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CLINICAL STUDY

Relationship between Depression and Proinflammatory Cytokine Levels in Hemodialysis Patients

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Abstract

Aim: To evaluate the presence of the relationship between depression and proinflammatory cytokine levels in hemodialysis (HD) patients. *Methods*: The study included 40 HD patients and 20 healthy controls. All participants were evaluated for the presence of depression using the structured clinical interview based on criteria defined by Diagnostic and Statistical Manual Mental Disorders (Fourth Edition, Text Revision) Axis I disorders. 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 antidepressants for 8 weeks. Blood samples were taken at baseline and after 8 weeks of antidepressant treatment for interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) levels. *Results*: A total of 9 (22.5%) of the 40 HD patients had depression. IL-1, IL-6, and TNF-α levels were significantly higher in HD patients compared with that in the control group, but were not significantly different between HD patients with and without depression. In the depressive patients, we observed no significant difference in proinflammatory cytokine levels after antidepressant treatment. The psychometric measurements in depressive patients decreased significantly after antidepressant treatment. *Conclusion*: We observed that depression is a common psychiatric disorder and has no significant effect on proinflammatory cytokine levels in HD patients; no important improvement in cytokine levels was observed after antidepressant therapy.

Keywords: antidepressant treatment, depression, hemodialysis, inflammation, proinflammatory cytokines

INTRODUCTION

Depression is the most common psychological disorder among patients with end-stage renal disease (ESRD).[1] It has been speculated that proinflammatory cytokines may play a role in the pathogenesis of depression.[2] Growing evidence suggests that the mood disorder is associated with inflammation.[3] In several studies, it was also shown that there is a positive relation between depression and proinflammatory cytokines and C-reactive protein (CRP).[4] Recent studies have suggested that the alterations of cytokines in hemodialysis (HD) may be related to depression.[5,6] It has also been reported that proinflammatory cytokines such as interleukin-1 (IL-1), interleukin 6 (IL-6), and CRP are activated in long-term HD patients.[7] In another study, serum proinflammatory cytokine levels in ESRD patients were 10 times higher than in the normal population.[8] Furthermore, antidepressant treatment alters serum cytokine levels in patients with depression.[9] However, conflicting results have also been described.[10,11] Many factors may explain these conflicting results, including variable factors such as age, gender, nationality, and methodological differences in the measurement of cytokine concentrations.

The aim of the study was to evaluate the presence of the relationship between depression and proinflammatory cytokine levels in HD patients.

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PATIENTS AND METHODS

Forty patients on HD (male/female 22/18, mean age 43.3 ± 14.6 years, mean HD duration 68.3 ± 52.3 months) and 20 healthy controls (male/female 11/9, mean age 42.6 ± 5.0 years) were included in the study. This prospective study was approved by the Ethics Committee of the Medical Faculty of Erciyes University. Written informed consent was obtained from all participants. All HD patients received 4 h of HD treatment three times weekly in our university hospital HD center, used bicarbonate-containing dialysis solutions, and were dialyzed with a high-performance diacetate hollow fiber membrane. Healthy control groups comprised the staff from the Department of Internal Medicine, Medical Faculty of Erciyes University, and the relatives of the patients.

The etiologies of ESRD were as follows: 42.5% unknown, 17.5% diabetes, 10% hypertension, 7.5% urologic causes (nephrolithiasis, obstruction, and vesicoureteral reflux), 7.5% interstitial nephritis/pyelonephritis, 5% amyloidosis, 2.5% glomerulonephritis, and 5.7% other causes. The mean Kt/V_{urea} of HD patients was 1.33 ± 0.49. Exclusion criteria for participation were as follows: age >65 years, severe illness (malignancy, severe heart, or respiratory failure), infection in the past 2 weeks, presence of any psychiatric illness, use of nonsteroidal anti-inflammatory drugs in the past 4 weeks, control subjects with any Diagnostic and Statistical Manual Mental Disorders (Fourth Edition, Text Revision; DSM-IV) diagnosis, and use of any other drug that could interfere with immunological parameters.

