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Association of inflammation with nutritional status, lean body mass, and physical activity in non-dialysis-dependent chronic kidney disease

Aysun Aksoy[1], Timur Selçuk Akpınar[2], Alattin Yıldız[3], Sebahat Usta Akgül[4], Ege Sinan Torun[5], Fatma Savran Oğuz[4], Halil Yazıcı[3], Nilgün Erten[6], Cemil Taşçıoğlu[6], Bülent Saka[6]

ABSTRACT

Objective: Patients with chronic kidney disease (CKD) are susceptible to systemic inflammation and nutritional disorders, which are associated with morbidity and mortality. The aim of the present study was to evaluate the relationship between nutritional status, lean body mass, physical activity, and systemic inflammation in patients with stage 3-5 non-dialysis-dependent CKD.

Methods: A total of 55 predialysis patients with CKD were included in this cross-sectional study. Patients were divided into two groups according to the Subjective Global Assessment: 35 with normal nutritional status (NN) and 20 with malnutrition (MN). Anthropometric measurements, fat-free mass, muscle strength, physical activity, biochemical parameters, and serum cytokine levels of the patients were compared.

Results: Patients with CKD and malnutrition (CKD-MN) had higher serum phosphate, interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α levels and lower serum albumin levels and blood lymphocyte counts than those with CKD-NN independent from glomerular filtration rate. Regression analysis showed a relationship between MN and serum phosphate level, blood lymphocyte count, and serum IL-6 and TNF-α levels. Muscle strength and gait speed showed a positive relationship with nutritional status and negative relationship with inflammation.

Conclusion: An increased inflammatory environment in patients with non-dialysis-dependent CKD was significantly associated with MN and decreased physical activity. An increased serum phosphate level appears to contribute to this MN-inflammation environment.

Keywords: Cytokine, inflammation, kidney failure, malnutrition, predialysis

ORCID ID of the author:
A.A. 0000-0002-8218-7109; T.S.A. 0000-0002-9591-4475; A.Y. 0000-0002-4066-929X; S.U.A. 0000-0003-0176-3344; E.S.T. 0000-0002-4842-0683; F.S.O. 0000-0002-6018-8936; H.Y. 0000-0003-2526-3483; N.E. 0000-0002-1113-9310; C.T. 0000-0003-3808-6957; B.S. 0000-0001-5404-5579

[1]Department of Rheumatology, Marmara University School of Medicine, İstanbul, Turkey
[2]Department of Internal Medicine, Memorial Bahçelievler Hospital, İstanbul, Turkey
[3]Department of Nephrology, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[4]Department of Medical Biology, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[5]Department of Rheumatology, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[6]Department of Internal Diseases, İstanbul University İstanbul School of Medicine, İstanbul, Turkey

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Corresponding Author:
Bülent Saka

E-mail:
drsakab@yahoo.com

Introduction

Chronic kidney disease (CKD) is an important public health problem. The Chronic REnal Disease In Turkey study showed that the prevalence of CKD in adults is 15.7% in Turkey, and that 1 out of every 666 persons has end-stage renal disease (1).

Markers of systemic inflammation are elevated in patients with CKD, which are associated with an increased prevalence of morbidity and mortality (2). Poor nutritional status, which is termed as malnutrition (MN), is also highly prevalent in patients with CKD. A number of evidence suggest that an increased inflammatory response with MN tends to coexist in patients undergoing chronic hemodialysis (3). Increased levels of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α are known to induce proteolysis and decreased protein synthesis, which can lead to decreased lean body mass (LBM) (3-5). In patients with CKD, an adverse consequence of MN is its potential detrimental effect on physical functioning. Since skeletal muscle mass, quality, and muscle strength are the main determinants of physical function, it is also possible that there is an interplay between exaggerated inflammatory response, MN, and physical functioning. In fact, Amparo et al. (6) showed a neg-

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ative correlation with muscle strength and MN-inflammation score in non-dialysis-dependent CKD.

The aim of the present study was to evaluate the relationship between nutritional status, as assessed by the Subjective Global Assessment (SGA), measurements of muscle mass, muscle strength, and physical activity, and inflammatory state, as assessed by serum proinflammatory cytokine concentrations, in patients with non-dialysis-dependent CKD.

