients with hip fractures, as defined by the criteria of the Asian Working Group on Sarcopenia (AWGS). **Methods and Study Design:** A total of 327 elderly patients with hip fractures were enrolled in this retrospective observational study. The main outcome measure was the nutritional status and nutritional risk factors for sarcopenia in elderly patients. Diagnosis of sarcopenia was made according to the guidelines of the AWGS. Whole body densitometry analysis was used to measure skeletal muscle mass, and muscle strength was evaluated by handgrip testing. Multivariable regression analysis was utilized to analyze the nutritional risk factors for sarcopenia in patients with hip fractures. **Results:** Of 327 patients with hip fractures (78 men and 249 women), the prevalence of sarcopenia was 60.3% and 30.1% in men and women, respectively. The rates of three indicators of malnutrition in men and women (low BMI, hypoalbuminemia, and hypoproteinemia) in sarcopenia patients with hip fractures were 23.4%, 31.9%, and 53.2% and 21.3%, 21.3%, and 37.3%, respectively. The prevalence of markers of chronic inflammation (increased CRP and ESR) in men and women with sarcopenia and hip fractures were 74.9% and 52.2%, and 49.3% and 85.1%, respectively. After adjusting for covariates, low BMI and hypoproteinemia in women were associated with a 2.9- and 2.1-fold greater risk of sarcopenia than non-sarcopenia, respectively. **Conclusions:** The present study revealed a strong relationship between sarcopenia and malnutrition and chronic inflammatory factors in elderly patients with hip fractures.

Key Words: chronic inflammation, hip fracture, malnutrition, sarcopenia, elderly

INTRODUCTION

Sarcopenia has its own International Classification of Disease in the Tenth Revision, Clinical Modification (ICD-10-CM). The assigned code is M62.84, and it was available for use as of October 1, 2016.[1] In the near future, studies related to sarcopenia will most likely become more popular.

So far, several studies have reported that development of sarcopenia is related to multifactorial and interrelated biological mechanisms, including age, physical inactivity, nutritional factors, and biological markers such as sex hormones, oxidative products, and inflammatory cytokines.[2,3] Of those mechanisms, chronic activation of the inflammatory response is the key physio-pathological substrate for anabolic resistance, sarcopenia, and frailty in older individuals.[4] ESR and CRP are recognized worldwide as biologic markers of infection or inflammation and can serve as useful predictors of sarcopenia.[4] Many studies have reported that chronic inflammation is associated with sarcopenia in patients with chronic diseases.[5-7]

Hip fracture is a common condition in patients with sarcopenia and results in high mortality, morbidity, and socioeconomic burden.[8,9] Recently, several epidemiological studies have reported a higher prevalence of sarcopenia in patients with hip fractures.[10,11] However, the relationship between nutritional status and chronic inflammation as risk factors for sarcopenia in elderly patients with hip fractures is not well understood.

The purpose of the present study was to evaluate the relationship between malnutrition and chronic inflammation and sarcopenia in elderly patients with hip fractures, as defined by the criteria of the Asian Working Group on Sarcopenia.

Corresponding Author: Dr Yong-Chan Ha, Department of Orthopaedic Surgery, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-ku, Seoul 156-755, South Korea.
Tel: +82-2-6299-1577; Fax: +82-2-822-1710
Email: hayongch@naver.com
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METHODS

The design and protocol of this retrospective study were approved by the Institutional Review Board of our hospital (IRB approved by Chung-Ang university hospital, C2016212 (1955)). All patients waived informed consent. Between November, 2011 and December, 2015, all patients with a fresh hip fracture who were at least 65 years of age and who were admitted to our hospital were eligible for this study. During the study period, 432 hip fracture patients aged 65 years and older were admitted to the institution. Of these, 25 (5.7%) were excluded because the injury originated from a high-impact event such as a traffic accident or industrial injury, 23 (5.2%) were excluded because there was no time to perform DXA preoperatively owing to the need for urgent surgical repair, 34 (7.7%) were excluded because of refusal of examination, and 23 (5.2%) were excluded owing to incorporation, such as dementia, delirium, and depression. A total of 327 hip fracture patients were finally included in this study (Figure 1).

