Impact of Skeletal Muscle Mass on Long-Term Adverse Cardiovascular Outcomes in Patients With Chronic Kidney Disease

Kazuhiro Harada, MD[a], Susumu Suzuki, MD[a,*], Hideki Ishii, MD, PhD[a], Toshijiro Aoki, MD[a], Kenshi Hirayama, MD[a], Yohei Shibata, MD[a], Yosuke Negishi, MD[a], Takuya Sumi, MD[a], Kazuhiro Kawashima, MD[a], Ayako Kunimura, MD, PhD[a], Yusaku Shimbo, MD, PhD[b], Yosuke Tatami, MD[a], Toshiki Kawamiya, MD[a], Dai Yamamoto, MD[a], Ryota Morimoto, MD[a,c], Yoshinari Yasuda, MD, PhD[c], and Toyoaki Murohara, MD, PhD[a]

Sarcopenia, defined as skeletal muscle loss and dysfunction, is attracting considerable attention as a novel risk factor for cardiovascular events. Although the loss of skeletal muscle is common in chronic kidney disease (CKD) patients, the relation between sarcopenia and cardiovascular events in CKD patients is not well defined. Therefore, we aimed to investigate the relation between skeletal muscle mass and major adverse cardiovascular events (MACE) in CKD patients. We enrolled 266 asymptomatic CKD patients (median estimated glomerular filtration rate: 36.7 ml/min/1.73 m^2). To evaluate skeletal muscle mass, we used the psoas muscle mass index (PMI) calculated from noncontrast computed tomography. The patients were divided into 2 groups according to the cut-off value of PMI for MACE. There were significant differences in age and body mass index between the low and high PMI groups (median age: 73.5 vs 69.0 years, $p = 0.002$; median body mass index: 22.6 vs 24.2 kg/m^2, $p < 0.001$, respectively). During the follow-up period (median: 3.2 years), patients with low PMI had significantly higher risk of MACE than those with high PMI (31.7% and 11.2%, log-rank test, $p < 0.001$). The Cox proportional hazard model showed that low PMI is an independent predictor of MACE in CKD patients (hazard ratio 3.98, 95% confidence interval 1.65 to 9.63, $p = 0.0022$). In conclusion, low skeletal muscle mass is an independent predictor of MACE in CKD patients. The assessment of skeletal muscle mass may be a valuable screening tool for predicting MACE in clinical practice. **(Am J Cardiol 2017;119:1275−1280)**

Sarcopenia, which is defined as skeletal muscle loss and dysfunction, is a serious problem and is associated with increased hospitalization and mortality in various clinical settings, including chronic kidney disease (CKD).[1−3] Moreover, several studies proposed sarcopenia as a new prognostic factor for cardiovascular disease.[4,5] However, skeletal muscle mass is not routinely assessed in clinical practice, and the possible relation between skeletal muscle mass and the incidence of cardiovascular event (CVE) in CKD patients remains to be assessed. The purpose of this study is to evaluate the predictive value of skeletal muscle mass, assessed using noncontrast computed tomography (CT), on future CVE in asymptomatic CKD patients.

Methods

All patients were seen in the outpatient clinic at the Department of Nephrology in Nagoya University Hospital from January 2008 to December 2012. Within the study period, a total of 392 patients had referred to our department. Exclusion criteria were 34 patients were not performed abdominal CT, 7 patients with active malignancy, 5 patients of lack of the value of height that was needed to calculate psoas muscle mass index (PMI), 1 patient with having undergone lumbar spinal fusion with pedicle screws and rods at the umbilical level, and 79 patients were estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2. After exclusion of these patients, a total of 266 patients were evaluated in this study.

Hypertension was defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, and/or use of antihypertensive medicine. Dyslipidemia was defined as triglycerides ≥150 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol ≤40 mg/dl, and/or use of medications to treat hyperlipidemia. Diabetes mellitus (DM) was defined as having a fasting plasma glucose concentration of >126 mg/dl, glycosylated hemoglobin concentration of ≥6.5% (National Glycohemoglobin Standardization Program), and/or the use of any antihyperglycemic medicine. Current smokers were

Departments of [a]Cardiology and [c]CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan; and [b]Department of Cardiology, Kariya Toyota General Hospital, Kariya, Japan. Manuscript received November 12, 2016; revised manuscript received and accepted January 3, 2017.

