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Original Research

Mediating Effects of Malnutrition on the Relationship between Depressive Symptoms Clusters and Muscle Function Rather than Muscle Mass in Older Hemodialysis Patients

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Abstract

OBJECTIVES: The purpose of this study was to investigate the association and mediation pathways among muscle mass, muscle function (muscle strength and physical performance), and malnutrition with depressive symptoms clusters in the older hemodialysis patients.
DESIGN: A multi-center cross-sectional study.
SETTING AND PARTICIPANTS: A total of 499 patients aged ≥ 60 on hemodialysis from seven facilities in Shanghai of China from 2020 to 2021.
MEASUREMENTS: Muscle mass was assessed by skeletal muscle index(SMI). Muscle strength was measured by handgrip strength, and physical performance was measured via gait speed and Timed Up and Go Test (TUGT). Nutritional status was assessed by Malnutrition Inflammation Score (MIS). Depressive symptoms were evaluated by the Patient Health Questionnaire-9 (PHQ-9). Logistic regression and mediation analyses fully adjusted for all potential confounding factors.
Results: Among 499 participants (312 men, mean age 69.2±6.6 years), 108 (21.6%) had depressive symptoms. The muscle strength, physical performance and malnutrition were associated with depressive symptoms. Furthermore, malnutrition significantly mediated the association of muscle function with total, cognitive-affective symptoms. The association of the muscle function with somatic symptoms were mediated by the nutritional status. The mediated proportions of malnutrition in the relationship between physical performance and depressive symptoms clusters were stronger in somatic symptoms than in cognitive-affective symptoms.
CONCLUSIONS: Our findings suggest that muscle function rather than muscle mass may contribute substantially to the development of depressive symptoms clusters in the hemodialysis via malnutrition. The malnutrition mediated stronger in the association of muscle function with somatic symptoms. These findings may help guide clinicians to better diagnose and manage depression in the context of concomitant muscle function and malnutrition.

Key words: Depressive symptoms clusters, hemodialysis, malnutrition, muscle function, physical performance.

Introduction

Depression is generally the most common psychological complication in patients receiving maintenance hemodialysis due to its relative prevalence and its association with other adverse medical outcomes (1). Many studies have reported that the prevalence of depression in dialysis population ranges from 20 to 30% (2). Evidence is accumulating that elevated depressive symptoms are not only a risk factor of poor adherence to treatment and increased hospitalization but also are associated with poorer quality of life and enhanced mortality in patients receiving hemodialysis (3, 4). However, depression often goes undetected, untreated or undertreated in patients undergoing hemodialysis (5). Therefore, it is essential to identify depressive symptoms early and evaluate the modifiable factors associated with it.

The patients undergoing hemodialysis experienced high risk for muscle wasting, which was associated to higher morbidity and mortality (6). Muscle wasting is the most common condition in older adults, especially those on hemodialysis, with a higher prevalence of declined muscle mass and muscle function, which ranges from 12.7% to 45.1% in patients receiving hemodialysis (7). It is reported that depression is common in older hemodialysis patients and is associated with impairment muscle mass and function (8-10). A recent report has suggested that muscle function such as muscle strength and physical performance are related to depression in hemodialysis patients (9). In contrast, researchers failed to found the relationships between mental health and physical performance (11). Furthermore, preliminary study suggest that muscle function may be more closely associated with mortality than muscle mass in dialysis patients (12), so the correlation between depression and muscle mass or muscle function needs to be further investigated. Studies to date have focused on the depression rather than on the depressive symptoms clusters. In closely related research areas, researchers have begun to

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compare the utility of depressive symptoms clusters including affective-cognitive and somatic clusters, which are associated with various health-related outcomes (13). Studies in which the depression construct is examined according to symptom clusters could help to elucidate the mechanisms underlying the relationship among muscle mass, muscle function and depression.