Body composition was measured by whole-body DXA (DPX-NT; GE Medical Systems Lunar, Madison, WI, USA). Bone mineral content, fat mass, and lean soft tissue mass were measured separately for each part of the body, including the arms and legs. The average lean soft tissue masses of the arms and legs were nearly equal to the skeletal muscle mass. As absolute muscle mass correlates with height, the skeletal muscle mass index (SMI) was calculated using the following formula: lean mass = [kg]/height^2 [m^2]; lean mass is directly analogous to body mass index (BMI = weight [kg]/height^2 [m^2]). Arm SMI was defined as (arm lean mass [kg]/height^2 [m^2]). Leg SMI was defined as (leg lean mass [kg]/height^2 [m^2]). Appendicular SMI was defined as the sum of arm and leg SMI.

Muscle strength was assessed by handgrip strength. The participant held a Jamar adjustable dynamometer (Asimov Engineering, Los Angeles, CA) in the dominant hand with his/her arm fully extended at an angle of 30° with respect to the trunk and the palm of the hand perpendicular to the shoulder line.

Serum 25(OH)D and parathyroid hormone (PTH) levels were measured using a radioimmunoassay kit (DiaSorin, Stillwater, MN, USA) and a chemiluminescence immunoassay kit (N-tact PTH Assay kit; DiaSorin), respectively.

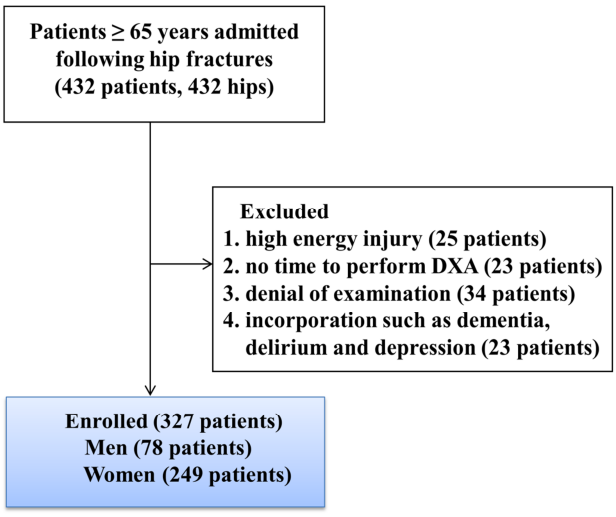

Figure 1. Flow chart of the study population.

Sarcopenia was defined according to the Asian Working Group for Sarcopenia (AWGS) criteria for low muscle mass strength (hand grip strength below 18 kg in women and below 26 kg in men) and low muscle strength (appendicular SMI below 5.4 kg/m^2 in women and below 7.0 kg/m^2 in men).[12]

To determine the relationship between malnutrition and sarcopenia, hypoalbuminemia was defined as a serum albumin level ≤3.4 g/dL.[13] Hypoproteinemia was defined as a serum protein level <6.5 g/dL.[14] Low BMI was defined as a BMI below 18.5 kg/m^2, according to WHO guidelines.

To determine the relationship between chronic inflammation and sarcopenia, increased CRP was defined as serum CRP ≥5.0 mg/dL. Increased ESR was defined as an increase in serum ESR ≥20 mm/hour.[15]

We used the Chi-square test for categorical variables and the t-test for numerical variables. All reported p values are two-sided, and a p value of <0.05 was taken to indicate statistical significance. To determine the nutritional risk factors for sarcopenia in women aged 65 years or over with hip fractures, multivariable regression analysis was performed. Variables that had a p value of <0.20 (25(OH)D, ALP, and CRP in women, and BMI, 25(OH)D, hypoalbuminemia, and hypoproteinemia in men) were included in the multivariable model. All statistical tests were two-tailed, and p<0.05 was considered statistically significant. Statistical analyses were carried out using SPSS software for Windows (version 22.0; SPSS, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Of 327 patients with hip fractures (78 men and 249 women), the prevalence of sarcopenia in men and women were 60.3% and 30.1%, respectively. The baseline demographic data of the patients are shown in Table 1.