See page 1279 for disclosure information.

*Corresponding author: Tel: (+81) 52-744-2147; fax: (+81) 52-744-2210.

E-mail address: susumusuzuki@med.nagoya-u.ac.jp (S. Suzuki).

0002-9149/17/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2017.01.003

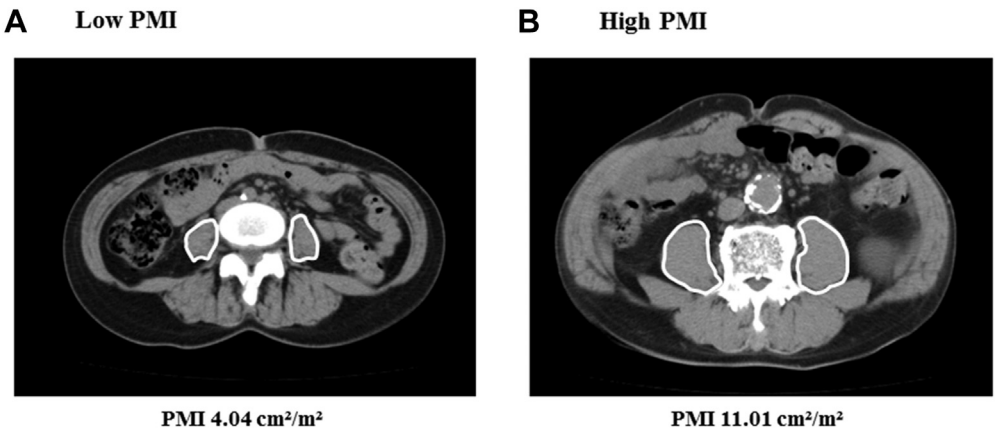


Figure 1. The image of cross-sectional CT and ROI at umbilical level. The *white line* shows bilateral psoas muscle measured by manual tracing. PMI = area of psoas muscle (cm^2)/height^2 (m^2). Representative cross-sectional images of the psoas muscle volume in patients with 4.0% low PMI (*A*) and 11.0% ACI (*B*). ROI = region of interest.

defined as those who declared active smoking. Blood samples were taken from all patients after a 12-hour overnight fast. eGFR was calculated using the equation for Japanese subjects recommended by the Japanese Society of Nephrology: eGFR (ml/min/1.73 m^2) = 194 × SCr − 1.094 × age − 0.287 × 0.793 (if woman).[6] This study was approved by the local ethics committee (Institutional Review Board/Ethics approval number 101, 2013) and conducted in accordance with the ethical principles stated by the Declaration of Helsinki. Written informed consent was obtained from all patients.

Renal morphology and skeletal muscle mass in our study population were assessed and quantified using noncontrast CT scan (Siemens Medical Solutions, Forchheim, Germany). The cross-sectional area of the bilateral psoas muscles as an indicator of skeletal muscle mass was measured using manual tracing at the umbilical level, and PMI was calculated as follows: PMI = cross-sectional area of bilateral psoas muscle/height^2 (cm^2/m^2).[7,8] Representative CT images of low and high PMI are listed in Figure 1. The measurement of PMI was independently conducted by 2 physicians who were blinded to the patient's clinical characteristics. The inter- and intrarater reliability, calculated using the intraclass correlation coefficient, was 0.97 (95% confidence interval [CI] 0.95 to 0.97, p <0.001) and 0.97 (95% CI 0.96 to 0.99, p <0.001), respectively. The cut-off value of PMI was selected on the basis of best accuracy in relation to major adverse cardiovascular events (MACE), which is defined as a composite of all-cause death, myocardial infarction, coronary revascularization, heart failure, and cerebral infarction. As the range of PMI was quite different according to gender, we established different cut-off values using receiver operating characteristic curves for MACE in men and women. The cut-off values of PMI were 7.17 (area under the receiver operating characteristic curve [AUC] = 0.57) and 5.13 cm^2/m^2 (AUC = 0.61) for men and women, respectively. On the basis of the previously mentioned cut-off values, we divided the patients into 2 groups: low PMI (n = 110) and high PMI (n = 156).

