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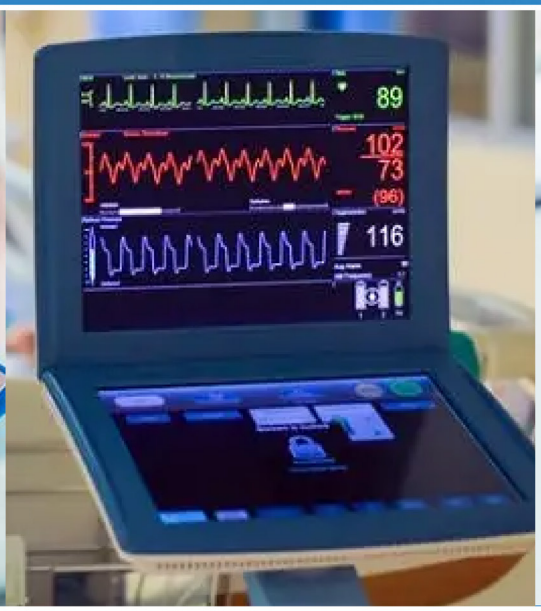

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Original Article

Assessment of nutritional parameters in elderly hemodialysis patients

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ABSTRACT

Aims: Malnutrition is a common and important condition in hemodialysis patients, associated with increased mortality and morbidity. This study aimed to identify parameters that may be associated with the level of malnutrition in elderly hemodialysis patients and to determine the most reliable parameter for detecting malnutrition in the elderly hemodialysis patient population.

Methods: This single-center, cross-sectional study evaluated 136 patients aged ≥65 years who were undergoing hemodialysis across four different units. We evaluated sociodemographic characteristics, laboratory parameters, and comorbidities. The Controlling Nutritional Status (CONUT), body-mass index (BMI), Geriatric Nutritional Risk Index (GNRI), Malnutrition Inflammation Score (MIS), subjective global assessment (SGA), and normalized protein nitrogen appearance (nPNA) scales were applied to assess the nutritional status of patients.

Results: The median age was 73 (IQR:69-77) years, hemodialysis duration was 4 (IQR:2-7) years, and BMI was 25.28 (IQR:22.08-28.39) kg/m^2. According to SGA, malnourished patients were older and had significantly lower abdominal skinfold thickness (ASF), triceps skinfold thickness (TSF), and waist circumference (all $p<0.01$). Malnutrition was detected in 22.8% of patients by BMI, 49.3% by MIS, 44.1% by SGA, 66.2% by CONUT, and 11.8% by GNRI. There was no significant difference between the malnourished and well-nourished groups regarding nPNA and hemodialysis duration ($p>0.05$).

Conclusion: MIS was found to be near-ideal tests for detecting malnutrition in elderly hemodialysis patients. GNRI was usable in identifying the healthy population. The validity of the CONUT test was weak. When anthropometric measurements were evaluated for detecting malnutrition in elderly hemodialysis patients, TSF and ASF were close to ideal.

Keywords: Malnutrition, chronic kidney disease, anthropometry

INTRODUCTION

Malnutrition is a common condition in end-stage renal disease (ESRD) patients, with a reported global prevalence of 28-54% in hemodialysis patients.[1] Malnutrition has a multifactorial origin and is strongly associated with increased mortality, morbidity and decreased quality of life.[2]

As a result of increased life expectancy, the world's population is aging. The elderly population (aged 65 and over) with chronic diseases who are dependent on others have difficulty ensuring healthy nutrition. Malnutrition is a significant health problem most seen in the elderly population.[3]

In the diagnosis of malnutrition, anthropometric measurements, biochemical tests, combined assessments of dietary intake and compliance, and combined nutritional indices can be used to evaluate body compartment status.[4]

This study aimed to determine the level of malnutrition in patients over 65 years of age undergoing hemodialysis treatment and to identify related laboratory parameters, comorbidities, medications used, and sociodemographic characteristics, and to compare malnutrition parameters. The aim was to find the most reliable parameter for detecting malnutrition in the elderly hemodialysis patient population.

METHODS

This study was conducted with the approval of the Non-interventional Clinical Researches Ethics Committee at Sivas Cumhuriyet University (Date: 27.07. 2022, Decision No: 2022-07/07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

Our cross-sectional, single-center study evaluated 136 patients aged 65 years and older who underwent hemodialysis treatment across four different units between August 1, 2022, and August 1, 2023. Patients under 65 years of age, those who did not sign the informed consent form, patients with malignancy, active inflammation, or oral feeding disorders, and patients receiving nutrition via percutaneous endoscopic gastrostomy (PEG) were excluded from the study. Patients were evaluated on dialysis days, prior to their dialysis sessions.

We recorded the patients' sociodemographic characteristics (age, gender, marital status, educational status, income status, place of residence, living environment, and smoking status) and clinical data, including comorbidities (diabetes mellitus [DM], hypertension [HT], coronary artery disease [CAD],

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chronic obstructive pulmonary disease [COPD], and the primary cause of chronic kidney disease). Additionally, we evaluated components of the Malnutrition Inflammation Score (MIS), such as weight change in the last 3 months, dietary intake, gastrointestinal symptoms, and functional capacity.[5] Physical examination findings (body weight, height, triceps skinfold thickness (TSF), abdominal skinfold thickness (ASF), waist circumference, and average interdialytic weight gain in the last month) and routine laboratory parameters (blood urea nitrogen [BUN], creatinine, total protein, albumin, complete blood count, lipid profile, and iron status) were obtained from the patient records.

Using the obtained data, the Controlling Nutritional Status (CONUT), Geriatric Nutritional Risk Index (GNRI), MIS, subjective global assessment (SGA), and normalized protein nitrogen appearance (nPNA) scales were applied to assess malnutrition.

Body-Mass Index (BMI)

BMI (kg/m²) is calculated using the formula: Body weight (kg)/height² (m²).[6]

Based on previous studies associating BMI<22 kg/m² with increased mortality risk in hemodialysis patients, this value was selected as the cut-off point for malnutrition diagnosis.[6]

Skin Fold Thickness Measurement

TSF and ASF were measured using a skinfold caliper according to standard anthropometric guidelines to assess body fat reserves.[7]

Waist Circumference Measurement

Waist circumference is an indicator of regional fat distribution. In older adults, waist circumference measurements have been shown to correlate highly with visceral and total fat amounts determined by computed tomography.[8]

Malnutrition Inflammation Score (MIS)

The MIS is a semi-quantitative scale assessing 10 components related to medical history, physical examination, and laboratory parameters. The total score ranges from 0 to 30, where higher scores indicate more severe malnutrition.[9]

Subjective Global Assessment (SGA)

SGA includes medical history, weight changes, changes in eating status, gastrointestinal symptoms lasting more than 2 weeks, and changes in 14 functional capacities. The physical examination assesses loss of subcutaneous fat tissue, muscle loss, ankle/sacral edema, and the presence of ascites. Patients were categorized into one of three groups: 'well-nourished' (A), 'moderately or possibly malnourished' (B), and 'severely malnourished' (C).[10]

SGA was established as the reference standard in this study, as it is a well-validated and widely recommended clinical tool by international guidelines for comprehensively assessing the nutritional status of patients with end-stage renal disease.[11]

Controlling Nutritional Status (CONUT)

CONUT is a practical and easy-to-use score that assesses patients' nutritional status using laboratory values (albumin, lymphocytes, cholesterol).

CONUT score 0-1=Normal; 2-4=Mild; 5-8=Moderate; 9-12=Severe malnutrition.[12]

Geriatric Nutrition Risk Index (GNRI)

GNRI, requires the evaluation of serum albumin and the calculation of ideal body weight using the Lorentz formula. The score is obtained according to the following equation.[13]

GNRI=(1.489×albumin (g/L))+(41.7×weight/ideal body weight)

Note: When weight exceeds ideal body weight, a score of 1 point is assigned based on the weight/ideal body weight ratio.

GNRI<92: Severe/moderate risk

GNRI=92-98: Low risk

GNRI>98: No risk

Normalized Protein Nitrogen Appearance (nPNA)

nPNA was calculated using the urea kinetic modeling approach described by Depner and Daugirdas to estimate daily protein intake. Based on the findings of the National Cooperative Dialysis Study (NCDS), an nPNA greater than 1.0 g/kg/day was accepted as adequate.[14]

Statistical Analysis

The data were analyzed using SPSS 23.0 and R Studio. The Kolmogorov-Smirnov test was used to assess normality of distribution. Since the data did not meet the assumptions of normal distribution, non-parametric tests were utilized. For the comparison of two independent groups, the Mann-Whitney U test was used. The Kruskal-Wallis test was used for non-parametric comparisons of multiple groups. Categorical variables were analyzed using the Chi-square test. When the assumption of expected frequencies was violated (expected count <5 in >20% of cells), the Likelihood ratio test was used. For descriptive statistics and baseline group comparisons, well-established literature cut-offs for nutritional indices and anthropometric measurements (e.g., BMI <22 kg/m², categorical CONUT scores, standard GNRI risk groups, and 25th percentiles for TSF and ASF) were utilized. Furthermore, to determine the maximum diagnostic accuracy specifically for this elderly hemodialysis cohort, ROC analysis was performed to evaluate the diagnostic performance of these parameters against SGA as the reference standard. The optimal cut-off values for each parameter were determined using the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) with 95% confidence intervals (CI) were calculated. Pairwise comparisons of the AUC values to determine statistical superiority among the indices were conducted using the DeLong test. Multivariate logistic regression analysis was performed to identify independent predictors of malnutrition. Our data are presented in tables as median, interquartile ranges (IQR, 25th-75th percentiles), number of individuals, and percentage, with a significance level of 0.05.

RESULTS

Our study included 136 patients aged 65 years and older undergoing hemodialysis treatment, with a median age of 73 (IQR: 69-77) years. Most patients (71.3%) were over 70 years of age. 51.5% of the patients were female. 82.4% of the patients had hypertension, 46.3% had DM, 37.5% had CAD, and 13.2%

had asthma/COPD. 86.8% of patients had been receiving hemodialysis treatment for more than 1 year, with a median dialysis duration of 4 (IQR: 2-7) years. DM (33.1%) was the most common etiology of chronic kidney disease among patients. Only 14.7% of patients were high school or university graduates. Only 14% had sufficient income.

In 22.8% of patients, BMI was below 22 kg/m², in 27.9% TSF was below the 25th percentile, and in 25% ASF was below the 25th percentile. Malnutrition was detected in 49.3% of patients according to MIS, 44.1% according to SGA, and 66.2% according to CONUT. Malnutrition risk was detected in 11.8% according to GNRI.

When sociodemographic characteristics were evaluated according to the SGA, statistically significant relationships were observed between the presence of malnutrition and both age groups (p=0.012) and smoking status (p=0.017). The prevalence of malnutrition was relatively lower in the 65-69 and 70-74 age groups (35.9% and 31.9%, respectively), but markedly increased in advanced age categories, reaching 68.2% in patients aged 80 years and older. Similarly, malnutrition was notably higher in current smokers (87.5%) compared to patients who had never smoked (45.3%) and former smokers (35.8%) (**Table 1**).

Patients with malnutrition according to SGA were found to be older (p=0.001). They had significantly lower BMI, TSF, ASF, and waist circumference (all p<0.01). While the duration of hemodialysis, HDL, nPNA, Kt/V, and urea reduction ratio (URR) did not differ, malnourished patients had lower lymphocyte counts (p<0.001), total cholesterol (p=0.012), LDL (p=0.001) and triglycerides (p=0.012) (**Table 2**).