The prevalence of malnutrition in men and women (low BMI, hypoalbuminemia, and hypoproteinemia) in patients with sarcopenia and in those with hip fractures were 23.4%, 31.9%, and 53.2%, and 21.3%, 21.3%, and 37.3%, respectively. Low BMI was significantly associated with sarcopenia in women (p=0.014). However, there was no association between sarcopenia and malnutrition in men (Table 2).

In men, ALP (p=0.008), CRP (p=0.002), and ESR (p=0.034) were significantly different in those with sarcopenia vs. those without. However, body mass index (p<0.001), 25(OH)D (p=0.042), ALP (p=0.035), CRP (p=0.043), and ESR (p=0.005) in women were significantly different given the presence of sarcopenia (Table 3).

The prevalence of chronic inflammation (increased CRP and increased ESR) in men and women in hip fracture patients with sarcopenia were 74.9% and 52.2%, and 49.3% and 85.1%, respectively. As a marker of increased inflammation, CRP in patients with sarcopenia and hip fractures was significantly higher than in the normal group (p=0.002 for men and p=0.049 for women) (Ta-

Table 1. Patient demographics

	Total	Men	Women	*p*-value
Number (%)	327 (100)	78 (23.9)	249 (76.1)	
Age (years)	77.76±9.7	76.12±8.57	78.29±9.99	0.004*
BMI (kg/m^2)	22.22±3.79	21.51±3.01	22.44±3.99	0.008*
ASA (≥Grade 3) (%)	279 (85.3)	67 (85.9)	212 (85.1)	0.869
Koval (≥Grade 4) (%)	75 (22.9)	18 (23.1)	57 (22.9)	0.973
Type of fracture (%)				0.213
Femoral neck	120 (36.7)	24 (30.8)	96 (38.6)	
Intertrochanteric	207 (63.3)	54 (69.2)	153 (61.4)	
Fracture treatment (%)				0.379
Arthroplasty	211 (64.5)	52 (66.7)	159 (63.9)	
Internal fixation	112 (34.3)	24 (30.8)	88 (35.3)	
Conservative treatment	4 (1.2)	2 (2.6)	2 (0.8)	
Sarcopenia (%)	122 (37.3)	47 (60.3)	75 (30.1)	<0.001*

BMI: body mass index; ASA: American Society of Anesthesiologists,
*p-value significant at <0.05.

Table 2. Association between malnutrition and sarcopenia in hip fracture patients

Gender	Characteristics	Normal group	Sarcopenia group	*p*-value
Men	Number of participants (%)	31 (39.7)	47 (60.3)	
	Low BMI (kg/m^2)†	3 (9.7)	11 (23.4)	0.122
	Hypoalbuminemia‡	5 (16.1)	15 (31.9)	0.118
	Hypoproteinemia§	10 (32.3)	25 (53.2)	0.069
Women	Number of participants (%)	174 (69.9)	7 5 (30.1)	
	Low BMI (kg/m^2)†	17 (9.8)	16 (21.3)	0.014
	Hypoalbuminemia‡	26 (14.9)	16 (21.3)	0.217
	Hypoproteinemia§	49 (28.2)	28 (37.3)	0.151

BMI: body mass index.
†Low BMI (kg/m^2): <18.5 kg/m^2.
‡Hypoalbuminemia: serum albumin <3.5 g/dL.
§Hypoproteinemia: serum protein <6.5 g/dL.

ble 4).

For women aged 65 years or over with hip fractures, those with low BMI had a 2.9-fold greater prevalence of sarcopenia after adjusting for 25(OH)D, ALP and CRP (OR=2.94; 95% CI=1.51-5.75). Also, hypoproteinemia increased the prevalence of sarcopenia by 2.1 times after adjusting for 25(OH)D, ALP and CRP (OR=2.10; 95% CI=1.02-4.32) (Table 5).