All statistical analyses were performed using SPSS software version 23 for Windows (SPSS, Inc., Chicago, IL) and R software version 3.3.1 (The R project for Statistical Computing). Data for continuous values are expressed as mean ± SD for normally distributed variables or as median (interquartile range) for asymmetrically distributed data. Categorical variables are shown as numbers (percentages). Statistical differences were assessed using the Student's *t* test (for normally distributed continuous variables) or the Mann−Whitney *U* test (for asymmetrically distributed variables). Differences in categorical variables were assessed using the chi-square test. The Kaplan−Meier analysis was used to estimate event-free survival, with comparisons performed using the log-rank test. In cases when multiple CVEs were reported for individual patients, only the day of the first occurrence was included in the Kaplan−Meier analyses. The Cox proportional hazards model was used to assess the associations. In addition, the C-index and the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indexes were calculated to assess the incremental prognostic value for MACE after adding PMI into the baseline model, along with traditional cardiovascular risk factors, including age, gender, hypertension, DM, dyslipidemia, and smoking status. The C-index was defined as AUC between individual predictive probabilities for MACE and was compared with the baseline model and the established risk factors plus the presence of low PMI, categorized using the corresponding PMI cut-off value.[9] The NRI index indicates the relative proportion of patients with improved predicted probabilities for MACE, whereas the IDI index indicates the average improvement in predicted probabilities for MACE after adding variables into the baseline model.[10] A p value <0.05 was considered statistically significant.

Results

A total of 266 patients were enrolled in the preset study. The median and interquartile ranges of age and eGFR levels were 71 (62 to 78) years and 36.7 (26.7 to 48.1) ml/min/1.73 m^2, respectively. The median and interquartile ranges of PMI were 7.55 (6.65 to 8.96) in men and 5.69 (4.57 to 6.64) cm^2/m^2 in women. Patients were divided into 2 groups

Table 1
Baseline characteristics of the study patients

Variable	ALL (n = 266)	Psoas Muscle Mass Index		P value
		Low (n = 110)	High (n = 156)	
Age (years)	71 (62-78)	73.5 (65-80)	69 (61-76)	0.0019
Men	197 (74%)	82 (75%)	115 (74%)	0.89
Body mass index (kg/m^2)	23.6 (21.5-25.4)	22.6 (20.2-24.7)	24.2 (22.4-25.9)	<0.001
Hypertension	229 (86%)	97 (88%)	132 (85%)	0.47
Diabetes mellitus	98 (37%)	44 (40%)	54 (35%)	0.44
Dyslipidemia	211 (79%)	82 (75%)	129 (83%)	0.11
Current smoker	23 (9%)	9 (8%)	14 (9%)	0.82
Previous coronary artery disease	24 (9%)	11 (10%)	13 (8%)	0.64
Previous stroke	28 (11%)	13 (12%)	15 (10%)	0.56
Serum creatinine (mg/dL)	1.44 (1.16-1.90)	1.41 (1.17-1.85)	1.47 (1.17-1.85)	0.80
eGFR (mL/min/1.73 m^2)	36.7 (26.7-48.1)	36.4 (26.4-46.9)	36.7 (27.0-48.2)	0.75
LDL cholesterol (mg/dL)	102 (85-122)	100 (81-118)	105 (87-126)	0.21
Triglycerides (mg/dL)	134 (99-185)	126 (92-170)	138.5 (101-196)	0.068
Hemoglobin A1c (%)	5.7 (5.4-6.3)	5.7 (5.4-6.3)	5.7 (5.4-6.3)	0.77
Serum albumin (mg/dL)	3.8 (3.5-4.1)	3.8 (3.5-4.0)	3.8 (3.6-4.1)	0.099
Hemoglobin (g/dL)	12.3 ± 1.9	11.9 ± 1.8	12.6 ± 2.0	0.0068
C-reactive protein (mg/dL)	0.054 (0.028-0.13)	0.048 (0.027-0.11)	0.060 (0.029-0.13)	0.39
Proteinuria	117 (44%)	43 (39%)	74 (47%)	0.18
Antiplatelet agents	93 (35%)	43 (39%)	50 (32%)	0.24
ACE-I or ARB	180 (68%)	72 (66%)	108 (69%)	0.52
Beta-blocker	39 (15%)	22 (20%)	17 (11%)	0.039
Calcium channel blocker	145 (55%)	65 (59%)	80 (51%)	0.21
Statin	108 (41%)	46 (42%)	62 (40%)	0.73

