

Relationship between the target dose for hemodialysis adequacy and nutritional assessment

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BACKGROUND: Some studies have shown an increased relative risk of death for patients with higher levels of Kt/V, which may be associated with marked malnutrition.

OBJECTIVE: The aim of this study was to investigate the relationship between the target dose for hemodialysis adequacy, as measured by Kt/V, and various nutritional parameters in hemodialysis patients.

DESIGN: Cross-sectional.

SETTINGS: Sakarya University Faculty of Medicine, Turkey between February 2014 and March 2014.

PATIENTS AND METHODS: For consecutive patients who met criteria, the following were recorded: nutritional status, dialysis malnutrition score (DMS), the geriatric nutritional risk index (GNRI), serum albumin level, anthropometric measurements, and bioelectrical impedance analysis. Patients were classified into two groups according to the target hemodialysis dose for single-pool Kt/V: patients with spKt/V ≥ 1.4 and patients with spKt/V < 1.4 .

MAIN OUTCOME MEASURE(S): Association of hemodialysis adequacy by nutritional assessment.

RESULTS: The prevalence of malnutrition in 286 patients with target dose hemodialysis (spKt/V ≥ 1.4) was significantly higher according to body mass index (BMI), DMS, and GNRI ($P=.001$, $P=.006$, and $P=.004$, respectively) compared with patients with a lower target dose (spKt/V < 1.4). BMI, biceps skinfolds, mid-arm circumference, calf circumference, fat free mass, and total body water were statistically significantly lower in patients at a higher target dose (spKt/V ≥ 1.4) ($P<.001$, $P=.034$, $P=.010$, $P<.001$, $P<.001$, and $P<.001$ respectively).

CONCLUSIONS: Malnutrition was more frequent in chronic hemodialysis patients who received the target hemodialysis. Evaluation of nutritional status in patients at the target hemodialysis dose should be considered.

LIMITATIONS: Data collected from a single region; small sample size; cross-sectional design is disadvantageous.

Malnutrition is one of the most important causes of mortality and morbidity among hemodialysis (HD) patients.¹ Loss of appetite, dietary limitations, depression, hypermetabolism, metabolic acidosis, decreased physical activity, decreased anabolism, comorbidities, and dialysis all contribute to the development of malnutrition in these patients.² The results of several studies suggest that the prevalence

of malnutrition among maintenance HD patients ranges between 20% and 70%.³ In addition to biochemical and anthropometric nutrition assessment tools, bioelectrical impedance analysis (BIA), the dialysis malnutrition score (DMS), the malnutrition inflammation score, and the geriatric nutritional risk index (GNRI) can be used to identify malnourished HD patients.³

The goal of HD is to effectively eliminate uremic

toxins from the body. The adequacy of HD is directly related to the patient's quality of life, morbidity, rate of hospital admissions, and mortality.^{3,4} The kinetic model of urea (Kt/V) is the standard of care for measurement method of HD efficiency.⁵ Furthermore, Kt/V urea is the primary prescription parameter in current guidelines for HD adequacy,^{6,7} and adequate Kt/V urea values significantly decrease mortality.⁸ In addition, a correlation between inadequate dialysis and poor outcomes among HD patients has also been demonstrated.^{3,4,8} On the other hand, some studies have showed an increased relative risk of death for patients with a high level of HD adequacy.⁹⁻¹¹ The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines currently recommend that the minimally adequate HD dose should be a single-pool Kt/V (spKt/V) of 1.2, and the target HD dose should be a spKt/V of 1.4 for HD patients with minimal residual renal function.⁶

In this context, we designed this study to investigate a possible association between the level of hemodialysis adequacy and malnutrition, which are both related to morbidity and mortality among our HD patients. There are a paucity of data on the relationship between the target HD dose of spKt/V and DMS and GNRI. In the current study, we also investigated the relationship between the target dose of HD and different nutritional assessment methods such as DMS, GNRI, biochemical and antropometric tools, and BIA.

