



저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

Low bone mineral density and low serum  
vitamin D levels are associated with low  
skeletal muscle mass in early stage  
chronic kidney disease



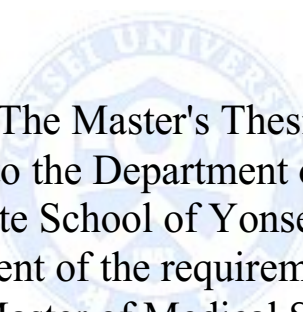
Jo Eun Kim

Department of Medicine

The Graduate School, Yonsei University

Low bone mineral density and low serum  
vitamin D levels are associated with low  
skeletal muscle mass in early stage  
chronic kidney disease

Directed by Professor Sung-Kil Lim



The Master's Thesis  
submitted to the Department of Medicine,  
the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree  
of Master of Medical Science

Jo Eun Kim

June 2015

This certifies that the Master's Thesis of  
Jo Eun Kim is approved.

Sung-Kil Lim

-----  
Thesis Supervisor : Sung-Kil Lim

Seong Hwan Moon

-----  
Thesis Committee Member#1 : Seong Hwan Moon

Tae Hyun Yoo

-----  
Thesis Committee Member#2 : Tae Hyun Yoo

The Graduate School  
Yonsei University

June 2015

## ACKNOWLEDGEMENTS

First of all, I would like to express the deepest appreciation to my committee chair Professor Sung-Kil Lim, who continually and convincingly conveyed his expertise, sincere and valuable guidance, and an excitement in regard to research and scholarship. Without his guidance and persistent help this thesis would not have been possible.

I would also like to thank my committee members, Professor Seong Hwan Moon and Professor Tae Hyun Yoo who provided expertise and comprehensive insight that greatly assisted the research and greatly improved the manuscript.

Furthermore, I am grateful to our colleagues from Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine for their assistance and support. Finally, I also thank my family for their unceasing encouragement and support.

<TABLE OF CONTENTS>

ABSTRACT .....	1
I. INTRODUCTION .....	2
II. MATERIALS AND METHODS .....	3
1. Study participants .....	3
2. Measurements of appendicular skeletal muscle mass and BMD ..	4
3. Measurement of biochemistry and hormones .....	4
4. Assessment of lifestyle and health-related behavior .....	5
5. Statistical analysis .....	5
III. RESULTS .....	5
1. Clinical characteristics of participants .....	5
2. BMD and geometry of femoral neck in patients with CKD .....	8
3. Clinical factors associated with low skeletal muscle mass .....	9
4. Effect of bone loss at total hip and vitamin D deficiency on skeletal muscle mass .....	11
IV. DISCUSSION .....	11
V. CONCLUSION .....	14
REFERENCES .....	16
ABSTRACT(IN KOREAN) .....	20
PUBLICATION LIST .....	21

## LIST OF FIGURES

Figure 1. Change of serum parathyroid hormone (PTH), vitamin D and HOMA-IR between control group and chronic kidney disease (CKD) group .....	8
---	---

## LIST OF TABLES

Table 1. Clinical characteristics of participants .....	6
Table 2. BMD and bone geometry in patients with CKD .....	9
Table 3. Association between appendicular skeletal mass/height <sup>2</sup> and clinical parameters .....	10
Table 4. Odds ratio for sarcopenia in patients with CKD .....	11

## ABSTRACT

Low bone mineral density and low serum vitamin D are associated with low skeletal muscle mass in early stage chronic kidney disease

Jo Eun Kim

*Department of Medicine  
The Graduate School, Yonsei University*

(Directed by Professor Sung-Kil Lim)

We previously identified that chronic kidney disease (CKD) stage 3 was strongly associated with sarcopenia. However, few studies have investigated sarcopenia in early-stage CKD. This study was designed to determine the prevalence of sarcopenia and analyze the factors associated with low skeletal muscle mass by focusing on bone mineral density (BMD) in early-stage CKD population. This cross-sectional study included the participants aged  $\geq 55$  years from the Korea National Health and Nutrition Examination Survey 2008–2010. As results, the prevalence of sarcopenia was 30.0% in control group and 38.4% in CKD in men. In control group, total hip BMD, serum vitamin D, insulin resistance, and total energy intake were associated with skeletal muscle mass in men, while total hip BMD, vitamin D, and total energy intake were associated with skeletal muscle mass in women. Meanwhile, in CKD group, only total hip BMD was associated with muscle mass in men, while total hip BMD and vitamin D level were associated with muscle mass in women. In conclusion, low hip BMD and low serum vitamin D levels are closely associated with low skeletal muscle mass in patients with early-stage CKD.

