Body Composition Analysis in Dialysis Patients: Nutrition Screening and Prediction of Outcome

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Abstract. *Background and objective: The prevalence of protein energy wasting is very high in dialysis patients and diagnosis is based on biochemical criteria, body composition and dietary intake. The body composition monitor (BCM) is crucial for early recognition of body composition disorders. Nutritional BCM parameters, as lean tissue index (LTI), skeletal muscle index (SMI), fat free mass index (FFMI) and fat tissue index (FTI), have been proved to be a validated markers for protein wasting. The aim of our study was to assess the relationship between BCM measured indices, antropometric measurements, biochemical markers of nutrition, inflammation and mortality in hemodialysis patients.*

Materials and methods: Sixty-three patients treated with maintenance hemodialysis for at least 3 months were included into the study in October 2014. Demographic, anthropometric, clinical, dialysis vintage data and comorbidities were recorded at the time of study enrollment. Assessment of body composition was performed using bioimpedance. Nutritional BCM parameters were directly measured and expressed as a percentage of total body mass, or normalized to the body surface area (m^2) as indices. The patients were followed until July 2017, the all-cause mortality being the primary outcome.

Results: The median age of the patients was 62 ± 15 years. There were 15 deaths (24% of the patients) during a median follow-up period of 25 months. Among the BCM measured nutritional markers, LTI, SMI and FFMI were significantly lower in the deceased patients group compared with alive patients, while nutritional parameters, expressed in percentages, and FTI did not differ between the groups. Deceased patients also were older, had lower creatinine and higher C-reactive protein (CRP) levels. Correlation analysis between body mass index (BMI) and nutritional BCM parameters showed that BMI had a strong positive correlation with FTI ($r = 0.875$, $P < 0.001$). Also, a very strong negative correlation was found between FTM and SM ($r = -0.991$, $P < 0.001$). A lower SMI was associated with an increased risk of death: this association was confrmed both in the univariate and the multivariate logistic regression model, when adjusted to age, creatinine and CRP. Kaplan-Meier analysis revealed that a higher SMI was associated with better survival during follow-up: the group of patients with SMI $\geqslant 10$ kg/m^2 had better survival than the group of patients with SMI < 10 kg/m^2 ($P = 0.006$).

Conclusions: Our data showed that, of all measured nutritional parameters, the skeletal muscle index was the most important predictor for survival derived. The lower skeletal muscle index was associated with the increased risk of death.

Introduction

The prevalence of protein energy wasting (PEW) is very high in dialysis patients [1] because of the synergic contribution of decreased protein and/or energy intake, chronic inflammation, physical inactivity, concurrent acute or chronic conditions or illness, and catabolism induced by the hemodialysis process [2]. PEW is strongly related to morbidity and mortality [3]. Diagnosis of PEW is based on abnormalities in 3 of 4 categories: biochemical criteria, body mass index (BMI) or fat mass (FM), muscle mass, and dietary intake [4].

BMI calculated from body weight and height does not differentiate fat mass (FM) from lean mass. Even when BMI is equal, body composition can significantly differ. In the general population, BMI strongly correlates with FM, whereas lean tissue mass (LTM) only slightly influences this parameter [5]. Furthermore, a decreasing amount of lean tissue can be masked by an increase of FM. Consequently, loss of muscle mass (sarcopenia) can coexist with an excess of adipose tissue.

Although both low muscle mass and low FM are associated with poor survival in hemodialysis (HD)

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patients, some authors have shown that lean body mass has even stronger influence on clinical outcomes [6]. In patients with chronic kidney disease (CKD), lean tissue loss can be masked by either adiposity or overhydration. Given the fact that PEW and sarcopenia in dialysis patients may be partly amendable to interventions such as optimal nutrition and excersice training, optimal diagnosis of change in body composition (BC) is of great clinical importance [7]. For this reason, body composition measurements are crucial for early recognition of body composition disorders, which can develop in PEW. Various methods are available to estimate BC in renal failure: dual-energy X-ray absorptiometry (DEXA), computed tomography, magnetic resonance and bioimpedance. The last one is easy applicable, simple and very informative.