PATIENTS AND METHODS

This was a cross-sectional study conducted on all consecutive patients at our HD centers who fulfilled inclusion criteria. Inclusion criteria were age >18 years old, receiving conventional HD treatment for at least three months, and a minimal residual renal function (<2 mL/min per 1.73 m²). The patients were recruited from the three HD centers in our city between February 2014 and March 2014. HD sessions required 4 hours and were performed three times per week for all patients. Patients received dialysis with a standard bicarbonate-containing dialysate bath using a biocompatible HD membrane (Polysulfone, FX series, Fresenius, Germany). Dialysate flow rates were 500 mL/min and blood flow rates were 250–350 mL/min. Exclusion criteria were pregnancy, active infection, malignancy, thyroid dysfunction, unstable clinical conditions such as severe cardiac-pulmonary-hepatic or neurological disease, having a metal prosthesis or a cardiac pacemaker (due to possible interference with the BIA), having fistula or catheter dysfunctions, major amputation of the leg (for BIA), and having advanced dementia that would prevent patients from answering questions. In addition, we

excluded patients who did not receive their prescribed dialysis dose, or were diagnosed with liver cirrhosis, or showed persistent non-compliance with their dialysis therapy such as missed and shortened dialysis sessions.

Patients followed a nutrition program with a diet appropriate for end-stage renal disease¹² and comorbidities (e.g. diabetes) under the control of a dietitian. The study was approved by the Ethics Committee of the our University Faculty of Medicine. Written informed consent was obtained from all participants before study inclusion.

Study patients were classified into two groups according to the target HD dose of spKt/V. While first group consisted of patients receiving the recommended target HD dose (spKt/V ≥1.4), second group consisted of patients receiving a non-target HD dose (spKt/V <1.4). Nutritional parameters and malnutrition rates were compared between these groups.

Definition of the target HD dose of spKt/V

Dialysis efficiency, expressed as spKt/V urea, was calculated according to the single-pool second generation equation of Daugirdas.⁵ Daugirdas second-generation formula is as following: $spKt/V = -\ln(R-0.008 \times t) + [(4-3.5 \times R) \times UF / W]$ (UF=ultrafiltration (in liters), W=post-dialysis weight (in kilograms), t=duration of dialysis session, R=Ct/Co, Ct=urea concentration at the end of dialysis session, Co=urea concentration at the start of dialysis session).⁵ Blood sample collection during pre- and post-dialysis used the slow flow/stop pump sampling method recommended by the guidelines.⁶ Arithmetic average of the last three months spKt/V urea values were calculated for all patients. In accordance with the KDOQI guidelines, the target HD dose Kt/V was defined as a value of spKt/V ≥1.4.⁶

Dialysis malnutrition score

Developed by Kalanter Zadeh et al,¹³ DMS is a method used for nutritional evaluation of HD patients on the basis of a subjective global assessment, including nutrition-related medical history and a brief physical examination. This modified quantitative subjective global assessment of nutrition has seven components: weight changes, gastrointestinal symptoms, dietary intake, functional capacity, comorbidities, loss of subcutaneous fat, and muscle wasting.¹³ Each component is scored between 1 (normal) and 5 (very severe). Therefore, the DMS score is a number between 7 (normal nutrition) and 35 (severe malnutrition). The DMS scores of patients were calculated and those with a score of 11–35 were considered to have malnutrition.¹³

Geriatric nutritional risk index

The GNRI was calculated as reported by Yamada et al: $GNRI = [14.89 \times \text{albumin (g/dL)}] \pm [41.79 \times (\text{body weight/ideal body weight})]$.¹⁴ We used the value at the end of the dialysis session as the body weight, and it was also used for the calculation of the body mass index (BMI). Body weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight.¹⁴ Ideal body weight was calculated using height and a BMI of 22 in accordance with the study by Yamada et al.¹⁴ Patients whose GNRI was lower than 92 were considered to have malnutrition.¹⁵

