Original Article

Exploring the Diurnal Course of Fatigue in Patients on Hemodialysis Treatment and Its Relation With Depressive Symptoms and Classical Conditioning

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Abstract

Context. Fatigue is one of the most prevalent symptoms among hemodialysis (HD) patients. To design effective treatments, it is crucial to understand the diurnal pattern of fatigue in this population.

Objectives. The objectives of this study were to assess diurnal changes in fatigue in patients undergoing hemodialysis and their relation with depressive symptoms and to explore whether fatigue may become a classically conditioned response to the hospital environment.

Methods. A prospective, observational study was conducted in 51 HD patients. Subjects repeatedly rated their current fatigue on three different days during one week of hemodialysis treatment to capture changes in momentary fatigue. First, on an HD treatment day, fatigue was measured one hour before and immediately before dialysis, as well as immediately after dialysis and again at 22:00 PM Second, on the postdialysis day and on the seventh weekday (when patients had not received treatment on the previous day), fatigue was measured at the same moments in time as the two measurements before dialysis on the treatment day. Beck Depression Inventory-II and Fatigue Severity Scale were administered to evaluate depressive mood and fatigue severity in daily life.

Results. Fatigue increased as a result of hemodialysis treatment over the entire sample. However, diurnal fatigue patterns differed significantly between individuals high and low in depressive symptoms, with the former being fatigued more constantly throughout the day, and the latter experiencing increases in fatigue due to treatment. Pretreatment fatigue experienced in the hospital environment followed a pattern consistent with the development of a classically conditioned response.

Conclusion. Diurnal fatigue patterns during hemodialysis treatment are associated with depressive symptoms, and classical conditioning may play a role in the experience of pretreatment fatigue. J Pain Symptom Manage 2019;57:890−898. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Hemodialysis, fatigue, momentary assessment, depression, classical conditioning

Introduction

The prevalence of renal replacement therapy in Europe and the U.S. is estimated to be 924 and 2274 per million population, respectively.[1,2] Hemodialysis (HD) is by far the most prevalent renal replacement therapy in the world.[3] The symptom burden of HD patients is comparable to that of terminal cancer patients.[4,5] Fatigue is one of the most common symptoms among

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HD patients, greatly affecting health-related quality of life.[6,7] Because 40%−80% of HD patients suffer from fatigue and HD treatment is usually received for many years, the need for effective fatigue interventions is beyond dispute.[7] It is therefore crucial to understand the development and course of fatigue in HD patients.

However, as an inherently subjective experience, fatigue is difficult to capture and define. A commonly used definition refers to fatigue as "an overwhelming, debilitating, and sustained sense of exhaustion that is likely to decrease one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles."[8,9] Fatigue in patients on HD treatment in particular is a complex and multidimensional phenomenon. For instance, different fatigue qualities can be distinguished, such as physical (weakness, tiredness, lack of energy) and mental (emotional, cognitive) fatigue, with the former being reported more frequently in this population.[10,11] Furthermore, fatigue in individuals undergoing HD treatment may be determined by multiple factors. Indeed, acute fatigue as a response to treatment may have different determinants than fatigue that is experienced more chronically by HD patients.[12] The difficulty to identify and study fatigue in HD patients is enhanced by the lack of a valid and reliable fatigue scale specifically developed for the end-stage kidney disease (ESKD) population. Recently, a systematic review on fatigue instruments used in hemodialysis found that fatigue was measured in 43 different ways across 123 studies.[13] Moreover, the most commonly used fatigue measures (e.g., Fatigue Severity Scale [FSS] or SF-36 vitality subscale) only evaluate the overall fatigue experience retrospectively, for instance, over the preceding week or month. As such, the implementation of novel measuring methods, such as ecological momentary assessment (EMA) procedures, taking into account the diurnal variability of fatigue by repeatedly collecting real-time measurements of fatigue over the course of several days, is warranted. To date, only a limited number of studies reported the use of EMA to evaluate the variability of fatigue in HD patients. These studies showed indeed differences in fatigue between and within individuals, for instance, on treatment versus nontreatment days. However, none of these reports investigated the relationship between diurnal fatigue patterns and variables that may explain these differences.[14−17]

In addition, research findings are inconsistent regarding the relation between fatigue in HD patients and physiological, psychological, sociodemographic, or dialysis-related variables. No causal association has been demonstrated yet.[18,19] As such, a better understanding of the factors contributing to fatigue in HD patients is crucial for the development of effective treatments. Interestingly, a biopsychosocial model of fatigue in HD patients has recently been proposed. In this model, fatigue is initially triggered by biochemical imbalances or stress and worrying and then maintained by a vicious cycle of negative beliefs, depression and anxiety, and maladaptive behavioral patterns such as avoidance of activity and sleep problems.[19] Previous reports already demonstrated a significant association between general, retrospectively reported fatigue and depression in HD patients.[20,21] However, the relationship between depressive symptoms and momentary changes in fatigue related to the dialysis treatment has not been investigated before. To better understand fatigue in response to treatment in patients who undergo hemodialysis thrice weekly, it is important to assess whether individual differences in depressive symptoms contribute to momentary fatigue related to hemodialysis. Therefore, the first aim of the present study was to assess the diurnal change in fatigue in response to hemodialysis and its relation with depressive symptoms.

