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# Amelioration of fatigue in chronic dialysis patients with dialysis solution employing electrolyzed water containing molecular hydrogen (H<sub>2</sub>) and its association with autonomic function balance

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## Abstract

**Background:** Enhanced oxidative stress is involved with fatigue in hemodialysis (HD) patients. Molecular hydrogen (H<sub>2</sub>) could improve the redox status. Thus, the study examines whether HD solution rendered by electrolyzed water containing H<sub>2</sub> (E-HD) could impact the fatigue and autonomic balance of patients.

**Methods:** This single-arm, prospective observational study examined 95 patients on chronic HD (54 males; mean age and HD duration; 71.4 years and 10.6 years). Fatigue status on HD and HD-free days was compared between control HD (CHD) and 8 weeks after commencement of E-HD, using a visual analog scale (VAS) and an original scale. Autonomic balance was analyzed with the degree of activities of the sympathetic and parasympathetic nervous system via frequency analysis of a continuous beat interval.

**Results:** Patients were classified into three groups according to the presence of subjective fatigue during the period of CHD: Group A (40.0%), fatigue only on HD days; Group B (11.6%), presence of fatigue on both HD and HD-free days; and Group C (48.4%), freedom from fatigue. During the 8-week observation period of E-HD, VAS scores were significantly decreased on HD days in Group A, while Group B showed no significant changes in VAS on HD days, but significant decreases on HD-free days. No consistent changes were found in Group C. Significant increases in percentages of patients who reported absence of fatigue were seen in Group A on HD days and in Group B on HD-free days in week 8. Regarding changes in autonomic balance parameters after E-HD commencement, a positive correlation was identified between changes in VAS and autonomic balance in Group A.

**Conclusion:** E-HD may ameliorate fatigue in patients with subjective symptoms on HD and HD-free days. The influence of autonomic balance by E-HD and its impact on fatigue needs to be elucidated.

**Keywords:** Dialysate, Biocompatibility, Oxidative stress, Quality of life, Molecular hydrogen, Dialysis fatigue

## Introduction

Fatigue is one of the most serious problems encountered by patients receiving chronic dialysis. Fatigue among those patients is closely related to low quality of life (QOL) [1–3] and constitutes an independent risk factor

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for patient survival [4–6]. Amelioration of fatigue in dialysis patients is thus a crucial issue. Multiple background factors affect the presence of fatigue, including medical factors (such as aging, anemia, malnutrition, inflammation, and comorbidities) and psychosocial factors (such as working status, socioeconomic status, and depression) [1, 7–12]. Various approaches have been trialed to address fatigue among dialysis patients, including use of erythropoietin-stimulating agents, supplementation with carnitine, exercise during dialysis, and intensive, short daily or nocturnal dialysis sessions [13–17]. However, clinically effective measures to suppress fatigue have not been established.

Bio-incompatibility of the dialysis system could be involved in the development of fatigue through the mechanism of enhanced oxidative stress during hemodialysis (HD) [18, 19]. In patients with cancer, enhanced oxidative stress via mechanisms such as reactive oxygen species, activation of the sympathetic nervous system, and disturbance of the balance between the sympathetic and parasympathetic nervous systems can result in fatigue development [20]. Changes in autonomic balance are commonly seen in dialysis patients [21]. This may indicate a causative relationship among oxidative stress, autonomic imbalance, and development of fatigue in HD patients.

An HD system employing electrolyzed water containing molecular hydrogen ( $H_2$ ) (E-HD system) has been developed to improve the biocompatibility of HD [22–26]. Oxidative stress is reportedly ameliorated using the

E-HD, such as an increase in the reduced/oxidized serum albumin ratio from a single HD session [27, 28], along with amelioration of fatigue in chronic HD patients [29]. The aim of the present study was thus to examine the influence of the E-HD system on fatigue and its association with autonomic balance.

