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ORIGINAL ARTICLE

Depression, quality of life, and body composition in patients with end-stage renal disease: a cohort study

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Objective: To prospectively evaluate depressive symptoms, nutritional status, and quality of life (QoL) and search for possible associations in patients with end-stage renal disease undergoing hemodialysis.
Methods: A cohort study of 104 adult patients with end-stage renal disease undergoing hemodialysis was conducted. Anthropometric, clinical, and biochemical variables were evaluated after a midweek hemodialysis session. The participants' body composition was assessed by direct segmental multi-frequency bioimpedance analysis. The WHOQOL-Bref questionnaire was used to evaluate QoL. Participants were separated into two groups - depressive symptoms and no depressive symptoms - at inclusion and evaluated annually for 2 years thereafter using the Beck Depression Inventory. Survival analysis used the Kaplan-Meier method and Cox regression analysis for the goodness of fit of associated factors. All-cause mortality was the outcome of interest.
Results: Participants' mean age was 55.3±15.6 years, 60% were male, and the median time on hemodialysis was 17.5 (8.0-36.8) months. Thirty-two patients had depressive symptoms and a significantly lower QoL compared with the 72 patients in the no depressive symptoms group. The fitted outcome model showed that lean body mass had a protective effect against all-cause mortality (hazard ratio [HR] = 0.89; 95%CI 0.80-0.99; p = 0.038).
Conclusion: Depressive symptoms were highly prevalent in the cohort, and correlated with the physical and psychological components of the QoL life questionnaire, as well as with C-reactive protein and phosphorus levels. Lean body mass was protective for the assessed outcome.

Keywords: Body composition; hemodialysis; mortality; quality of life; depression

Introduction

The term psychonephrology was coined to designate psychiatric problems affecting patients with chronic kidney disease (CKD) or renal transplant recipients.

Depressive symptoms (DS) are the most frequent comorbidity among patients with end-stage renal disease (ESRD).[1] Major attention is currently paid to the detection of DS in patients undergoing hemodialysis (HD). Early diagnosis of depression is often missed, owing to the similarities between DS and uremic symptoms. This might explain the lower prevalence of DS in the early stages of CKD.[2] In patients with ESRD, however, its prevalence is up to three times greater than in the general population.[3] Furthermore, the strong emotional burden of severe illness may have profound effects on quality of life (QoL). Occasionally, DS occur in response to such stress, in connection with some underlying psychiatric disease or in a manner dependent on personal characteristics.[4] Additionally, pro-inflammatory cytokine-related genes may be involved in the etiology of DS.[5]

Many patients with ESRD start HD with some degree of malnutrition, possibly related to decreased appetite, dietary restrictions, or to the catabolic consequences of uremia. These patients are more likely to experience poorer treatment outcomes[6] and to exhibit the so-called malnutrition-inflammation-depression and arteriosclerosis (MIDA) complex. MIDA has been shown to be an independent risk factor for cardiovascular disease, and is associated with higher morbidity and mortality.[7]

DS appear to be associated with a higher mortality rate since the start of renal replacement therapy: patients presenting with DS may have a 2.7-fold higher risk of death than those without DS.[8] As DS have a negative effect on QoL and are associated with increased morbidity and mortality, early diagnosis and treatment of these symptoms should be sought in all CKD patients, regardless of disease stage.[9,10]

The aim of the present study was to evaluate the presence of DS and their relationship with nutritional status, biochemical parameters, quality of life, and mortality in a cohort of ESRD patients undergoing HD.

Methods

This was a prospective cohort study of 104 prevalent and incident patients with ESRD undergoing HD at Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil. The study protocol was approved by the institutional Research Ethics Committee (protocol no. 10/05257), and written consent was obtained from all

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participants prior to their enrollment. Only stable (arteriovenous fistula as vascular access; no evidence of acute infection; ongoing treatment for 3 or more months; no recent hospitalization), adult, and literate patients were included. All participants were evaluated yearly after inclusion in the study. The following evaluation time points were defined: t0 (inclusion), t1 (1 year after inclusion), and t2 (2 years after inclusion). The cohort was censored for kidney transplantation for the sake of survival analysis. All-cause mortality was the outcome variable of interest.