Methods

Study population

The patients were recruited from the Nephrology Clinic in Istanbul University, Istanbul Medical Faculty Hospital, Turkey. Inclusion criterion was the presence of CKD with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (CKD stages 3, 4, and 5). eGFR was calculated using the Modification of Diet in Renal Disease formula (7).

Exclusion criteria were malignant cancer, hospitalization within the last 3 months, any ongoing infection, chronic inflammatory diseases, such as inflammatory rheumatoid diseases, immunosuppressive drug use, and maintenance dialysis treatment.

The participants completed a questionnaire regarding their health status, current comorbidities, and drug use. The study was approved by the Istanbul University Istanbul School of Medicine Ethics Committee (25/02/2015-459). Informed consent was obtained from the patients.

Characteristics of the patients and nutritional status

Demographic characteristics, smoking habits, body mass index (BMI), blood pressure measurements, comorbidities (e.g., hypertension, diabetes mellitus, and cardiovascular disease), and medications were recorded. The nutritional status of the patients was evaluated using the SGA by the same doctor working within the Clinical Nutrition Team of the hospital (8).

Anthropometric measurements

Mid-upper arm circumference (MUAC) is measured from the middle point of the upper arm between the acromion of the scapula at the posterior part of the shoulder and the olecranon process of the ulna at the elbow. Calf circumference (CC) is measured from the widest point of the calf.

Muscle strength, LBM, and physical performance measurements

Muscle strength was measured using a standardized handheld dynamometer (Jamar Hydrolic Hand Dinamometer, Lafayette Instrument, Lafayette IN 47903 USA), which was determined as the best of three measurements made in the dominant hand. In patients who had only one upper extremity or who could use only one extremity, measurements were made with this extremity. Bioelectrical impedance analysis (BIA) was used to measure fat-free mass (FFM, kg) (BIA, Tanita, Japan). Physical performance was measured using the 10-meter walking speed. Anthropometric measurements, BIA, and physical performance measurements were completed by the same two nurses of the Clinical Nutrition Team.

Blood sample analysis

Blood sample analyses were performed after overnight fasting. The complete blood count was determined using a Beckman Coulter LH 780 (hemoglobin by photometry and others by impedance method). Blood urea nitrogen, creatinine, albumin, C-reactive protein (CRP), and glucose were determined using spectrophotometry with a Roche Cobas 8000 c702 analyzer.

Serum cytokine levels

Serum levels of TNF-α, IL-6, IL-8, IL-10, and IL-1β were measured using an enzyme-linked immunosorbent assay with commercially available kits (Diaclone Research, Besancon, France). Serum samples were separated, immediately centrifuged at 3000 RPM for 10 min, and stored at −80°C until assay.

All assays were conducted according to the manufacturer's protocols. These experiments were performed in duplicate, and the concentrations of cytokines in each sample were determined by extrapolating absorbance values to cytokine concentrations using the standard curve.

Statistical analysis

Statistical analysis was performed using IBM Statistical Packages for the Social Sciences 21.0 (IBM SPSS Statistics, Corp., Armonk, NY, USA) version 21. Data are expressed as mean±SD. Chi-square test was used for comparison of the distribution of variables. An analysis of variance (ANOVA) was used to assess the difference between the arithmetical averages adjusted for multiple comparisons. ANOVA or Mann-Whitney U test was used for comparisons between the groups when results were distributed non-parametrically depending on the normality of the distribution of variables. The coefficient of variation is defined as the standard deviation percentage of the mean. Spearman coefficient (r) was calculated to determine the correlation between inflammatory markers and biochemical parameters. Linear and logistic regression analyses were used with appropriate samples. Significance tests were two-sided. A p-value ≤ 0.05 was considered as statistically significant.

Results

The demographic characteristics of the participants are shown in Table 1. The two main causes of CKD in our patients were hypertension and diabetes (43.6% and 36.4%, respectively).