The body composition monitor (BCM) based on the principle of bioimpedance has been widely applied in field of nephrology since 2007. The lean tissue index (LTI), a nutrition parameter measured with BCM, has been proved to be a validated marker for protein wasting and closely related to patients survival in many studies [8–12]. There are also reports about others indices: fat tissue, fat free mass and skeletal muscle mass (FTI, FFMI and SMI), and their relationship with PEW and influence on outcomes in dialysis patients. However, there are limited data about comparison of all these indices; therefore, the most important and influential index is not clear.

The aim of our study was to assess the relationship between BCM measured indices, antropometric measurements, biochemical markers of nutrition and inflammation and mortality in hemodialysis patients.

Materials and Methods

The longitudinal observational prospective study was conducted at a large university hospital. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (protocol number BE-10-2).

Study population

Sixty-three hemodialysis patients were included into the study in October 2014. All eligible patients were treated with maintenance hemodialysis (MHD) at the Hospital of the Lithuanian University of Health Sciences Kauno klinikos for at least 3 months. All the study patients were aged 18 years or older and were on MHD therapy thrice a week for 4 hours using synthetic or semisynthetic dialysis membranes, reverse osmosis purified water, and bicarbonate-base hemodialysis solution. The exclusion criteria were presence of big metal prostheses, an electrocardiostimulator, any form of limb amputation and clinical signs of an acute overt infection. We recorded demographic, anthropometric, clinical, dialysis vintage data and comorbidities at the time of study enrollment.

Application of BCM

BCM was used for the measurements of nutrition data in this study. Bioimpedance analysis was performed using InBody S10, Biospace Co., Ltd. (Korea) 20 minutes after HD in the supine position. Electrodes were placed in tetrapolar configuration (on a hand and a foot). The parameters measured by BCM included total body water, extracellular water, intracellular water, extracellular-to-intracellular water ratio, lean tissue, fat tissue, body cell, skeletal muscle, fat free, protein and mineral masses. The BCM delivered parameters related to nutrition consisted of lean tissue mass (LTM, unit kilogram [kg]), percentage of lean mass for the current body weight (LTM %) and lean tissue index (LTI, defined as LTM/ [body height]^2, unit kg/m^2), fat tissue mass (FTM, unit kilogram [kg]), percentage fat mass (FTM%) and fat tissue index (FTI, defined as FTM/ (body height)2, unit kg/m2), body cell mass (BoCM, unit kilogram [kg]), skeletal muscle mass (SM, unit kilogram [kg]), percentage of skeletal muscle mass for current body weight (SM%) and skeletal muscle mass index (SMI, defined as SM/ (body height)^2, unit kg/m^2), fat free mass (FFM, unit kilogram [kg]), percentage of fat free mass for current body weight (FFM%) and fat free mass index (FFMI, defined as FFM/ (body height)2, unit kg/m^2) and BMI (unit kg/m^2).

These calculated parameters were used as the main markers for the nutrition status in this study.

All the BCM tests were performed by specially trained personnel in our dialysis center to avoid bias from interperson variation of manipulation.

Laboratory Parameters

Data about routinely measured serum creatinine, albumin, transferin and C-reactive protein (CRP) levels were collected during the same month as bioimpedance analysis was performed.

Outcome Variable

The primary outcome was all-cause mortality. The patients were followed until July 2017.

Statistical Analysis

Baseline patient characteristics, clinical and laboratory data were compared between groups by using the chi-square test, the Student *t* test, or the Mann-Whitney rank sum test where appropriate. For correlations between parameters, the Pearson and Spearman correlation tests were performed reporting the correlation coefficients (r). Univariate analysis of overall survival was performed using the

Kaplan-Meier method with the log-rank test. Optimal cut off values for continuous variables were determined using receiver operating characteristic (ROC) analysis. Multivariate regression analysis was based on logistic regression modeling. All statistical analyses were performed using SPSS software version 23.0. Statistical significance was assumed at $P < 0.05$.