-----  
Key words: chronic kidney disease, sarcopenia, bone mineral density, vitamin D, muscle mass



# Low bone mineral density and low serum vitamin D are associated with low skeletal muscle mass in early stage chronic kidney disease

Jo Eun Kim

*Department of Medicine  
The Graduate School, Yonsei University*

(Directed by Professor Sung-Kil Lim)

## I. INTRODUCTION

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength that occurs with advancing age. It accompanies adverse outcomes such as the loss of independence, falls and fractures, poor quality of life, and eventually death.<sup>1-3</sup> The prevalence of sarcopenia is 6–26% according to age, sex, and skeletal muscle mass, but it generally increases with age, showing a >50% prevalence after age 80 years.<sup>4,5</sup> Sarcopenia has been explained as a multifactorial condition. Age-related factors such as decreased sex hormones, apoptosis, and mitochondrial dysfunction; endocrinopathies such as corticosteroid excess, abnormal thyroid function, and insulin resistance; neurodegenerative disease; physical inactivity; poor nutritional intake; and chronic disease and inflammatory status are associated with skeletal muscle loss.<sup>1,6-9</sup> In our previous study using data from the Korea National Health and Nutrition Examination Survey (KNHANES IV), we found that osteoporosis, insulin resistance, and chronic kidney disease (CKD) stage 3 were the most influential risk factors for sarcopenia in an elderly Korean population.<sup>10</sup> Among these factors, we especially noted that only a moderate decrease in estimated glomerular filtration rate (eGFR) has a substantial role in reducing skeletal muscle mass. After the adjustment for multiple confounding factors, participants with CKD stage 3 had an odds ratio (OR) of 3.13 (95% confidence interval [CI], 1.14–8.61) for sarcopenia compared to those with a

normal eGFR.

Sarcopenia is frequently observed in patients with CKD who are on dialysis, and it increases cardiovascular complications as well as CKD-related morbidity and mortality.<sup>11-14</sup> Muscle wasting in uremic patients is well described as “uremic sarcopenia,” emphasizing that uremia and sarcopenia are progressive diseases.<sup>15</sup> However, the majority of studies are limited to patients with end-stage renal disease; to date, sarcopenia in earlier stages of CKD has been insufficiently characterized and data are lacking. The number of patients with early-stage CKD is not small. In the United States, between 1999 and 2004, an estimated 6,500,000 (3.2%) people had CKD stage 2 and 15,500,000 (7.7%) had CKD stage 3.<sup>16</sup>

Therefore, the aims of this study were to determine the prevalence of sarcopenia and analyze the factors associated with low skeletal muscle mass focusing on bone mineral density (BMD) in a population of patients with mild to moderate CKD from the KNHANES 2008–2010. We also describe the sarcopenia-related clinical characteristics of early-stage CKD population.

## II. MATERIALS AND METHODS

### 1. Study participants

The KNHANES is a nationwide, population-based, and cross-sectional health examination and survey that is regularly conducted by the Korea Centers for Disease Control and Prevention using a multistage clustered and stratified random sampling method to monitor the general health and nutrition status of South Koreans.

A total of 29,235 individuals participated in the KNHANES between 2008 and 2010, and this study ultimately included 4,108 participants (1,844 men and 2,264 women) aged  $\geq 55$  years. Participants with missing data for muscle mass, BMD, or serum levels of creatinine and 25(OH)D were excluded. Due to the study aim, participants with an eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup> or eGFR  $< 30$  mL/min/1.73 m<sup>2</sup> or who were on dialysis were also excluded.

## 2. Measurements of appendicular skeletal muscle mass and BMD

Appendicular skeletal muscle mass (ASM) was measured by dual-energy X-ray absorptiometry (DXA; QDR 4500A; Hologic Inc.). ASM was calculated as the sum of the lean soft tissue masses of the arms and legs. Sarcopenia was defined as an ASM divided by height squared of <1 standard deviation (SD) below the sex-specific mean for a young reference group aged 20–39 years. The cutoff value for sarcopenia was 7.00 kg/m<sup>2</sup> for men and 4.96 kg/m<sup>2</sup> for women.

BMD at the femoral neck, total hip, and lumbar spine (L1–L4) was also examined using DXA (QDR 4500A; Hologic Inc.). The geometric structures of the femoral neck were further analyzed using the hip structure analysis program included with the APEX software (Hologic Inc.) as previously described.<sup>17,18</sup>

## 3. Measurement of biochemistry and hormones

Blood samples were obtained after 8 h of fasting by each subject, then immediately refrigerated and transported to the central testing institute (NeoDin Medical Institute). All blood samples were analyzed within 24 hours after transportation. Glycated hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography using an HLC-723G7 apparatus (Tosoh). Total cholesterol and fasting glucose were measured by an enzyme method, while serum creatinine and blood urea nitrogen were measured by colorimetric assay using an Automatic Analyzer 7600 (Hitachi). Serum 25(OH)D concentration was determined by radioimmunoassay (DiaSorin) using a  $\gamma$ -counter (1470 Wizard; PerkinElmer). The parathyroid hormone (PTH) assay was performed by chemiluminescence immunoassay (DiaSorin).