Table 1. Demographic characteristics of the participants

	CKD-NN (n=35)	CKD-MN (n=20)
Age (year)	63.06±13.117	59.3±20.59
Sex		
Male	22 (62.9%)	8 (40%)
Female	13 (37.1%)	12 (60%)
CKD stage		
3	13 (37.1%)	5 (25%)
4	16 (45.7%)	7 (35%)
5	6 (17.1%)	8 (40%)
CKD cause		
Hypertension	17 (48.6%)	7 (35%)
Diabetic nephropathy	13 (37.1%)	7 (35%)
PCKD	2 (5.7%)	1 (5%)
Others	3 (8.6%)	5 (25%)
ACEI/ARB usage	22 (62.9%)	8 (40%)
Ischemic heart disease	10 (28.6%)	7 (35%)
Statin usage	10 (28.6%)	7 (35%)
GFR (mL/min)	26.71±11.8	20.4±12.03
CKD duration (years)	7.8±8.5	6.43±8.36
Smoking (pack-year)	23.6±36.15	11.68±28.6
Height (m)	1.64±0.07	1.60±0.12
Weight (kg)	80.0±14.3	66.2±17.2§
BMI (kg/m^2)	29.66±5.96	26.02±7.71
SGA stage		
A (normal)	35 (100%)	0
B (moderate MN)	0	12 (60%)
C (severe MN)	0	8 (40%)

§Significant difference between patients with CKD with or without MN (p≤0.01). PCKD: polycystic kidney disease; CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; SGA: Subjective Global Assessment; BMI: body mass index; GFR: glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

According to the SGA, 20 (36%) patients had MN (CKD-MN), and 35 patients had normal nutritional status (CKD-NN). MN was more prevalent in the later stages of the disease. No significant difference was found between the two groups when GFR was taken into consideration (Table 1). The CKD-MN group had higher serum phosphate and parathyroid hormone levels and lower serum albumin levels and blood lymphocyte counts (Table 2).

Patients with CKD-MN had lower MUAC, CC, and muscle strength than those with CKD-NN. Although BIA-FFM was lower in the CKD-MN group, it did not reach statistical significance (Table 3).

The median cytokine levels of the patients in different CKD stages did not show any significant difference (Table 4). CKD-MN had higher serum IL-6, IL-10, and TNF-α

Table 2. Laboratory measurements of the patients according to nutritional status

	CKD-NN (n=35)	CKD-MN (n=20)
WBC (mm^3/mL)	8677±1773	7697±1703§
Lymphocytes (mm^3/mL)	2202±742	1719±390§§
Hemoglobin (g/dL)	12.1±1.4	10.19±1.57§§
Creatinine (mg/dL)	2.73±1.21	3.92±2.11§
GFR (mL/min)	26.7±11.9	20.5±12.0
Albumin (g/dL)	4.2 (2.8-4.7)	3.9 (2.4-4.5)§
CRP (mg/L)	3.95 (0.20-34.0)	2.25 (0.22-26.80)
Vitamin B12 (pmol/mL)	285 (171-2000)	475 (160-1023)
25-Hydroxyvitamin D (ng/mL)	15.5±8.47	24.36±18.9
Transferrin sat. (%)	27.75±15.94	30.5±16.67
Ferritin	117±117	142±141
Calcium (mg/dL)	9.2±0.49	8.59±0.73§§
Phosphate (mg/dL)	3.84±0.6	4.57±1.07§§
PTH (pg/mL)	164.4±156.2	330.8±288§
Proteinuria (g/day)	1.19±1.33	1.93±2.09

§Significant difference between patients with CKD with or without MN (p≤0.05). §§Significant difference between patients with CKD with or without MN (p≤0.01). CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; PTH: parathyroid hormone; WBC: white blood cell count; GFR: glomerular filtration rate; CRP: C-reactive protein

levels than CKD-NN (Table 5). Serum albumin showed a negative correlation with IL-6 and CRP. Proteinuria was positively correlated with TNF-α and IL-10. BIA-FFM, MUAC, and CC showed no correlation with serum cytokines (Table 6).