## Materials and methods

### Patients

Participants comprised patients on regular dialysis therapy who were treated at Inoue Hospital (Osaka, Japan) between October 2019 and May 2020. All patients had been receiving standard HD ( $n=62$ ) or online hemodiafiltration (HDF) (pre-dilution;  $n=33$ ) regularly three times a week for 4–5 h/session, using a high-performance membrane dialyzer. As of the end of November 2019, E-HD was introduced for all patients and was provided regularly thereafter.

Patient characteristics are shown in Table 1. The 95 patients (54 males and 45 females) had a mean age of 71.4 years, and mean duration of HD was 10.6 years. Twenty-nine patients (30.5%) had diabetes, and 19 patients (20.0%) had a history of cardiovascular disease.

Informed consent was obtained from all participants, and the study protocol was fully approved by the Ethics Review Committee at St Luke's International Hospital (approval date: June 19, 2019; research number: 18-RZ013). All methods were performed in accordance with the relevant guidelines and regulations.

**Table 1** Patients demographics

	Group-A HD-responsive type	Group-B chronic type	Group-C fatigue-free type	P
N	38 (40.0%)	11 (11.6%)	46 (48.4%)	
Age (years)	71.2 ± 8.8	66.9 ± 11.4	72.7 ± 9.8	NS
Male (%)	19 (50.0%)	5 (45.5%)	30 (65.2%)	NS
HD vintage (years)	11.4 ± 10.1	19.4 ± 12.6	7.8 ± 7.8	0.001 A versus C: 0.001 B versus C: 0.045
Modality (HD/OLHDF)	22/16	9/2	31/15	NS
Presence of DM	9 (23.7%)	2 (18.2%)	18 (39.1%)	NS
Body weight (kg)	54.8 ± 13.8	50.4 ± 11.5	55.3 ± 10.8	NS
SBP and DBP (mmHg) before HD	137 ± 20 73 ± 13	142 ± 38 75 ± 19	141 ± 25 76 ± 16	NS NS
UF volume/session (kg)	2.6 ± 0.8	2.0 ± 0.8	2.3 ± 0.8	NS
History CVD	5 (13.2%)	4 (36.4%)	10 (21.7%)	
Creatinine (mg/dL)	9.5 ± 2.0	8.6 ± 1.5	9.6 ± 2.2	NS
Hemoglobin (g/dL)	11.1 ± 1.2	11.4 ± 0.7	11.3 ± 1.2	NS
Albumin (g/dL)	3.41 ± 0.26	3.25 ± 0.34	3.42 ± 0.32	NS

HD hemodialysis, OLHDF online hemodiafiltration, DM diabetes mellitus, SBP systolic blood pressure, DBP diastolic blood pressure, UF ultrafiltration, NS not significant

### Assessments of fatigue

Patient fatigue was evaluated using both a visual analog scale (VAS) and our own original fatigue scale [29, 30] (Fig. 1). All questionnaires were provided in written format. The VAS is a unidimensional scale with the left end anchored to “no tiredness at all (0)” and the right end to “complete exhaustion (10).” Our original fatigue scale is a four-grade self-evaluation by the patient: Grade 1, no fatigue, patient acts in the ordinary way without any sense of fatigue; Grade 2, mild fatigue, patient acts in the ordinary way, but feels tired; Grade 3, moderate fatigue, patient feels tired even with light work; and Grade 4, intense fatigue, patient feels very tired and falls asleep.

Assessments of fatigue were performed by all patients at four time points: during HD within 2 weeks before commencement of E-HD (control HD [CHD] phase) and at 2 weeks, 4 weeks, and 8 weeks after commencing E-HD (E-HD phase). Assessments of fatigue were made on both HD day and HD-free day of the HD day at randomly selected at the week in both the CHD and E-HD phases. Cutoff VAS scores for the presence of substantial fatigue were based on analysis of the receiver operating characteristic (ROC) curve, in which fatigue with decreased activities of daily living was defined as Grade  $\geq 3$  on our original fatigue scale.