Blood samples were taken at baseline and after antidepressant treatment for biochemical examinations including serum levels of IL-1, IL-6, and tumor necrosis factor-α (TNF-α). In the morning, after an overnight fast, venous blood samples were drawn from the antecubital vein of each subject. The samples were immediately centrifuged and stored at −80°C. Serum IL-1, IL-6, and TNF-α were analyzed using enzyme immunoassay kits (Besançon Cedex, Diaclone, France). Analyses of all samples, standards, and controls were run in duplicate.

All psychiatric evaluations were performed by the same psychiatrist. Participants were evaluated for the presence of depression using the structured clinical interview for DSM-IV Axis I Disorders, Clinician Version.[12] The Turkish validation and reliability studies of the scale were performed by Corapcıoglu et al.[13] The severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI), which was developed by Beck and adapted for the Turkish population by Hisli[14,15]; the Hamilton Depression Rating Scale (HAM-D), which was developed by Hamilton and adapted for the Turkish population by Akdemir et al.[16,17]; and the Hamilton Anxiety Rating Scale (HAM-A), which was developed by Hamilton and adapted to Turkish population by Yazıcı et al.[18,19]

Sertralin 50 mg/day was given to nine patients who accepted the treatment protocol and gave informed consent. The depressive patients received antidepressant drug for 8 weeks. The psychometric measurements and proinflammatory cytokine levels were repeated after 8 weeks of antidepressant treatment.

Statistical Analysis

Data were analyzed by using the statistical program SPSS version 11.0 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. All data are expressed as mean ± SD (minimum–maximum) or median (minimum–maximum). Statistical analysis was performed using the Mann–Whitney *U*-test between two groups. Wilcoxon signed rank test was used to compare differences before and after antidepressant treatment. p-Value <0.05 was considered statistically significant.

RESULTS

The HD and control groups were not significantly different with respect to age and gender. The results of psychometric tests and proinflammatory cytokine levels in HD patients and controls are shown in Table 1. IL-1, IL-6, and TNF-α levels were significantly higher in HD patients compared with that in the control group ($p < 0.001$, $= 0.004$, and <0.001, respectively). BDI, HAM-D, and HAM-A scores were significantly higher in HD patients compared with that in the control group ($p = 0.005$, 0.003, and <0.001, respectively).

A total of 9 (22.5%) of the 40 HD patients had depression. The depressive patients received antidepressant drug treatment for 8 weeks.

Table 2 summarizes cytokine levels in HD patients with and without depression. The proinflammatory cytokine levels (IL-1, IL-6, and TNF-α) were not significantly different in HD patients with and without depression ($p > 0.05$). Although proinflammatory cytokine levels decreased after antidepressant treatment in the depressive patients, this was not statistically significant ($p > 0.05$).

BDI, HAM-D, and HAM-A scores were significantly higher in depressive patients compared with that in nondepressive patients ($p < 0.001$, <0.001, and <0.001, respectively). In depressive patients, the three scores were significantly decreased after antidepressant treatment ($p = 0.008$, 0.024, and 0.020, respectively).

During the 8 weeks of treatment, no adverse effect requiring drug cessation was seen in the study group.

DISCUSSION

In this study, we aimed to analyze the relationship between depression and inflammation in HD patients. We found that IL-1, IL-6, and TNF-α levels were significantly higher in HD patients compared with that

Table 1. Comparison of the inflammation markers and psychometric tests between HD patients and control subjects.

	Control group ($n = 20$)	HD group ($n = 40$)
Inflammation markers		
Tumor necrosis factor-α (pg/mL)*	53.05 ± 181.91 (0−800)	191.15 ± 294.66 (0−800)
Interleukin-1 (pg/mL)*	41.25 ± 117.94 (0−500)	167.75 ± 210.98 (0−500)
Interleukin-6 (pg/mL)*	29.00 ± 63.54 (0−200)	140.15 ± 82.74 (1−200)
Psychometric tests		
BDI*	4.5 (1−12)	8.0 (0−32)
HAM-D*	3.0 (1−12)	6.0 (0−30)
HAM-A*	1.0 (0−6)	4.0 (0−17)

Notes: *$p < 0.05$. HD, hemodialysis; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale.