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mg/dL)×fasting insulin (mIU/mL)/405. The eGFR was calculated using the equation from the Modification of Diet in Renal Disease Study (186×serum creatinine<sup>-1.154</sup>×age<sup>-0.203</sup> [×0.742 for women]). Control group was defined as

participants with an eGFR of 60–90 mL/min/1.73 m<sup>2</sup> and CKD group was defined as participants with an eGFR of 30–60 mL/min/1.73 m<sup>2</sup>.

#### 4. Assessment of lifestyle and health-related behavior

Smoking history was classified into categories of never smoker, ex-smoker, and current smoker by self-reporting. Limitation in daily activity was defined as a disability in day-to-day activities such as clothing oneself or bathing alone. Regular exercise was defined as vigorous physical activity (e.g., running, mountaineering, fast bicycling, fast swimming, soccer, basketball, and singles tennis) for at least 20 min for 3 days per week or moderate physical activity (e.g., slow swimming, volleyball, doubles tennis, badminton, and walking) for at least 30 min for 5 days per week. Nutrition intake status was evaluated using a 24-hour recall method. History of estrogen replacement therapy was collected for women.

#### 5. Statistical analysis

Clinical characteristics, bone density, and bone geometry according to CKD stage were analyzed using independent-sample Student's t tests for continuous variables and  $\chi^2$  tests for categorical variables. Data are presented as means±SD or percent of the people in Tables 1 and 2. The associations between relative ASM (ASM/height squared) and other clinical parameters in Table 3 were analyzed using a multiple linear regression model, and OR for sarcopenia in Table 4 were analyzed using a multiple logistic regression model. All data were analyzed using SPSS version 20.0 for Windows (IBM Corp.)

### III. RESULTS

#### 1. Clinical characteristics of participants

The clinical characteristics of the study sample are presented in Table 1. The mean age was higher in participants with CKD than control group. Body mass index, waist circumference, total fat mass, and total fat percent was increased

in men with CKD compared to control group. Relative ASM was reduced in patients with CKD compared to control group in both sexes, but statistical significance was seen in men only. The prevalence of sarcopenia was significantly higher in CKD group (38.4%) than in control group (30.0%) in men, although there was no difference between control group (5.2%) and CKD (4.7%) in women. Hypertension and diabetes mellitus were more prevalent in CKD than control group for both sexes. HOMA-IR was also increased in participants with CKD than control group. Serum vitamin D level did not differ between the two groups in both sexes. The mean PTH level was increased to 65.1 pg/mL in control group and 77.6 pg/mL in CKD for men and 68.7 pg/mL in control group and 83.5 pg/mL in CKD for women (Figure 1). Daily energy and protein intake were lower in CKD than in control, but there was no difference in daily calcium intake by CKD status. Fewer women with CKD than control group were engaging in regular exercise.

**Table 1.** Clinical characteristics of participants

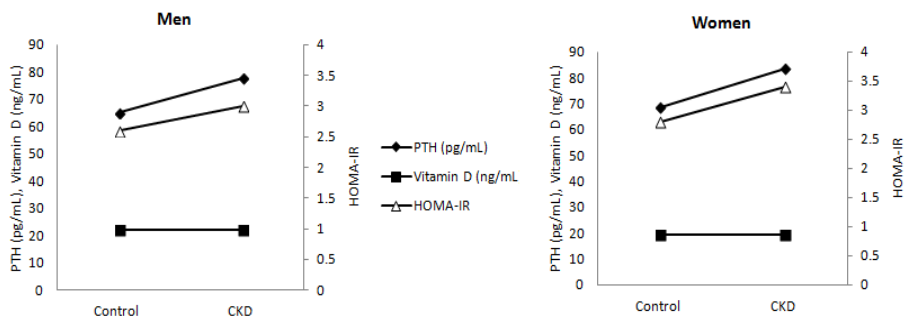
Variables	Men			Women		
	Control (n=1632)	CKD (n=203)	P-value	Control (n=2045)	CKD (n=211)	P-value
Age (years)	65.8±7.3	70.4±7.8	<0.001	66.4±7.4	72.5±8.3	<0.001
BMI (kg/m <sup>2</sup> )	23.7±2.9	24.3±2.9	0.004	24.4±3.2	24.5±3.4	0.634
Waist circ. (cm)	85.5±8.8	88.3±8.8	<0.001	83.1±9.1	84.1±9.9	0.123
Total fat mass (kg)	15.0±4.8	16.7±4.5	<0.001	19.7±5.2	19.5±5.6	0.584
Total fat (%)	22.6±5.1	25.0±4.9	<0.001	34.5±5.3	34.8±5.7	0.365
ASM (kg)	20.5±2.9	19.9±2.9	0.002	14.0±2.0	13.5±2.0	<0.001
ASM/Height <sup>2</sup> (kg/m <sup>2</sup> )	7.4±0.8	7.3±0.9	0.014	6.0±0.7	5.9±0.7	0.355
Sarcopenia	30.0%	38.4%	0.015	5.2%	4.7%	0.759
HTN (%)	39.1%	64.2%	<0.001	43.7%	71.9%	<0.001
DM (%)	13.7%	28.9%	<0.001	13.8%	27.6%	<0.001
HbA1c	7.2±1.3	7.4±1.5	0.203	7.2±1.3	7.1±1.2	0.511