### Assessment of autonomic functions

The autonomic nervous system function of participants was used as an objective measure of fatigue using the Fatigue Stress Measurement System (VM500; Fatigue Science Laboratory, Osaka, Japan) [31]. The VM500 is an autonomic nerve function measurement device that simultaneously measures pulse waves and electrocardiographic waveforms. In this test, heart rate variability in the resting state was recorded for 90 s under post-HD conditions. Heart rate measurements showing a > 10% rate of misdetection of R waves among total beats were considered unreliable and discarded from analysis. Regarding autonomic nerve function measurement, for the power spectral density gained via frequency analysis of a continuous beat interval, the integration of low-frequency (LF) components from the 0.04- to 0.15-Hz frequency band generally represents the degree of sympathetic nervous system activity. The integration of high-frequency (HF) components of the 0.15- to 0.4-Hz band generally represents the degree of activity of the parasympathetic nervous system. The LF/HF ratio thus represents the balance between sympathetic and parasympathetic nervous system activity.

#### Q.1

Please indicate your response by ticking one box for the question.

In the previous hemodialysis day (HD day), and the next day of hemodialysis (HD-free day), How did you feel tired?

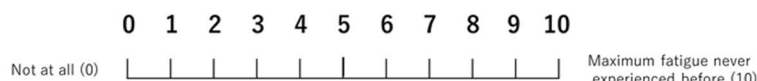
Grade	HD day	HD-free day
1. I did not feel tired at all, and I acted in the ordinary way.	<input type="checkbox"/>	<input type="checkbox"/>
2. I felt mildly tired, but I acted in the ordinary way.	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt tired even with light work.	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt very tired, and fell asleep.	<input type="checkbox"/>	<input type="checkbox"/>

#### Q.2

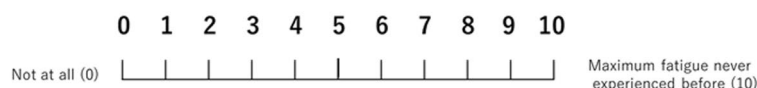
Please indicate your response by marking on the scale.

In the previous hemodialysis day (HD day), and the next day of hemodialysis (HD-free day), How did you feel tired?

(A) HD day



(B) HD-free day



**Fig. 1** Questionnaire on fatigue employed in the study

### Overview of the E-HD system [32]

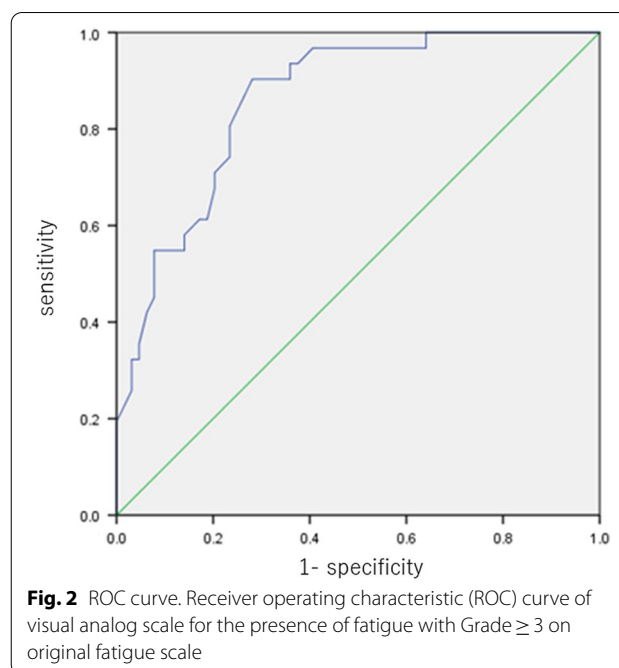
Briefly, E-HD solutions were prepared as follows: Tap water was supplied to the electrolyzed water-hemodialysis system (Trim Medical Institute Co., Osaka, Japan), where water was processed using activated charcoal filtration and water softening and then electrolyzed by direct current supply to the anode and cathode electrode plates. Water on the anode side was drained, and water from the cathode side (electrolyzed water) was collected to supply the reverse osmosis module. The intensity of electrolysis was adjusted to the target  $H_2$  concentration. Reverse osmosis water containing  $H_2$  produced by the electrolyzed water-hemodialysis system was supplied to prepare the HD solution. The composition of the inflow E-HD solution was the same as the CHD solution, with the exception of the presence of dissolved  $H_2$  in the E-HD, with no differences in terms of electrolyte levels or pH [24, 25, 27].  $H_2$  levels in dialysate were within the range of 120–163 ppb.