Within a biopsychosocial approach to fatigue in HD patients and as a second aim of this study, we put forward classical conditioning as another mechanism that may contribute to the maintenance of HD-related fatigue. Classical conditioning can be defined as a change in behavior to a stimulus or event due to its pairing with another stimulus or event.[22] Indeed, clinical evidence for fatigue as a classically conditioned response has already been shown in breast cancer patients receiving repeated infusions of chemotherapy. Bovbjerg et al. demonstrated that the repeated pairing of the hospital environment with chemotherapy and its undesirable side effects such as fatigue and nausea may result in the experience of these symptoms before chemotherapy. This can be explained as a classically conditioned response, where the hospital environment became a conditioned stimulus capable of eliciting these symptoms due to its previous pairing with chemotherapy. As such, classical conditioning may loosen the link between treatment and the experience of fatigue, thereby potentially contributing to the fatigue becoming a chronic symptom, above and beyond pathophysiological factors.[23,24] Therefore, our second aim was to explore whether hemodialysis-related fatigue may also in part be explained as a conditioned response to the hospital environment that has become associated with hemodialysis treatment. To this aim, we recorded fatigue ratings immediately before hemodialysis on treatment days in the hospital environment and compared these with fatigue measured at the same hour of the day on nontreatment days. We predicted that pretreatment fatigue would be higher on a treatment day in the hospital environment than fatigue on nontreatment days measured at the same time of day outside of the hospital environment.

Subjects and Methods

Study Population

All prevalent chronic patients of the HD unit of the Catholic University of Rome (Italy) between June and August 2018 were considered eligible for inclusion in this observational study. Exclusion criteria were as follows: <18 years of age, inability to answer the questionnaires because of hearing or reading problems, dementia, actual instability of clinical condition requiring hospitalization, or active cancer.

Data Collection

A fatigue diary was developed to prospectively and repeatedly measure momentary fatigue on eight different moments during one week of regular treatment. First, to assess diurnal changes in fatigue on an HD treatment day, fatigue was measured one hour before dialysis, as well as immediately before dialysis started at the dialysis unit. Fatigue was measured again after termination of the dialysis session at the dialysis unit, and finally at 22:00 PM. Second, to assess classical conditioning effects, fatigue was measured again on a postdialysis day at exactly the same moment as the fatigue measurement immediately before dialysis in the hospital environment. Fatigue rating was also collected one hour earlier as control measurement. These two measurements were repeated on the seventh weekday (when patients had not received treatment on the previous day) (Fig. 1). Fatigue was rated on an 11-point Likert scale from 0 (no fatigue at all) to 10 (extremely fatigued).

The Italian versions of the Beck Depression Inventory-II (BDI-II) and FSS were administered to evaluate depressive mood and the impact of general fatigue on the activities of daily living during the past seven days. The BDI-II is a 21-item, patient-rated scale that has been validated in the hemodialysis population.[25] Scores can range from 0 to 63, with higher scores indicating more severe depressive symptoms. The FSS is a nine-item questionnaire with a seven-point Likert scale. The total score is calculated by averaging the scores of the individual item responses. The scores can range from 1 (no fatigue) to 7 (maximum fatigue).[26] The FSS is one of the most frequently used measuring instruments to evaluate fatigue in renal patients.[27] Moreover, we preferred administering the FSS over other measuring instruments, such as the Edmonton Symptom Assessment System renal survey (ESAS-renal) or Integrated Palliative care Outcome Scale renal survey (IPOS-renal), as they evaluate the overall symptom burden of renal patients and dedicate only one item to fatigue in particular.

The following demographical, clinical, and laboratory information was obtained from medical records: age, gender, dialysis vintage, primary cause of ESKD, duration of dialysis, type and number of comorbidities assessed by the Charlson Comorbidity index,[28] self-reported functional status via the activity of daily living (ADL) scale,[29] and time of recovery after hemodialysis in minutes,[30] hemoglobin, sodium, calcium, phosphorus, PTH, creatinine, and dialysis dose as evaluated by Kt/V.

Procedure

After giving their informed consent, each participant received their personal diary along with verbal and written instructions and started data collection the following day. The BDI-II and FSS questionnaires were completed on the treatment day during dialysis. Demographical and clinical information was obtained at the moment of inclusion. Results of monthly routine biochemical and hematological investigation were obtained closest to the day on which the questionnaires were completed.