A validated Portuguese-language version of the Beck Depression Inventory (BDI) questionnaire[11] was used to evaluate the presence of DS.[12] The cutoff point for the presence of DS was set at 15, which appears to be the most sensitive and specific score.[13] Individual perception of QoL was evaluated by the World Health Organization Quality of Life instrument-Abbreviated version (WHOQOL-Bref), which comprises 26 questions, divided into four domains: physical health, psychological, social relationships, and environment.[14] Additionally, the malnutrition-inflammation score (MIS) was used to evaluate the malnutrition-inflammation syndrome.[15]

Anthropometric data (height and post-dialysis weight) were obtained at the end of a midweek HD session; the body mass index (BMI) was calculated as recommended (weight [kg]/ height squared [m^2]). Body composition analysis was performed by the direct segmental multi-frequency bioimpedance method (InBody 520®, Biospace Co., Seoul, South Korea) and results used to classify nutritional status as underfat, standard, overfat, or obese.[10,16] A venous blood sample was obtained at the start of the HD session. After centrifugation (10 minutes at 2,000 rpm), a serum aliquot was collected and frozen (-80 °C) for later estimation of high-sensitivity C-reactive protein (hs-CRP), using a high-sensitivity turbidimetric method (Vitros® 5.1 Fusion, Ortho Clinical Diagnostic, Rochester, NY, USA). Albumin, total cholesterol, HDL-cholesterol, triglycerides (LDL-cholesterol calculated by the Friedewald equation), creatinine, and phosphorus concentrations were determined by dry chemistry methods (Vitros® 5.1 Fusion, Ortho Clinical Diagnostic, Rochester, NY, USA) in the non-frozen aliquot. Blood cells were counted by flow cytometry (Sysmex XE-2100D, Sysmex Corporation, Kobe, Japan). Total iron-binding capacity was measured by a colorimetric ferrozine method (Labtest Diagnóstica S.A, Lagoa Santa, MG, Brazil).

Statistical analysis

Patients were allocated across two groups: DS and no DS. Variables are presented as mean and standard deviation (SD), median and interquartile range (IQR), or absolute and relative frequency, as appropriate. Between-group differences in continuous variables were analyzed by Student's *t* test or the Mann-Whitney *U* test (with post-hoc Tukey test). The chi-square test (χ^2) or Fisher's exact test were used to compare categorical variables. Correlations were analyzed by Pearson's correlation or Spearman's rank correlation coefficient. Survival and outcome-associated factors were analyzed by the Kaplan-Meier method (log rank test) and a Cox proportional hazards regression model.

To evaluate the effect of grouped data in the multiple measurements, a mixed linear model with adjustment for time on HD was employed. For variables with a normal distribution, changes over time are presented as mean and SD, while asymmetrically distributed variables were first log-transformed and then presented as median and IQR. Student's *t* test for repeated measures was used to evaluate changes in variables between groups over time. P-values $\leqslant 0.05$ were considered statistically significant. All statistical analyses were carried out in IBM SPSS Statistics for Windows version 21.0.

Results

Of the 104 patients included in the cohort, 60% were male. The mean age was 55.3±15.6 years, and the median time on HD was 17.5 (8.0-36.8) months. Laboratory tests revealed a well-nourished group, with a mean serum albumin level of 40.0±4.0 g/L, hemoglobin 110.0±15.0 g/L, hematocrit 33.8±4.4%, creatinine 0.84±0.27 mmol/L, phosphorus 1.90±0.58 mmol/L, and hs-CRP 7.0 (4.0-16.0) mg/L. At inclusion, the mean BMI was 25.3±4.5 kg/m^2; fat body mass, 29.4±9.9 kg; lean body mass, 26.2±5.0 kg; body water percentage, 52.0±7.3%; and the median MIS score was 3.5 (2.0-5.0) points, indicating normal nutritional status or mild malnutrition. According to the adopted body composition classification, eight patients were underfat, 34 standard, 32 overfat, and 30 obese. Table 1 shows the baseline and interim laboratory results.