### Analysis

Variables are expressed as mean  $\pm$  standard deviation (SD) or median (min, max), as appropriate. Statistical significance was set at the level of  $p < 0.05$ . On multivariate analysis, several confounding factors reported to be associated with fatigue in dialyzed patients, including age, sex, dialysis duration, blood pressure before dialysis, ultrafiltration volume (UV) by HD, hemoglobin (Hb), and serum albumin, were included. Comparisons between groups were performed using the paired t-test and non-parametric Wilcoxon paired rank test. Time courses were analyzed using repeated-measures analysis of variance and the Bonferroni procedure for multiple comparisons. All statistical analyses were performed using SPSS, version 22.0 (STATA Corporation, College Station, TX, USA).

### Results

According to the ROC for the presence of substantial fatigue (defined as Grade  $\geq 3$  on our original fatigue scale) on the HD day in the CHD phase, we defined patients with VAS  $\geq 4$  as presenting with fatigue (the cutoff level of VAS: 4.2; sensitivity: 90.3%; specificity: 71.9%; Fig. 2). As a result, 38 patients (40.0%; Group A) were defined as HD-responsive type (presence of fatigue on HD day and absence of fatigue on HD-free day), 11 patients (11.6%; Group B) as chronic type (presence of fatigue on both HD and HD-free days); and 46 patients (48.4%; Group C) as fatigue-free type (absence of fatigue on both HD and HD-free days). No significant differences in patient profiles were seen among the three groups, except for longer dialysis vintage in Group B (Table 1). We examined the possible contributing factors for the VAS score and the