DISCUSSION

To our knowledge, this is the first study to investigate the association between nutritional status and hip fracture in patients with sarcopenia. Low BMI and hypoproteinemia in women were used to assess nutritional status after adjusting for certain covariates (25(OH)D, ALP, and CRP); those factors led to a 2.9- and 2.1-fold greater risk of sarcopenia than non-sarcopenia, respectively. The levels of inflammatory markers such as CRP and ESR were increased in the sarcopenia group, and chronic inflammation is considered an important risk factor for hip fracture in patients with sarcopenia.

Many studies have reported an association between sarcopenia and malnutrition in the elderly population. A recent systemic review of 33 articles was performed on the relationship between sarcopenia and nutritional status in adults aged 60 and older. That study found that sarcopenia is correlated with poor nutritional status, including low body mass index, unfavorable nutritional risk screening results, decreased nutritional laboratory parameters, and anorexia.[16] However, elderly patients with hip fractures were not assessed for an association between sarcopenia and malnutrition. This study corresponds with previous studies done in elderly populations. A high prevalence (37.3%) (122/327 patients) of sarcopenia in elderly patients with hip fractures is most often related to malnutrition, as reflected by low BMI in both genders and hypoproteinemia in women. In addition, malnutrition in elderly patients with hip fractures is considered an independent risk factor for negative outcomes and failure of internal fixation of femoral neck fractures.[17-19] Therefore, management of sarcopenia caused by malnutrition, including nutritional support, in elderly patients after hip fracture, may be a vital step in improving outcomes and reducing perioperative complications.[20]

In this study, we found high levels of chronic inflammatory markers in elderly patients with hip fractures and sarcopenia. Chronic low-grade inflammation is an important causal factor in elderly individuals with sarcopenia. Aleman et al. performed a longitudinal observational study on 115 community-dwelling men and women aged 60-84 years. During a 5-year follow-up period, the authors observed a loss of total appendicular skeletal muscle with increasing inflammation, as indicated by increasing levels of serum IL-6 and CRP.[21] In addition, the relationship between chronic low-grade inflammation and sarcopenia in patients with chronic diseases such as COPD, Cachexia, and CKD has been reported.[5-7] Increased levels of inflammatory markers in patients with hip fractures

Table 3. Nutritional status of hip fracture patients given the presence of sarcopenia

	Men			Women		
Characteristics	Normal group	Sarcopenia group	*p*-value	Normal group	Sarcopenia group	*p*-value
Number (%)	31 (39.7)	47 (60.3)		174 (69.9)	75 (30.1)	
Age (yrs)	77.45±7.33	77.79±6.94	0.839	80.12±7.92	81.20±7.69	0.321
BMI (kg/m^2)	21.99±2.66	20.84±2.78	0.072	22.99±4.15	21.01±3.58	<0.001*
25(OH)D (ng/dL)	17.33±8.08	13.81±9.67	0.110	14.44±9.21	17.99±13.0	0.042*
PTH (ng/dL)	66.53±47.83	78.65±123.41	0.610	75.93±83.41	72.55±69.64	0.760
Albumin (g/dL)	3.78±0.38	3.68±0.4	0.299	3.87±0.44	3.76±0.44	0.084
Protein (mg/L)	6.72±0.62	6.42±0.73	0.067	6.69±0.60	6.64±0.70	0.533
Glucose (mg/L)	138.77±34.03	158.43±57.63	0.063	150.19±51.67	152.23±45.94	0.768
Bun (mg/dL)	23.81±19.33	24.17±14.20	0.924	19.21±6.97	20.67±12.26	0.335
Creatinine (mg/dL)	1.28±1.71	1.32±1.56	0.930	0.80±0.41	1.04±2.04	0.312
Uric acid (mg/dL)	5.19±1.50	5.29±1.55	0.778	4.57±1.54	4.45±1.83	0.611
AST (IU/L)	25.55±8.48	29.28±31.37	0.521	26.06±8.76	28.20±14.73	0.239
ALT (IU/L)	16.94±8.80	17.26±12.26	0.901	16.48±6.94	18.28±9.82	0.152
LDH (IU/L)	226.43±83.36	213.23±50.03	0.387	232.91±52.10	248.35 ±80.69	0.157
r-GT (IU/L)	21.73±16.79	37.15±61.97	0.188	20.87±18.87	24.87±31.33	0.216
ALP (IU/L)	146.30±97.03	221.96±129.77	0.008*	158.40±108.49	190.72±111.51	0.035*
P (mg/dL)	2.97±0.61	3.18±0.87	0.210	3.24±0.64	3.90±6.30	0.370
Calcium (mg/dL)	8.68±0.43	8.72±0.46	0.702	8.79±0.52	8.68±0.81	0.176
Cholesterol (mg/dL)	209.73±353.36	151.57±35.13	0.376	171.94±42.42	170.24±47.96	0.787
eGFR (mL/min)	85.61±32.79	77.15±36.48	0.309	81.30±28.73	83.69±34.58	0.572
CRP (mg/dL)	13.29±25.26	39.14±44.49	0.002*	15.38±32.80	26.40±40.70	0.043*
ESR (mm/hour)	19.23±16.33	30.39±28.54	0.034*	21.41±15.72	30.25±23.90	0.005*