Variables	Men			Women		
	Control (n=1632)	CKD (n=203)	P-value	Control (n=2045)	CKD (n=211)	P-value
Glucose (mg/dL)	104.9±27.0	110.9±30.6	0.008	102.6±24.5	105.4±30.3	0.194
Insulin (mg/dL)	9.7±5.4	10.7±5.7	0.016	10.7±7.2	12.7±9.7	0.004
HOMA-IR	2.6±1.8	3.0±2.0	0.005	2.8±3.1	3.4±3.1	0.008
Total cholesterol (mg/dL)	185.7±35.9	178.9±37.0	0.011	201.5±35.6	197.1±43.8	0.158
BUN (mg/dL)	16.5±4.3	21.2±6.2	<0.001	15.8±4.1	20.8±6.5	<0.001
Creatinine (mg/dL)	1.0±0.1	1.4±0.2	<0.001	0.8±0.1	1.1±0.2	<0.001
eGFR (MDRD)	76.9±7.7	51.9±6.6	<0.001	77.5±7.9	50.6±7.0	<0.001
25(OH) D (ng/mL)	21.9±7.5	21.9±8.9	0.958	19.2±7.4	19.2±7.2	0.963
PTH (pg/mL)	65.1±24.6	77.6±42.1	<0.001	68.7±30.3	83.5±45.1	<0.001
Current smoker	29.1%	20.4%	0.010	4.1%	7.6%	0.020
Daily energy intake (kcal)	2059±716	17767±605	<0.001	1519±591	1331±541	<0.001
Daily protein intake (g)	71.3±33.9	61.8±31.5	<0.001	50.0±25.5	42.7±23.6	<0.001
Daily calcium intake (mg)	533.6±357.7	507.3±485.3	0.372	402.4±297.9	425.3±982.6	0.744
Limitation in daily activities	20.6%	31.8%	<0.001	33.3%	40.2%	0.044
Regular exercise (yes)	61.4%	61.2%	0.954	51.8%	37.6%	<0.001

<sup>1</sup>Data are presented as means±SD or percent.

<sup>2</sup>Control group was defined as an eGFR of 60–90 mL/min/1.73 m<sup>2</sup> and CKD was defined as an eGFR of 30–60 mL/min/1.73 m<sup>2</sup>.

CKD, chronic kidney disease; BMI, body mass index; ASM, appendicular skeletal muscle mass; HTN, hypertension; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease study; PTH, parathyroid hormone



**Figure 1.** Change of serum parathyroid hormone (PTH), vitamin D and HOMA-IR between control group and chronic kidney disease (CKD) group. PTH and HOMA-IR were significantly increased in CKD compared to control group.

## 2. BMD and geometry of femoral neck in patients with CKD

Differences also existed in BMD and geometry of the femoral neck between control group and patients with CKD (Table 2). In men, total hip BMD tended to be lower in CKD than in control, while femoral neck BMD was significantly reduced in CKD group. Although femoral neck geometry did not differ by CKD status, lumbar spine BMD was increased in men with CKD compared to control. In women, total hip and femoral neck BMD were significantly decreased in CKD compared to control group, and bone geometry was deteriorated in those with CKD; femoral neck cross-sectional area and cortical thickness were more reduced in CKD than in control group.

**Table 2.** BMD and bone geometry in patients with CKD

Variables	Men			Women		
	Control (n=1632)	CKD (n=203)	P-value	Control (n=2045)	CKD (n=211)	P-value
<b>BMD</b>						
Total hip						
BMD (g/cm <sup>2</sup> )	0.918±0.128	0.910±0.125	0.393	0.759±0.113	0.711±0.119	<0.001
T-score	-0.2±0.9	-0.2±0.9	0.393	-0.8±1.0	-1.2±1.0	<0.001
Femoral neck						
BMD (g/cm <sup>2</sup> )	0.738±0.118	0.716±0.113	0.016	0.605±0.101	0.558±0.102	<0.001
T-score	-0.9±1.0	-1.0±0.9	0.016	-1.8±0.9	-2.3±1.0	<0.001
Lumbar spine						
BMD (g/cm <sup>2</sup> )	0.941±0.156	0.990±0.175	<0.001	0.785±0.134	0.772±0.125	0.199
T-score	-0.7±1.3	-0.3±1.5	<0.001	-1.9±1.2	-2.0±1.1	0.199
<b>Geometry</b>						
Cross-sectional area (cm <sup>2</sup> )	3.00±0.45	2.98±0.52	0.783	2.28±0.36	2.15±0.39	0.018
Width (cm)	3.65±0.22	3.67±0.20	0.548	3.24±0.22	3.24±0.26	0.971
Cortical thickness (cm)	0.17±0.03	0.16±0.03	0.609	0.14±0.02	0.13±0.03	0.033

<sup>1</sup>Data are presented as means±SD.