Data are indicated as median (interquartile range), or means ± SD, or number (percentages).
ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein.

according to the cut-off value of PMI. Baseline clinical characteristics are summarized in Table 1. There were significant differences in age, body mass index, hemoglobin levels, and β-blocker use between the 2 groups. During the median follow-up of 3.2 years, a total of 39 MACE occurred. The event-free survival curve for MACE is listed in Figure 2. The Kaplan−Meier analysis showed that patients with low PMI had significantly higher risk of MACE than those with high PMI (31.7% and 11.2%, log-rank test, p <0.001). Data for all clinical events are listed in Table 2. The incidence of all-cause death and coronary revascularization in patients with low PMI was significantly higher than in those with high PMI (13.3% and 3.3%, log-rank test, p = 0.035; 12.0% and 3.9%, p = 0.022, respectively). The incidence of myocardial infarction and heart failure in the low PMI group tended to be higher than that in the high PMI group but did not reach statistical significance. As a result, the rate of the composite of adverse cardiovascular outcomes in the low PMI group was numerically higher than that in the high PMI group. Cox proportional hazards models revealed that the presence of low PMI was independently associated with MACE (hazard ratio 3.98, 95% CI 1.65 to 9.63, p = 0.0022) (Table 3). In addition, current smoking and C-reactive protein levels were independently associated with MACE. When the presence of low PMI was added to the model along with the other risk factors for MACE, the C-index increased (0.71 vs 0.76) but did not reach statistical significance (p = 0.11). However, NRI and IDI for MACE significantly increased (0.53, p = 0.0014; 0.036, p = 0.015, respectively) (Table 4).

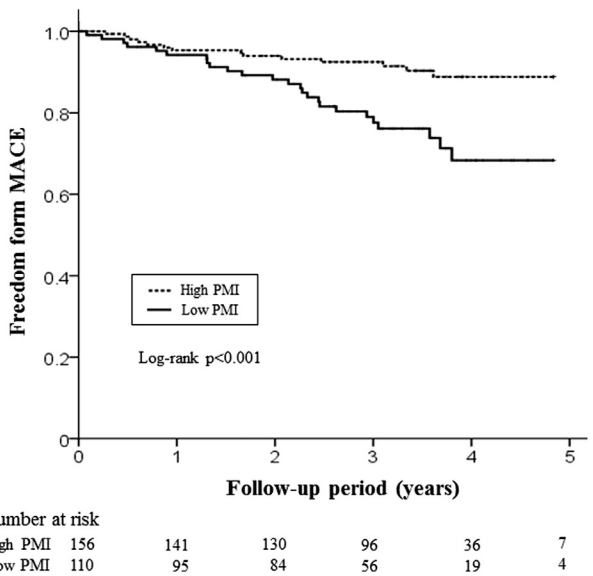


Figure 2. Event-free survival curve for major adverse cardiac events between low and high PMI.

We also estimated the combined effects of the PMI values (divided by optimal cut-off values) and eGFR grades (CKD stage G3 or G4, G5) for predicting MACE. After adjusting for conventional cardiovascular risk factors, hazard ratios (95% CI) for MACE were 2.90 (1.04 to 8.12, p = 0.043), 1.59 (0.49 to 5.12, p = 0.44), and 6.02 (2.00 to