The BDI score ranged from 0 to 51. Thirty-two patients presented with DS. The mean overall WHOQOL-Bref questionnaire score was 75.2±18.4 (range, 31.3 to 118.8 points). The lowest score was observed in the physical domain (10.7), which most significantly influenced QoL. The social relationships domain revealed better performance (65.7±19.0) compared with the remaining domains. The mean physical, psychological, and environmental domain scores were 56.4±16.3, 61.1±15.3, and 63.4±13.7 respectively.

Comparison of the DS and no DS groups revealed no difference in age (54.1±15.2 vs. 55.9±15.9; $p = 0.44$), gender (53 vs. 62.5%; $p = 0.37$) or time on HD (20.5 [8.3-49.0] vs. 17.0 [7.3-30.8]; $p = 0.30$). Furthermore, no significant differences were verified regarding intensity of DS, level of QoL, or MIS score among groups classified by body fat percentage, as shown in Table 2.

Changes in the selected variables at each follow-up time point were also assessed. The DS and no DS groups differed significantly with regards to QoL over time (Table 3). In addition, the general QoL score differed at inclusion and varied over time depending on group allocation. Scores on all four QoL domains diverged at inclusion, as well as between groups. Besides presenting a between-group difference, psychological and physical domain scores also varied over time. The physical domain correlated strongly with the other domains (general: $r = 0.591$, $p < 0.01$; psychological: $r = 0.563$, $p < 0.01$; social relationships: $r = 0.518$, $p < 0.01$; environment: $r = 0.591$, $p < 0.01$). As expected, all QoL aspects were related. The BDI score had a moderate to strong negative correlation with all QoL domains (physical: $r_s = -0.604$, $p < 0.01$; psychological: $r_s = -0.552$, $p < 0.01$; social relationships:

Table 1 Biochemical parameters and depressive symptoms over the follow-up period

Variable/time	BDI score		p-value	
	DS	No DS		
Albumin (g/L)				
t0	(n=32)	(n=72)	Baseline	0.67
	40.0±4.0	40.0±4.0	Group	0.10
t1	(n=10)	(n=39)	Time	0.96
	40.0±4.0	39.0±4.0	Time × group	0.42
t2	(n=9)	(n=20)		
	40.0±4.0	39.0±3.0		
Phosphorus (mmol/L)				
t0	(n=32)	(n=72)	Baseline	0.63
	1.84±0.55	1.90±0.58	Group	0.04
t1	(n=10)	(n=39)	Time	0.56
	1.68±0.39	1.87±0.65	Time × group	0.09
t2	(n=9)	(n=20)		
	1.55±0.42	2.13±0.58		
hs-CRP (g/L)				
t0	(n=32)	(n=71)	Baseline	0.43
	6.0 (3.0-15.0)	7.0 (4.0-18.0)	Group	<0.01
t1	(n=10)	(n=39)	Time	0.58
	4.0 (2.0-6.0)	10.0 (5.0-32.0)	Time × group	0.07
t2	(n=9)	(n=20)		
	5.0 (2.0-13.0)	12.0 (4.0-41.0)		
Total cholesterol (mmol/L)				
t0	(n=32)	(n=71)	Baseline	0.22
	4.00±1.12	4.32±1.23	Group	0.99
t1	(n=10)	(n=39)	Time	0.48
	4.08±1.37	4.30±1.44	Time × group	0.24
t2	(n=9)	(n=20)		
	3.85±1.31	4.20±1.26		
HDL-cholesterol (mmol/L)				
t0	(n=32)	(n=71)	Baseline	0.64
	1.08±0.30	1.04±0.27	Group	0.72
t1	(n=10)	(n=39)	Time	0.87
	1.09±0.27	1.09±0.28	Time × group	0.79
t2	(n=9)	(n=20)		
	1.13±0.27	1.08±0.28		
LDL-cholesterol (mmol/L)				
t0	(n=32)	(n=68)	Baseline	0.14
	1.92 (1.56-2.65)	2.36 (1.81-2.77)	Group	0.50
t1	(n=10)	(n=39)	Time	0.67
	1.63 (1.36-2.15)	2.05 (1.63-3.04)	Time × group	0.33
t2	(n=9)	(n=19)		
	1.56 (1.03-2.59)	2.30 (1.36-3.11)		
Triglycerides (mmol/L)				
t0	(n=32)	(n=71)	Baseline	0.32
	3.41 (2.15-5.66)	3.83 (2.65-5.93)	Group	0.57
t1	(n=10)	(n=39)	Time	0.17
	4.19 (3.41-6.65)	4.10 (3.11-6.21)	Time × group	0.22
t2	(n=9)	(n=20)		
	3.49 (2.30-6.50)	4.82 (2.47-6.06)		