<sup>2</sup>Control group was defined as an estimated glomerular filtration rate of 60–90 mL/min/1.73 m<sup>2</sup> and CKD was defined as an estimated glomerular filtration rate of 30–60 mL/min/1.73 m<sup>2</sup>.

BMD, bone mineral density; CKD, chronic kidney disease

### 3. Clinical factors associated with low skeletal muscle mass

Next, the association between skeletal muscle mass and clinical parameters including BMD, insulin resistance, and nutritional intake were evaluated using a multiple linear regression model (Table 3). After the adjustment for multiple confounding factors, total hip BMD ( $\beta=0.258$ ,  $p<0.001$ ), serum 25(OH)D level ( $\beta=0.152$ ,  $p<0.001$ ), HOMA-IR ( $\beta=-0.061$ ,  $p=0.002$ ), and daily total



energy intake ( $\beta=0.098$ ,  $p=0.001$ ) were positively associated with skeletal muscle mass in men in control group, while total hip BMD ( $\beta=0.288$ ,  $p<0.001$ ), 25(OH)D ( $\beta=0.079$ ,  $p<0.001$ ), and daily total energy intake ( $\beta=0.130$ ,  $p<0.001$ ) were positively associated in women in control group. Daily protein intake was negatively associated with skeletal muscle mass in women in control group. In contrast, only total hip BMD ( $\beta=0.284$ ,  $p=0.025$ ) was associated with skeletal muscle mass in men with CKD, while total hip BMD ( $\beta=0.432$ ,  $p<0.001$ ) and 25(OH)D ( $\beta=0.155$ ,  $p=0.008$ ) were associated in women with CKD.

**Table 3.** Association between appendicular skeletal mass/height<sup>2</sup> and clinical parameters

Variables	Control				CKD			
	Men		Women		Men		Women	
	$\beta$	<i>P</i> value	$\beta$	<i>P</i> value	$\beta$	<i>P</i> value	$\beta$	<i>P</i> value
Total hip BMD (g/cm <sup>2</sup> )	0.258	<0.001	0.288	<0.001	0.284	0.025	0.432	<0.001
25(OH)D (ng/mL)	0.152	<0.001	0.079	<0.001	0.003	0.962	0.155	0.008
Total energy intake (kcal)	0.098	0.001	0.130	<0.001	0.103	0.235	0.185	0.068
HOMA-IR	-0.061	0.002	-0.008	0.673	-0.037	0.502	0.045	0.432
Protein intake (g)	-0.026	0.380	-0.099	0.002	-0.086	0.321	-0.198	0.051

<sup>1</sup>Control group was defined as an estimated glomerular filtration rate of 60–90 mL/min/1.73 m<sup>2</sup> and CKD was defined as an estimated glomerular filtration rate of 30–60 mL/min/1.73 m<sup>2</sup>.

<sup>2</sup>Age, weight, femur neck BMD, lumbar spine BMD, parathyroid hormone, regular exercise were adjusted.

BMD, bone mineral density; CKD, chronic kidney disease

#### 4. Effect of bone loss at total hip and vitamin D deficiency on skeletal muscle mass

In a multiple logistic regression model of patients with CKD, after the adjustment for age, weight, femur neck BMD, lumbar spine BMD, PTH, regular exercise, daily total energy intake, HOMA-IR, history of hormone replacement therapy for women, the OR for sarcopenia increased to 8.94 (95% CI, 1.15–69.34) in men and 8.02 (95% CI, 1.11–57.8) in women with each 1 SD decrease in total hip BMD. However, vitamin D deficiency was not associated with the development of sarcopenia after the adjustment for multiple confounding factors (Table 4).

**Table 4.** Odds ratio for sarcopenia in patients with CKD

Variables (unit)	Men	Women
	OR (95% CI)	OR (95% CI)
Total hip BMD		
Decrease of 1SD	8.94 (1.15-69.34)	8.02 (1.11-57.8)
25(OH) D		
<20 ng/mL	1.15 (0.44-2.92)	1.495 (0.26-8.52)

<sup>1</sup>Values are after adjustment for age, weight, femur neck BMD, lumbar spine BMD, parathyroid hormone, regular exercise, total energy intake, homeostasis model assessment of insulin resistance, history of hormone replacement therapy if female. OR, odds ratio; CKD, chronic kidney disease; CI, confidence interval; BMD, bone mineral density; SD, standard deviation

#### IV. DISCUSSION

In the present study, we identified that the sarcopenia-related factors in patients with mild to moderate CKD using population-based data from KNHNES. Total hip BMD, serum 25(OH)D, daily energy intake, and insulin resistance were closely associated with skeletal muscle mass in control group. When the kidney function was aggravated, the association between total hip BMD and skeletal

muscle mass strengthened; meanwhile, the association with other factors was diminished. Sarcopenia was more prevalent in men than in women.