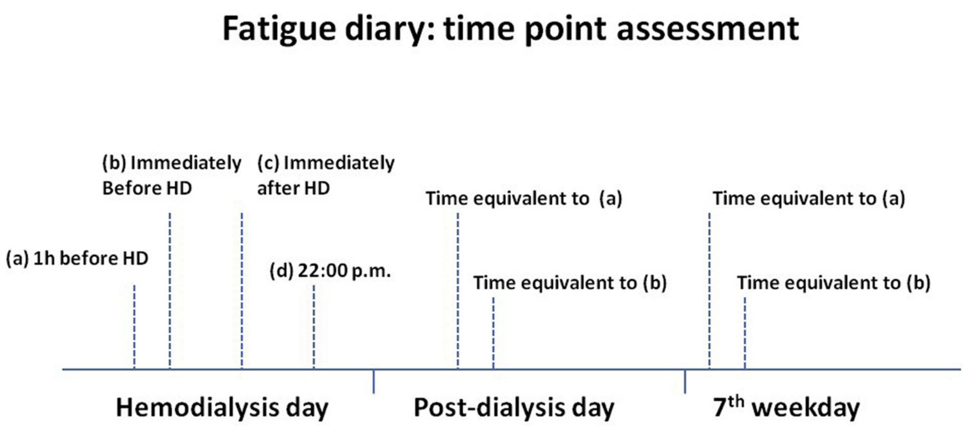

Fig. 1. Fatigue diary: time point assessment. HD = hemodialysis.

Hemodialysis

Patients received bicarbonate hemodialysis treatment between 3.5 and 4 hours, twice or thrice weekly. The blood flow ranged from 250 to 300 mL/minute with a dialysis rate flow of 500 mL/minute. High permeability membranes were used.

Statistical Analysis

Statistical analysis was performed by using the Statistical Package for Social Science (IBM SPSS Statistics 25). Data are presented as mean and SD, and statistical significance was assessed at $P < 0.05$. To investigate diurnal changes in fatigue in HD patients and their relation with depressive symptoms, we performed a mixed ANOVA with reported fatigue as dependent variable, measurement moment on the day of treatment as within-subjects factor and a low or high presence of depressive symptoms (BDI-II score ≤ 13 versus BDI-II > 14, corresponding to the cutoff score to classify for depressive mood according to the guidelines to interpret the BDI-II[31]), as between-subjects factor. Whenever Mauchly's test indicated that the assumption of sphericity was violated, F-ratio, degrees of freedom, and *P*-values are reported with the applied Huynh-Feldt corrections (all epsilons > 0.75). To evaluate the role of classical conditioning, we performed a mixed ANOVA with fatigue immediately before dialysis (or corresponding moment on nontreatment days) as dependent variable and day (treatment day, postdialysis day, seventh weekday) as within-subjects factor.

Results

Patient Characteristics

Sixty-three patients were approached of whom 57 individuals provided informed consent (90.5% consent rate). Subsequently, three withdrew owing to loss of interest, one patient withdrew owing to hospitalization, and two were excluded from the analyses owing to poor adherence to the study protocol (instead of recording momentary fatigue ratings throughout the week, these two subjects filled in the entire diary immediately before handing it in). The remaining 51 individuals with a mean age of 58.70 years (SD = 18.70) are included in this report. Baseline demographical, clinical, and laboratory characteristics as well as BDI-II and FSS scores are reported in Table 1. The fatigue severity score, reported by this HD population, is almost twice as high as compared to previous estimates of fatigue in healthy adults with a mean (+SD) FSS score of 2.3 (0.7).[26] Correlations between the aforementioned demographical and dialysis-related variables and the mean of all eight momentary fatigue ratings (representing the mean fatigue experienced during the week of the study) are reported in Supplemental Table 1. Mean fatigue only correlated significantly with time of recovery after hemodialysis, indicating that patients who report having to recover for a longer time after dialysis are on average more fatigued.

Table 1
Baseline Demographical, Clinical, and Laboratory Characteristics ($N = 51$)

