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To cite this article: Havva Cilan, Murat Hayri Sipahioglu, Nilüfer Oguzhan, Aydin Unal, Tayfun Turan, Ayse Nedret Koc, Bulent Tokgoz, Cengiz Utas & Oktay Oymak (2013) Association between Depression, Nutritional Status, and Inflammatory Markers in Peritoneal Dialysis Patients, Renal Failure, 35:1, 17-22, DOI: [10.3109/0886022X.2012.741643](https://doi.org/10.3109/0886022X.2012.741643)

To link to this article: <https://doi.org/10.3109/0886022X.2012.741643>



Published online: 14 Nov 2012.



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CLINICAL STUDY

Association between Depression, Nutritional Status, and Inflammatory Markers in Peritoneal Dialysis Patients

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Abstract

Background: To investigate the relationship between depression, nutritional status, and inflammatory markers in patients on peritoneal dialysis (PD). **Patients and Methods:** This prospective study included 40 PD patients and 20 healthy people. The severity of depressive symptoms was assessed using the Beck Depression Inventory, the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale. The depressive patients received antidepressant drug for 8 weeks. Blood samples were taken before and after antidepressant treatment for the high-sensitive C-reactive protein (hs-CRP), interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α) levels. **Results:** Ten (25%) of the 40 PD patients had depression. No significant difference was determined between depressive patients and nondepressive patients. The mean erythrocyte sedimentation rate was higher in depressive patients. There was no significant difference for other inflammation parameters, including hs-CRP, TNF- α , IL-1, and IL-6, between depressive patients and nondepressive patients. In the depressive patients, we did not observe any significant change in nutritional parameters after antidepressant treatment. When we evaluated inflammation parameters of the depressive patients before and after antidepressant treatment, only IL-1 and IL-6 levels were significantly increased after antidepressant treatment. **Conclusion:** The depressive disorder in PD patients is a common psychopathology and has no significant effects on nutritional status and inflammation.

Keywords: antidepressant treatment, depression, inflammation, nutrition, peritoneal dialysis

INTRODUCTION

Depression is the most common psychiatric problem in dialysis patients and it is estimated to be present in 20–30% of these patients.^{1,2} Depression is commonly associated with decreased food intake and this could increase malnutrition and anemia in dialysis patients. Malnutrition is a frequent problem in patients on peritoneal dialysis (PD) and is strongly associated with increased morbidity and mortality.^{3,4}

End-stage renal disease (ESRD) is a chronic inflammatory condition. It is suggested that serum proinflammatory cytokine levels of patients with ESRD is 10 times more than normal population.⁵ Causes of inflammation in PD patients are multiple and include bioincompatibility of conventional PD solutions, fluid overload, and reduction in residual renal function. In addition, genetic

factors may be implicated in the pathogenesis of inflammation influencing the expression and production of both proinflammatory and anti-inflammatory mediators.⁶ There is now evidence that depression is accompanied by the activation of the inflammatory response and proinflammatory cytokines might have a role in the cause of depression.⁷ In addition, it has been known that these cytokines trigger catabolism of the body protein, which results in a negative nitrogen balance that induces malnutrition and decrease of appetite.⁸ Several studies showed a positive relationship between depression and proinflammatory cytokines and C-reactive protein (CRP).^{9,10}

However, there are no sufficient data about the relationship between depression and malnutrition–inflammation in patients undergoing continuous ambulatory peritoneal

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Received 4 June 2012; Revised 1 October 2012; Accepted 9 October 2012

dialysis (CAPD). Therefore, the first aim of this study was to investigate the presence of the relationship between depression with nutritional status and inflammatory markers, and the second aim was to investigate the effects of antidepressant treatment on serum cytokines and nutritional status in PD patients.

SUBJECTS AND METHODS

Patients

Forty patients (mean CAPD duration = 59.5 ± 46.3 months) of >18-year-olds undergoing CAPD for at least 3 months in the Hospital of Erciyes University and 20 healthy volunteers from February 2006 to February 2007 were enrolled in the study. The study protocol was approved by the local ethics committee of the Medical Faculty of Erciyes University. Written informed consent was obtained from all participants. Healthy control groups comprise the staff from the Department of Internal Medicine, Medical Faculty of Erciyes University, and the relatives of the patients. CAPD patients were prescribed 2 L of exchanges 4–5 times daily (Baxter Healthcare Corporation, Deerfield, IL, USA). Standard solutions are used in CAPD. Eighteen patients were treated with recombinant erythropoietin and 10 patients used amino acid-based PD solution (Nutrineal, Baxter Healthcare Corporation).