Besides the role of muscle wasting, the nutritional status may also affect depressive symptoms. It is noteworthy that malnutrition is a common condition among chronic hemodialysis patients, with a prevalence of 18-76% (14). Several recent studies have indicated that low muscle strength (15, 16) and poor physical performance (17) are significant predictors of malnutrition in older adults. And previous studies have shown that malnutrition is related to depressive symptoms among hemodialysis patients (18-20), but some individual studies have no association (21, 22). Thus, it is reasonable to believe that muscle wasting and malnutrition may interact in some way and in turn have an effect on depression. However, to date the interrelationship of these three conditions of chronic hemodialysis patients remains controversial. Moreover, although physical impairment, malnutrition, and depression were examined in patients with advanced chronic kidney disease (23), no studies have yet investigated the potential mediation pathways among muscle mass, muscle function, nutritional status and depressive symptoms clusters in the patients undergoing hemodialysis.

Therefore, the aim of this study is to examine the complex association of depression with muscle mass, muscle function (muscle strength and physical performance) and nutrition status in patients receiving hemodialysis. Furthermore, we have explored that the possible mediating role of malnutrition in the association between muscle mass, muscle function and depressive symptoms clusters.

Methods

Subjects

This cross-sectional multicenter study enrolled patients undergoing hemodialysis from seven hemodialysis centers in Shanghai between July 2020 and April 2021. Patients were eligible to participate if they were over 60 years of age, receiving maintenance hemodialysis for at least 3months, and able to provide informed consent. Patients were excluded as following criteria: (1) inability to perform the handgrip strength test or the gait speed test; (2) unable to measure the body composition; (3) did not complete date on the depression and nutrition assessments; (4) patients with hearing impairment, or visual impairment difficulties; (5) presented with an infection, amputated limb, pulmonary edema, or malignancy; (6) unable to communicate with the study staff or provide informed consent. The final analytic sample consisted of 499 patients (men 312, women 187) after excluding 43 subjects. 19 patients refused to participant in depression assessment due to personal reasons; 1 were unable to complete the handgrip strength test due to hand disability; 13 were unable to perform the gait speed or TUGT test since they were unable to walk because of disability or total dependence on a wheelchair, or blindness; 10 unable to measure the body composition. The study was approved by the Ethics Committee of Shanghai University of Medicine and Health Sciences and the methods were carried out in accordance with the principles of the Declaration of Helsinki. The informed consent was obtained from all patients prior to enrollment in the study.

Muscle mass and function assessments

Muscle mass was measured using a direct segmental multi-frequency bioelectrical impedance analysis (BIA) (InBody S10; Biospace, Seoul, Korea) taken in the pre-dialysis period (24). Patients were placed in a supine position at least 10 min b efore measurement. Muscle mass was assessed by skeletal muscle index (SMI), which was calculated by dividing relative skeletal muscle mass index by height squared.

Muscle function included muscle strength and physical performance. Muscle strength was assessed on the non-fistula hand before a dialysis session, using a dynamometer (GRIP-D; Takei Ltd, Niigata, Japan). Participants were asked to exert maximum effort twice, and the result from the strongest handgrip strength was used for analysis. For patients with an indwelling dialysis catheter, we used the dominant hand to test handgrip strength. Physical performance was measured via gait speed and Timed Up and Go Test (TUGT). Gait speed was assessed with the 4-m walk test. Patients were instructed to stand with both feet touching the starting line and to begin walking at their usual pace after a verbal command. The patients were allowed to use a gait-assistance device (25). TUGT was used to evaluate the balance function and the TUGT assesses the number of seconds needed for an individual to stand up from a chair, then walk 3 m, turn around, walk back to the chair, and sit down again with his back against the chair (26). These tests were performed before a dialysis session.

Assessment of Nutritional Status

The Malnutrition Inflammation Score (MIS) is a comprehensive scoring system with significant associations with prospective hospitalization and mortality as well as measure of nutrition in hemodialysis patients (27). The MIS contains 10 items about the patient's nutritional and functional state, including seven components of the Subjective Global Assessment (28), and combined with three new parameters (body mass index (BMI), serum albumin, and total iron-binding capacity to represent serum transferrin). Each component of the MIS has four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components ranges from 0 to 30. A higher score reflects a more severe degree of malnutrition status. Previous studies suggested the MIS ≥ 6 indicates malnutrition in MHD patients (29, 30).