CKD and sarcopenia are both progressive diseases with aging-related increases in prevalence.<sup>5,16,19</sup> Sarcopenia has been associated with multiple conditions such as physical inactivity, poor nutritional intake, decline of anabolic hormone levels, chronic inflammation, and in addition, early CKD was revealed to associated with low skeletal muscle mass in our previous study.<sup>6-10</sup>

Several studies reported that mild renal insufficiency is associated with increased cardiovascular disease and mortality,<sup>20-22</sup> and sarcopenia itself represents an increased risk of fall and fractures, disabilities, morbidity, and death.<sup>1,3,23</sup> However, few studies have investigated sarcopenia in patients with early-stage CKD. Foley et al. reported that the prevalence of class I sarcopenia was 33.6% for CKD-2 and 50.7% for CKD-3 and beyond (eGFR <60 mL/min/1.73 m<sup>2</sup>), and multivariate associations including: older age; low income-to-poverty ratio; overweight; lack of exercise; low carbohydrate, fat, and protein intake; hypercalcemia, low 25-hydroxy-vitamin D; higher diastolic blood pressure; and insulin resistance.<sup>24</sup> Although the definition of sarcopenia differed, the authors found an association between increasing sarcopenia prevalence and declining GFR consistent with the finding of our study.

The prevalence of sarcopenia was much higher in men than women in early CKD participants. This tendency was also observed in a general population of elderly Korean and elderly Italian subjects.<sup>25,26</sup> However, no gender-specific prevalence of sarcopenia was found in an Austrian or New Mexican population.<sup>4,27</sup> This finding implicates gender and ethnicity differences in the development of sarcopenia. Gender specificity might be explained by differences in the effect of sex hormones on the bone-muscle relationship. The close relationship between muscle and bone mass appears to be weaker in women than in men. The reports studying bone and muscle relationship in elderly demonstrated that skeletal muscle mass was positively associated with BMD in men and fat mass in women.<sup>26-29</sup> The conversion of androgens to estrogens in the adipose tissue of postmenopausal women may have a positive effect on bone tissue and skeletal

muscle. Regarding ethnic differences, in Korea, peak muscle mass was obtained at 20–39 years of age in men, but peak muscle mass was reached at 40–59 years of age in women.<sup>25</sup> Since sarcopenia is defined compared to a young reference group aged 20–39 years, the prevalence of sarcopenia is naturally lower in women. The lack of physical activity and a growing tendency to prefer a thin body among young Korean women are reasons why peak muscle mass is achieved at middle age.

While musculoskeletal health of the CKD population has traditionally focused on bone and mineral disease, it was recently reported that sarcopenia also plays a critical role in poor outcomes in CKD. Similar to sarcopenia in the general population, multiple factors and different mechanisms seem to contribute to the muscle loss seen in patients with CKD. Increases in angiotensin II, metabolic acidosis, and inflammation as well as testosterone deficiency in CKD are expected to impair insulin/IGF-1 intracellular signaling and stimulate muscle protein degradation by the adenosine triphosphate–dependent ubiquitin-proteasome system, which is known to be the most important pathway for muscle breakdown.<sup>13,30</sup> Moreover, tissue necrosis factor- $\alpha$ , myostatin, glucocorticoid, nuclear factor of kappaB, and reactive oxygen species are involved in protein degradation, while immunologic and myocellular changes and impaired function of satellite cells are involved in the inhibited protein synthesis in patients with CKD.<sup>15</sup>

Interestingly, in our study, when the kidney function was aggravated to CKD stage 3, only total hip BMD was significantly associated with skeletal muscle mass. The correlations between bone and muscle and their pleiotropic factors are relatively well recognized. Muscle cells and osteoblasts are derived from a common mesenchymal precursor, and both components are regulated and controlled by common genes and mechanisms. The candidate genes and pathways for pleiotropic action on bone and muscle involve androgen receptor, estrogen receptor 1, insulin-like growth factor (IGF)-1, myostatin, vitamin D receptor, interleukin-6, bone morphogenetic protein-2, peroxisome proliferator-activated receptor- $\gamma$ , glucocorticoid receptor, and pleiotropin.<sup>31</sup>

Furthermore, sarcopenia and osteoporosis share common risk factors such as physical inactivity, cognitive decline, sedentary lifestyle, oxidative stress, chronic inflammatory conditions, and hormonal deficiencies.<sup>32,33</sup> Although bones and muscles have their own correlations, CKD seems to provide a susceptible environment for both bone and muscle. Increased pro-inflammatory cytokines, decreased exercise, inactivity, decreased sex hormones, growth hormone resistance, insulin resistance, and vitamin D deficiency aggravate the loss of bone and muscle mass.

Unexpectedly, of the three sites of BMD, only total hip BMD was associated with muscle mass. In men, lumbar spine BMD was increased in CKD compared to control group. Because of the way DXA works, subjects with osteophytes and vascular calcifications had greater spinal bone density.<sup>34,35</sup> In recent studies, early CKD stimulated early vascular calcification, vascular osteoblastic transition, and circulating levels of fibroblast growth factor-23.<sup>36,37</sup> This suggests that lumbar spine BMD by DXA could be overestimated due to extravertebral calcification and that its use may be inappropriate for assessing the status of bone loss in patients with early-stage CKD.

