Original Article

Fatigue Is Associated With Serum Interleukin-6 Levels and Symptoms of Depression in Patients on Chronic Hemodialysis

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Abstract

Context. Little is known about activated immune-inflammatory pathways and interleukin-6 (IL-6) in the development of fatigue and/or depression in patients with end-stage renal disease on chronic hemodialysis (HD).

Objectives. To evaluate the possible correlation between fatigue and serum levels of IL-6 in patients on chronic HD.

Methods. One hundred HD patients were assessed for the presence of fatigue using the SF-36 Vitality subscale and were administered the Beck Depression Inventory (BDI), the Hamilton Anxiety Rating Scale (HARS), the Mini-Mental State Examination (MMSE), the activities of daily living (ADL), and the instrumental activities of daily living (IADL). We also calculated the time of recovery after hemodialysis (TIRD) and the number/severity of comorbidities using the Charlson Comorbidity Index (CCI). Laboratory parameters were measured as well as serum IL-6.

Results. Forty-three patients constituted the fatigued group and 57 the nonfatigued group. Age, CCI, BDI, HARS, and TIRD were significantly higher in fatigued patients than in the nonfatigued patients. Conversely, the scores of ADL, IADL, and MMSE were significantly lower in fatigued than in nonfatigued patients. Serum IL-6 levels (pg/mL) were higher in the fatigued group (5.1 ± 3.4) than in the nonfatigued group (1.6 ± 1.5; $P < 0.001$); serum albumin and creatinine levels were significantly lower. Twenty-six patients (26%) had no symptoms of depression (BDI score <10), and 74 patients (74%) had symptoms of depression (BDI score >9). Patients with a BDI score >9 were older; had a higher CCI; a lower MMSE; a higher TIRD; lower serum albumin, creatinine, and urea levels; and higher serum IL-6 levels. The correlation analyses showed that the score of the SF-36 Vitality subscale was associated with age, dialytic age, TIRD, ADL, IADL, CCI, BDI, HARS, MMSE, serum urea, creatinine, albumin, and IL-6 levels. On multivariate general linear model analyses, with fatigue as the dependent variable and gender as a second factor, BDI and serum IL-6 levels were independently associated with the score of the SF-36 Vitality subscale. A canonical correlation analysis was performed including in the model fatigue, BDI, and biomarkers; the correlation was 0.679 ($R^2 = 0.462$). Fatigue, BDI, and IL-6 among biomarkers showed the strongest association with the underlying construct (standardized canonical coefficients = −0.989, 0.015, and 0.852, respectively), thus explaining a correlation of IL-6 with both depression and fatigue.

Conclusion. Fatigue was significantly associated with symptoms of depression and serum IL-6 levels in patients receiving chronic HD. J Pain Symptom Manage 2015;49:578–585.

Key Words
Hemodialysis, fatigue, inflammation, interleukin-6, depression

Introduction

In their daily lives, end-stage renal disease (ESRD) patients receiving hemodialysis (HD) often suffer from fatigue.[1–3] Fatigue is difficult to describe, and dialysis patients may express it in different ways, such as saying they feel tired, weak, exhausted, weary,

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worn-out, heavy, or slow.[1,2] Health professionals may use other terms such as asthenia, lassitude, prostration, exercise intolerance, lack of energy, and weakness to describe fatigue.[1,3,4]

Numerous physiological, sociodemographic, psychological, and dialysis-related factors have been suggested as possible factors implicated in the onset of fatigue in chronic HD patients such as age, sex, race, educational status, anemia, malnutrition, uremia, dialysis inadequacy, hyperparathyroidism, and symptoms of depression or depression.[1–3]

Interestingly, in the general population and in patients with chronic diseases, fatigue may be part of a depressive syndrome, whereas the occurrence of fatigue may lead to the development of depressive symptoms.[5–7] The comorbidity between depression and fatigue may be explained by activated immune-inflammatory pathways.[8] Depression is associated with cell-mediated immune activation, increased monocytic activation, a T helper (Th)-1- and Th-17-like cytokine response[9] and higher serum levels of proinflammatory cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor alpha [TNF-α]).[10,11] In patients with depression, peripheral activation of immune-inflammatory pathways may contribute to neuroinflammation and consequent neuroprogressive changes including decreased neuroplasticity, neurogenesis, increased neurodegeneration and neuronal apoptosis,[9,12,13] and reduced expression of key neurotransmitters (e.g., serotonin, noradrenaline). Accordingly, it has been shown that activated immune-inflammatory pathways may contribute to fatigue experienced by healthy individuals and patients with a variety of diseases. In fact, an association between fatigue and inflammatory markers (IL-6, TNF-α, and C-reactive protein [CRP]) has been documented in patients with cancer, autoimmune diseases, viral infections, mood disorders, chronic obstructive pulmonary disease, and neurologic disease.[14–24]