Data presented as mean ± standard deviation or median (interquartile range).
BDI = Beck Depression Inventory; DS = depressive symptoms; hs-CRP = high-sensitivity C-reactive protein.

r_s = -0.487, $p < 0.01$; environment: r = -0.528, $p < 0.01$; general: r_s = -0.501, $p < 0.01$).

Comparison of body composition between the DS and no DS groups showed no more than a trend toward significant difference, even after lean body mass and body fat percentage were independently evaluated (p = 0.07 and p = 0.07, respectively). Serum phosphorus concentration was significantly higher in the no DS group (p = 0.04), as was hs-CRP ($p < 0.01$), with an upward trend over time in both groups. MIS scores did not differ significantly between groups; however, they increased significantly over time ($p < 0.01$), independently from the presence of DS. Other clinical and biochemical parameters were not significantly different between groups at inclusion or over the follow-up

Table 2 Depressive symptoms, quality of life, and MIS scores at baseline, stratified by nutritional classification

Variable	Nutritional classification				p-value
	Underfat (n=8)	Standard (n=34)	Overfat (n=32)	Obese (n=30)	
WHOQOL					
General	71.9±20.9	77.0±17.1	77.4±18.9	71.7±18.8	0.56
Physical domain	54.0±28.4	58.8±15.7	59.4±14.3	51.1±14.4	0.16
Psychological domain	60.4±22.4	62.4±16.0	65.0±12.4	55.7±14.4	0.11
Social relationships domain	60.4±21.7	65.5±19.8	69.5±17.5	63.3±19.2	0.50
Environment domain	57.4±17.3	64.6±14.9	65.2±13.9	61.8±10.7	0.44
BDI	11.5 (5.5-33.0)	12.5 (7.5-20.7)	10.5 (7.5-14.2)	15.5 (9.0-18.8)	0.33
MIS	6.0 (2.7-7.5)	4.0 (2.8-6.0)	3.5 (2.5-5.2)	3.5 (2.5-5.5)	0.07

Data presented as mean ± standard deviation or median (interquartile range).
BDI = Beck Depression Inventory; MIS = malnutrition-inflammation score; WHOQOL = World Health Organization Quality of Life instrument.

period, nor in terms of the interaction between groups and time of follow-up.