To further identify the independent clinical predictors of malnutrition, a multivariate logistic regression analysis was performed including age, diabetes mellitus, dialysis duration, C-reactive protein (CRP), albumin, phosphorus, parathyroid hormone (PTH), and Kt/V. The analysis confirmed that advanced age was the only independent risk factor significantly associated with the presence of malnutrition (OR: 1.114, 95% CI: 1.040-1.194, p=0.002). Notably, while CRP and parathormone demonstrated statistically significant associations with malnutrition in the univariate analysis, they lost their significance in the multivariate model and were not independent predictors (p>0.05). Other variables in the model did not demonstrate statistical significance (**Table 3**).

The median age was 71 (IQR: 67-77) years for male and 74 (IQR: 70-78) years for female (p>0.05). BMI was significantly higher in female (25.73 [IQR: 23.09-29.65]) compared to men (24.12 [IQR: 21.62-27.35]) (p=0.021). TSF and waist circumference were lower in men, while ASF was higher in men, but no statistically significant differences were found (all p>0.05). The MIS score was significantly higher in female (7 [IQR: 4-9]) compared to male (4.5 [IQR: 2.75-7]) (p<0.01). GNRI was 108.5 (IQR: 102-116) in male and 113 (IQR: 104.75-121.75) in female (p>0.05).

Malnutrition according to SGA was found in 47.1% of female and 40.9% of men, but there was no statistically significant difference (p>0.05).

Among patients with SGA-defined malnutrition, 88.3% and 83.3% also had malnutrition according to MIS and the CONUT score, respectively (p<0.001 for both). Nutritional risk according to GNRI was identified in 18.3% of the patients with SGA-defined malnutrition (p=0.035). When anthropometric measurements were analyzed, TSF was below the 25th percentile in 56.7% and ASF was below the 25th percentile in 53.3% of the patients with SGA-defined malnutrition (p<0.001 for both). Furthermore, BMI was<22 kg/m² in 45% of the patients with SGA-defined malnutrition (p<0.001). No statistically significant relationship was found between SGA-defined nutritional status and gender (p>0.05) (**Table 4**).

The diagnostic performance, validity, and optimal cut-off points of the nutritional indices and anthropometric measurements were evaluated using ROC curve analysis according to SGA. The ROC curves of these analyses are illustrated in **Figure 1**. Furthermore, detailed diagnostic metrics such as sensitivity, specificity, PPV, NPV, and overall accuracy at the determined cut-off points are visually

Table 1. Evaluation of patients based on their sociodemographic characteristics and SGA

		SGA (malnutrition)		
		Absent	Present	p
		n (%)	n (%)	
Age (years)	65-69	25 (64.1)	14 (35.9)	0.012*
	70-74	32 (68.1)	15 (31.9)	
	75-79	12 (42.9)	16 (57.1)	
	>80	7 (31.8)	15 (68.2)	
Gender	Male	39 (59.1)	27 (40.9)	0.464*
	Female	37 (52.9)	33 (47.1)	
Marital status	Married	53 (55.8)	42 (44.2)	0.974*
	Single	23 (56.1)	18 (43.9)	
Education status	Illiterate	20 (50)	20 (50)	0.495†
	Literate	9 (69.2)	4 (30.8)	
	Elementary school	33 (56.9)	25 (43.1)	
	Middle school	2 (40)	3 (60)	
	High school	10 (55.6)	8 (44.4)	
	University	2 (100)	0 (0)	
Place of residence	Own residence	54 (58.7)	38 (41.3)	0.604*
	With family	9 (47.4)	10 (52.6)	
	Tenant	13 (52)	12 (48)	
Living arrangement	Alone	8 (61.5)	5 (38.5)	0.405†
	With family	68 (55.7)	54 (44.3)	
	With a caregiver	0 (0)	1 (100)	
Smoking	Non-smoker	41 (54.7)	34 (45.3)	0.017*
	Smoker	1 (12.5)	7 (87.5)	
	Ex-smoker	34 (64.2)	19(35.8)	
Hemodialysis duration (years)	<1	13 (72.2)	5 (27.8)	0.160*
	1-4	30 (51.7)	28 (48.3)	
	5-9	24 (63.2)	14 (36.8)	
	>10	9 (40.9)	13 (59.1)	
ESRD etiology	Unknown	14 (50)	14 (50)	0.090*
	DM	32 (71.1)	13 (28.9)	
	Hypertension	13 (50)	13 (50)	
	Other	17 (45.9)	20 (54.1)	

*Pearson Chi-square test was used. † Likelihood Ratio test was used. SGA: Subjective global assessment, BMI: Body-mass index, TL: Turkish lira, DM: Diabetes mellitus, ESRD: End-stage renal disease

Table 2. Comparison based on numerical measurements obtained from patients. laboratory parameters and SGA

	All patients	SGA (malnutrition)		
		Absent	Present	
	Median (IQR)	Median (IQR)	Median (IQR)	P
Age (years)	73 (69-77)	71 (68-74.75)	75.5 (70.25-79.75)	0.001
HD duration (years)	4 (2-7)	4 (1.16-7)	4 (2-8.75)	0.319
BMI (kg/m²)	25.28 (22.08-28.39)	27.04 (24.26-30.39)	22.39 (19.74-25.39)	<0.001
TSF (mm)	7.5 (5-10)	10 (7.25-12)	5 (4-6)	<0.001
ASF (mm)	10 (6-14.75)	14 (10.25-17)	6 (5-9)	<0.001
Waist circumference (cm)	98 (90.25-108)	103.5 (96-115)	92 (80-100)	<0.001
Interdialytic weight gain (kg)	2.5 (2-3)	2.75 (2-3.375)	2 (2-3)	0.052
MIS	5 (3.25-8)	4 (2-5)	8 (7-11)	<0.001
GNRI	110.5 (102.25-117)	115 (107.25-124.75)	105 (99-112)	<0.001
KT/V	1.46 (1.32-1.62)	1.41 (1.31-1.58)	1.54 (1.36-1.63)	0.083
nPNA (g/kg/day)	1.13 (0.94-1.28)	1.11 (0.91-1.289)	1.14 (0.98-1.33)	0.46
URR (%)	70.31 (66.83-74.11)	68.96 (65.21-73.78)	71.87 (67.83-74.6)	0.051
WBC (10⁹/L)	6.635 (5.18-8.16)	6.86 (5.26-8.315)	6.19 (4.76-8.06)	0.22
Neutrophils (10⁹/L)	4.13 (3.13-5.49)	4.33 (3.13-6.3)	3.68 (3.28-5.35)	0.551
Lymphocytes (10⁹/L)	1.41 (0.99-1.75)	1.62 (1.28-1.88)	1.15 (0.83-1.52)	<0.001
Hemoglobin (g/dl)	11.1 (10.07-12)	11.2 (10.13-12)	10.7 (9.8-11.8)	0.15
Hematocrit (%)	34.25 (30.3-37.335)	34.9 (31.7-37.475)	33.5 (29.5-36.38)	0.176
Platelets (10⁹/L)	186 (141.25-226.75)	181.5 (142.25-224.25)	192.5 (139.5-236.5)	0.334
Total cholesterol (mg/dl)	156 (137-179.75)	164 (139.5-196.5)	148.5 (127.5-166)	0.001
Triglycerides (mg/dl)	135.5 (104.25-211.5)	160 (116.25-232.75)	120.5 (92-175.5)	0.012
HDL (mg/dl)	38 (31-45)	38.5 (31-44)	36.5 (30.25-46.75)	0.951
LDL (mg/dl)	83 (66-103.5)	92.5 (73.25-118.75)	79 (60-93.75)	0.002
Ferritin (ug/L)	536 (269.5-725.75)	521.5 (248-702.25)	551.5 (276.25-804.25)	0.383
TS (%)	31.5 (21.25-40)	32 (20.25-42.5)	29.5 (22-38.75)	0.658
BUN (mg/dl)	69.04 (56.07-81.19)	69.19 (55.02-82.01)	68.22 (56.5405-80.4)	0.801
Creatinine (mg/dl)	6.87 (5.6-8.62)	7.16 (5.81-8.775)	6.43 (5.11-8.11)	0.128
Total protein (mg/dl)	70 (66-74.7)	70.12 (66-74.75)	69.91(65.835-74.71)	0.779
Albumin (mg/dl)	41 (37.63-44.96)	41.08(38-46.69)	40.79 (37.225-44.8)	0.372
Phosphor (mg/dl)	4.8 (3.91-5.26)	4.89 (4.05-5.25)	4.73 (3.9-5.34)	0.375
C-reactive protein (mg/L)	5.79 (1.7-17.84)	4.3 (1.06-13.72)	9.44 (2.11-34.91)	0.018
Parathormone (ng/L)	257 (169.25-409)	312 (185-467.25)	213(148.5-363.5)	0.037

SGA: Subjective global assessment, IQR: Interquartile range, HD: Hemodialysis, BMI: Body-mass index, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold thickness, GNRI: Geriatric Nutritional Risk Index, nPNA: Normalized protein nitrogen appearance, WBC: White blood cell, MIS: Malnutrition Inflammation Score, URR: Urea reduction ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TS: Transferrin saturation, BUN: Blood urea nitrogen

Table 3. Multivariate logistic regression analysis for predictors of malnutrition based on the SGA

	β	SE (β)	Wald	P	OR	%95 CI (lower-upper)
Age	0.108	0.035	9.447	0.002	1.114	1.040-1.194
DM	-0.528	0.412	1.642	0.200	0.590	0.263-1.323
HD duration	0.037	0.042	0.774	0.379	1.038	0.956-1.126
Kt/V	1.042	0.740	1.983	0.159	2.835	0.665-12.091
Albumin	-0.013	0.031	0.166	0.684	0.987	0.928-1.050
Phosphor	-0.093	0.183	0.260	0.610	0.911	0.637-1.304
CRP	0.011	0.006	3.075	0.080	1.011	0.999-1.024
Parathormone	0.000	0.001	0.435	0.510	1.000	0.998-1.001

SGA: Subjective global assessment, SE: Standard error, OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus, HD: Hemodialysis, CRP: C-reactive protein

compared in Figure 2 and comprehensively presented in Table 5.

When evaluated according to SGA:

- MIS found a PPV of 79.1%, an NPV of 89.9%, sensitivity of 88.3%, specificity of 81.6%, accuracy of 84.6% and AUC 0.934 for cut-off 5.5.
- TSF found a PPV of 78.0%, an NPV of 81.8%, sensitivity of 76.7%, specificity of 82.9%, and accuracy of 80.1% and AUC 0.878 for cut-off 6.5.
- ASF found a PPV of 72.5%, an NPV of 85.1%, sensitivity of 83.3%, specificity of 75.0%, and accuracy of 78.6% and AUC 0.872 for cut-off 10.5.
- BMI found a PPV of 67.2%, an NPV of 78.3%, sensitivity of 75.0%, specificity of 71.1%, and accuracy of 72.8% and AUC 0.792 for cut-off 25.2.
- GNRI found a PPV of 65.6%, an NPV of 73.3%, sensitivity of 66.7%, specificity of 72.4%, and accuracy of 69.8% and AUC 0.734 for cut-off 109.5.