Table 3. Assessment of anthropometric measurements, muscle mass, muscle strength, and gait speed of patients with CKD according to their nutritional status

	CKD-NN (n=35)	CKD-MN (n=20)	p
Weight (kg)	80.0±14.3	66.2±17.2	0.006
BMI (kg/m^2)	29.66±5.97	26.02±7.71	0.085
MUAC (cm)	31.9±4.4	28.7±4.2	0.013
CC (cm)	38.2±3.1	34.3±5.2	0.006
BIA fat (%)	28.5±11.7	23.6±12.9	0.164
BIA-FFM (kg)	50.5±11.7	44.2±14.8	0.091
BIA visceral fat (%)	12.2±4.0	8.3±5.8	0.008
Handgrip (kg)	31.3±8.8	25.3±9.2	0.029
Gait speed (m/s)	1.16±0.38	1.12±0.48	0.274

BIA: bioelectrical impedance analysis; BMI: body mass index; CC: calf circumference; CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; FFM: fat-free mass; MUAC: mid-upper arm circumference

Serum phosphate showed a positive correlation with IL-1β, IL-8, TNF-α, and weight loss and a negative correlation with serum albumin. In the regression analysis, serum phosphate levels showed an independent relationship with serum IL-1β (R^2=0.340), TNF-α (R^2=0.240), and IL-8 (R2=0.240). Logistic regression analysis showed a relationship between MN and serum phosphate level (p=0.003), lymphocyte count (p=0.005), IL-6 level (p=0.044), and TNF-α level (p=0.035).

Gait speed had a positive correlation with muscle strength (p=0.019) and a negative correlation with age, BMI, proteinuria, and serum IL-6 (Table 7). Muscle strength showed a positive correlation with serum protein levels and BIA-FFM and a negative correlation with age and serum IL-6 (Table 7). Both gait speed and muscle strength did not show any correlation with GFR.

Discussion

The prevalence of MN is between 20% and 50% in CKD (9, 10). Anorexia and cachexia in CKD can be related with

Table 4. Median cytokine levels of the patients in different disease stages

CKD stage	Stage 3 (n=17)	Stage 4 (n=22)	Stage 5 (n=13)	p
IL-1β (pg/mL)	5.73 (4.7-172)	6.6 (4.4-131.8)	7.28 (5.4-85.8)	0.054
IL-6 (pg/mL)	3.45 (1.1-201)	4.32 (0.9-171.9)	5.5 (1.3-287)	0.435
IL-8 (pg/mL)	10.78 (5.8-691)	16.1 (1.96-1326)	14.7 (2.5-814)	0.638
IL-10 (pg/mL)	0.80 (0.27-3.3)	1.1 (0.23-3.3)	0.98 (0.44-33.8)	0.474

CKD: chronic kidney disease; IL: interleukin

Table 5. Median cytokine levels of the patients according to nutritional status

	CKD-NN (n=35)		CKD-MN (n=20)	
	Median	25th-75th percentile	Median	25th-75th percentile
IL-8 (pg/mL)	11.76	7.8-19.6	24.51	8.8-546
IL-6 (pg/mL)	2.91	1.36-6.86	5.43§	3.15-47.6
IL-1β (pg/mL)	6.5	5.48-7.23	7.28	5.53-26.4
TNF-α (pg/mL)	12.5	11.5-19.8	17.38§	13.6-23.6
IL-10 (pg/mL)	0.77	0.54-1.63	1.47§	0.8-2.15

§Significant difference between CKD-MN and CKD-NN (p≤0.05). CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; IL: interleukin; TNF-α: tumor necrosis factor-α

uremia, metabolic acidosis, inflammation, decreased oral intake, inappropriate protein restrictions, polypharmacy, depression, dialysis complications, and comorbidities, such as diabetes and heart failure (11, 12). In the present study, 36% of patients with CKD had MN, and patients with MN showed no significant difference in GFR when

Table 6. Correlation analysis of serum cytokines and CRP with biochemical parameters and indirect measurement of muscle mass