Etiologies of ESRD were as follows: 35% hypertension, 32% diabetes, 5% amyloidosis, 5% urologic causes (nephrolithiasis, obstruction, vesicoureteral reflux), 2.5% cystic renal diseases, 7.5% glomerulonephritis, 10% unknown, and 3% others. Baseline sociodemographic profiles of these patients were recorded. Mean Kt/V_{urea} of PD patients was 2.37 ± 0.64 . Exclusion criteria for participation were as follows: age > 65 years, severe illness (malignancy, severe heart, or respiratory failure), infection in the last 2 weeks, the presence of any psychiatric illness, the use of nonsteroidal anti-inflammatory drugs in the last 4 weeks, control subjects with any Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revision (DSM-IV) diagnosis, and any other drug that could interfere with immunological parameters.

Assessment of Depression

All psychiatric evaluations were performed by the same psychiatrist. All participants were evaluated for the presence of depression using the Structured Clinical Interview for DSM-IV, Axis I Disorders (SCID-I), Clinician Version (SCID-CV).¹¹ The severity of the depressive symptoms was measured using the Beck Depression Inventory (BDI), which was developed by Beck¹²; the Hamilton Depression Rating Scale (HAM-D), which was developed by Hamilton¹³; and the Hamilton Anxiety Rating Scale (HAM-A), which was developed by Hamilton.¹⁴

Ten patients who were diagnosed with depression received an antidepressant drug (sertraline = 50 mg/day) for 8 weeks. The psychometric measurements and proinflammatory cytokine levels were repeated after 8 weeks of antidepressant treatment.

Assessment of Malnutrition–Inflammation

Subjective global assessment (SGA) of nutritional status in participants was performed based on their medical history and physical examination. Changes in weight, dietary intake, functional capacity, gastrointestinal symptoms, metabolic stress, loss of subcutaneous fat, muscle wasting, and ankle/sacral edema of patients were recorded. On the basis of total SGA scores, patients with a score of 25 or higher were classified as normal (SGA-A). Those with a score between 13 and 24 were classified as mildly-to-moderately malnourished (SGA-B). On the other hand, patients with a score of 12 or less were classified as severely malnourished (SGA-C).¹⁵ SGA evaluations were performed by the same physician. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). We measured the body weight of PD patients when their abdomen was empty.

Blood samples from CAPD patients and control subjects were taken from the antecubital vein under fasting conditions. The samples were immediately centrifuged and stored at -80°C . Hemoglobin and hematocrit values, erythrocyte sedimentation rate (ESR), serum total protein, serum albumin, and other biochemical variables were included in regular patient laboratory reports. Most blood chemistries were measured by standard techniques. Low density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. High-sensitive CRP (hs-CRP) was measured with a high sensitivity nephelometric method; serum interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α) were analyzed by an enzyme-linked immunosorbent assay (ELISA) kit (Diacione, Besançon, France). Kt/V_{urea} was calculated using RenalSoft (TM) version 2.0.1 (Baxter Healthcare Corporation).

Statistical Analysis

Data were analyzed by using the statistical program SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine the normality of distributions of variables. Continuous variables with normal distribution were presented as mean $\pm$ SD. Median deviation and minimum–maximum values were used when normal distribution was absent. The qualitative variables were given as percent. Statistical analysis was performed by the Student's *t*-test for the parametric variables, the Mann–Whitney *U* test for the nonparametric variables, and the χ^2 -test for qualitative variables between two groups. To compare variables before antidepressant therapy and after the therapy in patients with depressive disorder, paired *t*-test (for the parametric variables), Wilcoxon test (for the

nonparametric variables), and McNemar test (for categorized variables) were performed. A *p*-Value of <0.05 was considered as statistically significant.

RESULTS

A total of 40 patients consisted of 22 males (55%) and 18 females (45%), with a mean age of 41.88 ± 11.74 years. The study control subjects were 11 male (55%) and 9 female (45%) patients. The average age of the control subjects was 42.6 ± 5.041 years. The comparison of sociodemographic profiles between control subjects and CAPD patients (nondepressed patients and depressed patients) is shown in Tables 1 and 2. There was no significant difference between CAPD patients and control group in terms of gender, age, and educational and marital status. Table 3 shows the comparison of nutritional status parameters, inflammation markers, and results of psychometric tests between CAPD patients and the control

Table 1. Sociodemographic characteristics of the sample (*n*: 60).