Anthropometric measurements

The triceps skinfolds (TSF), biceps skinfolds (BSF), mid-arm circumferences (MAC), and calf circumferences (CC) of all patients were measured between 10–20 minutes after the dialysis session. Measurements were performed using standard techniques, and after three measurements, an average of these measurements was taken.¹⁶ All measurements were performed on the non-fistula arm. TSF and BSF were measured with a standard skinfold caliper, and MAC and CC were measured with a metal tape measure by the same trained researcher. Mid-arm muscle circumference (MAMC) was calculated using the following formula: $MAMC = MAC - (3.1415 \times TSF)$.¹⁶ BMI was calculated after dialysis as the body weight in kilograms divided by the square of the height in meters (kg/m^2).¹⁷ Patients with a BMI $< 18.5 \text{ kg/m}^2$ were considered malnourished in accordance with the World Health Organization criteria.¹⁷

Laboratory evaluation

All laboratory values were obtained from patients' dialysis records. Predialysis blood samples were taken after an overnight fast for serum total cholesterol, triglyceride, albumin, total protein, parathyroid hormone (PTH), calcium, phosphorus, C-reactive protein (CRP), creatinine, urea, uric acid, ferritin, total iron binding capacity, and hemoglobin. CRP was assayed using the immunoturbidimetric method (normal range of CRP: 0–5 mg/L), whereas the quantitative colorimetric method was used for serum albumin measurement. PTH was measured by chemiluminescence (reference values: 16–87 pg/mL). All other laboratory parameters were measured using standard laboratory methods. Patients with albumin $< 3.5 \text{ g/dL}$ were considered malnourished.¹⁵

Body composition measurements

Body compositions were analyzed using the Body Composition Analyzer (Tanita SC 330S) 30 minutes after dialysis. BIA measurements were performed while pa-

tients stood barefoot on the metal surface of the device and kept their arms loose and in parallel with the body. Measurement took 1–2 minute(s) for each patient, and results were automatically printed out from the device. Body fat percentage, fat free mass (FFM), and total body water (TBW) were measured by BIA.

Statistical analysis

Continuous variables with a normal distribution (based on the Kolmogorov–Smirnov test) were reported as mean and standard deviation (SD), whereas median and interquartile range (IR) were used for non-normally distributed data. Categorical variables were expressed as number and percentage. Normally-distributed continuous parameters were compared using the *t* test, and non-normally distributed parameters were compared using the Mann–Whitney U-test. Spearman's correlation test was used to determine the relationship between the markers of nutritional status and spKt/V . A *P* value of $< .05$ was considered as statistically significant. SPSS version 17.0 was used to conduct the statistical analyses.

RESULTS

Among the 286 patients included in the study, 168 were male (58.7%), and the average age was 60.8 (13.9) years. Patient demographics are presented in **Table 1**. The rate of patients with $\text{spKt/V} \geq 1.4$ was 73.7% among women and 46.4% among men ($P < .001$). **Table 2** shows the parameters related to the nutritional status of patients according to the target spKt/V . The anthropometric measurements such as BMI, BSF, MAC, and CC values were significantly lower in the $\text{spKt/V} \geq 1.4$ group ($P < .001$, $P = .034$, $P = .010$, and $P < .001$, respectively). Similarly, the mean FFM and TBW values from the BIA evaluation were lower in the $\text{spKt/V} \geq 1.4$ group ($P < .001$ and $P < .001$, respectively). While the mean DMS was higher in the group with $\text{spKt/V} \geq 1.4$, the mean GNRI was lower ($P = .011$ and $P = .001$, respectively). Prevalence of malnutrition in female and male patients were same according to albumin, BMI, and GNRI ($P = .133$, $P = .117$, and $P = .065$, respectively). However, according to DMS, malnutrition was higher in women compared to men (61% vs 41.6%, respectively) ($P = .001$).

The prevalence of malnutrition was significantly higher in the group with $\text{spKt/V} \geq 1.4$ according to BMI, DMS, and GNRI ($P = .001$, $P = .006$, and $P = .004$, respectively; **Table 3**). In the group with $\text{spKt/V} \geq 1.4$, a significant negative correlation was found between spKt/V and albumin, BMI, GNRI, MAMC, and CC, whereas there was a significant positive correlation between

Table 1. Characteristics of chronic hemodialysis patients.