Table 4. Comparison of nutritional parameters and scoring systems according to SGA malnutrition status

		SGA (malnutrition) (n)		
		Absent	Present	p
Gender	Male	39	27	0.464
	Female	37	33	
BMI (kg/m²)	<22	4	27	<0.001
	≥22	72	33	
MIS (malnutrition)	Absent	62	7	<0.001
	Present	14	53	
TSF (percentile)	<25	3	34	<0.001
	25-75	33	22	
	>75	40	4	
ASF (percentile)	<25	3	32	<0.001
	25-75	42	25	
	>75	31	3	
GNRI (risk)	Absent	71	49	0.035
	Present	5	11	
CONUT (malnutrition)	Absent	37	10	<0.001
	Present	39	50	

SGA: Subjective global assessment, BMI: Body-mass index, MIS: Malnutrition Inflammation Score, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold thickness, GNRI: Geriatric Nutritional Risk Index, CONUT: Controlling nutritional status

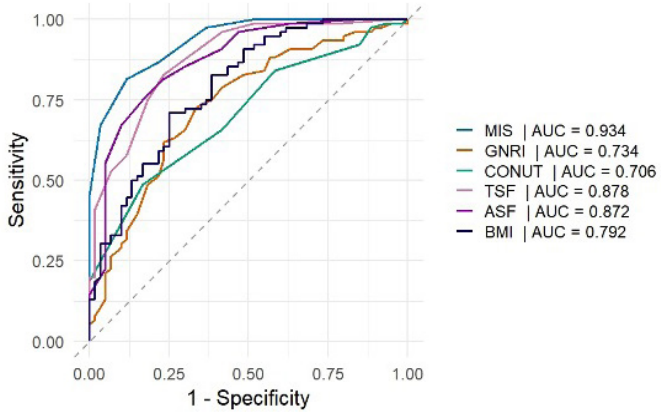

Figure 1. ROC curve analysis of various nutritional scores and anthropometric parameters for predicting malnutrition

ROC: Receiver operating characteristic, MIS: Malnutrition-inflammation score, GNRI: Geriatric Nutritional Risk Index, CONUT: Controlling nutritional status, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold, BMI: Body-mass index, AUC: Area under the curve

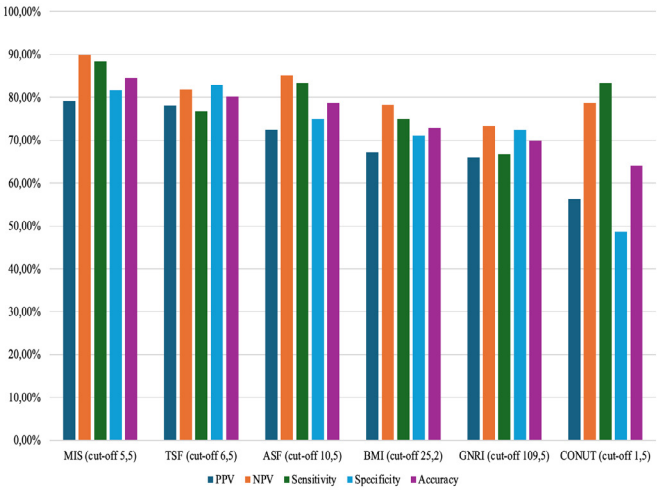

Figure 2. Evaluation of the validity of malnutrition parameters according to SGA

SGA: Subjective global assessment, MIS: Malnutrition-inflammation score, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold, BMI: Body mass index, GNRI: Geriatric Nutritional Risk Index, CONUT: Controlling nutritional status, PPV: Positive predictive value, NPV: Negative predictive value

- CONUT found a PPV of 56.2%, an NPV of 78.7%, sensitivity of 83.3%, specificity of 48.7%, and accuracy of 64% and AUC 0.706 for cut-off 1.5.

Finally, to compare the diagnostic performance of these parameters, the area under the ROC curves (AUC) was compared using the DeLong test. The analysis revealed that the AUC of the MIS was significantly higher than those of the GNRI, BMI and CONUT (all p<0.001) scores; however, the difference between the AUC of the MIS and other anthropometric measurements (TSF, ASF) did not reach statistical significance (p>0.05) (**Table 6**).

DISCUSSION

In this study, using the SGA as the reference standard, the MIS was identified as the most robust tool for assessing malnutrition in elderly hemodialysis patients, demonstrating the highest diagnostic validity. Furthermore, anthropometric measurements-specifically TSF and ASF-exhibited high diagnostic accuracy, presenting as viable and less time-consuming alternatives for clinical practice. While the BMI and GNRI provided high specificity, making them useful for confirming a well-nourished status, their clinical utility in detecting malnutrition is limited by suboptimal sensitivity. Conversely, although the CONUT score demonstrated high sensitivity, its overall diagnostic performance was compromised by low specificity, resulting in a higher rate of false positives compared to the other evaluated indices.

Malnutrition is commonly observed in hemodialysis patients, with a prevalence of 28-52% found in a meta-analysis study.[15] Many tests have been used to detect malnutrition in this patient population, but there are differing data on which one is superior.[12,16,17] In a study conducted on hospitalized patients, it was noted that the CONUT score is as useful as SGA in determining malnutrition.[12] Another study indicated that GNRI is a reliable assessment system for detecting malnutrition.[18] However, the diagnostic accuracy of these tools can vary significantly depending on the specific patient population. In our study, by utilizing SGA as the clinical reference standard, we clarified these literature discrepancies in the elderly hemodialysis population. Our findings demonstrate that the MIS is a near-ideal tool for assessing malnutrition, and that anthropometric measurements (TSF and ASF) also exhibit high diagnostic accuracy, whereas the overall diagnostic utility of the GNRI and CONUT is limited.

Studies have shown that malnutrition rates in hemodialysis patients range from 41.1% to 70% according to SGA.[19,20] According to the SGA, malnutrition was detected in 44.1% of our patients, of whom 24.3% had mild malnutrition, 17.6% had moderate malnutrition, and 2.2% had severe malnutrition.

In a study conducted by Kang et al.[21] on hemodialysis patients, it was stated that a MIS value below 5 is associated with mortality. In another study conducted in China with 257 hemodialysis patients, the MIS cut-off value was set at 5, and it was reported that mortality increased by more than 80% at MIS values above 5.[22] In a study conducted by Alipoor et al.[23] on hemodialysis patients, the MIS cut-off value was set at 8, and malnutrition was detected in 59% of patients. In our study, the MIS cut-off value was set at 5.5, and malnutrition was detected in 49.3% of patients. The lack of a

Table 5. ROC analysis of nutrition score results predicting malnutrition according to SGA

	Cut-off	Sensitivity	Specificity	PPV	NPV	Youden	AUC	95% CI (lower-upper)
MIS	5.5	0.883	0.816	0.791	0.899	0.699	0.934*	0.898-0.971
GNRI	109.5	0.667	0.724	0.659	0.733	0.390	0.734*	0.649-0.820
CONUT	1.5	0.833	0.487	0.562	0.787	0.320	0.706*	0.621-0.790
TSF	6.5	0.767	0.829	0.780	0.818	0.596	0.878*	0.821-0.935
ASF	10.5	0.833	0.750	0.725	0.851	0.583	0.872*	0.812-0.933
BMI	25.2	0.750	0.711	0.672	0.783	0.461	0.792*	0.716-0.867

*p<0.05

SGA: Subjective global assessment, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval: MIS: Malnutrition Inflammation Score, GNRI: Geriatric Nutritional Risk Index, CONUT: Controlling nutritional status, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold thickness, BMI: Body-mass index

Table 6. ROC DeLong test

	AUC 1	AUC 2	Z	p
MIS-GNRI	0.934	0.734	4.629	<0.001
MIS-CONUT	0.934	0.706	5.481	<0.001
MIS-TSF	0.934	0.878	1.740	0.081
MIS-ASF	0.934	0.872	1.190	0.055
MIS-BMI	0.934	0.792	3.420	<0.001
GNRI-CONUT	0.734	0.706	0.542	0.587
GNRI-TSF	0.734	0.878	-3.213	0.001
GNRI-ASF	0.734	0.872	-3.080	0.002
GNRI-BMI	0.734	0.792	-1.540	0.122
CONUT-TSF	0.706	0.878	-3.560	<0.001
CONUT-ASF	0.706	0.872	3.640	<0.001
CONUT-BMI	0.706	0.792	-1.570	0.116
TSF-ASF	0.878	0.872	0.235	0.814

ROC: Receiver operating characteristic, MIS: Malnutrition Inflammation Score, GNRI: Geriatric Nutritional Risk Index, CONUT: Controlling nutritional status, TSF: Triceps skinfold thickness, ASF: Abdominal skinfold thickness, BMI: Body-mass index

universally accepted cut-off value for MIS can be considered a shortcoming of this test.

In our study, ASF and TSF were found to be below the 25th percentile in 25% and 25.7% of patients, respectively. TSF and ASF were significantly lower in those with malnutrition according to SGA. In a study conducted with patients aged 20-63 at the only hemodialysis center in İstanbul, the mean was found to be 26.6±6.3 mm, and the difference between this and our study supports the loss of adipose tissue with aging.[24] In a study conducted by Pembegül Yiğit[25] and colleagues on elderly hemodialysis patients, a significant difference was found between TSF and ASF, similar to the findings in our study. We detected malnutrition in 91.9% of our patients below the 25th percentile of TSF and in 91.4% of patients below the 25th percentile of ASF according to SGA. The accuracy rates of 80.1% and 78.6% for both parameters indicate that these two tests may be ideal for detecting malnutrition.

The median age of the patients included in our study was similar to the age found in the study by Pembegül Yiğit et al.[25] on malnutrition in elderly hemodialysis patients in our country. Similarly to this study, a higher average age was found among those with malnutrition in our study, and a relationship was determined between age and malnutrition.[2]

The duration of hemodialysis treatment may be an effective factor in malnutrition. A study conducted in Palestine indicated that malnutrition was more prevalent in patients undergoing hemodialysis for more than 4 years.[26] However, in our study, no relationship was found between dialysis duration and malnutrition.

In our study, triglyceride levels were found to be 120.5 (IQR: 92-175.5) mg/dl and 160 (IQR: 116.25-232.75) mg/dl in malnourished and non-malnourished patients, respectively, according to SGA, and a statistical difference was detected. In a study conducted by Lee et al.[27] on hemodialysis patients, similarly to our study, lower triglyceride levels (81.5±30.9 mg/dl; 139±85.3 mg/dl) were found in malnourished patients. It is thought that evaluating the malnutrition status of patients using triglyceride levels would be beneficial.

Hypoalbuminemia has been reported to serve as a potential indicator of mortality and nutritional status in the hemodialysis patient population.[17] A study involving malnourished and non-malnourished patients have shown that serum albumin levels are similar.[28] In our study, we found that the serum albumin level was 41 (IQR: 37.63-44.96) mg/dl on average, and no significant difference was found according to SGA.

Although nPNA is a widely used marker reflecting recent dietary protein intake and nitrogen balance, we found no significant difference in nPNA levels between malnourished and well-nourished patients according to SGA (p>0.05). This finding suggests that while nPNA may indicate acute dietary compliance, it may not adequately capture the chronic, cumulative, and multifactorial tissue loss associated with malnutrition in the elderly hemodialysis population. Comprehensive tools like MIS and anthropometric measurements appear to be more reliable than recent protein intake markers for identifying true malnutrition in this age group.

In our study, when patients were examined according to CONUT, mild malnutrition was detected in 54.4%, moderate malnutrition in 9.6%, and severe malnutrition in 1.5% of patients, with a total of 65.4% of patients having malnutrition. In a study conducted on dialysis patients in our country, the CONUT score cut-off value was calculated as 2.5.[29] In a study conducted by Yılmaz Aydın and colleagues[30] in hemodialysis patients, the CONUT score cut-off value was calculated as 4.5. Both studies found a relationship between the CONUT score and malnutrition and mortality.[29,30] In our study, the defined values of the CONUT score (0-1: normal, 2-4: mild, 5-8: moderate, 9-12: severe) were used, and the optimal cut-off value was calculated as 1.5 based on ROC curve analysis. Further studies are needed to determine the cut-off value and the applicability of the CONUT score in hemodialysis patients.

Limitations

Although this study yielded important results in determining the most useful methods for detecting malnutrition in elderly hemodialysis patients, it has limitations such as a small number of cases, a single-center and cross-sectional design, and the lack of longitudinal mortality or follow-up outcome data.