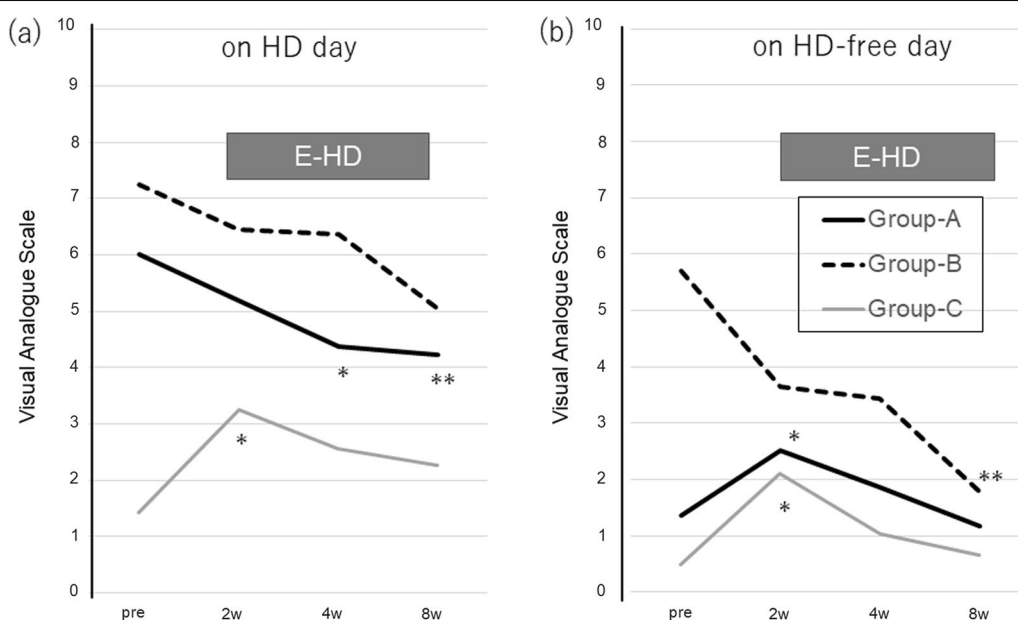


**Fig. 2** ROC curve. Receiver operating characteristic (ROC) curve of visual analog scale for the presence of fatigue with Grade  $\geq 3$  on original fatigue scale

presence of fatigue (VAS  $\geq 4$ ) at baseline data. In multiple regression analysis (stepwise method), HD vintage and male gender were identified as significant factors for the basal VAS score (HD vintage:  $R = 0.341$ ,  $p = 0.002$ ; male:  $R = -0.258$ ,  $p = 0.019$ , respectively) after adjusting for the possible confounding factors, such as age, albumin, hemoglobin, and LF/HF. In multiple logistic regression analysis, only male gender was identified as a significant factor for the basal absence of fatigue (VAS  $\geq 4$ ) (OR: 3.067; 95% CI 1.186–7.933,  $p = 0.021$ ) after adjusting for the possible confounding factors, such as age, albumin, hemoglobin, and LF/HF.

During the 8-week observation periods, Group A showed a significant decrease in VAS scores as a function of treatment time on the HD day, while Group B showed a significant decrease in VAS scores as a function of treatment time on the HD-free day (Fig. 3). Primarily significant differences in VAS scores were evident between Group A/B and Group C on HD days and between Groups B and C on HD-free days during the 8-week course. With respect to patient-reported outcomes using our original fatigue scale at 8 weeks, significant increases in the number of patients who reported absence of fatigue were seen in Group A on the HD day and in Group B on the HD-free day, as compared with the CHD phase ( $p < 0.05$  each) (Table 2).

Regarding autonomic balance, data were available in 68 cases among 95 patients (28 in Group A, 7 in Group B, and 33 in Group C) who agreed to the examinations. No significant changes in logLF, logHF,



**Fig. 3** Serial changes in visual analog scale scores for fatigue on dialysis day (a) and dialysis-free day (b). \* $p < 0.05$  versus Pre; \*\* $p < 0.01$  versus Pre VAS on HD day (mean  $\pm$  SD), Group-A:  $6.0 \pm 1.4$  (pre),  $5.2 \pm 2.2$  (2w),  $4.3 \pm 2.8$  (4w),  $4.2 \pm 2.7$  (8w); Group-B:  $7.2 \pm 1.6$  (pre),  $6.4 \pm 1.2$  (2w),  $6.3 \pm 1.9$  (4w),  $5.0 \pm 3.0$  (8w); Group-C:  $1.4 \pm 1.5$  (pre),  $3.2 \pm 2.5$  (2w),  $2.5 \pm 2.2$  (4w),  $2.2 \pm 2.4$  (8w). Comparisons, pre: A versus C; B versus C:  $p < 0.001$ , respectively; 2w: A versus C:  $p = 0.001$ , B versus C:  $p < 0.001$ ; 4w: A versus C:  $p = 0.002$ , B versus C:  $p < 0.001$ ; 8w: A versus C:  $p = 0.003$ , B versus C:  $p = 0.006$ . VAS on HD-free day (mean  $\pm$  SD), Group-A:  $1.3 \pm 1.0$  (pre),  $2.5 \pm 1.9$  (2w),  $1.8 \pm 2.1$  (4w),  $1.1 \pm 1.4$  (8w); Group-B:  $5.7 \pm 1.6$  (pre),  $3.6 \pm 1.9$  (2w),  $3.4 \pm 2.3$  (4w),  $1.7 \pm 2.1$  (8w); Group-C:  $0.4 \pm 0.7$  (pre),  $2.1 \pm 1.9$  (2w),  $1.0 \pm 1.1$  (4w),  $0.6 \pm 1.0$  (8w). Comparisons, pre: A versus C; A versus B; B versus C:  $p < 0.001$ , respectively; 2w: NS; 4w: B versus C:  $p < 0.001$ , A versus B:  $p = 0.034$ ; 8w: B versus C:  $p = 0.040$