Characteristic	Mean (±SD)
Age (yrs) (range)	58.7 (18.7) (20–91)
Sex: male/female (*n*)	28/23
Dialysis vintage, months (range)	70 (68.7) (7–386)
Hours of dialysis/week	11.4 (1.2)
Primary cause of ESRD (*n*)	
Hypertension	12
Glomerulonephritis	15
Diabetes	8
Interstitial nephritis	2
Polycystic kidney disease	5
Others/unknown	9
CCI (range)	1.5 (1.4) (0–6)
ADL (range)	5.8 (0.7) (2–6)
Morning/afternoon treatment (*n*)	23/28
BDI (range)	15.4 (8.4) (2–33)
FSS (range)	4.3 (1.5) (1.3–6.6)
TIRD (minutes) (median) (range)	180 (674) (10–4320)
UFR (/mL/kg/hour)	8.4 (3.2)
Kt/V	1.52 (0.4)
Hemoglobin (g/dL)	10.6 (1.0)
Serum creatinine (mg/dL)	10.5 (2.7)
Calcium (mg/dL)	9.2 (0.8)
Serum sodium (mmol/L)	138.9 (2.9)
Dialysate sodium (mmol/L)	138.7 (1.9)
PTH (pg/mL)	570 (455)
Phosphorus (mg/dL)	5.3 (1.4)

CCI = Charlson Comorbidity Index; ADL = activity of daily living; BDI = Beck Depression Inventory; FSS = Fatigue Severity Scale; TIRD = time of recovery after dialysis; UFR = ultrafiltration rate.

Fatigue Course in HD Patients

Mean fatigue scores (+SD) on the HD treatment day were 3.92 (2.59), 95% CI [3.19–4.65] one hour before dialysis, 4.14 (2.84), 95% CI [3.34–4.94] immediately before dialysis, 5.08 (2.53), 95% CI [4.37–5.79] immediately after dialysis, and 5.45 (2.75), 95% CI [4.68–6.22] at 22:00 PM Results of the mixed ANOVA showed a significant main effect of the measurement moment on fatigue rating, $F(2.67, 131.91) = 9.44$, $P < 0.001$, partial $\eta^2 = 0.159$. Planned comparisons of the four measurement moments revealed a significant fatigue increase from immediately before to immediately after hemodialysis treatment, $F(1, 50) = 6.75$, $P = 0.012$, partial $\eta^2 = 0.119$. There were no significant differences between the measurement one hour before dialysis and the second measurement immediately before treatment, $F(1, 50) = 0.97$, $P = 0.330$, partial $\eta^2 = 0.019$, nor between the postdialysis measurement moment and the measurement at 22:00 PM, $F(1, 50) = 1.07$,

$P = 0.305$, partial $\eta^2 = 0.021$ (Fig. 1). Furthermore, fatigue severity in daily life, assessed with the FSS, did not correlate with the momentary fatigue rating after HD treatment ($r = 0.12$, $P = 0.371$). Nevertheless, the FSS score was significantly, although moderately, associated with the average of all other fatigue ratings individuals reported ($r = 0.34$, $P = 0.017$).

Fatigue Course in HD Patients and Its Relation to Depression

For this analysis, depressive status (BDI-II) was added as a between-subjects factor, based on the cutoff score described earlier. Results are based on 50 subjects because one individual declined to fill in the questionnaire, resulting in a group high in depressive symptoms ($n = 25$) and a group low in depressive symptoms ($n = 25$). The low-depressed patient group had a mean (+SD) BDI-II score of 8.76 (2.99), whereas the high-depressed patient group had a mean (+SD) BDI score of 22 (6.68). Mean diurnal fatigue scores (+SD) on the consecutive measurement moments are reported in Table 2. We found no main effect of depression, $F(1, 48) = 3.95$, $P = 0.053$, partial $\eta^2 = 0.076$. However, there was a significant measurement moment × depression interaction, $F(2.71,130.18) = 3.36$, $P = 0.025$, partial $\eta^2 = 0.065$, showing that fatigue throughout the day of HD treatment differed depending on one's depressive symptoms. Comparison between low-depressed and high-depressed patients showed a significantly different fatigue rating one hour before dialysis and immediately before HD started, $F(1, 48) = 10.70$, $P = 0.002$, partial $\eta^2 = 0.182$ and $F(1, 48) = 4.12$, $P = 0.048$, partial $\eta^2 = 0.079$, respectively. It is noteworthy that this pattern of results was also found on nontreatment days. Here, fatigue ratings were collected at the same hours of the day as the fatigue ratings one hour before and immediately preceding hemodialysis on the treatment day to answer our research question about classical conditioning. Interestingly, individuals high in depressive symptoms reported higher fatigue than low-depressed individuals on all these time points as well (results in Supplemental Table 2). Furthermore, in the low-depressed group, there was a significant increase in fatigue from one hour before HD to immediately before HD, $F(1, 24) = 8.90$, $P = 0.006$, partial $\eta^2 = 0.270$. Similarly, there was a significant increase from pretreatment to posttreatment fatigue, $F(1, 24) = 12.39$, $P = 0.002$, partial $\eta^2 = 0.340$. There was no significant fatigue rating difference in this group between the measurement just after HD and the one at 22:00 PM, $F(1, 24) = 0.01$, $P = 0.930$, partial $\eta^2 = 0.000$. By contrast, in the high-depressed group, there were no significant differences in fatigue levels between any of the consecutive measurement moments, $F(1, 24) = 0.04$, $P = 0.846$, partial $\eta^2 = 0.002$ (measurement moment 1 vs. 2), $F(1, 24) = 0.09$, $P = 0.770$, partial $\eta^2 = 0.004$ (moment 2 vs. 3) and $F(1, 24) = 2.15$, $P = 0.156$, partial $\eta^2 = 0.082$ (moment 3 vs. 4) (Fig. 2).