	Control group (<i>n</i> : 20)	CAPD group (<i>n</i> : 40)
Sociodemographic characteristics		
Age (years)	42.60 ± 5.041	41.88 ± 11.741
Gender		
Male	11 (55%)	22 (55%)
Female	9 (45%)	18 (45%)
Marital status		
Single	3 (15%)	6 (15%)
Married	17 (85%)	32 (80%)
Divorced	0 (0%)	2 (5%)
Education status		
Illiterate	2 (10%)	4 (10%)
Primary school	4 (20%)	9 (22.5%)
Literate	12 (60%)	23 (57.5%)
High school	2 (10%)	4 (10%)

Note: CAPD, continuous ambulatory peritoneal dialysis.

Table 2. Sociodemographic characteristics of the CAPD group (*n*: 40).

Sociodemographic characteristics	CAPD group (<i>n</i> : 40)		<i>P</i>
	Nondepressive patients (<i>n</i> : 30)	Depressive patients (<i>n</i> : 10)	
Age (years)	41.63 ± 11.67	42.60 ± 12.55	NS
Gender*			0.025
Male	20 (66.7%)	2 (20%)	
Female	10 (33.3%)	8 (80%)	
Marital status			NS
Single	4 (13.3%)	2 (20%)	
Married	25 (83.3%)	7 (70%)	
Divorced	1 (3.3%)	1 (10%)	
Education status			NS
Illiterate	1 (3.3%)	3 (30%)	
Literate	6 (20%)	3 (30%)	
Primary school	19 (63.3%)	4 (40%)	
High school	4 (13.3%)	0 (0%)	

Notes: CAPD, continuous ambulatory peritoneal dialysis; NS, nonsignificant.

**p* < 0.05.

group. Levels of hemoglobin, total protein, and serum albumin were significantly lower in CAPD patients compared with the control group. ESR, IL-6, and HAM-A score were significantly higher in PD patients than in the control group. There was significant difference between two groups with regard to SGA classification. All of the control subjects were classified as SGA-A, whereas 26 and 14 of 40 PD patients were classified as SGA-A and SGA-B, respectively. On the other hand, there was no significant difference between two groups in terms of levels of total cholesterol, triglyceride, hsCRP, TNF- α , IL-1, BMI value, and BDI and HAM-D score.

Ten of the 40 CAPD patients had depression. There was significant difference between CAPD patients with depression and without depression in terms of gender. There was no significant difference between CAPD patients with depressive disorder and without depressive disorder in terms of age, education status, and marital status (*p*: 0.164, 0.590, and 0.052, respectively).

Table 4 summarizes the comparison of the nutritional status parameters, inflammation markers, and results of psychometric tests in CAPD patients with and without depressive disorder and after antidepressant treatment. ESR value and BDI, HAM-D, and HAM-A scores were significantly higher in depressed CAPD patients than in nondepressed (*p*: 0.037, <0.001, <0.001, and <0.001, respectively) patients. However, there was no significant difference between two groups in terms of all of nutritional parameters and inflammatory markers except ESR (*p* > 0.05). In the depressive patients, we did not observe any significant change in nutritional parameters after antidepressant treatment (*p* > 0.05). When we evaluated inflammation parameters of the depressive patients before and after antidepressant treatment, only IL-1 and IL-6 levels were significantly increased after antidepressant treatment (*p*: 0.014 and 0.028, respectively). On the other hand, the psychometric measurements, including BDI, HAM-D, and HAM-A, of the depressive patients decreased significantly after antidepressant treatment (*p*: 0.005, 0.005, and 0.005, respectively).

DISCUSSION

In this study, there were no significant differences between CAPD patients and the control group for triglyceride and cholesterol levels and BMI. Hemoglobin, total protein, and serum albumin were significantly lower in the CAPD group. CAPD group had worse nutritional status; 35% of the patients had mild-to-moderate malnutrition as assessed by SGA. Similar to observations of Li et al.,¹⁶ 35% of PD patients (*n*: 214) had mild-to-moderate malnutrition, whereas none of these patients had severe malnutrition. In a study, Prasad et al.¹⁷ evaluated the SGA score in PD patients and found that 192 of 283 PD (68%) patients had mild-to-moderate malnutrition and 20 of 283 PD (7%) patients had severe malnutrition.

Table 3. Comparison of the nutritional status parameters, inflammation markers, and results of psychometric tests between CAPD patients and control subjects.