	All patients (n=286)	Kt/V urea <1.4 (n=121)	Kt/V urea ≥1.4 (n=165)	P
Age (year)	60.8 (13.9)	59.8 (11.5)	61.6 (15.5)	.302
Gender (female/male)	118/168	31/90	87/78	<.001
Dialysis vintage (month)	42 (20-80)	34 (18-72.5)	50 (21-84.5)	.076
Diabetes %, (n)	33.6 (96)	33.9 (41)	33.3 (55)	.922
Hypertension %, (n)	73 (209)	74.3 (90)	72.1 (119)	.343
History of CAD %, (n)	18.5 (53)	20.7 (25)	17 (28)	.260
Previous CVD %, (n)	5.5 (16)	6.6 (8)	5.4 (9)	.363
spKt/V urea	1.5 (1.3-1.6)	1.3 (1.2-1.4)	1.6 (1.5-1.7)	<.001
Urea reduction rate (%)	71 (67-76)	66 (63-68)	75 (71-78)	<.001
Creatinine (mg/dL)	7.2 (6-8.8)	7.4 (6.4-9)	7.1 (5.8-8.5)	.090
Hemoglobin (g/dL)	10.8 (1.2)	10.8 (1.2)	10.7 (1.2)	.378
Total protein (g/dL)	6.6 (6.2-7)	6.6 (6.2-7.1)	6.6 (6.3-6.9)	.534
LDL cholesterol (mg/dL)	103 (35)	104 (39)	102 (32)	.507
Triglyceride (mg/dL)	139 (105-193)	146 (105-219)	137 (105-180)	.517
PTH (pg/mL)	350 (181-564)	360 (210-535)	332 (176-591)	.722
Calcium (mg/dL)	8.5 (0.8)	8.5 (0.8)	8.5 (0.8)	.995
Phosphorus (mg/dL)	4.8 (3.8-5.7)	4.9 (3.9-5.6)	4.7 (3.7-5.8)	.594
Uric acid (mg/dL)	5.5 (4.8-6.1)	5.5 (5-6.1)	5.4 (4.8-6.3)	.708
TIBC (µg/dL)	177 (153-205)	177 (157-221)	176 (152-201)	.163
Ferritin (ng/mL)	439 (287-650)	417 (276-568)	470 (293-669)	.063
CRP (mg/L)	5.6 (2.2-11.3)	7.3 (3.2-11.2)	4.6 (1.9-12.1)	.200

CAD: Coronary artery disease; CVD: Cerebrovascular disease; LDL: low density lipoprotein; PTH: parathyroid hormone; TIBC: total iron binding capacity; CRP: C reactive protein.

Table 2. Nutritional parameters of hemodialysis patients according to target hemodialysis dose of spKt/V urea.

	All patients (n=286)	Kt/V urea <1.4 (n=121)	Kt/V urea ≥1.4 (n=165)	P
Albumin (g/dL)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	.603
Total cholesterol (mg/dL)	172 (46)	173 (50)	171 (44)	.707
BMI (kg/m ²)	24.8 (4.9)	26.1 (4.9)	23.9 (4.7)	<.001
Height (cm)	165 (156-170)	168 (163-175)	160 (155-168)	<.001
Weight (kg)	67.2 (15.1)	74.1 (14.6)	62.1 (13.5)	<.001
TSF (mm)	11 (8-15)	11 (8-14)	10 (7-15)	.507
BSF (mm)	10 (8-14)	10 (8-10)	9 (7-14)	.034
MAMC (cm)	22.3 (2.9)	22.9 (3.1)	21.9 (2.7)	.003
MAC (cm)	26.1 (24-28.2)	26.2 (24-29)	25.2 (23-28)	.010
Calf circumference (cm)	32.5 (4.1)	34 (4)	31.4 (3.9)	<.001
Percentage body fat	25.3 (9.9)	23.7 (9)	26.5 (10.4)	.058
Fat mass (kg)	16.6 (10.8-23.2)	16.6 (10.9-22.3)	16.7 (10.7-23.8)	.943
Fat free mass (kg)	49 (9.6)	54.9 (8.1)	44.9 (8.3)	<.001
Total body water (kg)	36 (6.7)	40.2 (5.9)	36 (6.7)	<.001
DMS	10 (9-13)	10 (9-12)	11 (9-14)	.011
GNRI	105.6 (11.9)	108.2 (12.1)	103.6 (11.5)	.001

BMI: body mass index; TSF: triceps skinfold thickness; BSF: biceps skinfold thickness; MAMC: mid-arm muscle circumference; MAC: mid-arm circumference; DMS: dialysis malnutrition score; GNRI: geriatric nutritional risk index.