Results

In total, 63 hemodialysis patients (52% men and 48% women) participated in our study. The median age of the patients was 62 ± 15 years. The median (interquartile range) duration of dialysis was 52 (22.202) months. The main characteristics of our patiens: mean BMI 25.6 ± 4.7 kg/m^2, SM 39.1 ± 7.5%, SMI 9.8 ± 1.4 kg/m^2, LTM 67.2 ± 12.1%, LTI 16.8 ± 2.1 kg/m^2, FFM 71.4 ± 12.8%, FFMI 17.8 ± 2.2 kg/m^2, FTM 28.6 ± 12.8%, FTI 7.8 ± 4.6 kg/m^2, creatinine 934 ± 250 μmol/L, albumin 35.6 ± 2.2 g/L, C-reactive protein (CRP) 7.5 ± 8 mg/L, and hemoglobine 110.5 ± 11.6 g/L. There were 15 deaths (24% of the patients) during a median follow-up period of 25 months.

Of the 63 patients, 7.9% had a BMI < 19 kg/m^2, 17.5% had a BMI ⩾ 30 kg/m^2. The mean LTI (17.7 vs. 15.8 kg/m2) and SMI (10.4 vs. 9.0 kg/m^2) were higher in men as compared with women ($P < 0.001$). In contrast, FMI (8.9 vs. 6.7 kg/m^2) and FM percentage (33.0 vs. 24.6%) were higher in women ($P < 0.05$), although BMI was similar (25.6 vs. 25.5 kg/m^2) in both groups.

When comparing deceased and alive patients, deceased were older and had lower creatinine and higher CRP levels (Table 1). There were no statistically significant differences in the weight, BMI, albumine and hemoglobin levels between the two groups. Among the BCM measured nutritional markers, LTI, SMI and FFMI were significantly lower in deceased patients while nutritional parameters, expressed in percentages, and FTI did not differ between the groups (Table 2).

Correlation analysis between BMI and nutritional BCM parameters showed that BMI had a strong positive correlation with FTI ($r = 0.875$, $P < 0.001$) and a strong negative correlation with BoCM ($r = -0.743$, $P < 0.001$), but not with others parameters. The inflammatory marker, such as CRP, showed a positive correlation with BMI ($r = 0.265$, $P < 0.05$). FTI negatively correlated with BoCM ($r = -0.952$, $P < 0.001$). A very strong negative correlation was also found between FTM and SM ($r = -0.991$, $P < 0.001$).

Nutritional BCM parameters had no significant correlation with albumin and hemoglobin. Creatinine had a negative correlation with patient's age ($r = -0.341$, $P < 0.01$), but did not correlate with nutritional BCM parameters.

Table 1. Comparison of patient characteristics in alive and deceased groups

Variable	Alive	Deceased	*P* value
Age	**58.9 ± 15.5**	**70.8 ± 11.3**	**0.008**
Creatinine	**972 ± 260**	**816 ± 160**	**0.04**
Albumin	35.7 ± 2.2	35 ± 2.1	0.29
CRP	**5.9 ± 6.8**	**12.4 ± 10.3**	**0.04**
Hemoglobin	110 ± 11.8	113 ± 11.6	0.85
Duration of dialysis	43 ± 38	78.8 ± 64	0.05
BMI	25.6 ± 4.8	25.5 ± 4.6	0.94
Weight	75 ± 16.8	67.8 ± 14.8	0.14

Age (year); Creatinine (μmol/L); albumin (g/L); CRP, C-reactive protein (mg/L); hemoglobin (g/L); duration of dialysis (year); BMI, body mass index (kg/m^2); weight (kg).

Table 2. Comparison of bioimpedance measured nutritional parameters in alive and deceased groups

Variable	Alive	Deceased	*P* value
SM	40.1 ± 7.6	35.9 ± 6.1	0.05
SMI	**10 ± 1.4**	**8.96 ± 1.0**	**0.009**
LTM	68.4 ± 12.4	63.3 ± 10.5	0.154
LTI	**17 ± 2.2**	**15.8 ± 1.7**	**0.03**
FFM	72.6 ± 13.1	67.3 ± 11.3	0.165
FFMI	**18.1 ± 2.3**	**16.8 ± 1.8**	**0.04**
FTM	27.3 ± 13.1	32.6 ± 11.3	0.167
FTI	7.4 ± 4.6	8.7 ± 4.4	0.345

SM, skeletal muscle mass (%); SMI, skeletal muscle mass index (kg/m^2); LTM, lean tissue mass (%); LTI, lean tissue index (kg/m^2); FFM, fat free mass (%); FFMI, fat free mass index (kg/m^2); FTM, fat tissue mass (%); FTI, fat tissue index (kg/m^2).