There were 34 deaths overall, 11 (32%) in the DS group. No statistically significant difference in mortality rate was detected between groups (no DS = 76% vs. DS = 59%, p = 0.17) in the 2-year evaluation period. Neither gender nor time on HD were among the factors possibly associated with outcome. Age (hazard ratio [HR] = 1.04; 95%CI 1.01-1.08; p = 0.01) was directly related to the outcome, and lean body mass (HR = 0.89; 95%CI 0.80-0.99; p = 0.038)

Table 3 Quality of life domains and depressive symptoms over the follow-up period

WHOQOL/time	BDI score		p-value	
	DS	No DS		
General				
t0	(n=32)	(n=72)	Baseline	< 0.01
	65.7±15.0	79.4±18.3	Group	0.22
t1	(n=10)	(n=38)	Time	0.26
	75.1±19.8	76.7±16.6	Time × group	0.02
t2	(n=9)	(n=19)		
	80.0±17.1	78.0±13.7		
Physical domain				
t0	(n=32)	(n=72)	Baseline	< 0.01
	45.0±15.0	61.5±14.2	Group	< 0.01
t1	(n=10)	(n=38)	Time	0.94
	52.5±8.3	58.4±11.6	Time × group	0.06
t2	(n=9)	(n=19)		
	53.2±11.8	56.6±11.3		
Psychological domain				
t0	(n=32)	(n=72)	Baseline	< 0.01
	50.0±15.1	66.0±12.7	Group	0.02
t1	(n=10)	(n=38)	Time	0.89
	57.9±14.3	60.5±13.1	Time × group	< 0.01
t2	(n=9)	(n=19)		
	58.8±12.2	59.7±14.4		
Social relationships domain				
t0	(n=32)	(n=72)	Baseline	< 0.01
	55.7±19.0	70.1±17.4	Group	0.02
t1	(n=10)	(n=38)	Time	0.83
	62.5±25.0	64.7±25.6	Time × group	0.32
t2	(n=9)	(n=19)		
	58.3±22.8	71.1±16.5		
Environment domain				
t0	(n=32)	(n=72)	Baseline	< 0.01
	55.5±11.6	67.0±13.1	Group	0.03
t1	(n=10)	(n=38)	Time	0.71
	61.3±16.3	62.4±16.5	Time × group	0.15
t2	(n=9)	(n=19)		
	59.4±14.0	66.1±13.6		

Data presented as mean ± standard deviation.
BDI = Beck Depression Inventory; DS = depressive symptoms; t0, t1, and t2 = evaluation at inclusion, at 1 year, and at 2 years, respectively; WHOQOL = World Health Organization Quality of Life instrument.

had a protective effect. Conversely, DS, when stratified by nutritional status, did not relate to mortality.

Discussion

Significant DS occurred in 31% of the participants. These symptoms were strongly associated with hs-CRP and serum phosphorus concentration and weakly correlated with QoL. Patients with DS tended to have a lower survival rate in the 2-year evaluation period. DS prevalence was within the expected range even if a higher DS prevalence had been previously observed in a similar cohort, with the same evaluation instrument, but using a BDI score of 14 as the cutoff point.[17] Adopting different diagnostic criteria or cutoff points may produce significant variation in the prevalence of DS.[13,18] Specific cutoff points have been recommended when using the BDI questionnaire to evaluate DS in patients with CKD - generally higher than those applied to the general population.[19] Scores in our study cohort ranged from 0 to 51 (out of a possible 63).[11] Some individuals did not exhibit DS, whereas others reported more intense symptoms. Although the difference was not statistically significant, participants in the DS group had been on HD for a longer period than those in the no DS group. Previous studies suggest that incident HD patients - during the first treatment year - are exposed to a higher DS burden.[20,21] However, this finding is contradictory, as DS have been suggested to vary with CKD progression, being particularly dependent on clinical outcomes, complications, and adverse effects of HD.[22] Possibly due to illness severity and to the demands of renal replacement therapy, patients with ESRD become frail and ineffective in the use of compensatory mechanisms to overcome the minor conflicts of daily life. This may reinforce the impression that patients who have been on dialysis for longer experience more DS.