A primary role in the activated immune pathways is played by IL-6. IL-6 is crucial for interaction between the immune system and the central nervous system in inflammatory disease, particularly for mediating common clinical symptoms such as fatigue, sleep disturbances, and excessive daytime sleepiness.[15,16] IL-6 belongs to a family of 10 cytokines, which act via receptor complexes containing the cytokine receptor subunit gp130. On cells, IL-6 first binds to a specific membrane-bound IL-6R, and the complex of IL-6 and IL-6R interacts with gp130, leading to signal initiation.[25,26] Although gp130 is widely expressed throughout the body, the IL-6R is only found on some cells including hepatocytes and some leucocytes. A soluble form of the IL-6R is an agonist capable of transmitting signals through interaction with the gp130 protein.[25,26] *In vivo*, the IL-6/soluble IL-6R complex stimulates several types of target cells, which are unresponsive to IL-6 alone, as they do not express the membrane-bound IL-6R. This process has been named trans-signaling.[25,26] Increased IL-6 and sIL-6R in depression indicate that IL-6 trans-signaling is increased in depression and allows IL-6 to modulate signaling in cells in which the plasma membrane IL-6R is not typically expressed. Increased IL-6 levels in depression are related to increased hypothalamic-pituitary-adrenal axis activity, increasing cortisol, which in turn activates tryptophan 2,3-dioxygenase and leads to decreased tryptophan availability for serotonin *N*-acetylserotonin, and melatonin synthesis.[25,26]

Unfortunately, little is known about activated immune-inflammatory pathways and IL-6 in the development of fatigue and/or depression in patients with ESRD on chronic HD.[27,28] Thus, the aims of the present study were to delineate the associations between fatigue and depression and immune-inflammatory markers, including CRP, IL-6, and albumin in HD patients.

Methods

All prevalent patients affected by ESRD who received chronic HD at the Hemodialysis Unit were eligible for inclusion in the study. Exclusion criteria were dialysis duration of one year or less, diagnosis of dementia based on Diagnostic and Statistical Manual of Mental Disorders-IV criteria,[29] previous diagnosis of psychotic disorders, clinical instability requiring hospital admission, infective disease, rheumatic disease, inflammatory bowel disease, autoimmune disease, acute hepatitis/liver failure, and active cancer. Incident patients considered eligible and included in the study were evaluated after 12 months of HD treatment. The study was approved by the local ethics committee, and written informed consent was obtained from all patients before enrollment in the study.

The following demographic, clinical, and laboratory data were recorded for each patient at the moment of inclusion in the study: age, gender, underlying renal disease, HD regimen, duration on dialysis, type and number of comorbidities, symptom of depression and anxiety (using the Beck Depression Inventory [BDI] and the Hamilton Anxiety Rating Scale [HARS]), cognitive function (using the Mini-Mental State Examination [MMSE]), time of recovery after the HD session (TIRD), disability determined through activities of daily living (ADL) and instrumental activities of daily living (IADL), weight, height, and body mass index. The following laboratory parameters were measured: hemoglobin, hematocrit, serum

albumin, creatinine, urea, calcium, phosphorus, CRP, IL-6, parathyroid hormone (PTH), vitamin D, fibrinogen, and ferritin.

Hemodialysis

All patients were receiving conventional four hour HD, three times a week. Blood flow ranged from 250 to 300 mL/minute with a dialysis rate flow of 500 mL/minute. All patients were treated with high-permeability membranes. Most patients were taking recombinant human erythropoietin, antihypertensive medications (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors), and other commonly used drugs such as phosphate binders and vitamin D.