CONCLUSION

As a result, the most useful information for detecting malnutrition in the elderly hemodialysis patient population may be provided by the MIS and anthropometric measurements such as TSF and ASF. BMI and GNRI are more suitable for identifying the well-nourished (healthy) population due to their high specificity. The effectiveness of the CONUT in detecting malnutrition is low. Although we determined specific optimal threshold values for nutrition scores in this population in our study, larger-scale research is needed to validate these threshold values in broader clinical settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Non-interventional Clinical Researches Ethics Committee at Sivas Cumhuriyet University (Date: 27.07. 2022, Decision No: 2022-07/07).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: MFA, YK; Design: MFA, YK; Control: MFA, YK; Data Collection and/or Processing: MFA; Analysis and/or Interpretation: MFA; Literature Review: MFA; Article Writing: MFA, YK; Critical Review: All Authors.

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Original Article

SIADH-associated hyponatremia in hospitalized COVID-19 patients: relationship with inflammatory and stress response markers

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ABSTRACT

Aims: Hyponatremia observed during the course of COVID-19 infection is closely associated with disease prognosis. The objective of this study is to determine the prevalence of syndrome of inappropriate antidiuretic hormone secretion (SIADH) in patients diagnosed with COVID-19 and to analyze the relationship between this condition and inflammatory markers and stress response parameters.

Methods: The study included 50 patients hospitalized with a diagnosis of COVID-19 who were found to have hyponatremia (Na<135 mEq/L). The diagnosis of SIADH was based on the criteria of clinical euvolemia, low plasma osmolarity (<275 mOsm/kg), and high urinary sodium (>40 mEq/L). TSH and cortisol levels were evaluated to rule out secondary causes in the differential diagnosis. Patients were divided into two groups: SIADH-positive (n=37) and non-SIADH (n=13). The Mann-Whitney U test was used for intergroup comparisons, and the Spearman test was used for correlation analyses.

Results: The mean age of the patients was 62.1±12.3 years, and a higher proportion of female patients was observed in the SIADH group (p=0.038). Serum sodium levels (median: 130.0 mEq/L) were significantly lower in the SIADH (+) group compared to the Non-SIADH group (p<0.01). Among inflammatory markers, ferritin levels were found to be significantly higher in the SIADH group (741.0 vs 335.0 ng/ml; p=0.029), and serum cortisol levels were also found to be markedly elevated in this group (7.5 vs 1.6 µg/dl; p=0.017). In the correlation analysis, a significant negative correlation was found between serum sodium levels and cortisol (r=-0.325, p=0.021) and ferritin (r=-0.284, p=0.046).

Conclusion: The primary etiological factor for COVID-19-associated hyponatremia is SIADH. Elevated ferritin and cortisol levels accompanying this condition indicate that systemic inflammation and the stress response are associated with the severity of hyponatremia. Preserved urinary sodium and elevated cortisol levels are key clinical clues supporting the diagnosis of SIADH in the course of COVID-19.

Keywords: COVID-19, SIADH, hyponatremia, ferritin, cortisol

INTRODUCTION

COVID-19 is a viral infection that primarily affects the respiratory system but can also involve multiple organ systems.[1,2] Electrolyte imbalances, along with hematological, inflammatory, and metabolic abnormalities, are commonly observed during the course of the disease.[3] The most common of these electrolyte abnormalities is hyponatremia; it has been reported that hyponatremia develops in approximately 20-35% of patients hospitalized for COVID-19 at the time of admission or during the course of the illness.[4,5]

Hyponatremia has been associated with increased mortality, prolonged hospital stay, and poor clinical prognosis in COVID-19 patients.[6,7] Although the etiology of COVID-19-associated hyponatremia is multifactorial, inappropriate antidiuretic hormone secretion syndrome (SIADH) stands out as a key mechanism alongside gastrointestinal fluid losses, inadequate oral intake, cardiac dysfunction, and renal causes.[8,9]

SIADH is a condition characterized by the inability to suppress antidiuretic hormone secretion despite low serum osmolality, the formation of inappropriately concentrated urine, and ongoing renal sodium excretion.[10,11] The primary mechanism responsible for the development of SIADH in COVID-19 is thought to be pulmonary inflammation and cytokine-mediated neurohormonal activation. It has been reported that proinflammatory cytokines, particularly interleukin-6 (IL-6), can stimulate ADH secretion.[12,13] This mechanism may explain the relationship between increased levels of inflammatory markers, such as ferritin, and hyponatremia. Additionally, it has been demonstrated that the marked increase in ferritin levels in severe COVID-19 infection serves as an indicator of systemic inflammation.[14] In patients with euvolemic hyponatremia, secondary causes such as adrenal insufficiency and hypothyroidism must be ruled out before diagnosing SIADH. Therefore, serum cortisol levels are important not only for assessing adrenal function but also as an indicator of the systemic stress response.[15]

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The aim of this study is to evaluate the relationship between serum sodium levels and inflammatory burden (ferritin) and stress response (cortisol) in patients with COVID-19 pneumonia who present with hyponatremia consistent with SIADH.

METHODS

Ethics

This study was conducted with the approval of the Non-interventional Clinical Researches Ethics Committee at Van Yüzüncü Yıl University (Date: 12.02.2021, Decision No: 2021/02-18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patient Selection

This retrospective observational study included a total of 50 patients who were hospitalized for COVID-19 pneumonia at a tertiary care center between January 2021 and December 2021 and in whom hyponatremia (serum sodium <135 mEq/L) was detected during follow-up. SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) performed in the microbiology laboratory of our hospital using the Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen R&D Technologies, Istanbul, Türkiye) on nasopharyngeal swab specimens. Pneumonia was confirmed by chest computed tomography (CT) demonstrating findings compatible with COVID-19 pneumonia.

Diagnostic Criteria and Classification

The diagnosis of SIADH was established based on the presence of hypotonic hyponatremia (calculated plasma osmolality <275 mOsm/kg), clinically euvolemic status, urinary sodium concentration >40 mEq/L, normal thyroid function tests, and the exclusion of adrenal insufficiency, renal failure, and other secondary causes of hyponatremia. In addition, a urine specific gravity >1.010 was considered a supportive finding for the diagnosis of SIADH.

Patients meeting these criteria were classified into the SIADH (+) group (n=37), while those who did not meet the criteria or whose hyponatremia could be explained by alternative causes were classified into the Non-SIADH group (n=13).

Data Collection

Demographic data, comorbid conditions, and laboratory parameters were retrospectively obtained from the hospital information management system. Laboratory assessments included serum sodium, potassium, creatinine, CRP, ferritin, LDH, TSH, free T4, and morning serum cortisol levels.

Plasma osmolarity was calculated using the following formula:

Plasma osmolarity=2×Na+glucose/18+BUN/2.8

Statistical Analysis

The date were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare continuous variables, while the Chi-square or Fisher's exact test was used to analyze categorical variables. Continuous variables were expressed as the median (interquartile range, IQR), while categorical variables were expressed as counts and percentages. Relationships between variables were assessed using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographic and baseline clinical characteristics of the 50 patients included in the study are presented in Table 1. The median age of the patients was 64.0 years in the SIADH (+) group and 58.0 years in the Non-SIADH group; no statistically significant difference in age was observed between the groups (p=0.166). When gender distribution was examined, the proportion of female patients in the SIADH (+) group (56.7%) was found to be significantly higher than in the Non-SIADH group (23.1%) (p=0.038).

All patients (100%) had radiologically confirmed COVID-19 pneumonia (lung involvement). In the clinical volume assessment, all patients (100%) in the SIADH group were euvolemic, whereas this rate was 69.2% in the Non-SIADH group (p=0.004). No significant difference was observed between the groups in terms of baseline renal function markers (serum creatinine; p=0.194) or the nutritional/inflammatory marker albumin (p=0.312). The mean length of hospital stay was 11.5 days in the SIADH group and 9.0 days in the control group, showing statistical similarity (p=0.214). A total of 5 patients (10%) died during the study period, and mortality rates were found to be similar between the groups (p=0.741) (Table 1).

Table 1. Demographic and clinical characteristics of the patients

Variable	SIADH (+) (n=37)	Non-SIADH (n=13)	p-value
Age (years), median (IQR)	64.0 (57-72)	58.0 (49-62)	0.166
Gender (female), n (%)	21 (56.7)	3 (23.1)	0.038
Clinical findings, n (%)			
Lung involvement (pneumonia)	37 (100)	13 (100)	1.000
Volume status (euvolemia)	37 (100)	9 (69.2)	0.004
Baseline laboratory data, median (IQR)			
Serum creatinine (mg/dl)	0.81 (0.6-0.9)	0.92 (0.7-1.2)	0.194
Serum albumin (g/dl)	3.2 (2.9-3.6)	3.4 (3.1-3.8)	0.312
Length of hospital stay (days)	11.5 (8-16)	9.0 (7-14)	0.214
Mortality (exitus), n (%)	4 (10.8)	1 (7.6)	0.741

Data are presented as median (interquartile range, IQR) or number (%). Statistical comparisons were performed using the Mann-Whitney U test, Chi-square test, or Fisher's exact test where appropriate. SIADH: Syndrome of inappropriate antidiuretic hormone secretion, IQR: Interquartile range

The laboratory parameters of the groups included in the study are presented in a comparative format in Table 2. While the median serum sodium level in the SIADH (+) group was 130.0 mEq/L (IQR: 127.0-132.0), it was 133.0 mEq/L (IQR: 131.0-134.0), and the difference between the two was found to be highly statistically significant (p<0.001). Similarly, plasma osmolarity levels were also significantly lower in the SIADH group (268.5 vs 276.0 mOsm/kg; p=0.002).

When examining the stress and inflammation parameters, which were the focus of the study, it was found that serum cortisol levels in the SIADH group (median: 7.5 µg/dl) were approximately 4.5 times higher than in the control group (median: 1.6 µg/dl), and this difference was statistically significant (p=0.017). Serum ferritin levels, an inflammatory

marker, were also found to be statistically significantly higher in the SIADH group compared to the Non-SIADH group (741.0 vs 335.0 ng/ml; p=0.029). However, no significant differences were observed between the groups regarding CRP, LDH, TSH, and complete blood count parameters (WBC, lymphocytes) (p>0.05) (Table 2).

Table 2. Comparison of laboratory parameters between groups

Parameter	SIADH (+) (n=37)	Non-SIADH (n=13)	p-value
Serum sodium (mEq/L)	130.0 (127.0-132.0)	133.0 (131.0-134.0)	<0.001
Serum cortisol (µg/dl)	7.5 (4.2-13.6)	1.6 (1.1-4.3)	0.017
Serum ferritin (ng/ml)	741.0 (489.0-1250.0)	335.0 (274.0-511.0)	0.029
Plasma osmolarity (mOsm/kg)	268.5 (262.0-272.5)	276.0 (273.5-281.0)	0.002
C-reactive protein (mg/L)	102.0 (63.0-161.0)	96.0 (47.0-129.0)	0.682
LDH (U/L)	464.0 (318.0-618.0)	419.0 (327.0-642.0)	0.706
WBC ($\times10^3$/µL)	9.0 (7.0-12.3)	7.9 (6.7-9.0)	0.388
Lymphocyte count ($\times10^3$/µL)	630 (460-970)	620 (500-700)	0.674
TSH (mU/L)	0.8 (0.4-1.5)	0.9 (0.6-1.3)	0.535

Continuous variables are expressed as median (IQR). p-values were calculated using the Mann-Whitney U test. SIADH: Syndrome of inappropriate antidiuretic hormone secretion, mOsm: Milliosmole, LDH: Lactate dehydrogenase, WBC: White blood cell, TSH: Thyroid-stimulating hormone

The results of the Spearman correlation analysis conducted to determine the relationship between serum sodium levels and various clinical and laboratory parameters are presented in Table 3. The analysis revealed a moderate, negative, and statistically significant correlation between serum sodium levels and serum cortisol levels (r=-0.325, p=0.021). Similarly, a significant negative relationship was also found between sodium levels and ferritin levels (r=-0.284, p=0.046).