Determination of depressive symptoms clusters

The Patient Health Questionnaire-9 (PHQ-9) was administered to assess depressive symptoms over the last two weeks (31). Using a 4-point scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day), patients reported the frequency with which they had experienced the following nine symptoms of major depressive disorder: (1) anhedonia, (2) depressed mood, (3) sleep disturbance, (4) fatigue, (5) appetite changes, (6) low self-esteem, (7) concentration problems, (8) psychomotor disturbances, and (9) suicidal ideation. Total scores range from 0 to 27, with scores ≥10 representing clinically significant depressive symptoms(32). It was proved to be reliable and valid to detect depressive disorder determined by this cut-off in dialysis patients (sensitivity= 92%, specificity =92%) (33).

In addition to computing the PHQ-9 total score by summing the nine items, we also calculated PHQ-9 cognitive-affective and somatic subscale scores. The cognitive-affective subscale score was computed by summing items 1, 2, 6, 7 and 9, and the somatic subscale score was calculated by summing the items 3, 4, 5 and 8. Previous studies supported a one-factor structure comprised of all nine items (34); however, recent confirmatory factor analyses have established that a two-factor structure provides a better fit (13).

Covariates

All participants were invited to a face-to-face interview to answer a standardized questionnaire. Baseline date of socio-demographic characteristics, health behaviors, condition of chronic diseases were considered as covariates. Demographic characteristics included age, gender, post-dialysis weight, dialysis vintage, education level. Health behaviors included smoking and drinking habits. Physical activity was assessed using the short form of the International Physical Activity Questionnaire (IPAQ) (35). Charlson comorbidity index (CCI) was used to assess the comorbidity, which accounted for multiple comorbidities by creating a sum score according to the presence of 19 comorbid conditions (36). In addition, all blood samples were drawn pre-dialysis. Kt/V was used as indicator of dialysis quality and monitored in every dialysis treatment using the OCM® (On-line Clearance Monitor; Fresenius Medical Care, Bad Homburg, Germany).

Statistical analyses

Baseline sociodemographic and health-related characteristics were compared between patients with and without depressive symptoms using an independent t-test for numeric variables and a chi-square test for categorical variables. Data with a normal distribution are expressed as the mean ± SD, whereas data with a non-normal distribution are expressed as the median, with the 25%–75% interquartile ranges given in parentheses. Categorical variables are expressed as proportions. Depressive symptoms were dichotomized according to the score of ≥ 10 on PHQ-9. A logistic regression analysis for the association between depressive symptoms with muscle mass and function, was performed after controlling for all confounding factors. We also explored the relationship of depressive symptoms and malnutrition using a logistic regression analyses with the fully-adjusted model.

Mediating effect of nutritional status was investigated on the association between muscle mass, muscle function and depressive symptoms. In the mediation analysis, the mediation analysis method recently developed by Hayes et. Al (37) is used, which used the nonparametric resampling bootstrapping procedure to evaluate the indirect effect of potential mediators in a regression model. In our analyses, we used boot-strapping with 5000 resamples to obtain a bias-corrected and accelerated 95% confidence interval of the mediation effect. In each mediation model with full adjustment, we included SMI, handgrip strength, gait speed, and TUGT as independent variables, PHQ-9 total, cognitive-affective, and somatic score all in the form of continuous variables as dependent variables, and the MIS variable as a potential mediator. In addition, we have also analyzed MIS variable as an independent variable, and the SMI, handgrip strength, gait speed, and TUGT as potential mediators.

We used the PROCESS V2.16.3 developed by Hayes and Preacher (http://www.afhayes.com) to performed the mediation analysis. We examined the significance of the mediating effect to confirm that the effect of independent variable on mediator, the effect of mediator on dependent variable and the total effect of independent variable on dependent variable were significant, respectively. In addition, the effect of all bootstrapped 95% confidence of the mediating intervals for indirect effects in the above-mentioned mediations did not contain zero. All statistical analyses were performed using IBM SPSS Statistics v26.0 (SPSS Inc., Chicago, Illinois, United States). The statistical significance was determined as $p < 0.05$.