Table 2. Comparison of the inflammation markers and psychometric tests in HD patients with and without depressive disorder.

		Depressive patients ($n = 9$)	
	Nondepressives ($n = 31$)	Before treatment	After treatment
Inflammation parameters			
Tumor necrosis factor-α (pg/mL)	214.94 ± 303.69 (0−800)	109.22 ± 260.15 (0−800)	56.56 ± 162.61 (0−490)
Interleukin-1 (pg/mL)	177.00 ± 222.79 (0−500)	135.89 ± 171.46 (0−500)	127.11 ± 216.27 (0−500)
Interleukin-6 (pg/mL)	139.09 ± 83.25 (2−200)	143.78 ± 85.84 (3−200)	54.63 ± 83.71 (3.5−200)
Psychometric tests			
BDI	6.0 (0−16)*	19.5 (17−32)†	14.0 (10−24)
HAM-D	5.0 (0−9)*	14.5 (8−30)†	9.0 (7−32)
HAM-A	3.0 (0−8)*	9.5 (3−17)†	5.0 (1−10)

Notes: *$p < 0.05$ in patients without depressive disorder compared with those with depressive disorder, †$p < 0.05$ in depressive patients, evaluations before antidepressive treatment compared with evaluations after antidepressive treatment. HD, hemodialysis; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale.

in the control group. This result is similar to other studies, in which it was found that IL-1 and TNF-α levels were higher among HD patients than among controls.[20,21] Similarly, in another study, Kamimura et al.[22] found that serum CRP and IL-6 levels were significantly higher in the HD patients than in the control group.

In many studies, different rates of depression in dialysis patients have been reported because of different populations, different diagnostic criteria, different psychometric scales, and a strong overlap between uremic and depressive symptoms. In our study, a total of 9 of 40 HD patients (22.5%) had depression. By using BDI, Weisbord et al.[23] found that the prevalence of depression in 162 HD patients was 25.9%. In another study performed by Taşkapan et al.[24] in Turkish patients, it was found that the prevalence of depression in HD patients was found to be 35%.

We found that there was no significant difference between HD patients with and without depression with regard to proinflammatory cytokine levels. In addition, we observed no significant difference in cytokine levels after antidepressant treatment in the depressive patients, although cytokine levels decreased. A possible cause of this situation may have been small number of subjects treated ($n = 9$). Similarly, Rothermundt et al.[25] found that there was no meaningful difference between depressive patients and controls in terms of serum IL-1 level. Also Kagaya et al.[26] observed that serum IL-1, IL-6, and TNF-α levels were not significantly different between depressive patients with healthy subjects and TNF-α level was increased after pharmacotherapy in depressive patients. In a study performed by Tuglu et al.,[27] serum IL-1, IL-6, TNF-α, and CRP levels were compared between depressive patients and healthy subjects and it was found that levels of TNF-α and CRP were significantly higher in depressive patients and decreased significantly after antidepressant treatment. Because different methods for measuring serum cytokines were used in these studies and/or these studies were mostly single-centered and consisted of a small number of patients, the results are not similar. Moreover, there are insufficient data on this subject in dialysis patients.

Lee et al.[28] 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 for 8 weeks, while serum TNF-α and CRP did not change significantly. In addition, in another recent study performed by Kalender et al., it was found that levels of serum cytokine including IL-1, IL-6, and TNF-α were similar in peritoneal dialysis (PD) patients with depression and without depression. Although the mean CRP level was higher in patients with depression than in patients without depression, there was no statistical significance between the two groups.[29] In another study, serum IL-6 and TNF-α levels were not significantly different among

chronic renal failure patients [HD, PD, and chronic kidney disease] with and without elevated depressive symptoms.[30]

This study has several limitations. The number of the 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.

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