Table 3. The relationship between bioimpedance indices and outcomes in logistic regression univariate analysis

Variable	Coefficient	Odds ratio (95% CI)	*P* value
SMI	−0.648	0.523 (0.309 to 0.885)	0.016
LTI	−0.323	0.724 (0.526 to 0.996)	0.047
FFMI	−0.298	0.7 (0.549 to 1.002)	0.052
FMI	0.060	1.062 (0.938 to 1.202)	0.342

SMI, skeletal muscle mass index; LTI, lean tissue index; FFMI, fat free mass index; FTI, fat tissue index.

For selection of the most important nutritional BCM measured parameter related to survival, we performed univariate logistic regression analysis. Binary logistic regression analysis showed that SMI and LTI were significantly related to outcomes: lower SMI and lower LTI were associated with an increased risk of death (Table 3).

Table 4. Multivariate logistic regression analysis

Variable	Coefficient	Hazard ratio (95% CI)	*P* value
Age	0.05	1.05 (0.99 to 1.1)	0.1
SMI	–0.634	0.53 (0.29 to 0.97)	0.04
CRP	0.08	1.08 (0.99 to 1.2)	0.09
Creatinine	–0.002	0.998 (0.994 to 1.002)	0.4

SMI, skeletal muscle index; CRP, C-reactive protein.

The factors, which were significant in univariate analysis, were used in the multivariate logistic regression model (Table 4).

As we found a very strong linear correlation between SMI and LTI (Pearson correlation coefficient r = 0.99, $P < 0.001$), we could not use both variables in one multivariate model. As SMI difference was more pronounced between deceased and alive patients, we chose this factor for further multivariate analysis. Even when adjusted to age, creatinine and CRP, lower SMI remained significantly related to worse survival in the multivariate logistic regression model.

Kaplan-Meier analysis revealed that higher SMI was associated with better survival during follow-up. We divided all the patients into two groups according to the 10 kg/m^2 cut-off of SMI detected by the ROC curve: the group of patients with SMI $\geqslant$ 10 kg/m^2 had better survival than the group of patients with SMI < 10 kg/m^2 ($P = 0.006$) (Figure). The latter group was significantly older (mean age 64.9 vs. 56.8 years), had higher fat mass (33.1 vs. 21.8%) and a higher fat mass index (8.7 vs. 6.2 kg/m^2), although BMI did not differ.

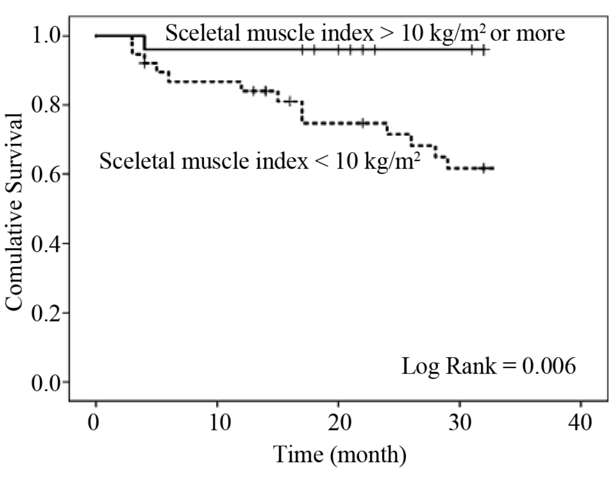

Figure. Kaplan-Meier survival curves according to skeletal mass index in hemodialysis patients

Discussion

In this study, we compared 8 different BCM measured nutritional parameters and found that the skeletal muscle index was the strongest predictor of survival compared with other parameters: the higher skeletal muscle index was associated with better survival. Our results showed that directly measured BCM nutritional parameters, expressed as a percentage of total body mass, were not good markers predicting survival. However, when BCM parameters were normalized to the body surface area (m^2), these indices were associated with patients' outcomes in univariate analysis.