Fatigue in HD Patients and Classical Conditioning

This analysis was based on 48 subjects because three individuals did not report their fatigue rating on either the postdialysis day or the seventh weekday. Mean fatigue scores (+SD) were 4.10 (2.79), 95% CI [3.29−4.16] immediately before HD started on the treatment day, 3.00 (2.70), 95% CI [2.22−3.78] on the postdialysis day, and 3.38 (2.76), 95% CI [2.57−4.18] on the seventh weekday, measured at the same time of day. Mixed ANOVA revealed a main effect of day, $F(2, 94) = 5.58$, $P = 0.005$, partial $\eta^2 = 0.106$. Planned comparisons revealed that fatigue immediately before hemodialysis in the hospital environment was significantly higher than fatigue at the same time on the postdialysis day, $F(1, 47) = 9.34$, $P = 0.004$, partial $\eta^2 = 0.166$, and the seventh weekday $F(1, 47) = 4.48$, $P = 0.040$, partial $\eta^2 = 0.087$. No significant difference in fatigue rating was found between the postdialysis day and the seventh weekday, $F(1,47) = 0.44$, $P = 0.512$, partial $\eta^2 = 0.009$. By contrast, a mixed ANOVA with the control fatigue measurement taken in a different environment than the hospital one hour earlier revealed no differences in fatigue between the treatment day, postdialysis day, or the seventh weekday, $F(2, 96) = 1.94$, $P = 0.149$, partial $\eta^2 = 0.039$ (Fig. 3).

Discussion

The present study was conducted to assess diurnal changes in fatigue in response to hemodialysis treatment and their relation with depressive symptoms.

Table 2
Fatigue Difference Between High- and Low-Depressed Individuals According to the Beck Depression Inventory-II (BDI-II) on a Hemodialysis (HD) Treatment Day

Hemodialysis Day	Low BDI-II Mean (SD) 95% CI	High BDI-II Mean (SD) 95% CI	*P*-Value
One hour before HD	2.92 (2.50) [1.89−3.95]	5.08 (2.16) [4.19−5.97]	0.002
Immediately before HD	3.44 (2.75) [2.30−4.58]	5.00 (2.68) [3.90−6.11]	0.048
Immediately after HD	5.04 (1.93) [4.25−5.84]	5.16 (3.09) [3.88−6.44]	0.87
22:00 PM	5.00 (2.86) [3.82−6.18]	6.00 (2.60) [4.93−7.07]	0.20

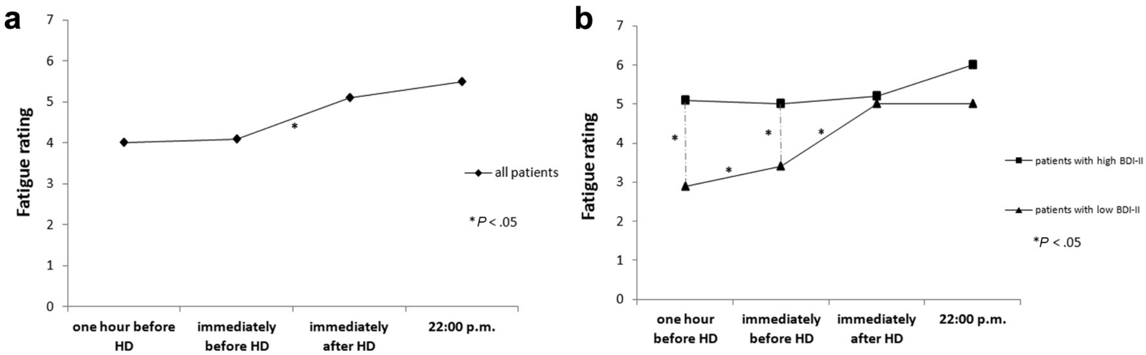

Fig. 2. Course of fatigue on a hemodialysis (HD) treatment day (a) and its relation to depressive symptoms (b). a) Fatigue levels in HD patients vary according to the measurement moment on the HD day. A marked increase in fatigue was found immediately after the HD session. b) Individuals high in depressive symptoms (BDI-II score of >14) reported continuously high levels of fatigue. Low-depressed individuals (BDI-II score ≤ 13) were significantly less tired than high-depressed individuals before treatment but showed a marked increase in fatigue after HD treatment. BDI-II = Beck Depression Inventory-II.