Table 3. The prevalence of malnutrition according to target hemodialysis dose of spKt/V urea.

Nutritional evaluation	All patients %, (n=286)	Kt/V urea <1.4 %, (n=121)	Kt/V urea ≥1.4 %, (n=165)	P
Albumin <3.5 gr/dL	12.5 (36)	12.3 (15)	12.7 (21)	.541
BMI <18.5 kg/m ²	8.7 (25)	2.4 (3)	13.3 (22)	.001
DMS 11-35	49.6 (142)	40.4 (49)	56.3 (93)	.006
GNRI <92	11.8 (34)	5.7 (7)	16.3 (27)	.004

BMI: body mass index; DMS: dialysis malnutrition score; GNRI: geriatric nutritional risk index.

spKt/V and DMS (Table 4). However, while there were positive correlations between spKt/V and albumin and GNRI in the group with spKt/V <1.4, a negative correlation was observed between the same parameters in the group with spKt/V ≥1.4 (Table 4).

DISCUSSION

Among the chronic HD patients evaluated in the current study, we found that the prevalence of malnutrition was significantly higher in those in whom the spKt/V value was ≥1.4 as compared with those whose spKt/V value was <1.4 using DMS, GNRI, and BMI. To the best of our knowledge, the current study is the first to examine the relationship between the target adequate HD dose of spKt/V and DMS and GNRI in chronic HD patients. The nutritional status impairment observed in dialysis patients is strongly associated with increased morbidity and mortality.^{1,3,4} In addition, nutritional status is an important predictor of survival in HD patients.^{1,3} Protein-energy wasting (PEW) may develop in HD patients for multifactorial reasons mentioned above.² On the other hand, there is an increased relative risk of death for patients with a high level (>1.6) of Kt/V.^{9,10} This increased death rate may be associated with marked malnutrition in such patients.^{9,10} Similarly, Salahudeen et al defined a "paradox of Kt/V urea" as having a Kt/V urea >1.6 associated with higher mortality compared to patients whose Kt/V urea was 1.2-1.3.¹¹ In this prospective study of 9 months on 1151 patients, it was postulated that the paradox of Kt/V urea was common in HD patients whose weight was lower than 70 kg and who had low values of prealbumin.¹¹ In the current study, malnutrition was more frequent among patients whose spKt/V values were higher by comparison.

The results of our study indicated that anthropometric parameters, such as BMI, BSF, MAC, and CC, were lower in patients whose spKt/V value was ≥1.4 as compared with those in whom spKt/V value was <1.4. BMI has been correlated with body fat and can be used as a nutritional status indication.¹⁸ Low BMI is an independent risk factor for death in HD patients.³ Lowrie

Table 4. Correlation coefficients between spKt/V urea and nutrition related parameters in chronic hemodialysis patients.

Parameters	Kt/V urea (Kt/V urea <1.4 group)	Kt/V urea (Kt/V urea ≥1.4 group)
Albumin (gr/dL)	0.306 (P=.001)	-0.212 (P=.006)
BMI (kg/m ²)	0.057 (P=.532)	-0.105 (P=.180)
GNRI	0.209 (P=.021)	-0.210 (P=.007)
Dialysis malnutrition score	-0.111 (P=.227)	0.198 (P=.011)
MAMC (cm)	0.094 (P=.306)	-0.195 (P=.012)
Calf circumference (cm)	-0.039 (P=.672)	-0.192 (P=.013)

BMI: body mass index; GNRI: geriatric nutritional risk index; DMS: dialysis malnutrition score; MAMC: mid arm muscle circumference; CC: calf circumference.