Results

Characteristics of the patients for depressive symptoms

Among 499 participants (312 men, 187 women; mean age 69.2±6.6 years) who were available to be analyzed, 108 (21.6%) had depressive symptoms, in which 21.8% for men and 21.4% for women respectively. Socioeconomic and health-related characteristics of patients undergoing hemodialysis stratified by depressed status were presented in Table 1. Handgrip strength, gait speed, TUGT, IPAQ, MIS and CCI significantly differed between groups ($P<0.05$, Table 1).

Association of muscle mass, muscle function, malnutrition and depressive symptoms

We investigated the association between muscle mass, function and depressive symptoms in hemodialysis patients using logistic regression analysis (Table 2). After adjustments for potential confounders (age, sex, BMI, Kt/V, IPAQ, MIS and

Table 1. Baseline Characteristics of Study Participants According to the Presence of Depressive Symptoms

Characteristics	Total (n=499)	Not Depressed (n=391)	Depressed (n=108)	P value
Age (y)	69.2±6.6	69.1±6.4	69.7±7.0	0.371
Sex (%)				0.915
Male	312(62.5)	244(62.4)	68(63.0)	
Female	187(37.5)	147(37.6)	40(37.0)	
Dry weight (kg)	61.8±10.8	62.0±10.8	60.6±11.1	0.237
BMI (kg/m2)	23.4±3.4	23.4±3.4	23.4±3.6	0.999
Vintage (months)	44.7(23.1,83.2)	44.7(24.8,83.2)	44.7(16.5,83.2)	0.521
Cause of ESRD (%)				0.206
Diabetic	118(23.6)	83(21.2)	35(32.4)	
Hypertensive	82(16.4)	67(17.1)	15(13.9)	
Glomerulonephritis	139(27.9)	115(29.4)	24(22.2)	
Polycystic kidney	24(4.8)	21(5.3)	3(2.7)	
Other	136(27.3)	105(26.9)	31(28.7)	
Handgrip strength	22.0±7.4	22.6±7.4	19.9±6.8	<0.001
SMI (kg/m2)	6.8±1.2	6.9±1.1	6.7±1.2	0.370
Gait speed (m/s)	0.91±0.30	0.95±0.29	0.79±0.30	<0.001
TUGT	11.2±6.9	10.4±5.7	13.9±9.7	<0.001
IPAQ (Met-min/wk)	1386(462,2772)	1386(693,3066)	693(198,2336)	0.007
MIS	4.6±3.0	4.2±2.9	5.8±3.5	<0.001
Malnutrition (%)	153(30.7)	100(25.6)	53(49.1)	<0.001
Education (%)				0.386
Less than high school	145(29.1)	110(28.1)	35(32.4)	
High school or higher education	354(70.9)	281(71.9)	73(67.6)	
Drinking (%)	7(1.4)	7(1.8)	0(0.0)	0.192
Smoking (%)	94(18.8)	77(19.7)	17(15.7)	0.335
CCI	4.2±1.7	4.0±1.7	4.8±1.9	<0.001
Number of medications (n)	4.6±2.5	4.4±2.5	5.0±2.8	0.053
Laboratory parameters				
Hemoglobin (g/dL)	111.4±14.9	112.0±14.7	109.5±15.4	0.129
Albumin (g/L)	39.2±3.4	39.4±3.3	38.3±3.7	0.006
PTH(pg/dL)	316.9±285.0	308.5±282.4	348.2±293.8	0.208
Calcium (mg/dL)	2.3±0.3	2.3±0.3	2.2±0.2	0.301
Phosphorus (mg/dL)	1.9±0.6	1.9±0.6	2.0±0.6	0.121
Kt/V	1.39±0.35	1.40±0.36	1.36±0.29	0.309

BMI, body mass index; ESRD, end stage renal disease; SMI, muscle mass index; TUGT, timed up and go test; MIS, malnutrition inflammation score; IPAQ, international physical activity questionnaire; Met-min/wk, metabolic equivalent task minutes per week; CCI, Charlson Comorbidity Index; PTH, parathyroid hormone, Kt/V, fractional clearance index for urea.

CCI), we observed that handgrip strength (OR =0.94, 95% CI = 0.90–0.98), gait speed (OR = 0.21, 95% CI = 0.08–0.56) as well as TUGT (OR = 1.04, 95% CI = 1.01–1.08) were significantly correlated with depressive symptoms. Furthermore, malnutrition was highly associated with depressive symptoms in hemodialysis patients (OR = 2.30, 95% CI = 1.43–3.70).