**Table 2** Changes of fatigue grade on HD day and HD-free day in respective groups

Group: fatigue grade	HD day			HD-free day		
	Pre N (%)	8w	p value	Pre N (%)	8w	p value
A:1 (none)	4 (10.5)	11 (28.9)	< 0.05	31 (81.6)	30 (78.9)	NS
A:2 (mild)	16 (42.1)	13 (34.2)		6 (15.8)	8 (21.1)	
A:3 (moderate)	14 (36.8)	9 (23.7)		1 (2.6)	0 (0.0)	
A:4 (intense)	4 (10.5)	5 (13.2)		0 (0.0)	0 (0.0)	
B:1 (none)	0 (0.0)	0 (0.0)	NS	0 (0.0)	8 (72.7)	< 0.05
B:2 (mild)	1 (9.1)	1 (9.1)		4 (36.4)	3 (27.3)	
B:3 (moderate)	3 (27.3)	6 (54.5)		6 (54.5)	0 (0.0)	
B:4 (intense)	7 (63.6)	4 (36.4)		1 (9.1)	0 (0.0)	
C:1 (none)	31 (67.4)	33 (73.3)	NS	41 (91.3)	40 (88.9)	NS
C:2 (mild)	12 (26.1)	7 (15.6)		3 (8.7)	4 (8.9)	
C:3 (moderate)	3 (6.5)	4 (8.9)		0 (0.0)	1 (2.2)	
C:4 (intense)	0 (0.0)	1 (2.2)		0 (0.0)	0 (0.0)	

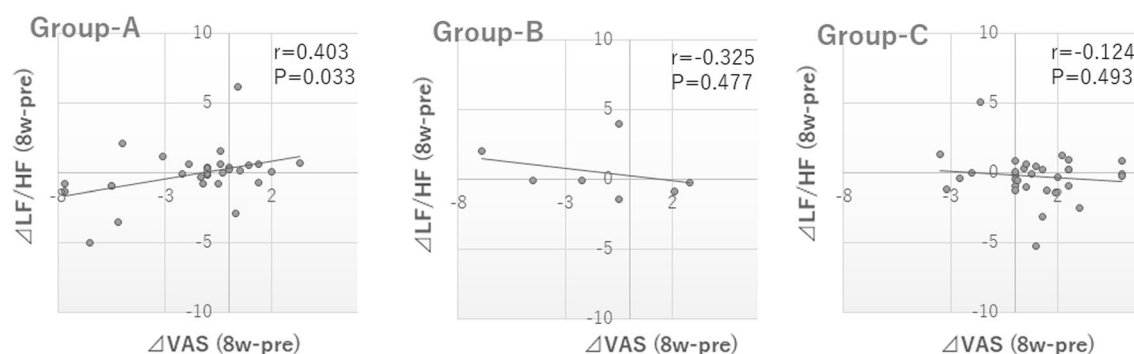
log(LF + HF), or LF/HF were apparent between CHD and E-HD phases in each group (Table 3). Changes in VAS and LF/HF between CHD and E-HD phases were calculated as:  $\Delta$  = value in E-HD phase (8w)—value in

CHD phase. A mild but significant positive correlation was seen between  $\Delta$ VAS and  $\Delta$ LF/HF in Group A ( $r = 0.403$ ,  $p < 0.05$ ) (Fig. 4).