	Control group (<i>n</i> : 20)	CAPD group (<i>n</i> : 40)	<i>p</i>
<i>Nutritional parameters</i>			
Hemoglobin (g/dL)*	14.65 ± 1.09	10.34 ± 1.67	<0.001
Total protein (g/dL)*	6.93 ± 0.45	6.37 ± 0.71	0.002
Albumin (g/dL)*	4.39 ± 0.21	3.51 ± 0.52	<0.001
Total cholesterol (mg/dL)	180.4 ± 43.2	186.6 ± 59.8	0.682
Triglyceride (mg/dL)	142.5 ± 53.8	167.9 ± 76.2	0.188
BMI (kg/m ²)	25.95 ± 3.9	25.18 ± 5.1	0.555
SGA*	A = 20 (%100)	A = 26 (%65) B = 14 (%35)	0.030
<i>Inflammation markers</i>			
ESR (mm/h)*	7.55 ± 5.39	69.83 ± 31.25	<0.001
hs-CRP (mg/dL)	3.17 (3.17–15.10)	3.17 (3.17–57.90)	0.209
TNF-α (pg/mL)	7.00 (2.00–50.00)	24.50 (1.00–800.00)	0.097
IL-1 (pg/mL)	13.00 (1.00–41.00)	17.50 (1.00–500.00)	0.311
IL-6 (pg/mL)*	9.00 (1.00–58.00)	28.00 (1.00–200.00)	0.008
<i>Psychometric tests</i>			
BDI	4.5 (1–12)	3.5 (1–28)	0.241
HAM-D	3.0 (1–12)	3.0 (1–30)	0.499
HAM-A*	1.0 (0–6)	2.0 (0–9)	0.040

Notes: PD, peritoneal dialysis; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; BMI, body mass index; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitive C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; CAPD, continuous ambulatory peritoneal dialysis.

**p* < 0.05.

Table 4. Comparison of the nutritional status parameters, inflammation markers, and results of psychometric tests in PD patients with and without depressive disorder.

	Nondepressive patients (<i>n</i> : 30)	Depressive patients (<i>n</i> : 10)	
		Before treatment	After treatment
Nutritional parameters			
Hemoglobin (g/dL)	10.60 ± 1.74	9.53 ± 1.11	9.55 ± 2.35
Total protein (g/dL)	6.38 ± 0.63	6.35 ± 0.94	6.21 ± 0.62
Albumin (g/dL)	3.55 ± 0.48	3.40 ± 0.60	3.21 ± 0.44
Total cholesterol (mg/dL)	179.7 ± 58.5	207.1 ± 61.9	200.5 ± 48.2
Triglyceride (mg/dL)	160.5 ± 63.4	189.8 ± 107.3	165.8 ± 92.0
BMI (kg/m ²)	25.2 ± 4.8	25.1 ± 6.2	24.7 ± 5.6
SGA	<i>A</i> = 21 (%70) <i>B</i> = 9 (%30)	<i>A</i> = 5 (%50) <i>B</i> = 5 (%50)	<i>A</i> = 5 (%50) <i>B</i> = 5 (%50)
Inflammation markers			
ESR (mm/h)	63.93 ± 31.21*	87.50 ± 25.14	95.10 ± 29.84
hsCRP (mg/dL)	3.17 (3.17–20.50)	9.01 (3.17–57.9)	6.48 (3.17–41.40)
TNF- α (pg/mL)	24.50 (1.00–800.00)	25.50 (1.00–800.00)	220.00 (2.00–800.00)
IL-1 (pg/mL)	14.00 (1.00–500.00)	25.00** (3.00–340.00)	374 (3.00–500.00)
IL-6 (pg/mL)	27.00 (1.00–200.00)	46.50** (5.00–200.00)	200.00 (160.00–200.00)
Psychometric tests			
BDI	3.0 (1–5)*	23.5 (19–28)**	14.5 (8–25)
HAM-D	2.5 (1–6)*	24.5 (20–30)**	12.5 (6–25)
HAM-A	2.0 (0–4)*	6.5 (3–9)**	3.0 (1–4)

Notes: PD, peritoneal dialysis; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitive C-reactive protein; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; SGA, subjective global assessment; BMI, body mass index; TNF-α, tumor necrosis factor-α; IL, interleukin.

p* < 0.05 in patients without depressive disorder compared to those with depressive disorder. *p* < 0.05 in depressive patients; evaluations were performed before antidepressive treatment compared to evaluations after antidepressive treatment.

We found that ESR and serum IL-6 were higher in the CAPD group compared to the control group. hs-CRP, serum TNF-α, and IL-1 were similar between two groups. Although there was no significant difference

between CAPD patients and the control group in terms of TNF-α and IL-1, TNF-α and IL-1 were higher in CAPD patients. This may reflect typical type 2 statistical error. Increasing the number of cases seems to achieve

statistical significance. In one study by Borazan et al.,¹⁸ the serum TNF- α , IL-6, IL-10, and CRP levels were higher than the control group in the CAPD and HD patients for the beginning values and the third month of dialysis treatment.