Furthermore, we explored whether HD-related fatigue may in part be explained as a conditioned response to the hospital environment. We found that fatigue increases significantly during HD treatment, but only in low-depressed individuals according to the BDI-II. By contrast, individuals high in depressive symptoms already reported high levels of fatigue before treatment, and these were not significantly increased afterward. We also showed that patients reported higher fatigue levels in the hospital environment before treatment relative to other environments that are not associated with hemodialysis, which is in line with the development of a classically conditioned fatigue response.

First, our results show that fatigue increased significantly during a treatment day and especially during the dialysis session. These findings are in line with a previous study of Abdel-Kader et al. who also demonstrated diurnal increases in fatigue in HD patients.[14] However, their study did not specifically investigate fatigue levels immediately before and after HD, nor did they investigate the relationship of fatigue with depressive symptoms. In addition, we found that postdialysis fatigue did not correlate with fatigue severity in general as measured with the FSS. However, FSS scores were moderately associated with the average of all other (i.e., not postdialysis) fatigue ratings in our study. This supports the finding of different fatigue patterns (i.e., more general fatigue vs. fatigue as a response to treatment) and may suggest that these should, at least partially, be distinguished in HD patients.[12,17] It also emphasizes the need for a reliable

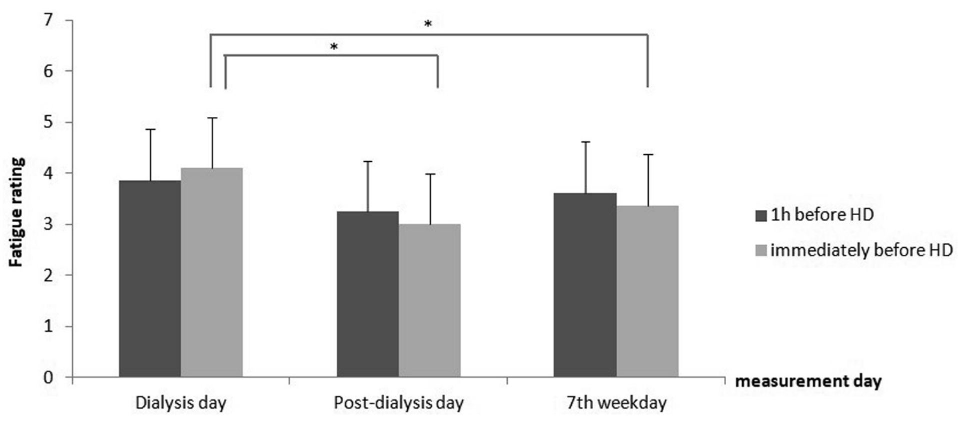

Fig. 3. Exploration of classical conditioning in hemodialysis (HD)-related fatigue ($N = 48$). Momentary fatigue measurements one hour before and immediately before HD on a treatment day, postdialysis day, and the seventh weekday. Fatigue levels immediately before HD in the hospital environment were significantly higher than fatigue at the same time of the day on a postdialysis day and the seventh weekday. On the contrary, control fatigue measurement in a different environment than the hospital one hour earlier showed no differences in fatigue between the different days. To control for carryover effects, the order of the day in which individuals completed the fatigue diary varied: one-third of participants started on a dialysis treatment day, another third started on a postdialysis day, and the remaining third started on the seventh weekday. They all completed the diary within one week of regular treatment. $*P < 0.05$.

fatigue measuring instrument adapted to the HD population, taking into account the general and treatment-related fatigue qualities in these individuals.[19] Moreover, conventional fatigue scales, evaluating fatigue retrospectively, are liable to recall bias and do not accurately reflect momentary fatigue.[32] Interestingly, a new outcome measure for fatigue in hemodialysis is being developed by the International Standardized Outcomes in Nephrology (SONG) initiative, which identified fatigue as a core outcome domain in HD, to facilitate consistent measurement of fatigue in HD patients and facilitate comparison of the effects of interventions for fatigue across trials.[33]

Second, previous studies have revealed an association between general fatigue and depressive symptoms in HD patients.[11,20,21,34,35] Here, we found that individuals high and low in depressive symptoms reported similar levels of fatigue after HD treatment, but high-depressed individuals showed significantly higher fatigue before treatment relative to their low-depressed counterparts. Moreover, individuals high in depressive symptoms also experienced more fatigue than low-depressed individuals on nontreatment days. Thus, individuals high in depressive symptoms reported continuously high levels of fatigue, which appeared to be no longer directly affected by the HD treatment. By contrast, low-depressed individuals were less tired than high-depressed individuals but showed a marked increase in fatigue after HD treatment. This may be seen as an adaptive response by inducing rest to conserve energy and thus allow recovery to take place.[36] These findings are in line with the recently proposed biopsychosocial model of fatigue in ESKD.[19] That is, fatigue symptoms may initially be triggered by chemical imbalances or may be caused by HD treatment itself but may eventually be perpetuated by other factors such as depressive mood. To the extent that depressive mood contributes to the maintenance of fatigue in HD patients, interventions aimed at decreasing depressive symptoms may also be effective in alleviating fatigue. An interesting hypothesis is that successful treatment of depression may lead to a pattern similar to what was found in low depressed individuals in this study, where fatigue increases after HD treatment but is less present before treatment or on nontreatment days.