Assessment of Fatigue

The Italian version of the SF-36® questionnaire[30] was offered to the patients by the attending physician. Patients completed the questionnaire at home and returned it during the next dialysis session. Participants were screened for fatigue status using the Vitality scale of the SF-36. Standardized Vitality scale scores range from 0 to 100, with higher scores indicating better functioning. Scores above the midpoint of 50 represent well-being (nonfatigued group), whereas scores ≤50 represent limitations or disability related to fatigue (fatigued group).[18]

Assessment of Symptoms of Depression and Anxiety

We used the Italian version of the BDI[31] to assess the presence of symptoms of depression. The BDI is a 21-item patient-rated scale that has been validated in the HD population.[32–34] Scores can range from 0 to 63, with higher scores indicating more severe depression. In patients with ESRD, the BDI correlates highly with diagnostic criteria of depression, quality of life, functional status, severity of illness, and mortality over time.[32–34] The standard cutoffs are 0–9 indicates minimal depression, 10–18 indicates mild depression, 19–29 indicates moderate depression, and 30–63 indicates severe depression. Higher total scores indicate more severe depressive symptoms. To assess the presence and degree of symptoms of anxiety, we used an Italian version of the HARS.[35] The HARS comprises 14 items that evaluate the physical, psychological, and behavioral aspects of anxiety.

Assessment of Comorbidity

Each patient was evaluated for the presence of the following comorbidities included in the Charlson Comorbidity Index (CCI)[36] and according to the guidelines of the CCI itself: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, mild liver disease, diabetes without end-organ damage, diabetes with end-organ damage, malignant tumor without metastases (exclude if five years or more from diagnosis), malignant tumor with metastases, acute or chronic leukemia, moderate or severe liver disease, and AIDS. The CCI was then calculated for each patient.

Assessment of Cognitive Function

Cognitive function was assessed with the MMSE.[37] The MMSE is a brief 30-point questionnaire that is used to screen for cognitive impairment. It is also used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The MMSE has 11 questions that test five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE has been extensively used in ESRD patients on chronic HD.[38–40]

Other Variables

Patients underwent assessment of disability through the determination of daily activities using ADL[41] and IADL.[42] We calculated the TIRD following the methods used by Lindsay et al.[43] Patients were invited to answer the following single open-ended question: "How long does it take you to recover from a dialysis session?" Responses were converted to number of minutes, according to the study by Lindsay et al.[43]

Laboratory Measurements

Blood samples were obtained from HD patients directly through the arteriovenous fistula or the central venous catheter immediately before their scheduled HD session at the beginning of the week. The plasma was separated within 30 minutes, and samples were kept frozen at −70°C if not analyzed immediately. Laboratory parameters were measured by routine methods at the Department of Laboratory Medicine, Catholic University of Rome. High-sensitivity CRP was measured by means of nephelometry (Beckman Instruments, Fullerton, CA); limit of detection: 0.02 mg/dL; intra-assay CV: 1%. Plasma IL-6 was measured by a commercially available human high-sensitivity *in vitro* enzyme-linked immunosorbent assay kit (Abcam, Cambridge, UK); sensitivity: <0.8 pg/mL; intra-assay CV: 4.4%.

Table 1
Patient Demographic, Clinical, and Laboratory Characteristics, Stratified According to the Presence of Fatigue