These findings indicate that as the severity of hyponatremia increases (as sodium levels decrease), both the systemic inflammatory burden (ferritin) and the physiological stress response (cortisol) increase. Furthermore, the expected strong positive correlation between sodium levels and plasma osmolarity was confirmed (r=+0.642, p<0.001). On the other hand, no statistically significant relationship was found between sodium levels and age or CRP levels (Table 3).

Table 3. Correlation analysis of serum sodium levels with clinical parameters

Variable Pair	Correlation coefficient (spearman's rho)	p-value
Serum Na & serum cortisol	-0.325	0.021
Serum Na & serum ferritin	-0.284	0.046
Serum Na & plasma osmolarity	+0.642	<0.001
Serum Na & CRP	-0.154	0.285
Serum Na & age	-0.222	0.120

Correlation analyses were performed using Spearman's correlation test. A p-value <0.05 was considered statistically significant. Na: Sodium, CRP: C-reactive protein

DISCUSSION

This study demonstrated that SIADH is the most common underlying mechanism of hyponatremia developing during COVID-19 infection and that markers of inflammation and the stress response are more pronounced in patients with SIADH. In particular, the finding that serum ferritin and cortisol levels were significantly elevated in the SIADH group suggests that COVID-19-associated hyponatremia is not merely a simple electrolyte imbalance but a complex process associated with systemic inflammation and a neuroendocrine stress response. Furthermore, the negative correlation observed between serum sodium levels and ferritin and cortisol supports the notion that as the severity of hyponatremia increases, so do the inflammatory burden and the physiological stress response.

Previous studies have reported that hyponatremia is quite common in COVID-19 and is associated with a poor clinical prognosis. Machiraju et al.[16] demonstrated that hyponatremia is common in COVID-19 patients and may be particularly associated with severe clinical course. Similarly, Tzoulis et al.[17] reported that dysnatremia holds independent prognostic significance regarding morbidity and mortality in COVID-19 patients. Tezcan et al.,[18] on the other hand, demonstrated that electrolyte abnormalities at the time of presentation are associated with a poor prognosis. In our study as well, the significantly low serum sodium levels in the SIADH group support the clinical significance of COVID-19-associated hyponatremia.

Although the development of hyponatremia in COVID-19 infection is multifactorial, SIADH stands out as one of the most significant mechanisms. Lippi et al.[19] reported that electrolyte disturbances are common, particularly in severe COVID-19 cases, and that these may be associated with systemic inflammation. In the case reported by Ayat et al.,[20] it was emphasized that SIADH could be the first and only presentation of a COVID-19 infection. In our study as well, the fact that all patients in the SIADH group were euvolemic and had markedly low plasma osmolarity is consistent with the classic pathophysiology of SIADH.

Ferritin is an acute-phase reactant that has been associated with disease severity and adverse clinical outcomes in patients with COVID-19. Kurian et al.[21] demonstrated that serum ferritin levels are associated with COVID-19 severity and clinical outcomes. In our study as well, the finding that ferritin levels were significantly elevated in the SIADH group and the detection of a negative correlation between serum sodium levels and ferritin suggest that hyponatremia worsens as the inflammatory burden increases. This finding is consistent with previous studies demonstrating that higher ferritin concentrations are associated with greater inflammatory burden and more severe COVID-19.

Given that IL-6 levels were not directly measured in our study, ferritin was evaluated as a surrogate marker of systemic inflammation. Previous studies have demonstrated a significant positive correlation between serum IL-6 and ferritin levels in patients with COVID-19, suggesting that elevated ferritin may indirectly reflect cytokine-mediated inflammatory activity. Therefore, the significantly higher ferritin levels observed in the SIADH group should be interpreted as indirect evidence of enhanced inflammation rather than direct evidence of increased IL-6 activity.[22]

Another notable finding in our study is that serum cortisol levels were significantly elevated in the SIADH group. Excluding adrenal insufficiency is of critical importance in the diagnosis of SIADH. Therefore, the detection of elevated rather than low cortisol levels supports the notion that the

hyponatremia is not due to adrenal insufficiency. Additionally, this finding may be interpreted as an indicator of the systemic stress response developing during COVID-19 infection. Pal and Banerjee reported that COVID-19 may activate the hypothalamic-pituitary-adrenal axis through systemic inflammation, leading to alterations in cortisol secretion and adrenal function.[23] Similarly, Jensterle et al.[24] reported that COVID-19 may be associated with both glucocorticoid insufficiency and excessive HPA-axis activation depending on disease severity.[24] The negative correlation observed in our study between serum sodium and cortisol levels suggests that deeper hyponatremia may be associated with a more intense physiological stress response.

It is noteworthy that while ferritin levels showed significant differences in our study, CRP levels were found to be similar. This suggests that ferritin may be a more sensitive marker than CRP for indicating the inflammatory burden in COVID-19. It is particularly known that ferritin levels are more closely associated with macrophage activation and hypercytokinemia.[25] Therefore, it is possible that the inflammatory mechanisms associated with the development of SIADH are better reflected through ferritin.

In our study, no significant differences were observed between the groups in terms of mortality and length of hospital stay. One of the main reasons for this may be the relatively small number of patients. Additionally, the fact that only hyponatremic patients were included in the study may have limited the clarity of prognostic differences between the groups. However, the presence of more pronounced biochemical abnormalities in the SIADH group suggests that these patients developed a more intense inflammatory and metabolic stress response. Adekanmbi et al.[26] demonstrated that the inflammatory burden is a determining factor in clinical outcomes among patients hospitalized due to COVID-19. Therefore, the independent effect of SIADH on the prognosis of COVID-19 could be more clearly established through prospective studies with larger sample sizes.

Limitations

Our study has some limitations. First, it has a retrospective, single-center design. The relatively small number of patients may have limited its statistical power. Additionally, the failure to measure IL-6 and ADH levels prevented a direct demonstration of the pathophysiology of SIADH. Therefore, the proposed inflammatory mechanism should be interpreted as indirect and based on previous literature. However, the study's strengths include the evaluation of the SIADH diagnosis using systematic criteria, the exclusion of adrenal and thyroid causes, and the detailed analysis of the relationship between inflammation/stress parameters and serum sodium levels.

CONCLUSION

As a result, this study demonstrates that SIADH is one of the primary etiological mechanisms of COVID-19-associated hyponatremia and that the inflammatory burden and stress response are more pronounced in patients who develop SIADH. The finding that ferritin and cortisol levels are inversely correlated with serum sodium suggests that hyponatremia may be a biochemical reflection of the systemic inflammatory process in COVID-19. In COVID-19 patients, particularly in the presence of euvolemic hyponatremia, SIADH should be considered, and ferritin and cortisol levels may be evaluated as helpful biomarkers in clinical assessment.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Non-interventional Clinical Researches Ethics Committee at Van Yüzüncü Yıl University (Date: 12.02.2021, Decision No: 2021/02-18).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: OÖ, MA; Design: OÖ, MA; Control: OÖ, MA; Data Collection and/or Processing: OÖ, MA; Analysis and/or Interpretation: OÖ, MA; Literature Review: OÖ, MA; Article Writing: OÖ, MA; Critical Review: OÖ, MA.

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Original Article

Changes in anthropometric and metabolic parameters related to gastroesophageal reflux disease in non obese cases

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ABSTRACT

Aims: Central obesity associated with visceral adiposity is considered to increase reflux symptoms. This study aimed to investigate the effects of anthropometric and visceral fat-related measurements on reflux symptoms in non-obese patients with gastroesophageal reflux disease (GERD) and a body-mass index (BMI)<30 kg/m².

Methods: The study included 120 non-obese patients with dyspeptic complaints, BMI<30, and GERD diagnosed according to the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), and 50 non-obese controls with BMI<30 kg/m², no dyspeptic complaints, and no GERD according to the FSSG. Demographic data and extraesophageal symptoms were assessed using a questionnaire. Serum biochemical findings were recorded. Body composition and anthropometric measurements were evaluated using bioelectrical impedance analysis (TANITA).

Results: Significant differences were found between the GERD and healthy control groups in waist circumference, BMI, low-density lipoprotein cholesterol (LDL), body fat percentage, fat mass, total body water (TBW), metabolic age, visceral fat, obesity grade, reflux score, acid reflux score, and total FSSG score ($p<0.05$). Sore throat, apnea, and teeth grinding also differed significantly between the groups ($p<0.05$). In the patient group, acid reflux scores were positively correlated with BMI ($r=0.298$, $p=0.001$), LDL ($r=0.387$, $p<0.001$), and visceral fat ($r=0.180$, $p=0.049$), and negatively correlated with TBW ($r=-0.273$, $p<0.003$).

Conclusion: Reflux symptom frequency and severity are closely associated with body fat composition in non-obese as well as obese patients. Increased abdominal and visceral fat may increase GERD risk independently of obesity.

Keywords: Non-obese, GERD, FSSG, bioelectrical impedance

INTRODUCTION

Gastroesophageal reflux (GER) increasingly draws attention in recent years due to its prevalence, heterogeneity of its clinical presentation, morbidity and economic consequences. Considering multiple previous consensus definitions, gastroesophageal reflux disease (GERD) is defined as symptoms and complications resulted from retrograde flow of gastric contents into the esophagus, oral cavity (including larynx) and/or lungs.[1] Obesity is a potential risk factor for several chronic disorders including gastroesophageal reflux disease. Although various pathological mechanisms, including increased intragastric pressure, decreased lower esophageal sphincter (LES) pressure and esophageal acid exposure, can underly GERD, obesity has also been suggested to play an important role in the development of GERD.[2-3] Obesity can facilitate transient LES relaxation and cause GERD by increasing intraabdominal pressure and altering the structure and function of gastroesophageal junction.[4] Other possible obesity-linked mechanisms that may underlie GERD include increased levels of circulating inflammatory cytokines and delayed gastric motility.[5] Recently, visceral fat accumulation associated with abdominal obesity has been implicated in the development of gastrointestinal disorders as visceral fat accumulation increases intraabdominal pressure leading to the release of several bioactive substances known as adipocytokines such as TNFα, IL-6, resistin, leptin and adiponectin. Several mediators released by visceral adipose tissue, including adiponectin, leptin, TNFα, IL-6 impact the stomach and esophagogastric junction.[6] Proinflammatory cytokines IL-1 and TNFα have been reported to induce gastrin release from antral segments of the stomach.[7] Therefore, as with adipocytokines, proinflammatory mediators can enhance or perpetuate local inflammation at the gastroesophageal junction following local injury associated with esophageal acid exposure.[2]

In the assessment of obesity, body fat percentage, fat amount and fat distribution are far more important than total body weight alone. Bioelectrical impedance analysis is among

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the most efficient methods to estimate body fat ratio. This analytical method is based on electrical conductivity differences between fat-free tissue and fat tissue.[8-10]

Making an accurate diagnosis of GERD can be challenging in routine clinical practice. In clinical assessment, the self-assessment scale is an important part of diagnostic process. Japanese studies have demonstrated that FSSG might be beneficial for monitoring GERD in symptomatic patients.[11] A diagnosis of GERD is made in patients with a FSSG score of 8 or higher. FSSG is a diagnostic tool previously validated by public health and primary care physicians for use in Chinese populations to diagnose GERD.[12]

This study aims to demonstrate that the presence of insulin resistance (HOMA-IR>2.7) and alterations in anthropometric and metabolic parameters may be associated with an increased incidence of GERD in non-obese (BMI<30 kg/m²) populations. This study aims to assess potential associations between GERD and alterations in anthropometric and metabolic parameters in non-obese (BMI<30 kg/m²) populations.

METHODS

This study was conducted with the approval of the Clinical Researches Ethics Committee at Kırıkkale University (Date: 29.11.2016, Decision No: 23/14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Necessary permissions were obtained for the use of study materials, and it was essential that participants gave their free consent. This article is based on the internal medicine postgraduate dissertation no.466521.