This study has some limitations. First, it was cross-sectional, so we could not conclude a causal relationship of bone mass and muscle mass, although a 1 SD reduction of total hip BMD increased the OR for sarcopenia by 8 times in multiple logistic regression model. Second, low muscle function and low physical performance were not used to define sarcopenia, unlike recommendations of the European Working Group on Sarcopenia or the International Working Group on Sarcopenia.<sup>1,38</sup> Third, we could not use data of sex hormones, inflammatory cytokines that can affect both bone and muscle.

## V. CONCLUSION

In conclusion, low total hip BMD and low vitamin D levels are closely associated with low skeletal muscle mass in patients with early-stage CKD, and the association between BMD and muscle mass strengthened as the kidney function aggravated. Chronic inflammation, deficiency of anabolic hormone, impaired

insulin/IGF-1 signaling, myostatin, oxidative stress might simultaneously affect the bone and muscle in CKD patients during aging process, although further studies are needed to identify the causal relationship. Preventing osteoporosis and vitamin D deficiency may slow the progression of sarcopenia in patients with mild to moderate CKD at a stage when musculoskeletal complications may still be reversible.



## REFERENCES

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39:412-23.
2. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;29:154-9.
3. Cawthon PM, Marshall LM, Michael Y, Dam TT, Ensrud KE, Barrett-Connor E, et al. Frailty in older men: prevalence, progression, and relationship with mortality. *J Am Geriatr Soc* 2007;55:1216-23.
4. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755-63.
5. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J Gerontol A Biol Sci Med Sci* 2002;57:M772-7.
6. Roth SM, Metter EJ, Ling S, Ferrucci L. Inflammatory factors in age-related muscle wasting. *Curr Opin Rheumatol* 2006;18:625-30.
7. Jo E, Lee SR, Park BS, Kim JS. Potential mechanisms underlying the role of chronic inflammation in age-related muscle wasting. *Aging Clin Exp Res* 2012;24:412-22.
8. Scott D, Jones G. Impact of nutrition on muscle mass, strength, and performance in older adults. *Osteoporos Int* 2014;25:791-2.
9. Kim SH, Kim TH, Hwang HJ. The relationship of physical activity (PA) and walking with sarcopenia in Korean males aged 60 years and older using the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV-2, 3), 2008-2009. *Arch Gerontol Geriatr* 2013;56:472-7.
10. Kim JE, Lee YH, Huh JH, Kang DR, Rhee Y, Lim SK. Early-stage chronic kidney disease, insulin resistance, and osteoporosis as risk factors of

sarcopenia in aged population: the fourth Korea National Health and Nutrition Examination Survey (KNHANES IV), 2008-2009. *Osteoporos Int* 2014;25:2189-98.

11. Pupim LB, Heimbürger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. *Kidney Int* 2005;68:2368-74.

12. Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. *Clin Nutr* 2014;33:64-8.

13. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010;91:1128s-32s.

14. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Barany P, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 2008;27:557-64.

15. Fahal IH. Uraemic sarcopenia: aetiology and implications. *Nephrol Dial Transplant* 2014;29:1655-65.

16. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *Jama* 2007;298:2038-47.

17. Kim KM, Lim JS, Kim KJ, Choi HS, Rhee Y, Oh HJ, et al. Dissimilarity of femur aging in men and women from a Nationwide Survey in Korea (KNHANES IV). *J Bone Miner Metab* 2013;31:144-52.

18. Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW. Structural trends in the aging femoral neck and proximal shaft: analysis of the Third National Health and Nutrition Examination Survey dual-energy X-ray absorptiometry data. *J Bone Miner Res* 2000;15:2297-304.

19. Chien MY, Huang TY, Wu YT. Prevalence of sarcopenia estimated using a bioelectrical impedance analysis prediction equation in community-dwelling elderly people in Taiwan. *J Am Geriatr Soc* 2008;56:1710-5.

20. Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, et al.



Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney Int* 2002;62:1402-7.

21. Leoncini G, Viazzi F, Parodi D, Ratto E, Vettoretti S, Vaccaro V, et al. Mild renal dysfunction and cardiovascular risk in hypertensive patients. *J Am Soc Nephrol* 2004;15 Suppl 1:S88-90.

22. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285-95.

23. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* (1985) 2003;95:1851-60.

24. Foley RN, Wang C, Ishani A, Collins AJ, Murray AM. Kidney function and sarcopenia in the United States general population: NHANES III. *Am J Nephrol* 2007;27:279-86.

25. Huh JH, Song MK, Park KH, Kim KJ, Kim JE, Rhee YM, et al. Gender-specific pleiotropic bone-muscle relationship in the elderly from a nationwide survey (KNHANES IV). *Osteoporos Int* 2014;25:1053-61.