Mediating effects of nutritional status in the association between muscle function and depressive symptoms clusters

In the mediation analysis, MIS had a significant mediating role in the muscle function (handgrip strength, gait speed and TUGT) and PHQ-9 total score (Table 3, Fig. 1A). We also observed that MIS was a significant mediator of the association

Table 2. Associations of depressive symptoms (PHQ-9 score ≥10) with muscle mass, muscle function and malnutrition in a logistic regression analysis

Variables	OR(95%CI) Crude	P	Adjusted model	P
SMI	0.92(0.76,1.11)	0.369	0.79(0.57,1.09)	0.147
Handgrip strength	0.95(0.92,0.98)	0.001	0.94(0.90,0.98)	0.003
Gait speed	0.16(0.08,0.34)	<0.001	0.21(0.08,0.56)	0.002
TUGT	1.07(1.03,1.10)	<0.001	1.04(1.01,1.08)	0.028
Malnutrition	2.84(1.83,4.42)	<0.001	2.30(1.43,3.70)	0.001

Adjusted model: Adjusted for age, sex, BMI, Kt/V, IPAQ, MIS, CCI; PHQ-9, patient health questionnaire-9; SMI, muscle mass index; TUGT, timed up and go test; MIS, malnutrition inflammation score; BMI, body mass index; Kt/V, fractional clearance index for urea; IPAQ, international physical activity questionnaire; CCI, Charlson Comorbidity Index.

Table 3. Mediation pathways among muscle mass, muscle function, MIS and PHQ-9 score

IV	M	DV	IV on M			M on DV			IV on DV						Mediating effect of M				
			Effect of IV on M	Boot SE	P	Effect of M on DV	Boot SE	P	Direct effect of IV on DV	Boot SE	P	Total effect of IV on DV	Boot SE	P	Indirect effect	Boot SE	Boot LLCI	Boot ULCI	Proportion of effect mediated
SMI	MIS	PHQ-9 score	0.157	0.185	0.399	0.339	0.079	<0.001	0.247	0.324	0.446	0.300	0.329	0.362	0.053	0.081	-0.083	0.239	-
Handgrip strength*			-0.084	0.022	0.001	0.311	0.080	0.001	-0.089	0.039	0.025	-1.115	0.039	0.004	-0.026	0.009	-0.048	-0.011	22.7%
Gait speed*			-2.607	0.489	<0.001	0.272	0.081	0.001	-3.269	0.890	0.001	-3.977	0.874	<0.001	-0.708	0.273	-1.328	-0.245	17.8%
TUGT*			0.100	0.020	<0.001	0.299	0.081	0.001	0.085	0.036	0.019	0.115	0.036	0.001	0.030	0.014	0.010	0.063	26.0%
SMI		Cognitive-affective score	0.164	0.187	0.379	0.143	0.049	0.003	0.138	0.199	0.487	0.162	0.200	0.420	0.024	0.037	-0.029	0.123	-
Handgrip strength*			-0.082	0.022	0.001	0.121	0.049	0.014	-0.070	0.024	0.004	-0.080	0.024	0.001	-0.010	0.005	-0.023	-0.002	12.4%
Gait speed*			-2.591	0.491	<0.001	0.101	0.049	0.041	-2.039	0.545	0.001	-2.301	0.532	<0.001	-0.262	0.159	-0.618	-0.001	11.4%
TUGT*			0.100	0.020	<0.001	0.121	0.050	0.015	0.046	0.022	0.038	0.058	0.022	0.008	0.012	0.007	0.002	0.031	20.7%
SMI		Somatic score	0.146	0.187	0.435	0.200	0.041	<0.001	0.095	0.169	0.573	0.124	0.173	0.471	0.029	0.047	-0.059	0.128	-
Handgrip strength			-0.083	0.022	0.001	0.195	0.042	<0.001	-0.018	0.021	0.374	-0.035	0.021	0.098	-0.016	0.005	-0.027	-0.008	-
Gait speed*			-2.596	0.491	<0.001	0.177	0.042	<0.001	-1.104	0.467	0.018	-1.565	0.462	0.001	-0.460	0.143	-0.798	-0.229	29.4%
TUGT*			0.100	0.020	<0.001	0.182	0.042	<0.001	0.037	0.019	0.044	0.055	0.019	0.003	0.018	0.008	0.007	0.038	32.9%