Table 2
Details of major adverse cardiovascular events

Major adverse events	All (n = 266)	Psoas Muscle Mass Index		P value
		Low (n = 110)	High (n = 156)	
All cause death	15 (5.6%)	10 (9.0%)	5 (3.2%)	0.040
Cardiovascular death	6 (2.3%)	3 (2.7%)	3 (1.9%)	0.66
Myocardial infarction	8 (3.0%)	5 (4.5%)	3 (1.9%)	0.22
Coronary revascularization	13 (4.9%)	9 (8.2%)	4 (2.6%)	0.036
Heart failure	8 (3.0%)	5 (4.5%)	3 (1.9%)	0.22
Cerebral infarction	5 (1.9%)	2 (1.8%)	3 (1.9%)	0.95

Table 3
Cox proportional hazards models for major adverse cardiovascular events

Variables	Univariate		Multivariate	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age	1.01 (0.98-1.04)	0.39		
Gender, men	1.71 (0.75-3.87)	0.20		
Body mass index	0.98 (0.91-1.10)	0.98		
Hypertension	3.42 (0.82-14.18)	0.091		
Diabetes mellitus	1.73 (0.92-3.23)	0.088		
Dyslipidemia	1.31 (0.64-2.70)	0.46		
Hemoglobin	0.95 (0.80-1.12)	0.55		
Estimated glomerular filtration rate	0.97 (0.95-0.99)	0.024	0.98 (0.95-1.01)	0.19
Current smoking,	3.75 (1.78-7.91)	<0.001	5.63 (1.81-17.50)	0.0028
Serum albumin	0.47 (0.27-0.81)	0.0060	0.52 (0.21-1.27)	0.52
C-reactive protein (log-transformed)	1.46 (1.14-1.86)	0.0025	1.66 (1.14-2.43)	0.0089
Proteinuria	0.98 (0.50-1.94)	0.98		
Low psoas muscle mass	2.88 (1.49-5.54)	0.0016	3.98 (1.65-9.63)	0.0022

CI = confidence interval.

18.09, p = 0.0065) for patients with low PMI and G3, high PMI and G4 to G5, and low PMI and G4 to G5, respectively (Figure 3).

Discussion

The main finding of the present study is that sarcopenia, denoted in our study by low skeletal muscle mass, is significantly associated with adverse cardiovascular outcomes in CKD patients, even during the early phase of the disease. Our findings indicate the considerable significance for asymptomatic CKD patients, because evaluation of skeletal muscle mass by noncontrast CT scan is a noninvasive and useful screening tool for predicting adverse cardiovascular outcomes.

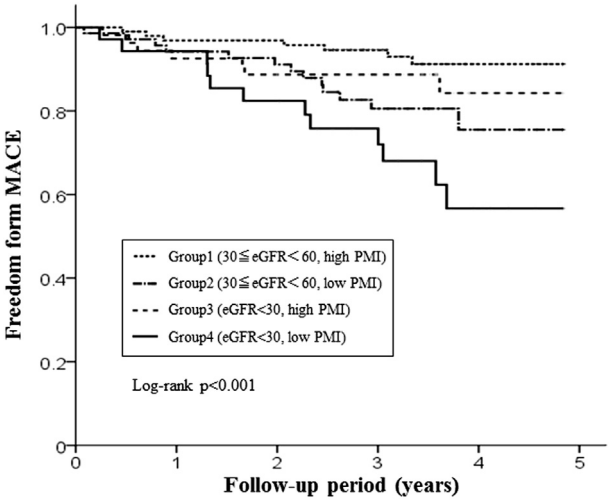
Sarcopenia is defined as the age-related loss of muscle mass and function.[11] Recently, the European Working Group on Sarcopenia in Older People defined sarcopenia as "low skeletal muscle mass plus low muscle strength and/or low physical performance."[1,4] In addition, sarcopenia is a devastating complication because it not only promotes a sedentary life style and leads to decreased quality of life, but also jeopardizes cardiovascular health by increasing morbidity and mortality.[5,12] Several large cohort studies suggested that sarcopenia is more commonly observed in patients with end-stage renal disease receiving hemodialysis.[13,14] In addition, a number of recent studies have suggested that these physical and functional abnormalities may have already started in early-stage CKD.[3,15] Our combined analysis indicated that subjects with low PMI in the relatively early phase of CKD (stage G3) had a 2.9-fold higher risk for adverse cardiovascular outcomes than those with high PMI. Furthermore, these relations were clearly supported by the finding that the model that included both PMI and eGFR levels could more accurately predict adverse cardiovascular outcomes, as shown by the increased C-index and the NRI and IDI significance values. These results suggest that assessment of skeletal muscle mass in addition to renal function is useful to improve our ability to identify patients at high risk of future adverse cardiovascular events and highlight the importance of implementing treatment strategies to improve sarcopenia before CKD reaches advanced stages.