This study included 120 patients who attended Gastroenterology Outpatient Clinics of the School of Medicine at Kırıkkale University for dyspeptic complaints and gave consent to take part in this study. Study participants were male and female patients aged between 18 and 65 years and had a BMI of<30 kg/m². 50 individuals who attended internal medicine outpatients clinics (general medicine, gastroenterology, endocrinology and rheumatology outpatients clinics) for reasons other than dyspepsia were included in this study as a control group. Laboratory data including fasting glucose, insulin, uric acid, TSH, ALT, HDL, LDL, triglyceride and total cholesterol levels were noted in addition to descriptive data such as age, gender, occupational status, smoking status and the presence of hypertension. HOMA-IR values were derived from fasting glucose and insulin levels (HOMA-IR=fasting glucose level (mg/dl) x fasting insulin level (uIU/ml)/405).

The F-scale FSSG (Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease) was used in each participant to standardize the evaluation of gastroesophageal reflux disease. Each item in this scale was rated from 1 to 5 as never (1), rarely (2), occasionally (3), often (4) and sometimes (5) and items assessing dyspeptic symptoms (5 items) were excluded from the scale whereas participants responded to 7 questions assessing reflux symptoms. Participants who scored 8 points or more in the 7-item scale were included in the GERD group. Total scores were calculated as follows: reflux symptoms: (max:7x5=35 points) and acid reflux symptoms (dyspepsia) (max:5x5=25 points); Total score (max:7x5=35 points)+(max:5x5=25 points). An additional survey form was filled for extraesophageal symptoms (chronic cough, chest pain, hoarseness, sore throat, apnea, choking sensation, teeth grinding).

TANITA (bioelectrical impedance) was used for anthropometric assessments and height, weight, body-mass index (BMI), fat percentage, fat mass (in kg), fat-free mass (FFM), muscle mass (in kg), total body water (TBW), TBW percentage, bone mass weight (bone mineral mass), basal metabolic rate (BMR), metabolic age, visceral fat rating and obesity grade were noted. All measurements were performed using the same device. In addition, waist circumference was measured using a non-stretching measuring tape in a standing position and using the ribs and longest horizontal line that passes across both iliac crests as references.

People with a BMI of ≥30 kg/m², diabetes mellitus, thyroid dysfunction, chronic obstructive pulmonary disease, chronic kidney failure, coronary artery disease or liver cirrhosis, people who were on proton pump inhibitors, NSAIDs, anticoagulants, antiplatelet or any herbal medicine or people who had a history of abdominal surgery (cholecystectomy, gastric surgery, colon surgery, C-section, reflux surgery, hiatal hernia repair, etc.) were excluded from the study.

Statistical Analysis

The SPSS 20.0 (IBM Corporation, Armonk, New York, United States) and Medcalc 14 (Acacialaan 20, B-8400 Ostend, Belgium) statistical software packages were used in data analysis. Normality of data distribution and homogeneity of variances were assessed by the Shapiro-Wilk test and Levene's test, respectively. In comparisons of quantitative data between two independent groups, bootstrapping was used with Independent-Samples T test whereas Monte Carlo simulations were used with the Mann-Whitney U test. Variables were tested using the backward elimination method. In comparisons of categorical variables, Pearson's Chi-square and Fisher's Exact tests were used with Monte Carlo simulations and Exact test results. The odds ratio was used to identify the most important risk factor among significant risk factors. The logistic regression test was used with backward method to determine cause and effect associations between dichotomous or multinomial categorical response variable and explanatory variables. The sensitivity and specificity of the cutoff was analyzed in a receiver operating curve (ROC) analysis based on the associations between the classification determined by the cutoff value calculated based on patient and control groups' variables and true classification. Spearman's rho test was used to analyze correlations between variables. Quantitative variables were presented as mean±standard deviation and median (range, maximum- minimum) and categorical variables were presented as counts (n) and percentages (%). Variables were analyzed at 95% confidence level and p-values less than 0.05 were considered significant.

RESULTS

The study included a total of 170 participants with 44 male (25.9%) and 126 female (74.1%) and the mean age in the study population was 30.45±10.77 years. The mean age in the patient group (31.65±11.45 years) was comparable to that of the control group (30.22±7.27 years) (p=0.054). Significant intergroup differences were found in BMI (p=0.022) and waist circumference (p=0.001) whereas intergroup differences were not significant in height, weight, gender, occupational

status, smoking status, alcohol consumption, and in the rate of hypertensive participants (p>0.05) (Table 1).

Table 1. Sociodemographic data

	Controls (n=50) mean±SD	Patients (n=120) mean±SD	Total (n=170) mean±SD	p-value
Age (years)	30.22±7.27	31.65±11.45	30.45±10.77	0.054
Height (cm)	167.68±10.14	164.47±10.16	165.41±10.23	0.064
Weight (kg)	63.12±11.29	64.25±10.66	63.92±10.82	0.537
BMI (kg/m$^{2)}$	22.43±3.43	23.79±3.60	23.43±3.59	0.022
Waist circumference (cm)	74.63±5.62	79.94±10.60	78.38±9.71	0.001
	n (%)	n (%)	n (%)	
Gender				
Female	39 (78.0)	87 (72.5)	126 (74.1)	0.565
Male	11 (22.0)	33 (27.5)	44 (25.9)	
Occupational status				
Unemployed	38. (76.0)	87 (72.5)	125 (73.5)	0.706
Employed	12 (24.0)	33 (27.5)	45 (26.5)	
Smoking status				
Non-smoker	37 (74.0)	72 (60.0)	109 (64.1)	0.114
Smoker	13 (26.0)	48. (40.0)	61 (35.9)	
Alcohol consumption				
No	48 (96.0)	110 (91.7)	158 (92.9)	0.513
Yes	2 (4.0)	10 (8.3)	12 (7.1)	
Hypertension				
No	49 (98.0)	115 (95.8)	164 (96.5)	0.72
Yes	1 (2.0)	5 (4.2)	6 (3.5)	

Independent T test (bootstrapped)-Person's Chi-square test (exact)-Fisher exact test (exact). SD: Standard deviation, BMI: Body-mass index

LDL levels (p=0.035), fat (p=0.016), fat mass (p=0.012), metabolic age (p=0.002), visceral fat (p<0.001), obesity grades (p=0.015), reflux scores (p<0.001), acid reflux scores (p=0.020) and total scores were statistically significantly higher in patient group compared to control group whereas TBW (%) was statistically significantly lower in patient group compared to control group (p=0.018). There were no statistically significant intergroup differences in glucose, insulin, HDL, triglyceride, total cholesterol, uric acid, TSH, ALT levels and FFM, muscle mass, TBW, bone mass, BMR and HOMA-IR values (p>0.05) (Table 2).

In ROC analysis, out of the analyzed variables, total score displayed the highest performance in distinguishing patient and control groups with an AUC value of 0.928±0.019 (p<0.001), followed by visceral fat (AUC=0.673±0.045; p<0.001), metabolic age (AUC=0.652±0.044; p=0.001), waist circumference (AUC=0.631±0.042; p=0.002), fat mass (AUC=0.621±0.043; p=0.005), obesity grade (AUC=0.619±0.046; p=0.012), fat (AUC=0.617±0.043; p=0.008), TBW (%) (AUC=0.617±0.043; p=0.008), BMI (AUC=0.614±0.046; p=0.015) and LDL (AUC=0.602.±.0.045; p=0.025). The most appropriate cutoff values for these variables were determined as 79 cm, 22.8 kg/m², 107 mg/dl, 29 years, 10,3, 29,7, 19,4, 1, 25 and 50.7 respectively (Table 3).

The prevalence of sore throat, apnea and teeth grinding was significantly higher in the patient group compared to the control group (p=0.006, p=0.019 and p=0.029, respectively). Participants experiencing sore throat were 3.2 times more likely to be in the patient group (OR=3.2; 95% CI: 1.3-7.3). Likewise, participants experiencing teeth grinding were 3.3 times more likely to be in the patient group (OR=3.3; 95% CI: 1.1-10.1). Nevertheless, the prevalences of chronic cough, non-cardiac chest pain, hoarseness, bronchospasm and insulin resistance did not statistically significantly differ between the patient and control groups (p=0.557, p=0.255, p=0.528, p=0.069 and p=0.255, respectively). Multiple logistic regression analysis was performed using backward elimination method (backward stepwise [wald]) in a model including statistically significant variables for patients experiencing dyspepsia in this population aged 18 to 65 years. Variables identified as statistically significant by our logistic model included LDL, fat, total score and sore throat (p model<0.001) (Table 4).

Spearman's correlation analysis showed moderate, significant negative correlations between reflux scores and total scores and height in the control group (r=-0.365; p=0.009). Significant positive correlations were found between reflux scores and total scores and triglyceride (r=0.305; p=0.031), total cholesterol (r=0.354; p=0.012) and LDL (r=0.281; p=0.048) levels and significant negative correlations were found between reflux scores and total scores and TSH levels (r=-0.347; p=0.014). Other biochemical or body composition parameters did not significantly correlate with reflux scores (p>0.05). In the patient group, significant negative correlations were found between the height and reflux scores (r=-0.197; p=0.031), acid reflux scores (r=-0.252; p=0.006) and total scores (r=-0.261; p=0.004). Significant positive correlations were found between total cholesterol levels and reflux scores (r=0.295; p=0.001), acid reflux scores (r=0.293; p=0.001) and total scores (r=0.333; p<0.001) and between LDL levels and reflux scores (r=0.378; p<0.001), acid reflux scores (r=0.387; p<0.001) and total scores (r=0.427; p<0.001). ALT levels positively correlated with reflux scores alone (r=0.190; p=0.038). In anthropometric assessments, positive correlations were found between acid reflux scores and total scores and waist circumference (r=0.244-0.275), BMI (r=0.269-0.298), fat percentage (r=0.217-0.262), fat mass (r=0.188-0.241), metabolic age (r=0.232-0.255), obesity grade (r=0.269-0.278) and visceral fat; significant negative correlations were found between TBW percentage and acid reflux scores (r=-0.273; p=0.003) and total scores (r=-0.232; p=0.011).

DISCUSSION

The prevalence of obesity is increasing worldwide because of inadequate physical activity and overeating. The surge in the number of people living with obesity gave rise to an increase in the prevalence of metabolic syndrome. In addition to established associations between metabolic syndrome and several disorders such as ischemic heart disease and diabetes mellitus, numerous studies have also demonstrated associations between metabolic syndrome and gastrointestinal disorders.[2] Although several studies have reported conflicting results, many studies conducted in Japan and other developed countries have demonstrated strong associations between GERD symptoms and obesity and high BMI.[3,13] Nevertheless, associations between high BMI and obesity and reflux symptoms should be further discussed due to the conflicted results mentioned above.