All estimated effect values, P-values, standard errors, and confidence intervals were obtained from the mediation analysis by Hayes and Preacher (2014); A significant mediating effect is represented as bold-face with an asterisk ($P < 0.05$); DV, dependent variable; M, mediator; IV, independent variable; Boot SE, boot-strapped standard error; Boot LLCI/ULCI, lower level (LL) or upper level (UL) confidence interval (CI) for boot-strapped effect value in the mediation analysis based on 5000 bootstrap samples; SMI, muscle mass index; TUGT, timed up and go test; MIS, malnutrition inflammation score; PHQ-9, patient health questionnaire-9.

of handgrip strength/gait speed/TUGT with cognitive-affective score (Table 3, Fig. 1B). The correlation of gait speed and TUGT with somatic score were mediated by MIS, while the relationship between handgrip strength and somatic score was not mediated by MIS (Table 3, Fig. 1C). The ratio of the indirect effect of nutritional status in the relationship between gait speed/TUGT and depressive symptoms clusters were stronger for the somatic symptoms (29.4%/32.9%) than for the cognitive-affective symptoms (11.4%/20.7%).

Mediating effects of muscle function in the association between nutritional status and depressive symptoms clusters

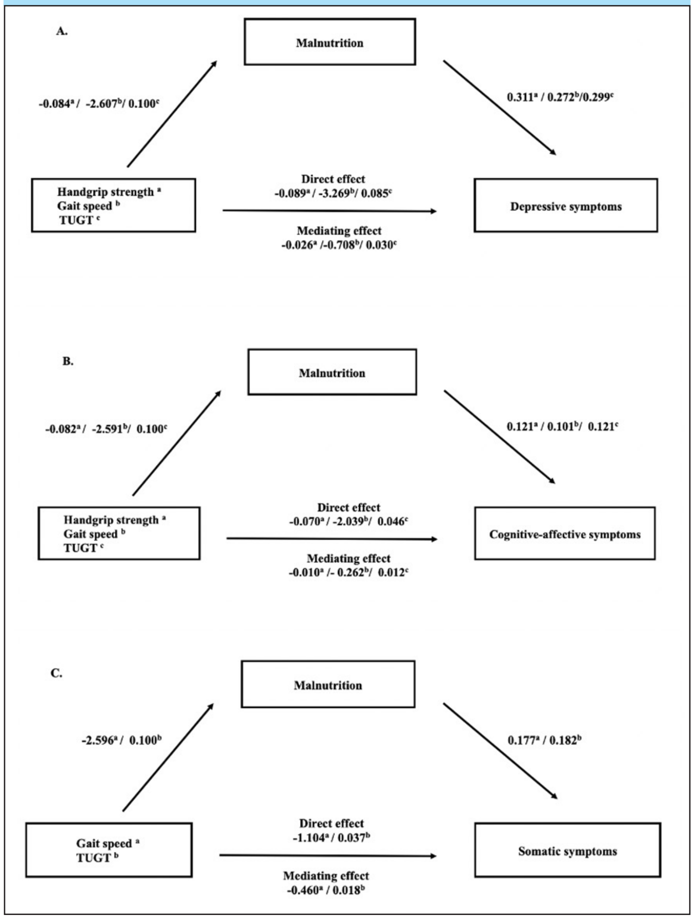
In supplementary analyses, we explored the potential mediating effect of muscle function on the association between nutritional status and depressive symptoms clusters using the same mediation analysis method. We observed significant partial mediation pathways between MIS and PHQ-9 score through muscle function (handgrip strength, gait speed, TUGT, Supplementary Table).