Third, to assess fatigue as a classically conditioned response, we used a different approach to that used by Bovbjerg and colleagues.[23] In their study, patients were followed from the start of treatment onward, and evidence for a conditioned fatigue response was inferred from an increase in prechemotherapy fatigue over the course of treatment. In our study sample, however, prevalent HD patients were recruited, with a median dialysis vintage of 48 months, so an increase in pretreatment fatigue over the course of our study was not to be expected. Therefore, we chose an alternative approach that consisted of comparing fatigue on a treatment day to fatigue on nontreatment days. To the extent that the hospital environment—through repeated pairings with hemodialysis and ensuing fatigue increase—had effectively become a conditioned stimulus for fatigue, one would predict higher levels of fatigue in this environment relative to other environments that have not been paired with treatment. Results are in line with this prediction, thereby providing preliminary clinical evidence for fatigue as a conditioned response in individuals undergoing HD treatment.

However, some caution is warranted when interpreting these results as they allow alternative explanations. For instance, coming to the hospital (e.g., by means of transport) may require effort that also leads to increases in fatigue that do not necessarily require an explanation in terms of classical conditioning (but neither would it oppose such explanation, in that transport before treatment may also become a conditioned stimulus). However, given that most individuals in our sample engaged in professional or social activities on nontreatment days, it is unlikely that results should be explained solely in terms of day-dependent levels of activity or effort. Similar to Bovbjerg's study, future studies could include incident dialysis patients, which would allow assessing classical conditioning in terms of an increase in pretreatment fatigue over the course of treatment. Future studies could also investigate the extent to which other conditioned responses than fatigue may develop. For instance, through repeated pairings with HD treatment, the hospital environment may not only trigger fatigue as a conditioned response but also (and perhaps even more likely) as learned responses such as the expectancy of fatigue, and fear of fatigue to the extent that fatigue is experienced as an aversive symptom. Based on the literature on placebo and nocebo responses, it follows that the expectancy of fatigue may contribute to the fatigue experience.[37] Moreover, anxious anticipation of fatigue may be associated with stress responses that may also increase fatigue.

This study adds to the existing literature by capturing the diurnal variability of fatigue by means of repeated measurements in the context of daily life. However, some limitations should be highlighted. First, because patients completed the fatigue diary without supervision, we could only assess compliance in terms of responses completed, but not in terms of the requested time of day of those responses. Future studies using EMA procedures incorporated into a Web-application that record time stamps for each response can control for this.[14] Second, we did not differentiate between different fatigue qualities such as mental or physical fatigue. Third, this was a single-center study with a rather small study sample that was followed for a period of one week. The generalizability of this study needs to be confirmed in future research. Fourth, we cannot draw any conclusions about a causal relationship between fatigue and depressive mood because our study design does not allow causal inferences.

Future studies using EMA procedures might help to better understand the course and development of fatigue in HD patients, the relation to hemodialysis treatment, and the association with other factors. In addition, this opens a window for psychological intervention studies to assess the effect on fatigue in HD patients by improving their mood, or vice versa.

Disclosures and Acknowledgments

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There are no conflicts of interest.

Ethical approval: The local ethics committee approved the study protocol (13,615/18—22,147/18). All participants gave their informed consent.

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Appendix

Supplemental Table 1
Correlation Analyses Between the Mean of All Eight Momentary Fatigue Ratings and Demographical, Clinical, and Laboratory Variables ($N = 48$)