Protein-energy-wasting, malnutrition, and chronic systemic inflammation are well-known major problems associated with atherosclerosis and increased overall morbidity and mortality in CKD patients.[16] Recent evidence suggests that malnutrition and inflammation are important causes of muscle wasting in hemodialysis patients.[17,18] However, even after adjusting for these 2 factors, our data show that low skeletal muscle mass is strongly associated with MACE in nondialyzed CKD patients. Several researches showed that standard approaches to the management of sarcopenia include nutritional support and exercise training.[19,20]

Table 4
Discrimination of each predictive model for major adverse events using C-index, NRI, and IDI

Predictive model	C-index (95 % CI)	P value	NRI (95 % CI)	P value	IDI (95 % CI)	P value
Established risk factors	0.71 (0.62-0.80)	Reference	Reference		Reference	
+eGFR	0.74 (0.65-0.82)	0.27	0.42 (0.089-0.75)	0.013	0.019 (0.0007-0.038)	0.042
+Low PMI	0.76 (0.68-0.84)	0.11	0.53 (0.21-0.86)	0.0014	0.036 (0.0069-0.066)	0.015
+eGFR+Low PMI	0.77 (0.70-0.85)	0.077	0.55 (0.22-0.88)	0.0010	0.059 (0.021-0.096)	0.0021

Established risk factors included age, gender, hypertension, diabetes, dyslipidemia, and smoking status.
CI = confidence interval; IDI = integrated discrimination improvement; NRI = net reclassification improvement; PMI = psoas muscle mass index.



	Adjusted hazard ratio	95 % CI	P value
Group1	Reference		
Group2	2.90	1.04-8.12	0.043
Group3	1.59	0.49-5.12	0.44
Group4	6.02	2.00-18.09	0.0065

Figure 3. Event-free survival curve for major adverse events according to both CKD stage and PMI (Group 1: CKD stage G3 [30 ≦ eGFR < 60 ml/min/1.73 m^2] and high PMI; Group 2: CKD stage G3 and low PMI; Group 3: CKD stage G4, G5 [eGFR < 30 ml/min/1.73 m^2] and high PMI; and Group 4: CKD stage G4, G5 and low PMI).

Recently, supplementation with branched chain amino acids and vitamin D has been reported to be of benefit.[21,22] According to Kim et al,[23] this intervention together with controlled nutrition and exercise are beneficial for elderly Japanese women. To the best of our knowledge, the present study is the first to indicate a predictive role for skeletal muscle mass on future adverse CVE in asymptomatic CKD patients. Although further large studies are required to confirm our findings, our results allow us to conclude that sarcopenia can be a useful therapeutic target for cardiovascular risk reduction in these patients, and the close monitoring of nutritional status is recommended as treatment strategies for sarcopenia in CKD patients.

The pathogenesis of sarcopenia is complex and multifactorial, which remains not to be fully understood. Several mechanisms and factors of sarcopenia in CKD patients were proposed in recent researches such as hormonal imbalances (insulin resistance, decreased sex hormones, and growth hormone resistance), metabolic acidosis, excess angiotensin II, interleukin-6, tumor necrosis factor-alpha, and vitamin D.[16,24–26] Unfortunately, because we did not have the opportunity to measure these important biomarkers related to atherosclerosis, any association between the incidence of adverse CVE and these biomarkers could not be determined in the present study. To improve the prognosis of CKD patients, further investigation is therefore needed.