Discussion

The present results showed that the muscle function (muscle strength and physical performance) and malnutrition were significantly associated with depressive symptoms in the multicenter older hemodialysis patients. In addition, we also found that nutritional status both significantly mediated the association of muscle function rather than muscle mass with total depressive symptoms. With regard to the depressive symptoms clusters, malnutrition significantly mediated the association of physical performance with cognitive-affective, somatic symptoms as well as overall depressive symptoms, with a greater contribution from the somatic symptoms (i.e., sleep disturbance, fatigue, appetite changes, and psychomotor disturbances).

In our study, the prevalence of depressive symptoms using the PHQ-9 was 21.6%, which is consistent with other studies. King-Wing Ma et al. (1) and Mapes et al. (38) reported that the prevalence of depressive symptoms in patients undergoing hemodialysis was 22.8%-39.3% and 20%, respectively. However, some studies have shown high prevalence of depression among hemodialysis patients. There are significant disparities in the prevalence of depression among patients receiving hemodialysis in previous literature, mainly due to differences in the characteristics of the study population, the timing of initiation of hemodialysis treatment and the tools used to screen for depression.

Figure 1. Mediation models of muscle function, malnutrition and depressive symptoms in hemodialysis patients



Our study revealed that depressive symptoms were associated with muscle function, including handgrip strength, gait speed and TUGT. This is consistent with several studies in dialysis population, which showed a significantly association between handgrip strength and gait speed with depression (9). Hemodialysis patients had poor physical performance which may decrease physical activity and also cause depressive symptoms. However, there were inconsistencies. Tao et al. failed to find the relationship among muscle function measured by handgrip strength, gait speed and TUGT with mental health in the peritoneal dialysis (11). This may be due to different assessment criteria for mental health and different dialysis treatment or populations. To date, rare study focus on the relationship between TUGT and depression in the hemodialysis population, which encourages further research to identify possible common underlying determinants of these two conditions. Several hypothetical underlying mechanisms can explain the association between muscle function and depressive symptoms. Low muscle strength and poor physical performance reflects poor overall physical activity, and is associated with increases the risk in feeling of helplessness, fatigue, and fewer social activities, which can result in depressive symptoms. Furthermore, the association between muscle function with depression can be explained by sharing several common pathophysiological pathways such as oxidative stress, chronic inflammation, metabolic dysfunction, and reduced concentration of brain-derived neurotropic factor (39). It's worth noting that muscle function has been widely identified as practical mortality predictor in the dialysis patients (12, 40). Hence, these tests have been proposed as a useful tool for the continuous and systematic assessment of muscle function in this population.

Moreover, the study suggested that malnutrition in hemodialysis patients was nearly 2-fold risk associated with depressive symptoms, which are in line with some previous studies (18-20). It is reported that the lack of appetite and reduced dietary adherence have been suggested as the underlying causes for the relationship between the malnutrition and depression. However, conflicting results have also been reported (21, 22). The inconsistent results are likely due to the small sample size in a single dialysis center and incomplete assessment measures of nutritional status in previous studies. The etiology of dialysis-related depression is multifactorial and is associated with biological and psychosocial mechanisms. Biological mechanisms involve enhanced cytokine levels and neurotransmitters influenced by uremia. Psychosocial factors include a sense of well-being, loss of freedom, altered family and social relationships, etc (20).

To our knowledge, this is the first study that evaluates the mediation relationship between muscle function, malnutrition and depressive symptoms in patients on hemodialysis. This implies that muscle function (muscle strength and physical performance) may cause poor nutritional status, leading to depressive symptoms among hemodialysis patients independent of the direct effects of physical performance on depressive symptoms. Several recent studies suggested that low muscle strength (15, 16) and poor physical performance (17) are significant predictors of malnutrition in older adults. Moreover, some studies have suggested that malnutrition is related to the risk of depressive symptoms in hemodialysis population (18-20). Similar results shown in our recent studies among the elderly population, one study revealed a significant association between grip strength and gait speed with depression (41), and another study showed that physical performance was associated with malnutrition and depression (42). These results make it conceivable that poor nutritional status mediates poor muscle function and depressive symptoms. On the other hand, our additional results also demonstrated that muscle function significantly mediated the association between malnutrition and depressive symptoms (Supplementary Table). Several factors explain the occurrence of poor muscle function in older adults and how they may create a vicious cycle resulting in malnutrition. Reduced physical activity and functional decline commonly observed in older adults contribute to poor muscle function (15). It further affects the gastrointestinal function, leading to appetite changes, which in turn reduces food intake and leads to malnutrition. In addition, in the malnourished state, skeletal muscle is the body's preferential fuel source, which causes a loss of protein stores and a resultant decline in muscle function (16). In fact, the relationship between muscle function and malnutrition is complex, and it remains unclear whether low muscle function is the cause or the consequence of impaired nutritional status. Further studies are needed to confirm the relationship.