In many studies, different rates of depression in dialysis patients have been reported because of different population, different diagnostic criteria, different psychometric scales, and strong overlap between uremic and depressive symptoms. In a study by Wuerth et al., the prevalence of depression in 320 CAPD patients was investigated by using BDI, HAM-D, and DSM-IV. In 60 (18.8%) of these patients, clinical depression was diagnosed.¹⁹ In addition, Atalay et al.²⁰ indicated that 32 of 124 CAPD patients (25.8%) had depression based on BDI. Similarly, in our study, 10 (25%) of 40 patients had depression disorder.

In this study, we found that there was no significant difference between patients with and without depressive disorder for nutritional parameters. In patients with depression disorder, we did not observe any significant change in nutritional parameters after antidepressant treatment. Kalender et al.²¹ showed that chronic kidney disease (CKD) patients with depression had lower hemoglobin, hematocrit, and serum albumin levels than CKD patients without depression. In a study by Einwohner et al.,²² it was found that depressed PD patients had significantly lower serum albumin levels compared to nondepressed PD patients.

Cytokines such as IL-1, IL-6, and TNF- α are potent modulators of corticotrophin-releasing hormone, which produces heightened hypothalamic–pituitary–adrenal (HPA) axis activity characterized by increases in adrenocorticotropin hormone and cortisol, both of which are reported to be elevated in major depression.²³ Although hs-CRP level, IL-1, and IL-6 were higher in patients with depression than in patients without depression, we found no significant difference between depressive patients and nondepressive patients in terms of all of inflammatory markers except ESR. These findings suggest that a relatively small number of patients who are included in the PD group might lead to statistical insignificance.

Similarly, in a recent study, Barros et al.²⁴ suggested that nutritional status with malnutrition–inflammation was not associated with depressive symptoms in HD patients. Kalender et al.²⁵ found that serum cytokine (IL-1, IL-6, and TNF- α) levels were similar in depressed and nondepressed PD patients. On the other hand, in another study, a significant positive correlation between the severity of depressive symptoms and serum inflammation markers such as CRP and ferritin in patients with CRF was observed.²⁶ In a study by Sonikian et al.,²⁷ it was found that serum IL-6 levels were correlated with depression scores in dialysis patients. Ko et al.²⁸ showed that TNF- α level was higher in patients with depressive symptoms than patients without depressive symptoms.

In this study, 50 mg of sertraline was used for the treatment of depressive patients. Sertraline is a selective serotonin reuptake inhibitor. As a result of its proven efficacy, good tolerability, and lack of pharmacokinetic interactions, sertraline is considered as a first-line treatment option for anxiety and depressive disorders.²⁹ It does not require dosage adjustment in case of renal functional impairment and the usual starting dose is 50 mg/day. This starting dose can be escalated up to 200 mg/day depending on the response of the patient. All of our patients successfully completed the 8-week treatment course, and we did not note any side effects serious enough to require cessation of the drug.

It has recently been suggested that antidepressants decrease the secretion of pro-inflammatory cytokines such as CRP, IL-1, IL-2, and TNF- α and have negative immunoregulatory effects.^{30,31} Interestingly, in this study, IL-1 and IL-6 levels were significantly increased; however, ESR, hs-CRP, and TNF- α levels were not significantly changed after antidepressant treatment. It was previously reported that after antidepressant treatment, IL-6 was decreased; however, a study showed that after antidepressant treatment, IL-6 was significantly increased.^{30,32} Lee et al.³¹ investigated the effects of antidepressant treatment on serum cytokines in 28 HD patients and found that serum IL-1 decreased and serum IL-6 increased after treatment in the response group, whereas serum TNF- α and CRP were not significantly changed. They explained the increase in IL-6: while the increased cortisol keeps IL-6 at lower level, stabilization of the HPA axis by antidepressant treatment will decrease the cortisol level, and after then these changes may increase IL-6 level paradoxically.

In conclusion, the results of this study have clearly not confirmed the relationship between depression with nutritional status and inflammatory cytokines in CAPD patients. We also did not observe any important improvement in nutritional parameters and inflammatory markers after antidepressant therapy.

This study has several limitations. The number of subjects was small. In addition, because the dosage of the antidepressant was fixed for all patients with depression, the amount of antidepressant treatment might not have been sufficient to optimally investigate the effects of treatment for depression. We believe that further studies are required to clarify this subject.

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

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