There is evidence that ESRD patients have compromised QoL, which deteriorates further as the DS burden increases.[23,24] HD therapy is critical for survival in ESRD, with patients unavoidably requiring at least one full-day session, three days a week. Devoting such a long time entirely to health maintenance certainly affects QoL. At inclusion, QoL scores differed between the DS and no DS groups; over time, QoL improved in the DS group, with increases in all WHOQOL scores, while patients in the no DS group had sustained or declining scores, which nevertheless remained higher than those of the DS group. These effects imply that QoL in patients undergoing HD may vary over time and in association with DS. All WHOQOL domains correlated with BDI scores, demonstrating consistency between the questionnaires.[25]

An association between inflammation and DS has been previously suggested. Pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor-α) have been measured at higher concentrations in patients presenting with DS as compared with non-depressed individuals. Cytokines are involved in the acute phase of the inflammatory response, but there is no evidence of a causal relationship in individuals with DS. However, DS may be accompanied by activation of the inflammatory response system.[26] A higher hs-CRP level was found in the DS group in another cohort study, suggesting an association between inflammation and DS.[27] A similar relationship between inflammation and DS was verified in a cross-sectional study of patients undergoing HD. Those with DS had higher interleukin-6 and lower albumin levels.[28] No association between hs-CRP and serum albumin level was observed in the present cohort. Cilan et al. reported higher concentrations of pro-inflammatory cytokines in an HD population compared with a control group; however, no significant difference between patients with or without DS was demonstrated.[29] Based on the available data, a relationship between DS, inflammation, and ESRD cannot be clearly demonstrated.

No significant difference in MIS scores was observed between the DS and no DS groups, although malnutrition and inflammation have been previously related to depression.[7] There was a positive and significant variation of MIS score over time, independent of the presence of DS, reinforcing the contribution of inflammation to the metabolic derangement that accompanies ESRD. Again, no relationship with DS prevalence was observed across nutritional status groups. The DS group had a significantly lower phosphorus concentration and a trend toward lower serum albumin levels, suggesting dietary inadequacy, which supports prior data.[30]

A relationship between BMI, serum albumin, and DS has been previously described.[31,32] However, the present study does not corroborate those findings. Our results only suggest a protective effect of lean body mass against all-cause mortality. Depressed individuals appear to have more body fat and less lean mass - a trend observed in this cohort. By jointly analyzing this observation and the strong correlation of BDI scores with WHOQOL physical domain scores, we may assume that patients in the DS group were less physically active.

DS and mortality are possibly associated in CKD. Occurrence of DS has been deemed a cause for increased risk of death in similar populations.[33,34] However, no statistically significant difference in mortality rates was observed between groups. Zimmermann et al. followed a similar cohort of 125 patients for 8 years, and demonstrated that mortality rate was associated with age, treatment modality (HD or peritoneal dialysis), and occurrence of DS; kidney transplantation was the main mortality-lowering factor.[35] It is likely that after, a successful kidney transplant, patients who previously had DS experienced remission or reduction of their symptoms. The study underscores a correlation between age and all-cause mortality, which is to be expected in such a population.

This study's strength derives from its prospective enrollment of participants with similar characteristics, recruited from a single HD unit, in a large enough number to support the observed differences. Nonetheless, some limitations must be mentioned. First, we enrolled prevalent and incident patients equally. However, time on HD did not correlate with the outcome of interest. Second, participants were not evaluated by a psychiatrist to establish a clinical diagnosis of depression - only a DS questionnaire (although validated and widely used) was administered.[8]

In conclusion, the present study demonstrated a high prevalence of DS in the analyzed cohort. Some patients

managed the imposed limitations of ESRD and HD in a positive manner, while others seemed unable to cope with the added burden. An association was found between DS and serum phosphorus concentration. BDI scores were significantly associated with the physical and psychological components of the WHOQOL-Bref questionnaire and with serum hs-CRP level, suggesting a relationship between DS and systemic inflammation. Nutritional markers did not correlate with DS. Lean body mass seemed protective for all-cause mortality. Properly designed, sequential evaluations of QoL and DS in patients with ESRD undergoing HD may establish new approaches for coping with this severe condition.

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Disclosure

The authors report no conflicts of interest.

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