There are several potential explanations for the reason that malnutrition is a stronger mediator between physical performance and somatic symptoms than cognitive-affective symptoms. In our study, MIS was used to assess the nutritional status, which is a comprehensive scoring system that has been significantly associated with prospective hospitalization and mortality, as well as measures of inflammation in addition to nutritional status (27). The somatic cluster may have stronger links with the putative mechanisms underlying the depression–inflammation relationship, such as autonomic dysfunction, hypothalamic–pituitary–adrenal axis (HPA) hyperactivity (43). Secondly, the somatic symptoms may be more likely to be a consequence of systemic inflammation than the cognitive-affective symptoms. Increasing evidence supports the role of inflammation in the etiology of some cases of depression. Dantzer et al. (44) reported that patients treated with interferon-a (which produces elevated pro-inflammatory cytokines) suffered physical symptoms similar to the somatic depressive symptoms, including sleep disturbance, fatigue, and appetite changes. Finally, given that the residual symptoms that persist after treatment for depression are usually somatic, it is possible that an elevated somatic symptom score may be a sign of greater depression severity or a positive history of depressive disorder. Therefore, it is plausible that elevations in poor nutritional status evaluated by MIS preceded and contributed more to increases in the somatic depressive symptoms in our study. In particular, we found that muscle strength was associated with total and cognitive-affective symptoms, rather than somatic symptoms in this study. The exact reason is unclear, the mechanisms between muscle strength and somatic symptoms need to be further observed. Future studies are needed to determine whether measurement invariance of the selected two-factor solution for the PHQ-9 holds overtime among the hemodialysis patients.

Exploration of these mediation pathways may clearly identify underlying associations, which may provide an opportunity for early detection, intervention, and monitoring of the most vulnerable older hemodialysis patients. These findings highlight the importance of integration consideration of muscle function as well as nutritional aspects into clinical practice throughout the lifetime of the hemodialysis patients to prevent psychological disorder. We believe that the current findings may have a very important role for nephrology physicians and co-medical staff in clinical practice. Exercise and nutrition therapy are recommended to improve the muscle function and nutritional status in order to improve depression. In the future, much greater attention must be paid to mental health during the renal rehabilitation and multifaceted interventions require to be considered.

Strengths and limitations

This study has several strengths. This is the first multicenter design to examine the relationship between muscle function, malnutrition and depression among the older patients undergoing hemodialysis, which increases the generalizability of our findings to other Chinese facilities. Moreover, findings may provide new insights for renal rehabilitation in this population. Despite extensive efforts to curb study limitations, some limitations of this study should be considered. This study is based on a cross-sectional design. Therefore, it is not possible to elucidate clear causal associations among muscle function, malnutrition and depressive symptoms in the older patients receiving hemodialysis. In addition, the relationship between physical performance and malnutrition is complex, and this study focused on exploring the association between malnutrition-mediated muscle function and depression, rather than concentrating on the mediating role of muscle function on the relationship between nutrition and depression. Future studies with longitudinal designs will provide more robust evidence regarding the causal association between malnutrition, muscle function and depressive symptoms.

Conclusion

In summary, we explored the complex relationship between muscle function, malnutrition and depressive symptoms clusters in Chinese hemodialysis patients, and found that muscle function rather than muscle mass, as well as malnutrition showed a strong positive correlation with depressive symptoms. Furthermore, malnutrition significantly mediated the association of physical performance with total, cognitive-affective, and somatic symptoms. The mediated proportions of malnutrition in the relationship between physical performance and depressive symptoms clusters were stronger in somatic symptoms than in cognitive-affective symptoms. A future longitudinal study may disentangle this complex issue.

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