	IL-1β		IL-6		IL-8		IL-10		TNF-α		CRP	
	r	p	r	p	r	p	r	p	r	p	r	p
Calcium	-0.30	0.030*	-0.326	0.018*	-0.172	0.223	-0.326	0.018*	-0.134	0.342	-0.170	0.239
Phosphate	0.386	0.005*	0.234	0.095	0.388	0.005*	0.265	0.057	0.378	0.006*	0.253	0.076
GFR	-0.238	0.089	-0.124	0.383	-0.180	0.200	-0.228	0.103	0.042	0.769	-0.255	0.074
Albumin	-0.262	0.060	-0.307	0.027*	-0.283	0.042*	-0.252	0.071	-0.093	0.511	-0.329	0.020*
Proteinuria	0.273	0.052	0.167	0.241	0.196	0.168	0.326	0.020*	0.319	0.022*	0.175	0.253
PTH	0.191	0.180	0.121	0.399	0.139	0.331	0.326	0.019*	-0.017	0.903	0.075	0.606
Lymphocytes	0.073	0.605	-0.195	0.166	-0.087	0.540	-0.085	0.547	0.022	0.874	-0.130	0.367
MUAC	0.076	0.598	0.126	0.378	-0.016	0.913	-0.063	0.663	0.057	0.590	0.158	0.277
CC	-0.035	0.809	-0.040	0.778	-0.145	0.309	-0.173	0.225	-0.056	0.694	0.095	0.516
BIA-FFM	0.078	0.587	0.001	0.995	-0.064	0.657	-0.030	0.837	0.033	0.816	-0.052	0.725

*p≤0.05. BIA-FFM: fat-free mass measurement according to bioelectrical impedance analysis; CC: calf circumference; GFR: glomerular filtration rate; MUAC: mid-upper arm circumference; PTH: parathyroid hormone; TNF-α: tumor necrosis factor-α; IL: interleukin; CRP: C-reactive protein

Table 7. Correlation analysis of gait speed and muscle strength with anthropometric measurements, BIA measurements, biochemical parameters, and cytokines

	Gait speed (m/s)		Muscle strength (kg)	
	r	p	r	p
Age (years)	−0.443	0.001*	−0.568	0.001*
GFR (mL/min)	0.188	0.174	−0.039	0.779
BMI (kg/m^2)	−0.279	0.047*	−0.213	0.126
MUAC (cm)	0.185	0.180	−0.016	0.908
CC (cm)	0.041	0.769	0.150	0.285
BIA-FFM (kg)	0.080	0.578	0.383	0.005*
Albumin (g/dL)	−0.008	0.956	0.289	0.036*
Prealbumin (g/dL)	0.472	0.056	0.531	0.023*
Calcium	0.066	0.647	0.094	0.501
Phosphate (mg/dL)	−0.006	0.967	−0.173	0.217
PTH (pg/mL)	−0.098	0.493	0.046	0.746
Proteinuria (g/day)	−0.304	0.027*	0.159	0.269
CRP (mg/L)	−0.160	0.288	−0.160	0.276
IL-6 (pg/mL)	−0.491	0.001*	−0.296	0.037*

*Significant relationship (p≤0.05). BIA-FFM: fat-free mass measurement with bioelectrical impedance analysis; BMI: body mass index; CC: calf circumference; GFR: glomerular filtration rate; MUAC: mid-upper arm circumference; PTH: parathyroid hormone; IL: interleukin; CRP: C-reactive protein

compared with those with NN. Serum phosphate levels were higher in CKD-MN.

In our patients, MN was associated with decreased MUAC, CC, muscle strength, and visceral fat. In patients with CKD, decreased muscle and/or fat revealed lower survival rates, which was related with age, uremia-related metabolic acidosis, systemic inflammation, decreased appetite, dietary restrictions, MN, dialysis-related factors, comorbidities, and increased insulin and insulin-like growth hormone resistance. CKD-related cachexia causes FFM loss (13-15). Muscle strength is also important for evaluation of sarcopenia in CKD. It was found to be correlated with muscle mass in patients undergoing hemodialysis and peritoneal dialysis (16). Although FFM was lower in our patients with CKD-MN, it did not reach statistical significance. This might be related with the low number of patients in the study groups.

TNF-α, IL-1β, IL-6, and IL-8 are proinflammatory cytokines, and IL-10 is an anti-inflammatory cytokine. In the current study, IL-6 was found to be significantly higher in patients with MN. TNF-α and IL-10 levels were also higher in patients with CKD-MN than in those with CKD-NN. We found no relationship between serum cytokines and CKD stage or GFR. In patients with CKD, inflammation can be related with underlying disease, cardiovascular diseases, comorbidities, dialysis complications, and infections; each disease is related with increased morbidity and mortality (17). An experimental study by Tsujinaka et al. (18) demonstrated that proinflammatory cytokines cause anorexia by directly affecting the satiety center. Giving TNF and IL-6 to rats resulted in muscle wasting that could be reversed by anti-IL-6 antibodies. A negative relationship was shown between GFR and serum cytokine levels (19, 20).