BMI: body mass index; PTH: parathyroid hormone; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; r-GT: r glutamyl transferase; ALP: alkaline phosphatase; P: phosphorus; Cholesterol: total cholesterol; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.
*p-value significant at <0.05.

Table 4. Association between inflammatory markers and sarcopenia in hip fracture patients

Gender	Characteristics	Normal group	Sarcopenia group	*p*-value
Men	Number of participants (%)	31 (39.7)	47 (60.3)	
	Increased CRP (mg/dL)†	12 (38.7)	34 (73.9)	0.002
	Increased ESR(mm/hour)‡	11 (36.7)	24 (52.2)	0.185
Women	Number of participants (%)	174 (69.9)	75 (30.1)	
	Increased CRP (mg/dL)†	62 (35.8)	36 (49.3)	0.049
	Increased ESR(mm/hour)‡	73 (64.6)	40 (85.1)	0.072

†Increased CRP: ≥5.0 mg/dL.
‡Increased ESR: ≥20 mm/hour.

Table 5. Multivariable logistic regression analysis for sarcopenia in women aged 65 years or over with hip fractures

	Regression coefficient	Standard error	OR†	95% CI	*p*-value
Low BMI (kg/m^2)	1.09	0.35	2.94	1.51-5.75	0.002
Hypoproteinemia	0.75	0.37	2.12	1.02-4.32	0.043
25(OH)D	-0.41	0.015	0.96	0.93-0.99	0.006
ALP	-0.004	0.001	0.99	0.99-1.00	0.007
CRP	-0.003	0.005	0.99	0.98-1.00	0.487

ALP: alkaline phosphatase; CRP: C-reactive protein; CI: confidence interval.
†Adjusted for age.

were also found to be related to sarcopenia. Cauley JA et al reported that an increase in inflammatory markers in 2,985 well-functioning elderly men and women was a risk factor for osteoporotic fracture.[22] Therefore, high levels of inflammatory markers should be considered an important risk factor for sarcopenia in elderly patients with hip fractures.

There were several limitations to this study. First, it was cross-sectional and retrospective in design. Therefore, selection bias is practically inevitable. Second, we could not evaluate the ability of those with hip fractures to walk. Therefore, severe sarcopenia was not defined and we could not observe the relationship between severe sarcopenia and malnutrition. Finally, the ability to compare our results with those of other studies is quite limited owing to different definitions of sarcopenia. However, the AWGS recently suggested guidelines for Asian populations. Thus, it is possible to compare our results with those of other studies done on Asians. However, there is no standard body composition in Korean patients.

In conclusion, the present study showed a strong relationship between sarcopenia, malnutrition, and chronic inflammatory factors in elderly patients with hip fractures. Further study on the risk factors for sarcopenia is needed to improve outcomes after treatment in patients with hip fractures.

AUTHOR DISCLOSURES

The authors declare that they have no competing interests. This study was funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC15C1189). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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