Characteristic	All Patients ($n = 100$)	Fatigued ($n = 43$)	Nonfatigued ($n = 57$)	*P*
Age (yrs)	63 ± 16	68 ± 11	60 ± 18	0.012
Sex (male:female)	37:63	15:28	22:35	0.864
Marital status				
Married/partner	73	31	42	
Widowed/single	27	12	15	0.960
Primary cause of ESRD				
Hypertension	38	18	20	
Glomerulonephritis	25	13	12	
Diabetes	12	5	7	
Interstitial nephritis	13	5	8	
Polycystic renal disease	8	3	5	
Others/unknown	4	2	2	0.959
Dialytic age (months)	55 ± 59	60 ± 64	52 ± 56	0.508
Body mass index	25.0 ± 4.4	25.9 ± 5.1	24.5 ± 3.8	0.119
CCI	3.1 ± 2.7	4.5 ± 2.6	2.1 ± 2.3	<0.001
MMSE	25.6 ± 3.4	22.6 ± 3.3	24.3 ± 3.3	0.012
ADL	6 (2–6)	5.1 ± 1.3	5.5 ± .9	0.072
IADL	8 (1–8)	6.2 ± 2.0	7.0 ± 1.6	0.029
TIRD (minutes)	198 ± 191	302 ± 227	137 ± 136	<0.001
BDI	15.9 ± 9.2	21.9 ± 8.3	11.8 ± 7.3	<0.001
HARS	14 ± 6	18 ± 5	12 ± 5	<0.001
Cardiac ejection fraction (%)	58.0 ± 8.4	57.5 ± 9.4	58.3 ± 8.0	0.647
Albumin (g/dL)	4.0 ± .3	3.9 ± .3	4.1 ± .3	0.001
Creatinine (mg/dL)	10.4 ± 3.1	9.2 ± 1.9	11.2 ± 3.4	<0.001
Urea (mg/dL)	83 ± 21	76 ± 16	89 ± 22	0.001
Kt/V	1.4 ± .3	1.4 ± .5	1.4 ± .2	0.984
Hemoglobin (g/dL)	11.0 ± .9	11.1 ± 1.0	10.9 ± .9	0.297
Calcium (mg/dL)	9.2 ± .6	9.2 ± .6	9.3 ± .5	0.366
PTH (pg/mL)	301 ± 367	328 ± 509	281 ± 221	0.534
Phosphorus (mg/dL)	5.1 ± 1.6	4.7 ± 1.1	5.4 ± 1.7	0.021
Vitamin D (ng/mL)	9.6 ± 2.1	9.3 ± 2.1	9.9 ± 2.1	0.160
CRP (mg/dL)	10.4 ± 11.9	9.6 ± 9.7	10.9 ± 13.1	0.586
IL-6 (pg/mL)	3.3 ± 3.2	5.1 ± 3.4	1.6 ± 1.5	<0.001
Fibrinogen (mg/dL)	324 ± 75	340 ± 83	312 ± 300	0.554
Ferritin (mg/dL)	391 ± 357	317 ± 300	448 ± 391	0.071

ESRD = end-stage renal disease; CCI = Charlson Comorbidity Index; MMSE = Mini-Mental State Examination; ADL = activities of daily living; IADL = instrumental activities of daily living; TIRD = time of recovery after hemodialysis; BDI = Beck Depression Inventory; HARS = Hamilton Anxiety Rating Scale; PTH = parathyroid hormone; CRP = C-reactive protein; IL-6 = interleukin-6.
Values are expressed as mean ± SD or median (min–max).

Statistical Analyses

Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), version 15.0 (SPSS Inc./IBM Corp., Armonk, NY). All data were first analyzed for normality of distribution using the Kolmogorov-Smirnov test of normality. Continuous variables are expressed as mean ± SD, categorical variables displayed as frequencies, and the appropriate parametric (Student t-test) or nonparametric (Mann-Whitney U-test or χ^2 test) test was used to assess significance of the differences between subgroups. After correction for multiple comparison, a *P*-value of less than 0.01 was considered statistically significant.

Moreover, we performed multivariate general linear model (GLM) analyses to examine the relationship between 1) fatigue and gender as the second factor and 2) fatigue and BDI scale, including in the model, based on the univariate analyses, the significant explanatory variables. In case of not normally distributed data (i.e., ADL, IADL), we used logarithmic transformation.

Finally, canonical correlation analyses were carried out to decipher the reciprocal correlations between fatigue, depression (BDI) and biomarkers (albumin, urea, creatinine, and IL-6).

Results

A total of 124 patients were screened for study participation. Of these, 24 were excluded because of a dialysis duration of less than one year ($n = 10$), diagnosis of dementia based on DSM-IV criteria ($n = 2$), previous diagnosis of psychotic disorders ($n = 1$), clinical instability requiring hospital admission ($n = 3$), infective disease ($n = 3$), rheumatic disease ($n = 1$), inflammatory bowel disease ($n = 1$), autoimmune disease ($n = 1$), acute hepatitis/liver failure ($n = 1$), and active cancer ($n = 1$). Baseline laboratory and clinical characteristics of the 100 HD patients included in the study are listed in Table 1. As noted, values of the variables are typical of ESRD patients.