Sarcopenia is a syndrome characterized by the progressive loss of muscle mass and strength [13]. Initially, the term "sarcopenia" was introduced by Rosenberg to describe the age-related progressive loss of muscle mass (primary sarcopenia as a geriatric sindrome) [14]. Recently, the debate has occured as to whether sarcopenia should include all others forms of muscle wasting related to chronic medical disease, endocrine derangement, starvation, immobilization, or cachexia (secondary sarcopenia). The criteria for sarcopenia were defined for elderly patients according to the EWGSOP (European Working Group on Sarcopenia in older people), but not for hemodialysis patients [15]. Malhotra et al. [16] highlight the need to develop appropriate cut-off values of muscle and fat mass for predicting mortality in MHD patients. The cut-off we chose by the ROC curve was 10 kg/m^2. Survival in these groups was significantly different in univariate and multivariate analyses, when adjusted to age, CRP and creatinine.

BMI, commonly used as a nutritional marker, has an impact on the clinical outcome in CKD. BMI values lower than 23 are associated with a high death risk in maintenance dialysis patients. But BMI is related mostly to fat mass rather than lean mass; furthermore, this value does not differentiate body composition from fluid compartment. Consequently, stable BMI does not mean stable body composition. Reduction of lean mass including skeletal mass can be masked by an increment of fat mass and/or extracellular water. Therefore, BMI is not a sensitive nutritional marker, and early nutritional disorders can be missed when only BMI is being monitored. In our study, no relationship was observed between BMI and outcomes.

Our results showed a strong negative correlation between SM and FM (r = –0.991, $P < 0.001$). A reduced amount of lean body mass and skeletal muscle as a part of LTM with an increased amount of FM is called sarcopenic obesity (SO) and is associated with increased morbidity and mortality in geriatric and oncological patients [15, 16]. In a sample of 122 HD patients, Malhotra et al. [17] showed that there were many sarcopenic obesity criteria and they were of limited utility in predicting all-cause mortality in prevalent MHD patients. They explained that the different ratios for lean to fat mass may have different outcomes and further we need to find new criteria for SO definitions. The importance of lean muscle and fat mass was evaluated in the study of body composition and survival by Marcelli et al. [18], where patients with both lean muscle and fat mass within 10th–90th percentile of health population were associated with the best survival, whereas patients with low muscle and low fat indices were associated with poor outcomes. We demonstrated that patients with low SMI had higher mortality, but we did not find any significant relationship between FM and survival groups. We showed that the group of deceased patients had a tendency of higher FM percent, but this was not statisticaly confirmed.

Among biochemical analyses, serum albumin concentration is widely used in nutritional status assesments both in clinical practice and for scientific purposes. However, in patients with CKD, the serum albumin concentration is influenced by fluid overload, protein loss with urine, and dialysate. Many studies show a weak association between serum albumin and other nutritional markers [19]. Supporting this trend, our study did not reveal a significant correlation between serum albumin and BCM measured nutritional markers.

The nutritional status of dialysis patients is influenced by inflammation. Chronic inflammation can induce catabolic processes including protein degradation in muscle through the activation of the ubiquitin-proteosome system, insulin resistance, reduced protein synthesis, and increased resting energy expenditure. Following these data, Kaizu et al. [20] revealed an inverse correlation between inflammatory markers and muscle mass. In our study, we did not observe a correlation between SMI and CRP in any of the groups. However, a low-grade chronic inflammation may not influence albumin and CRP concentration, but at the same time can stimulate the slow process of muscle loss. In our study, a significantly higher CRP level was detected in the group of deceased patients, and a positive, although not very strong, correlation was found between CRP and BMI.

Serum creatinine is a surrogate marker of muscle mass, but it is considered to be inaccurate and dialysis dose dependent. Thus, it is not recommended to use the creatinine level as a nutritional marker [21]. Nonetheless, in some studies, an association between lean tissue and creatinine was observed. Noori et al. [22] reported a positive correlation between serum creatinine and lean body mass measured by dual-energy X-ray absorptiometry. Similar results were noted by Patel et al. [23]. Contrary to these observations, in our study we did not find any correlation between serum creatinine and any BCM measurement nutritional marker in any groups.

The present study has several limitations. First, the relatively small sample size of our MHD database precludes our ability to perform detailed analysis and detect significant associations between body composition indices and mortality. Second, body composition measurements were obtained only at baseline. It might be that body composition of the patients changed during follow-up. Thus, the association between repeated BCM measurements and survival is a target of our future longitudinal research.

In conclusion, our data showed that, of all measured nutritional parameters, the skeletal muscle index was the most important predictor for survival derived. The lower skeletal muscle index was associated with the increased risk of death.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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