et al found that smaller HD patients had an increase in mortality risk with lower dialysis doses.¹⁹ Furthermore, additional studies demonstrated that patient mortality depended on both body size and a dialysis dose parameter.²⁰ Similar to results obtained in the current study, Nunes et al reported that height and weight values for HD patients whose Kt/V value was <1.2 were higher.²¹ Malnutrition may cause a smaller body mass, and therefore, a lower volume and a higher Kt/V value. Patients with severe malnutrition generally have a reduced body weight, and therefore, might appear to have a high Kt/V value.²¹ Many studies have reported a relationship between the increase in Kt/V and hospitalization and mortality.²⁰⁻²⁴

Body composition measurements provide important information on the nutritional status of dialysis patients.²⁴ Muscle mass is important for HD patients, as it is a marker of protein nutritional status.²⁴ In addition, the decrease in muscle mass in HD patients is significantly correlated with higher mortality.²⁵ In the current study, we found significantly lower FFM and TBW values in patients with spKt/V ≥1.4 than in those with spKt/V <1.4

in the BIA evaluation. Serum creatinine levels were also lower in patients with $\text{spKt/V} \geq 1.4$. Various factors affect protein metabolism in HD patients, and as catabolism increases, a decrease in lean body mass ensues.² A low plasma creatinine level may indicate decreased muscle mass in malnourished patients. Serum creatinine may also affect hydration status, residual renal function, and dietary protein intake.³ On the other hand, Kt/V is not an independent variable; it may be affected by protein intake and body composition. For example, some studies have reported that Kt/V is high when the muscle mass of patients is low, regardless of HD efficacy.^{10,26} Therefore, all of these conditions should be taken into consideration when Kt/V values of patients are evaluated.

In the current study, target $\text{spKt/V} \geq 1.4$ was higher in female patients than in male patients. Dialysis efficiency is inversely proportional with urea distribution volume. Therefore, lower dialysis efficiency is expected in patients with greater body surface areas. As the body surface areas of males are genetically larger than those of females, dialysis efficiency may be lower in males in general. In addition, the HEMO study reported a lower mortality rate in female patients receiving a high dose of HD as compared with those who received a standard dose of HD.²⁷ However, this difference has not been determined for males.²⁷ Although this difference may be attributable to differences in body size, some currently unidentified factors may also be involved. Similarly, no relationship was found between dialysis dose and age, diabetes, other comorbidities, and serum albumin in the HEMO study.²⁷

In the current study, spKt/V was found to be sig-

nificantly and negatively correlated with albumin, BMI, GNRI, MAMC, and CC among patients with $\text{spKt/V} \geq 1.4$, whereas it was found to be significantly and positively correlated with DMS. While high rates of BMI, GNRI, MAMC, and CC indicate good nutritional status, the increase in DMS demonstrates a malnutrition status. These results have collectively indicated that there is a relationship between an increase in spKt/V and malnutrition in patients with $\text{spKt/V} \geq 1.4$. In other words, severe PEW may occur with weight loss and muscle mass loss in patients with target spKt/V values. Nunes et al. reported a negative correlation between Kt/V and BMI, but did not find a correlation between most anthropometric parameters and Kt/V .²¹ Our study shows that patients with high spKt/V might have poor nutritional status. On the other hand, adequate HD and good nutritional status are associated with better survival.^{3,4} Thus, we suggest that patients who have adequate HD but poor nutritional status might benefit from expert nutritional support.

Limitations of our study were that data were from a single center, the sample size was relatively small, and the cross-sectional study design is disadvantageous.

In conclusion, the current study demonstrated that malnutrition is significantly higher in HD patients with $\text{spKt/V} \geq 1.4$. When spKt/V is considered as dialysis adequacy in patients on maintenance HD, it is important to review the nutritional status of such patients, along with factors such as dialyzer size, blood flow, HD treatment duration, and fistula integrity.⁶ Therefore, it may be beneficial to evaluate the nutritional status of patients whose Kt/V value is on or above the target HD dose with parameters such as BMI, GNRI, DMS, MAMC, and CC.

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