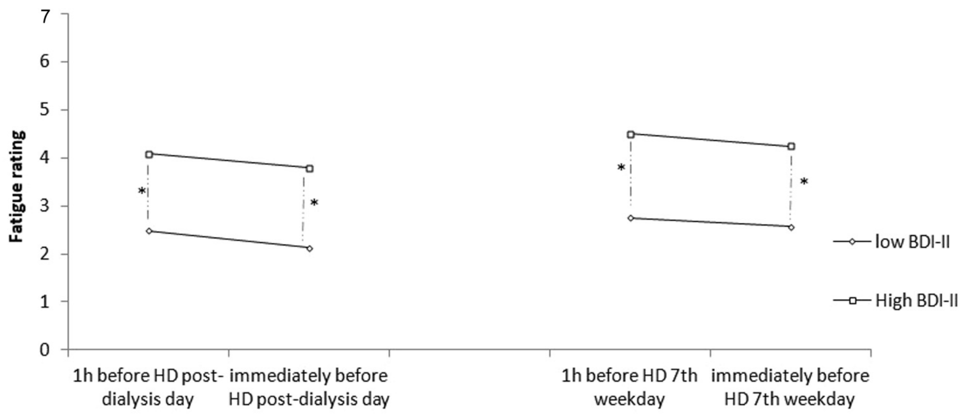
	Mean of All Eight Momentary Fatigue Ratings	
Variable	r	P
Age	0.200	0.173
ADL	−0.036	0.809
TIRD (minutes)	0.385[a]	0.007
Dialytic age	0.249	0.088
Hours HD/week	0.060	0.686
Kt/V	0.040	0.825
Hemoglobin g/dL	0.223	0.136
Calcium mg/dL	0.139	0.356
Creatinine mg/dL	−0.198	0.187
Sodium serum mmol/L	−0.045	0.768
Phosphorus mg/dL	−0.168	0.263
PTH pg/mL	−0.073	0.634

ADL = activity of daily living; TIRD = time of recovery after dialysis; Kt/V = urea clearance; PTH = parathyroid hormone.
Mean (+SD) of all eight momentary fatigue ratings: 3.96 (2.14).
A one way ANOVA with the following variables was computed: 1) Sex: $F(1, 47) = 2.543$, $P = 0.124$, partial $\eta^2 = 0.051$; 2) morning-afternoon dialysis session: $F(1, 47) = 1.334$, $P = 0.254$, partial $\eta^2 = 0.028$.
[a]$P < 0.01$.

Supplemental Table 2
Fatigue Difference Between High- and Low-Depressed Individuals on Nontreatment Days

	Low BDI-II Mean (SE)	High BDI-II Mean (SE)
Postdialysis Day		
One hour before HD	2.48 (0.45)	4.08 (0.63)
Immediately before HD	2.13 (0.42)	3.79 (0.63)
Seventh Weekday		
One hour before HD	2.75 (0.50)	4.50 (0.53)
Immediately before HD	2.57 (0.50)	4.24 (0.60)

Beck Depression Inventory-II (BDI-II) score (low ≤ 13, high > 14). On the postdialysis day at exactly the same time point as one hour before HD on the treatment day, patients with depressive symptoms experienced a higher fatigue level (M = 4.08, SE = 0.63) than patients without depressive symptoms according to the BDI-II (M = 2.48, SE = 0.45). This difference was significant, $t(47) = -2.09$, $P = 0.044$. The same was found one hour later corresponding to the time point immediately before dialysis on the treatment day, with $t(46) = -2.20$, $P = 0.034$ (*Supplemental Fig. 1*: *$P < 0.05$).
On the seventh weekday, at the same time points as one hour before and immediately before HD on the treatment day, patients with depressive symptoms experience higher fatigue levels (M = 4.50, SE = 0.53 and M = 4.24, SE = 0.60, respectively) than patients without depressive symptoms (M = 2.75, SE 0.50 and M = 2.57, SE = 0.50). These differences were also significant with $t(46) = 0.239$, $P = 0.021$ and $t(46) = -2.12$, $P = 0.040$ (*Supplemental Fig. 1*: *$P < 0.05$). Noteworthy, an additional correlation was found between BDI-II score and age in our patient group ($r = 0.369$, $P = 0.008$). The older the patients were, the more they experienced depressive symptoms.



Supplemental Fig. 1. Fatigue rating in high- and low-depressed individuals on nontreatment days.

Fatigue Severity Scale

Data________ **Nome_____________**

1: Fortemente in disaccordo
7: Fortemente d'accordo

Legga e segni un numero	**Fortemente in disaccordo → Fortemente d'accordo**
1. La mia motivazione è più bassa quando mi sento affaticato	1 2 3 4 5 6 7
2. L'esercizio aumenta il mio senso di fataica	1 2 3 4 5 6 7
3. Mi affatico facilmente	1 2 3 4 5 6 7
4. Il senso di fatica interferisce con il mio funzionamento fisico	1 2 3 4 5 6 7
5. Il senso di fatica mi provoca frequenti problemi.	1 2 3 4 5 6 7
6. Il mio senso di fatica impedisce il mio funzionamento fisico sostenuto	1 2 3 4 5 6 7
7. Il senso di fatica interferisce con la realizzazione di alcune mansioni e responsabilità	1 2 3 4 5 6 7
8. Il senso di fatica è tra i miei sintomi più invalidanti.	1 2 3 4 5 6 7
9. Il senso di fatica interferisce con il mio lavoro, la mia famiglia e la mia vita sociale.	1 2 3 4 5 6 7