Our study presents several limitations. First, it includes a relatively small sample and was conducted in a single center. Second, we assessed only skeletal muscle mass. We did not measure objective parameters of frailty such as handgrip strength or gait speed in the present study. Third, because we conducted only medical records' surveys, we could not obtain patients' information on the duration of dyslipidemia, DM, and hypertension, all of which may have affected the observed outcomes. Finally, another potential limitation of our study is that we were not able to measure in our patients some molecular factors (e.g., sex hormones, interleukin-6, tumor necrosis factor-alpha, vitamin D, and so on) known to be unbalanced or dysregulated in sarcopenia, which are also correlated to CVEs. In future research, assessing these important biomarkers and establishing their possible association with MACE on the background of sarcopenia is advised.

Acknowledgment: We express our sincere appreciation to all the patients, collaborating physicians, and other medical staff for their important contributions to the study.

Disclosures

The authors have no conflicts of interest and accept responsibility for all contents.

1. Avin KG, Moorthi RN. Bone is not alone: the effects of skeletal muscle dysfunction in chronic kidney disease. *Curr Osteoporos Rep* 2015;13:173–179.
2. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol* 2007;18:2960–2967.
3. Moon SJ, Kim TH, Yoon SY, Chung JH, Hwang HJ. Relationship between stage of chronic kidney disease and sarcopenia in Korean aged 40 years and older using the Korea National Health and Nutrition Examination Surveys (KNHANES IV-2, 3, and V-1, 2), 2008-2011. *PLoS One* 2015;10:e0130740.
4. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39:412–423.
5. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R,

Rahman O, Swaminathan S, Iqbal R, Gupta R, Lear SA, Oguz A, Yusoff K, Zatonska K, Chifamba J, Igumbor E, Mohan V, Anjana RM, Gu H, Li W, Yusuf S; Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015;386:266−273.
6. Matsuo S, Imai E, Horio Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GER. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53: 982−992.
7. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* 2015;157:1088−1098.
8. Hamaguchi Y, Kaido T, Okumura S, Fujimoto Y, Ogawa K, Mori A, Hammad A, Tamai Y, Inagaki N, Uemoto S. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. *Liver Transpl* 2014;20:1413−1419.
9. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837−845.
10. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157−172.
11. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. *J Nutr Health Aging* 2005;9:408−419.
12. Arango-Lopera VE, Arroyo P, Gutiérrez-Robledo LM, Pérez-Zepeda MU, Cesari M. Mortality as an adverse outcome of sarcopenia. *J Nutr Health Aging* 2013;17:259−262.
13. Domanski M, Ciechanowski K. Sarcopenia: a major challenge in elderly patients with end-stage renal disease. *J Aging Res* 2012;2012: 1−12.
14. 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;27:279−286.
15. 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;25:2189−2198.
16. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010;91:1128−1132.
17. Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, Bergström J. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int* 1998;53: 773−782.
18. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. *Am J Kidney Dis* 2001;38:1343−1350.
19. Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. *J Am Med Dir Assoc* 2013;14:10−17.
20. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. *Ageing Res Rev* 2010;9:226−237.
21. Komar B, Schwingshackl L, Hoffmann G. Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. *J Nutr Health Aging* 2015;19:437−446.
22. Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, McMurdo ME, Mets T, Seal C, Wijers SL, Ceda GP, De Vito G, Donders G, Drey M, Greig C, Holmbäck U, Narici M, McPhee J, Poggiogalle E, Power D, Scafoglieri A, Schultz R, Sieber CC, Cederholm T. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;16:740−747.
23. Kim H, Suzuki T, Saito K, Kojima N, Hosoi E, Yoshida H. Long-term effects of exercise and amino acid supplementation on muscle mass, physical function and falls in community-dwelling elderly Japanese sarcopenic women: a 4-year follow-up study. *Geriatr Gerontol Int* 2016;16:175−181.
24. Storz P, Döppler H, Wernig A, Pfizenmaier K, Müller G. TNF inhibits insulin induced STAT5 activation in differentiated mouse muscle cells pmi28. *FEBS Lett* 1998;440:41−45.
25. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, Johnson MA, Schwartz GG, Kritchevsky SB. Association between vitamin D status and physical performance: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2007;62:440−446.
26. Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. *Mol Aspects Med* 2005;26:203−219.