Table 2. Intergroup comparisons of biochemical data

	Controls (n=50) median (min-max)	Patients (n=120) median (min-max)	Total (n=170) median (min-max)	p-value
Glucose	90.50 (77-165)	92 (53-165)	91.50 (53-165)	0.508
Insulin	8.05 (1.90-93)	8.35 (1.32-108)	8.20 (1.32-108)	0.553
HDL	51.50 (3.10-99)	47.50 (3.10-90)	48.50 (310-99)	0.066
LDL	74.50 (42-129)	87 (11-243)	80 (1-243)	0.035
Triglycerides	81 (33-350)	97 (28-404)	95 (28-404)	0.184
Total cholesterol	146.50 (73-222)	161 (19-310)	159 (19-310)	0.216
Uric acid	4.05 (1.20-41)	4.30 (1.20-59)	4.20 (1.20-59)	0.471
TSH	1.68 (0.07-7.56)	1.54 (0.02-10)	1.58 (0.02-10)	0.476
ALT	12.50 (5-39)	13 (5-65)	13 (5-65)	0.213
Fat	19.30 (3-41.80)	24.75 (3-95.20)	22.55 (3-95.20)	0.016
Fat mass	12.80 (1.10-36.20)	15.15 (1.10-43.40)	14.20 (1.10-43.40)	0.012
FFM	45.95 (19-75.10)	46.05 (36.80-74.20)	45.95 (19-75.10)	0.613
Muscle mass	43.95 (35-70.50)	43.90 (34.90-516)	43.90 (34.90-516)	0.520
TBW	32.70 (25.10-52.60)	32.50 (25.10-52.60)	32.55 (25.10-52.60)	0.341
TBW percentage	55.80 (41.60-80.90)	52.50 (41.60-80.90)	53.80 (41.60-80.90)	0.018
Bone mass	2.40 (1.90-3.70)	2.40 (1.90-4)	32.55 (25.10-52.60)	0.442
BMR	5.858 (55.94-9.138)	5.851.50 (55.94-8.996)	5.858 (55.94-9.138)	0.586
Metabolic age	16 (12-64)	27 (12-66)	22 (12-66)	0.002
Visceral fat	1 (1-12)	3 (1-10)	3 81-12)	<0.001
Obesity grade	0.70 (-29.90-35.90)	10.95 (-29.90-35.90)	8.80 (-29.90-35.90)	0.015
HOMA-IR (mg/dl)	1.90 (0.42-19.06)	1.84 (0.27-22.93)	1.88 (0.27-22.93)	0.495
Acid reflux scores	13.50 (5-23)	15 (8-23)	14 (5-23)	0.020
Reflux scores	7 (7-7)	19 (9-35)	15 (7-35)	<0.001
Total scores	20.50 (12-30)	33 (17-53)	29 (12-53)	<0.001

Mann Whitney U Test (Monte Carlo). Min: Minimum, Max: Maximum, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormone, ALT: Alanine aminotransferase, FFM: Fat-free mass, TBW: Total body water, BMR: Basal metabolic rate, HOMA-IR: Homeostatic model assessment of insulin resistance

Table 3. ROC analysis of variables that showed significant differences between patient and control groups

	Control group (n=50)			Patient group (n=120)		AUC+SE	p-value
	Cutoff	n	%	n	%		
Waist circumference	≤79	43	86.0%	70	58.3%	0.631±0.042	0.002
	>79	7	14.0%	50	41.7%		
BMI	≤22.8	32	64%	48	40.0%	0.614±0.046	0.015
	>22.8	18	36.0%	72	60.0%		
LDL	≤107	44	88.0%	82	68.9%	0.602±0.045	0.025
	>107	6	12.0%	37	31.1%		
Metabolic age	≤29	41	83.7%	66	55.0%	0.652±0.044	0.001
	>29	8	16.3%	54	45.0%		
Obesity grade	≤10.3	36	73.5%	57	47.5%	0.619±0.46	0.012
	>10.3	13	26.5%	63	52.5%		
Fat	≤29.7	46	92.0%	77	64.2%	0.617±0.043	0.008
	>29.7	4	8.0%	43	35.8%		
Fat mass	≤19.4	46	92.0%	80	66.7%	0.621±0.043	0.005
	>19.4	4	8.0%	40	33.3%		
Visceral fat	≤1	31	63.3%	38	31.7%	0.673±0.045	<0.001
	>1	18	36.7%	82	68.3%		
Total score	≤25	49	98.0%	39	32.5%	0.928±0.019	<0.001
	>25	1	2.0%	81	------		
TBW percentage	>50.7	43	86.0%	69	57.5%	0.617±0.043	0.008
	≤50.7	7	14.0%	51	42.5%		

ROC analysis [Hanley & McNell-Youden Index (J)] ROC: Receiver operating characteristic, AUC: Area under the curve; SE: Standard error, BMI: Body-mass index, LDL: Low-density lipoprotein, TBW: Total body water

Table 4. Multiple logistic regression analysis of study data

					%95 CI for OR	
	B	SE	p-value	OR	Lower limit	Upper limit
LDL	2.318	0.916	0.011	10.160	1.690	61.220
Fat (>29.7)	-2.201	0.902	0.015	9.030	1.540	52.940
Total score (>25)	-5.838	1.200	<0.001	342.970	32.630	3.605.150
Sore throat (+)	-1.485	0.722	0.040	4.410	1.070	18.170

Dependent variable: Groups, predicted (patient)=88.2, predicted (control)=86.3, predicted =86.3, p model <0.001

Multiple logistic regression-method: backward stepwise (Wald). CI: Confidence interval, OR: Odds ratio, B: Regression coefficients, SE: Standard error, LDL: Low-density lipoprotein

Based on available evidence, waist circumference, which is used to assess central obesity, is associated with esophageal acid exposure as much as BMI does. In a case-control study that included 1.679 patients, a multifactorial analysis demonstrated that metabolic syndrome was an independent risk factor for GERD.[14] In a cross-sectional study in one hundred patients, Kallel et al.[15] demonstrated that metabolic syndrome components, abnormal waist circumference and elevated fasting blood glucose levels were independent risk factors for GERD using 24-hour pH monitoring. Although several studies in patients with obesity have demonstrated associations between metabolic syndrome and GERD, these studies have failed to demonstrate a direct association between BMI and GERD, supporting the hypothesis that GERD is associated with central obesity rather than BMI.[16] In a study conducted in 2008 with 475 patients, Danjo et al.[17] reported that FSSG scores could reflect the severity of endoscopic findings in GERD and FSSG could be used to monitor clinical course of GERD and assess treatment efficacy. In a study conducted in 2015, Fujiwara et al.[18] compared several variables including height, weight, BMI, body fat ratio, visceral fat, waist circumference, triglyceride, ALT, AST/ALT, HOMA-IR and FSSG scores (reflux scores, acid reflux scores, total scores) in 50 patients with NAFLD to those of a control group of 228 healthy participants and FSSG was found to be associated with BMI. They reported that FSSG scores were higher in participants with a BMI of >30 kg/m^2. Statistically significant intergroup difference was found in FSSG scores and the sensitivity and specificity of FSSG scores were determined as 81.7% and 90%, respectively. These findings suggest that our findings are valuable for explaining associations between intergroup differences and gastroesophageal reflux. In another study conducted in 2012 in 96 patients with NAFLD and 139 controls to investigate the prevalence of GERD symptoms and potential risk factors for GERD in patients with NAFLD, Fujikawa et al.[19] found that total scores, reflux scores and acid reflux scores were higher in patients with NAFLD compared to healthy controls. In 2009, Danjo et al.[17] conducted a study to compare GERD symptoms scales FSSG and QUEST to each other and found that reflux scores were higher in the GERD group compared to functional dyspepsia, stomach ulcer and duodenal ulcer group. In our study, total reflux scores were higher in the GERD group compared to the healthy control group. Our results demonstrate that FSSG is a reliable diagnostic tool for gastroesophageal reflux disease. The prevalence of GERD was found to be higher in overweight participants and in those with obesity compared to non-obese participants in a study conducted by Icitovic et al.[5] in 19.819 participants, in 2016. Our study was conducted in non-obese participants with a BMI less than 30 kg/m^2. BMI values statistically significantly differed between the subgroup of participants with higher reflux symptom scores and the control group. In the patient group, a significant positive correlation was found between acid reflux scores and BMI (r=0.298; p=0.001). In our study group, any increases in BMI, even the increases with the normal range, were found to be associated with increased reflux symptom scores, independently from obesity. Our findings support literature reports from previous studies and indicate that BMI can significantly contribute to the increases in reflux symptom scores. In 2007, a study conducted by Corley et al.[20] in 316 patients with GERD and 317 controls demonstrated associations between waist circumference and GERD symptoms and reported that abdominal obesity might contribute to GERD. In 2007, Corley et al.[21] investigated potential associations between GERD symptoms and waist circumference and BMI by ethnicity in a cross-sectional study conducted in 80.110 persons in the US and increased abdominal diameter was identified as an independent risk factor for gastroesophageal reflux symptoms. As for waist circumference, we found a statistically significant difference between the subgroup of patients with higher reflux scores and the control group. In the patient group, a significant positive correlation was found between acid reflux scores and waist circumference (r=0.275; p=0.002). Likewise, a significant positive correlation was found between total scores and waist circumference in the patient group (r=0.244; p=0.007). Previous studies have demonstrated that intraabdominal pressure driven by central obesity stimulates proinflammatory mediators and adipocytokines and these are important factors in the pathophysiology of GERD. In our study a positive correlation was found between waist circumference and reflux scores. Our study provides further evidence on the assumption that any increase in waist circumference may be an important factor in the development of reflux symptoms, even in non-obese people. Positive correlations between serum lipids levels and NEGERD were demonstrated by Matsuzaki et al.[22] in a study conducted in Japan, in 2010. Associations were found between the severity of gastroesophageal reflux symptoms and serum triglyceride levels in men and LDL levels in female. These findings indicate that the severity of GERD increases with the severity of dyslipidemia. In a study conducted in 2012, Fujikawa et al.[19] found that serum total cholesterol and triglyceride levels were risk factors for GERD symptoms in Japanese patients with NAFLD. Our study has supported these study reports. Serum LDL levels were found to be higher in the GERD group compared to the healthy control group in our study. A significant positive correlation was found between acid reflux scores and LDL levels in the patient group (r=0.387; p<0.001). There are literature reports indicating that inflammatory cytokines might be increased in conditions associated with increased levels of dlDL and other lipid parameters.[23] Proinflammatory mediators such as TNFα and IL-6 stimulated by increased levels of LDL can increase acid production by dilating LES and promoting gastrin secretion.[7] Significant associations between LDL levels and reflux scores in our study provided further evidence for these pathophysiological mechanisms. In a study conducted in 2015, Abdelkader et al.[24] compared overweight participants

and participants with obesity to normal-weight participants using a formula that included intraabdominal, subcutaneous abdominal and total body fat tissue areas by BMI. All three parameters mentioned above were found to be higher in the overweigh and obesity groups compared to the normal-weight group.[21] In another multicenter study conducted in 2015, Matsuzaki et al.[25] demonstrated that visceral fat tissue area might be an independent risk factor for reflux esophagitis. In 2017, Kutlu et al.[26] conducted a study aimed at assessing body compositions in our country and compared anthropometric measures in participants with obesity to those in non-obese participants. Fasting blood glucose, LDL, triglyceride, total cholesterol, visceral fat, BMI, waist circumference, BMR, FFM, bone mass, muscle mass measurements were found to be higher in the obesity group compared to the control group. A negative correlation was found between BMI and TBW levels. A direct link was found between BMI and visceral adiposity and fat and visceral fat accumulation and fat ratio were found to be increased as BMI increased.[7,26] In a study conducted in 2013, Peppa et al.[27] found a positive correlation body fat percentage and BMI whereas no significant differences were found between healthy and patient phenotypes in peripheral fat distribution and fat-free body mass (FFM) indices. Martin et al.[28] demonstrated that laparoscopic repair of gastrogastric fistula (GGF) following Roux-en-Y gastric bypass (RYGB) was associated with significant weight loss, resolution of reflux symptoms, and metabolic improvements, even after attempts at medical or endoscopic management. In a study by Salminen et al.,[29] sustained weight loss was observed at 10 years following laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG), and the cumulative incidence of Barrett's esophagus (BE) was found to be substantially lower than that reported in previous studies. Patients with non-severe GERD generally respond well to lifestyle modifications and optimized pharmacological therapy, whereas patients with severe GERD often require long-term anti-reflux management. In patients with persistent symptoms despite these measures, a precision approach to treatment escalation is recommended. This approach should be guided by factors including the integrity of the anti-reflux barrier, the presence of visceral hypersensitivity, confirmation of PPI-refractory GERD, symptom profile, BMI, and esophageal and gastric motor function.[30] Our study was the first study assessing GERD and anthropometric values analyzed using bioelectrical impedance. In our study fat, fat mass, visceral fat, metabolic age and obesity grades were higher in the GERD group compared to the healthy control group. Furthermore, TBW percentage was lower in the GERD group compared to the healthy control group.