According to our data, serum albumin was found to be negatively correlated with IL-6 and IL-8, which was also reported in previous studies (3, 21). Decreased serum albumin levels result in a vicious cycle of MN and inflammation by triggering oxidative stress and inflammation. IL-10 is an anti-inflammatory cytokine, and its level increases together with proinflammatory cytokines in patients with CKD (22). In our study, IL-10 level was higher in patients with CKD-MN ($p<0.05$). Thus, an increased inflammation in patients with CKD-MN may trigger IL-10 production to control proinflammatory activity.

Leukocytes are mainly active during infectious diseases. Uremia can induce leukocytosis. Sela et al. (23) indicated a positive relationship between the degree of kidney failure and total blood leukocyte and neutrophil counts. Our patients with CKD-MN had lower leukocyte and lymphocyte counts than those with CKD-NN ($p<0.05$). As such, MN can cause lymphopenia. Patients with anorexia nervosa showed changes in bone marrow histology, such as hypoplasia and aplasia, which were found to be correlated with weight loss (24, 25). Accordingly, MN and weight loss can cause leukopenia and lymphopenia in CKD.

Serum phosphate levels showed an independent relationship with MN, lymphocyte count, IL-6, and TNF-α in our patients. A cell culture and animal study on phosphate and inflammation-MN showed diet phosphate load-induced MN and increased serum TNF-α levels (26). In addition, serum phosphate level was found to be correlated with each MN-inflammation-atherosclerosis component, such as phosphate load-induced inflammation, decreased albumin synthesis, increased albumin degradation, and muscle atrophy. All of these contribute to MN (26). Our results support the fact that serum phosphate level contributes to MN-inflammation. Our patients with CKD-MN had higher serum phosphate levels than those with CKD-NN.

Assessment of nutritional status in patients with CKD can be difficult. As GFR decreases, fluid retention causes edema; therefore, patients and physicians cannot realize their weight loss. The present study also showed some important clues about anthropometric measurements in the diagnosis of MN. Simple measurements during follow-up can be useful in determining patients at risk for MN, such as serum albumin with CRP, serum phosphate, MUAC, and CC.

Decreased GFR was found to be related with immobility, frailty, and increased mortality in CKD (27). Lower gait speed was related with increased all-cause mortality (13). Our results showed a negative correlation between 10-meter walking speed (m/s), age, BMI, fat mass, and IL-6 and a positive correlation with muscle strength, blood hemoglobin level, and serum transferrin saturation ($p<0.05$). An association between gait speed and muscle strength was shown in previous studies (28). Thus, the lower gait speed, MUAC, CC, muscle strength, and higher IL-6/TNF-α in our patients with CKD-MN indicate a possible relationship of MN, inflammation, and sarcopenia in these patients.

The present study had a few limitations. First, the study had a low number of patients in the study groups. MN is particularly seen in severe renal insufficiency on renal replacement therapy and occurs in patients with multiple comorbidities. Exclusion of such patients resulted in a reduced number of patients recruited to the study groups. Second, dual-energy X-ray absorptiometry and magnetic resonance imaging are the gold standards for evaluation of muscle mass; however, both cost and difficulty in appli-

cation forced the use of BIA in our patients, which is also used effectively in many studies.

In conclusion, to the best of our knowledge, this was the first study to evaluate inflammation in non-dialysis stage CKD according to nutritional status, muscle mass, muscle strength, and physical activity of the patients. As a result, patients with CKD showed increased inflammatory environment that was significantly aggravated with MN. Increased serum phosphate levels appear to contribute to this MN-inflammation environment. Serum albumin level, blood lymphocyte count, and anthropometric measurements can also be used to predict patients at increased risk for MN and sarcopenia. It appears that decreased muscle mass was mainly related with MN. Muscle strength and gait speed showed a relationship with MN and inflammation. Further studies are needed with more patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine (25/02/2015- 459).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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