26. Gonnelli S, Caffarelli C, Cappelli S, Rossi S, Giordano N, Nuti R. Gender-specific associations of appendicular muscle mass with BMD in elderly Italian subjects. *Calcif Tissue Int* 2014;95:340-8.

27. Kirchengast S, Huber J. Sex-specific associations between soft tissue body composition and bone mineral density among older adults. *Ann Hum Biol* 2012;39:206-13.

28. Shin D, Kim S, Kim KH, Park SM. Importance of fat mass and lean mass on bone health in men: the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV). *Osteoporos Int* 2014;25:467-74.

29. Gonnelli S, Caffarelli C, Tanzilli L, Alessi C, Tomai Pitinca MD, Rossi S, et al. The associations of body composition and fat distribution with bone mineral density in elderly Italian men and women. *J Clin Densitom* 2013;16:168-77.

30. Wang XH, Mitch WE. Muscle wasting from kidney failure-a model for catabolic conditions. *Int J Biochem Cell Biol* 2013;45:2230-8.
31. Karasik D, Kiel DP. Evidence for pleiotropic factors in genetics of the musculoskeletal system. *Bone* 2010;46:1226-37.
32. Rolland Y, Abellan van Kan G, Benetos A, Blain H, Bonnefoy M, Chassagne P, et al. Frailty, osteoporosis and hip fracture: causes, consequences and therapeutic perspectives. *J Nutr Health Aging* 2008;12:335-46.
33. Crepaldi G, Maggi S. Sarcopenia and osteoporosis: A hazardous duet. *J Endocrinol Invest* 2005;28:66-8.
34. Orwoll ES, Oviatt SK, Mann T. The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. *J Clin Endocrinol Metab* 1990;70:1202-7.
35. Reid IR, Evans MC, Ames R, Wattie DJ. The influence of osteophytes and aortic calcification on spinal mineral density in postmenopausal women. *J Clin Endocrinol Metab* 1991;72:1372-4.
36. Fang Y, Ginsberg C, Sugatani T, Monier-Faugere MC, Malluche H, Hruska KA. Early chronic kidney disease-mineral bone disorder stimulates vascular calcification. *Kidney Int* 2014;85:142-50.
37. Manghat P, Fraser WD, Wierzbicki AS, Fogelman I, Goldsmith DJ, Hampson G. Fibroblast growth factor-23 is associated with C-reactive protein, serum phosphate and bone mineral density in chronic kidney disease. *Osteoporos Int* 2010;21:1853-61.
38. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, 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;12:249-56.

## ABSTRACT(IN KOREAN)

조기 만성신질환 환자에서 근육량과 골밀도, 비타민 D의 연관성

<지도교수 임승길>

연세대학교 대학원 의학과

김조은

이전 연구에서 3기 만성신질환이 근감소증과 강한 연관성이 있다는 것을 밝혔지만, 아직까지 조기 만성신질환과 근감소증에 대한 연구는 드물다. 그러므로 이번 연구에서는 경·중등도 만성신질환에서 근감소증의 유병률과 근육량과 관련된 인자들을 분석하고자 하였다. 본 연구는 국민건강영양조사 2008년에서 2010년 자료를 이용하여, 55세 이상의 남녀를 대상으로 한 단면적 연구이다. 그 결과, 근감소증의 유병률은, 남성의 경우, 대조군에서 30.0%, 조기 만성신질환에서는 38.4%였고, 여성의 경우, 대조군에서는 5.2%, 조기 만성신질환에서는 4.7% 였다. 대조군의 남성에서는 대퇴부 골밀도, 비타민 D 수치, 인슐린저항성, 총 에너지 섭취량이 근육량과 관련이 있었고, 대조군의 여성에서는 대퇴부 골밀도, 비타민 D 수치, 총 에너지 섭취량이 근육량과 관련이 있었다. 반면, 조기 만성신질환이 있는 남성에서는 오직 대퇴부 골밀도만이 근육량과 관련성을 보였고, 조기 만성신질환이 있는 여성에서는 대퇴부 골밀도, 비타민 D 수치가 근육량과 연관이 있었다. 결론적으로, 조기 만성신질환 환자에서는 낮은 대퇴부 골밀도, 낮은 혈청 비타민 D 수치가 낮은 근육량과 깊은 관련성이 있다는 것을 확인하였다.

---

핵심되는 말: 만성신질환, 근감소증, 골밀도, 비타민 D, 근육량

## PUBLICATION LIST

Kim JE, Lee YH, Huh JH, Kang DR, Rhee Y, Lim SK. Early-stage chronic kidney disease, insulin resistance, and osteoporosis as risk factors of sarcopenia in aged population: the fourth Korea National Health and Nutrition Examination Survey (KNHANES IV), 2008-2009. *Osteoporos Int* 2014;25:2189-98.

Huh JH, Song MK, Park KH, Kim KJ, Kim JE, Rhee YM, et al. Gender-specific pleiotropic bone-muscle relationship in the elderly from a nationwide survey (KNHANES IV). *Osteoporos Int* 2014;25:1053-61.