Table 2
Patient Demographic, Clinical, and Laboratory Characteristics, Stratified According to Beck Depression Inventory Score

Variable	BDI <10 ($n = 26$)	BDI ≥10 ($n = 74$)	*P*
Age (yrs)	56 ± 17	66 ± 15	0.023
Sex (male:female)	10:20	27:43	0.786
Marital status			
Married/partner	18	46	0.682
Widowed/single	8	28	
Dialytic age (months)	54 ± 59	55 ± 59	0.942
Body mass index	25.3 ± 4.1	25.0 ± 4.5	0.741
CCI	1.7 ± 2.1	3.5 ± 2.6	0.002
MMSE	25.1 ± 3.2	23.1 ± 3.2	0.011
ADL	6 (4–6)	6 (2–6)	0.016
IADL	8 (4–8)	8 (1–8)	0.015
TIRD	150 ± 131	271 ± 212	0.002
HARS	8.9 ± 4.2	16.3 ± 5.5	<0.001
Cardiac ejection fraction (%)	59 ± 7	58 ± 9	0.573
Albumin (g/dL)	4.1 ± .2	3.9 ± .3	0.008
Creatinine (mg/dL)	11.8 ± 3.2	9.8 ± 2.9	0.009
Urea (mg/dL)	90 ± 18	79 ± 19	0.016
Kt/V	1.3 ± .2	1.4 ± .3	0.050
Hemoglobin (g/dL)	10.8 ± 1.0	11.1 ± .9	0.143
Calcium (mg/dL)	9.3 ± .6	9.2 ± .5	0.566
PTH (pg/mL)	303 ± 224	262 ± 337	0.510
Phosphorus (mg/dL)	5.4 ± 2.0	5.0 ± 1.4	0.392
Vitamin D (mg/dL)	9.9 ± 2.4	9.2 ± 1.9	0.226
CRP (mg/dL)	11.6 ± 16.5	10.0 ± 9.9	0.654
IL-6 (pg/mL)	2.8 ± 1.8	4.9 ± 3.1	<0.001
Fibrinogen (mg/dL)	297 ± 66	328 ± 73	0.061
Ferritin (mg/dL)	351 ± 312	380 ± 354	0.708

BDI = Beck Depression Inventory; CCI = Charlson Comorbidity Index; MMSE = Mini-Mental State Examination; ADL = activities of daily living; IADL = instrumental activities of daily living; TIRD = time of recovery after hemodialysis; HARS = Hamilton Anxiety Rating Scale; PTH = parathyroid hormone; CRP = C-reactive protein; IL-6 = interleukin-6.
Values are expressed as mean ± SD or median (min–max).

Table 3
Correlation Analyses Between Fatigue and Demographic, Clinical, and Laboratory Variables

Variable	Correlation Coefficient	*P*-value
Age (yrs)	−0.252	0.015
BMI	−0.127	0.223
TIRD	−0.379	0.001
Gender	−0.128	0.220
Log ADL	0.287	0.005
Log IADL	0.303	0.003
Marital status	−0.067	0.526
Dialytic age (months)	−0.209	0.046
Urea	0.322	0.012
Calcium	0.182	0.084
Phosphorus	0.152	0.149
Creatinine	0.347	0.001
Fibrinogen	−0.216	0.097
Ferritin	0.146	0.266
Albumin	0.223	0.040
PTH	0.149	0.248
Vitamin D	0.253	0.115
Kt/V	0.040	0.710
Hb	−0.182	0.084
CRP	−0.161	0.135
IL-6	−0.660	<0.001
CCI	−0.555	<0.001
MMSE	0.287	0.010
BDI	−0.657	<0.001
Ejection fraction	0.087	0.624
HARS	−0.595	<0.001

BMI = body mass index; TIRD = time of recovery after hemodialysis; ADL = activities of daily living; IADL = instrumental activities of daily living; PTH = parathyroid hormone; Hb = hemoglobin; CRP = C-reactive protein; IL-6 = interleukin-6; CCI = Charlson Comorbidity Index; MMSE = Mini-Mental State Examination; BDI = Beck Depression Inventory; HARS = Hamilton Anxiety Rating Scale.
We report Spearman coefficients and significance.