Studies available in literature have found associations between gastroesophageal reflux and increased body fat area, subcutaneous fat tissue thickness, abdominal fat tissue area although these results were obtained using conventional methods. In our study, statistically significantly higher levels of fat, fat mass, visceral fat, metabolic age, obesity grades measured using bioelectrical impedance and positive correlations in the subgroup of patients with higher reflux scores demonstrated that a tendency to gastroesophageal reflux might occur as body fat ratio increased in non-obese study participants. In our study, a significant negative correlation was found between TBW percentage and acid reflux scores in the patient group (r=-0.273; p=0.003). In the patient group, a significant negative correlation was also observed between TBW percentage and total scores (r=-0.232; p=0.011). TBW ratio decreased with weight gain and increased body fat ratios and their negative correlations with reflux scores and significantly lower TBW ratio in the subgroup of patients with higher reflux scores further supported other results of our study. In this study, we did not find any statistically significant intergroup differences in FFM, muscle mass, bone mass and BMR. Considering that our patient group consisted of non-obese participants and ages were matched, this was an expected result. In our study, there were no significant differences between the patient group and control group in glucose, insulin, uric acid, TSH, ALT, Homa-IR (mg/dl) levels. Lack of significant differences between the patient group and control group in biochemical parameters could be explained by the study population constituted of non-obese participants with BMI values of 29 kg/m² or lower. Being the first study using bioelectrical impedance to assess potential associations between GERD and anthropometric values was an important aspect of our study. GERD diagnosis was based solely on the FSSG scale, which evaluates patients' symptoms, and objective diagnostic methods such as upper gastrointestinal endoscopy or ambulatory pH monitoring were not routinely used. Therefore, the possibility of symptom-based misclassification cannot be completely excluded. The limitations of this study included the lack of biomarkers of adipose tissue inflammation, the absence of BMI categorization according to obesity grades, and the reliance on the FSSG scale alone for the diagnosis of GERD.

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CONCLUSION

This study suggests that visceral fat accumulation and a higher body fat ratio may be associated with gastroesophageal reflux symptoms, even in non-obese individuals. This study also identifies an association between GERD and fat tissue and body fat composition, which are implicated in and investigated in the pathophysiology of several diseases. Further studies with larger sample sizes are needed to clarify the potential associations between GERD symptoms and adipocytokines related to visceral fat accumulation, as well as to assess the relationship between GERD and BMI categorized according to obesity grade.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Clinical Researches Ethics Committee at Kırıkkale University (Date: 29.11.2016, Decision No: 23/14).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All

participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: ŞY; Design: ŞY; Control: ŞY, ÖGU; Data Collection and/or Processing: ŞY; Analysis and/or Interpretation: ŞY, ÖGU, DO; Literature Review: ŞY, BE; Article Writing: ŞY; Critical Review: All Authors.

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Case Report

A rare case of *Streptococcus pneumoniae* urinary tract infection in a chronic hemodialysis patient

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ABSTRACT

We report a rare case of urinary tract infection (UTI) caused by *Streptococcus pneumoniae (S. pneumoniae)* in a chronic hemodialysis (HD) patient with a long-standing tunneled dialysis catheter. A 28-year-old female on thrice-weekly HD developed dysuria accompanied by genital pruritus. Urinalysis demonstrated leukocyturia and hematuria, and urine culture yielded *S. pneumoniae.* She had no systemic signs of infection but exhibited elevated C-reactive protein (CRP) levels. Based on antimicrobial susceptibility testing, a 7-day course of ceftriaxone 1000 milligram (mg) resulted in culture negativity. This case highlights the need to consider unusual pathogens in UTIs with complex urogenital risk factors.

Keywords: *Streptococcus pneumoniae*, urinary tract infection, hemodialysis

INTRODUCTION

S. pneumoniae (S. pneumoniae) is a gram-positive bacterium that is most commonly linked with respiratory infections such as pneumonia and otitis media, and life-threatening infections such as meningitis and bacteremia.[1] It has not been commonly associated with UTIs. It has rarely been isolated from urine cultures in both adults and children.[2] The isolation of this pathogen has been noted at low rates of ~0.18% in adults and ~0.08% in pediatrics, prompting debate on its clinical importance.[3] Its isolation has been noted from individuals with urinary abnormalities and other predisposing factors.[4] There is further controversy due to the possibility of contamination or pneumococcosuria without actual infection.

In view of the low rates of isolation and sparse literature on *S. pneumoniae* being a uropathogen, particularly in immunocompromised or chronic illness settings such as HD, awareness among clinicians plays an essential role in diagnosing and treating this condition appropriately.

CASE

A 28-year-old female with end-stage renal disease (ESRD) receiving maintenance HD three times weekly through a tunneled dialysis catheter complained of dysuria, urinary pruritus, and discomfort while urinating. She denied fever, chills, rigors, flank pain, and other systemic complaints. She had a history of ESRD on chronic HD but no history of urogenital tract abnormalities.

Vital signs were within normal limits. Urinalysis revealed pyuria and microscopic hematuria. In addition, laboratory investigations demonstrated evidence of infection, with elevated inflammatory markers in the blood and significant pyuria on urinalysis (Table 1). The patient had no respiratory symptoms, and the posteroanterior chest radiograph was unremarkable. Simultaneous blood cultures obtained from the tunneled catheter and peripheral vein were negative.

Table 1. Key laboratory and microbiological findings

Parameters	Value	Reference range
White blood cell count (×10³/L)	12.56	4.0-10.0
Hemoglobin (g/dl)	12.5	12.0-16.0
Platelet count (×10³/L)	225	150-400
C-reactive protein (mg/L)	58	<5
Blood urea nitrogen (mg/dl)	106	9-23
Serum creatinine (mg/dl)	13.09	0.5-1.1
Urine leukocytes (/HPF)	38	0-5
Urine erythrocytes (/HPF)	8	0-3

HPF: High-power field

The patient had a daily residual urine output of approximately 200-300 ml. To minimize the risk of contamination, the urine sample for culture was collected under sterile conditions using a clean-catch midstream urine specimen. Urine culture yielded pure growth of *S. pneumoniae* at a concentration >10^5 CFU/ml. To confirm the diagnosis, a repeat urine specimen collected the following day was cultured and demonstrated pure growth of *S. pneumoniae* at the same concentration. Antimicrobial susceptibility testing was performed and reported in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards (Table 2). After a 7-day course of ceftriaxone 1000 milligram

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(mg) therapy, the urine culture was sterile and clinical symptoms improved.

Table 2. Identification and antimicrobial susceptibility results of the *Streptococcus pneumoniae* isolates

Test	Interpretation
Optochin	S
Bile solubility	Positive
Oxacillin (1 µg)	R
Benzylpenicillin	I
Cefotaxime	S
Ceftriaxone	S
Cefepime	S
Erythromycin	S
Clindamycin	S
Cotrimoxazole	S
Levofloxacin	S
Vancomycin	S
Linezolid	S

S: Susceptible, I: Intermediate, R: Resistant

DISCUSSION

S. pneumoniae is typically associated with respiratory infections and serious diseases, but its involvement in UTIs is infrequent and not well-documented.[5] In many microbiological studies, finding pneumococcus in urine cultures is rare, and it is important to determine if the presence of bacteria is due to contamination, colonization (referred to as "pneumococcosuria"), or an actual infection.[6] Various observational studies and case reports have shown that pneumococcus can be found in urine, particularly in patients with urinary tract structural issues, underlying renal disease, or a history of recurrent UTIs, indicating that certain factors may allow this uncommon pathogen to invade or colonize the urinary tract. One laboratory study identified *S. pneumoniae* in a small number of urine samples out of 110.000 collected over five years, affecting both children and adults, especially those with kidney dysfunction or those who had undergone kidney transplants.[7]

Although the patient reported genital pruritus and dysuria at presentation, no formal gynecological evaluation was performed because there were no accompanying findings suggestive of a gynecological infection. The absence of a gynecological examination should therefore be acknowledged as a limitation of this case. Elevated CRP levels are relatively common among patients undergoing chronic HD and are not specific for urinary tract infection. Therefore, in this case, the elevated CRP level should be interpreted cautiously and was not considered a specific indicator of infection.

Correct diagnosis relies on identifying significant bacteriuria, having supportive symptoms, and ruling out contamination. Treatment should be based on susceptibility testing, as pneumococcal strains can show different resistance patterns. This case highlights the importance of considering rare pathogens like *S. pneumoniae* in high-risk patients who show urinary symptoms, particularly when cultures repeatedly identify the same organism and clinical evidence suggests an infection rather than simple colonization.

CONCLUSION

Although rare, *S. pneumoniae* should be considered a potential causative pathogen in UTIs in patients who have certain risk factors, like having HD access devices or structural issues in the urinary system. Diagnosis and treatment should be based on the patient's symptoms and the bacteria's resistance to antibiotics.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

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Letter to the Editor

Resetting the gut-brain axis in AN: the promise and pitfalls of FMT

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Keywords: Anorexia nervosa, fecal microbiota transplantation, gut-brain axis

Dear Editor,

Anorexia nervosa (AN) is an eating disorder characterized by persistent dietary restriction and an intense fear of weight gain despite maintaining low body weight. It remains one of the most lethal psychiatric disorders, yet therapeutic advancements continue to lag behind its clinical burden. With its onset in the early teen years, AN affects up to 4% of adolescent girls[1] and disproportionately affects young women, with 90% of sufferers being female.[2] Currently, the bidirectional link between the gastrointestinal tract and the central nervous system, known as the "microbiota-gut-brain axis," has attracted increased research interest in metabolic and psychiatric diseases such as AN.

Complex microbial communities can be found in the human digestive tract, and the gut microbiota (GM) plays an important role in host metabolism. Growing evidence shows that in the active phase of illness, individuals with AN have a dysbiotic GM, with lower microbial diversity and reduced stool levels of serotonin, GABA, dopamine, butyrate, and acetate compared to healthy controls (HCs).[3] The process of communication between the gut and brain takes place via neural, endocrine, and immune systems.[4] Microbial metabolites have an effect on gut-brain communication through activation of vagal afferent signaling and on secretion of appetite-regulating hormones like glucagon-like peptide-1 (GLP-1).[4]

Fecal microbiota transplantation (FMT) is a promising new procedure that involves the transfer of GM from a healthy donor to a recipient to restore microbial balance and improve health outcomes. FMT is a standard procedure used to treat recurrent C. difficile infections. Microbial diversity and production of microbial metabolites are restored with FMT, potentially normalizing the communication between the gut and the brain, leading to better gastrointestinal homeostasis and the alleviation of symptoms, including constipation, but the role of FMT in the regulation of appetite is still being investigated. FMT has shown promising findings in adult case reports of AN, with improvements in gut microbial diversity, gut barrier function and participants experiencing weight gain despite no reported increase in caloric intake.[5]

Despite increasing interest in FMT in AN, current evidence is still limited and unclear. Most available data comes from animal studies and small pilot human studies, while randomized controlled trials are still lacking. Existing research is also limited by the lack of standardized protocols for donor selection, route of administration, and the frequency of treatment, resulting in reduced reproducibility across studies.[6]

FMT in AN also brings up important ethical and safety concerns, especially because adolescents and young adults represent a vulnerable patient population. Obtaining informed consent can be difficult in severely malnourished individuals with impaired cognitive and psychological functioning. Additionally, the long-term neurodevelopmental, metabolic, and psychiatric consequences of altering the gut microbiome are not understood properly.

Although there is increased evidence that the gut microbiome plays a role in AN, there are key knowledge gaps, such as whether the timing of onset affects the relationship between genetic susceptibility, diet and gut microbiome. Future work should therefore extend beyond the observational studies towards understanding how certain microbial taxa interact with the host in order to develop microbiome-based interventions (e.g., probiotics, and FMT) as adjuncts to standard therapy.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

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