Forty-three patients (43%) constituted the fatigued group and 57 (57%) the nonfatigued group. The age of fatigued patients was significantly higher than that of the nonfatigued patients. The scores of CCI, BDI and HARS, and the TIRD were significantly higher in fatigued patients than in nonfatigued ones (Table 1). Conversely, the scores of ADL, IADL, and MMSE were significantly lower in fatigued than in those not fatigued. Serum IL-6 levels (pg/mL) were significantly higher in the fatigued group (5.1 ± 3.4) than in the nonfatigued group (1.6 ± 1.5; $P < 0.001$), whereas serum albumin and creatinine levels were significantly lower. Twenty-six patients (26%) had BDI scores <10, and 74 patients (74%) had BDI scores >9. The characteristics of these two groups of patients are listed in Table 2. Patients with BDI scores >9 were older and had a higher CCI; a lower MMSE; higher TIRD; lower serum albumin, creatinine, and urea levels; and higher serum IL-6 levels.

The correlation analyses showed that the score of the SF-36 Vitality subscale was associated with age, dialytic age, TIRD, ADL, IADL, CCI, BDI, HARS, MMSE, serum urea, creatinine, albumin, and IL-6 levels (Table 3). In the multivariate GLM analyses, with fatigue as the dependent variable and gender as a second factor, BDI and serum IL-6 levels were independently associated with the score of the SF-36 Vitality subscale (Table 4).

A canonical correlation analysis was performed, including in the model fatigue, BDI, and biomarkers (Table 5). The canonical correlation was 0.679 ($R^2 = 0.462$). Fatigue, BDI, and IL-6 among biomarkers showed the strongest association with the underlying construct (standardized canonical coefficients = −0.989, 0.015, and 0.852, respectively), thus explaining a correlation of IL-6 with both depression and fatigue.

Discussion

The present study shows that fatigue is very frequent in patients on chronic HD and is associated with symptoms of depression and serum IL-6 levels. These results support the need for longitudinal studies to investigate if symptoms of depression and serum IL-6 levels may have a causative role in fatigue for patients on chronic HD. Such efforts may help identify mechanisms by which renal providers can more effectively assess and treat fatigue in HD patients.

Table 4
Multivariate General Linear Model Analyses—Dependent Variables: Fatigue and Gender

Covariates	Fatigue (*P*)	Gender (*P*)
Age (yrs)	0.993	0.147
Dialytic age (yrs)	0.043	0.300
Time of recovery after hemodialysis (minutes)	0.080	0.733
Charlson Comorbidity Index	0.069	0.361
Mini-Mental State Examination	0.448	0.171
Beck Depression Index	<0.001	0.710
Hamilton Anxiety Rating Scale	0.574	0.345
Creatinine (mg/dL)	0.836	0.086
Albumin (g/dL)	0.341	0.574
Urea (mg/dL)	0.636	0.527
IL-6 (pg/mL)	<0.001	0.549
Logarithmic ADL scale	0.852	0.044
Logarithmic IADL scale	0.387	0.036

IL-6 = interleukin-6; ADL = activities of daily living; IADL = instrumental activities of daily living.
We included in the model variables with significant correlation with fatigue in the univariate analyses. Fatigue $R^2 = 0.701$ (adjusted = 0.652), gender $R^2 = 0.226$ (adjusted = 0.099).

The pathogenesis of fatigue in chronic HD patients is essentially unknown.[1–3] It has been suggested that fatigue may be correlated with sociodemographic (age, sex, race, employment status, marital status, education, and social support), clinical (anemia, malnutrition, sleep disorders, secondary hyperparathyroidism, physical inactivity, and the number and severity of comorbidities), psychological (anxiety, stress, and depression), and dialysis-related factors.[1–3,38,39,44–47]

Cytokines and activated immune-inflammatory pathways may cause fatigue through direct activation of the central nervous system, hypothalamus, pituitary gland, and adrenal glands or indirectly by inducing sleep disorders, depression, or anxiety.[15] In healthy individuals, fatigue does not seem to be associated with higher serum IL-6 levels.[48] The Whitehall II study, a large-scale cohort study conducted in 20 civil service departments in London that examined the health of 10,308 civil servants aged 35 to 55 years, has shown that the odds ratios for new-onset fatigue, assessed using the Vitality subscale of the SF-36, were 1.28 for high CRP and 1.24 for high IL-6.[49] Also, there is evidence of a significant correlation between fatigue and circulating levels of IL-6 in patients with other chronic diseases such as polycystic ovary syndrome,[19] diabetes,[20] psoriasis,[21] rheumatoid arthritis,[22] and the geriatric syndrome of frailty.[50] In cancer-related fatigue, two recent reviews have shown a strong association between high levels of fatigue and elevated systemic inflammatory markers and high cytokine (IL-6, IL-1β) concentrations.[23,24] In rheumatoid arthritis, studies on etanercept and tocilizumab showed reduction of fatigue within days and weeks, which is well before anti-inflammatory effects on joint disease alone could account for this effect.[51,52]

Table 5
Multivariate General Linear Model Analyses—Dependent Variables: Fatigue and BDI

Covariates	Fatigue (*P*)	BDI (*P*)
Age (yrs)	0.889	0.679
Dialytic age (yrs)	0.034	0.493
Time of recovery after hemodialysis (minutes)	0.019	0.119
Charlson Comorbidity Index	0.018	0.139
Mini-Mental State Examination	0.734	0.013
Hamilton Anxiety Rating Scale	0.006	<0.001
Creatinine (mg/dL)	0.484	0.461
Albumin (g/dL)	0.129	0.171
Urea (mg/dL)	0.541	0.667
IL-6 (pg/mL)	<0.001	0.045
Logarithmic ADL scale	0.851	0.916
Logarithmic IADL scale	0.552	0.996

BDI = Beck Depression Inventory; IL-6 = interleukin-6; ADL = activities of daily living; IADL = instrumental activities of daily living.
We included in the model variables with significant correlation in the univariate analyses. Fatigue $R^2 = 0.632$ (adjusted = 0.582), gender $R^2 = 0.585$ (adjusted = 0.529).

The finding that fatigue was independently associated with symptoms of depression is in accordance with studies in the general population[53,54] and confirms previous observations of our group.[27,28,55] However, one could question if an HD patient becomes depressed because of the effects of being also fatigued or because of the reverse and if there is a bidirectional relationship between the two symptoms. The observation from the canonical correlation analyses that fatigue, symptoms of depression, and serum IL-6 levels showed the strongest association with the underlying construct (standardized canonical coefficients = −0.989, 0.015, and 0.852, respectively), thus explaining a correlation of IL-6 with both depression and fatigue, may help to answer the previously cited question. However, longitudinal studies are needed to assess an eventual causal relationship between serum IL-6 levels and depression/fatigue in patients on chronic HD.

Fatigue also was not associated with most laboratory parameters (serum hemoglobin, calcium, phosphorus, PTH, vitamin D levels, albumin, and Kt/V). These data are in accordance with previous studies including patients receiving HD or peritoneal dialysis.[1–3,38,39,44–47] As an explanation, we can hypothesize that the serum levels of hemoglobin, calcium, phosphorus, PTH, and the Kt/V were relatively homogeneous in the study population as a consequence of the fact that all patients received erythropoietin to maintain hemoglobin levels between 11 and 12 g/L and were treated to target serum PTH and albumin levels and Kt/V according to the Kidney Disease Outcomes Quality Initiative guidelines.[56]

This study has certain limitations. First, the assessment of fatigue was made using the Vitality scale of

the SF-36, an instrument that measures the experience of fatigue during a period ranging from weeks to months, and may fail to recognize daily or weekly fatigue fluctuations. The SF-36 Vitality subscale is one of the most used tools to assess fatigue in ESRD patients receiving chronic dialysis and also has been used with people with chronic obstructive pulmonary disease, Sjogren syndrome, chronic fatigue syndrome, and systemic lupus erythematosus.[57] Second, we measured the serum levels of IL-6 only and not those of IL-6R, which are needed to evaluate the IL-6 transsignaling. Third, we cannot establish a causal relationship between fatigue and various variables using a cross-sectional study design.

In summary, we found that fatigue was significantly associated with symptoms of depression and serum IL-6 levels in ESRD patients receiving chronic HD. In addition, a correlation of IL-6 with both depression and fatigue was observed. The findings of this exploratory analysis should help generate additional longitudinal studies to possibly demonstrate the causative role of activated immune-inflammatory pathways and IL-6 in the onset of fatigue and depression in ESRD patients receiving chronic HD.

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