**Table 3** Comparisons of autonomic balance between control and E-HD phase in respective groups

N	All patients			Group-A			Group-B			Group-C		
	68			28			7			33		
	pre	8w	p	pre	8w	p	pre	8w	p	pre	8w	p
Log (HF)	1.94±0.80	2.03±0.74	0.412	1.99±0.77	2.08±0.78	0.620	2.00±0.97	1.51±0.67	0.175	1.89±0.82	2.09±0.70	0.132
Log (LF)	1.74±0.74	1.75±0.80	0.916	1.72±0.73	1.81±0.83	0.566	1.82±0.92	1.25±0.77	0.166	1.74±0.75	1.81±0.77	0.631
Log (HF + LF)	2.22±0.73	2.27±0.71	0.558	2.26±0.69	2.33±0.74	0.660	2.24±0.94	1.80±0.62	0.162	2.18±0.74	2.33±0.67	0.243
LF/HF	1.17±1.38	1.05±1.50	0.582	1.22±1.63	1.12±1.78	0.789	0.79±0.47	1.27±1.57	0.520	1.21±1.30	0.95±1.25	0.359
LogLF/LogHF	0.94±0.34	0.87±0.35	0.173	0.90±0.32	0.88±0.36	0.717	0.92±0.11	0.83±0.54	0.713	0.97±0.39	0.87±0.29	0.183

**Fig. 4** Correlations between changes in autonomic balance and visual analog scale of fatigue

## Discussion

Fatigue is one of the most prevalent subjective symptoms among dialysis patients, reported in 40–80% [1, 2], and is associated with decreased QOL in patients. However, with respect to the degree of daily and weekly fluctuations in fatigue among HD patients, exact data remain lacking, although fatigue time has been examined [33, 34]. In the present study, we administered the questionnaire regarding the degree of fatigue on both HD and HD-free days separately. In terms of fatigue presentation, patients were classified into three groups: Group A (40.0%), presence of fatigue only on the HD day; Group-B (11.6%), presence of fatigue on both HD and HD-free days; and Group C (48.6%), freedom from fatigue. Thus, two types of fatigue symptoms exist, as reported elsewhere [35–37]. One is fatigue that develops with HD and subsides thereafter and has commonly disappeared by the day after HD (HD-responsive type), and the other is fatigue that exists continuously irrespective of HD performance (chronic type). In the present study, 77.5% of fatigue patients were classified into the former type and the remaining 22.5% into the latter type. While various factors associated with fatigue in dialysis patients have been identified, HD vintage was the only different background characteristic in the chronic type (Group B) in the present study. In analysis of contributing factors for

fatigue, HD vintage and gender difference were identified. The pathological roles of these factors for fatigue are unknown. Regarding the causal possibility, we speculate that long-term HD vintage along with aging of patients may be associated with frailty, malnutrition, and depressive state, which could develop chronic fatigue. But this remains to be elucidated. Regarding the impact of female gender, there were several studies which pointed out female as risk of dialysis-related fatigue [38]. Since no significant differences were found in serum albumin, hemoglobin, blood pressure, or body weight in the study, the present results underlined the potential issue of psychological/mental factors in dialysis patients [12], which we think needs to be clarified, especially with respect to gender differences.

Regarding the influence of E-HD on fatigue in patients during the 8-week observation period, VAS scores were significantly decreased on HD day in Group A, while no significant changes in VAS were seen on HD-free day. Conversely, significant decreases in VAS were found on HD-free day in Group B. We have recently reported that HD-responsive fatigue is related to the enhancement of oxidative stress during HD, and E-HD could ameliorate the degree of fatigue as well as oxidative stress [32]. The present results, specifically regarding the significant decrease in VAS scores for Group A, support the

interpretation of previous findings. On the other hand, the present data did not confirm clinical benefits of E-HD in patients who presented with chronic fatigue (Group B). Taking together the observations that VAS tended to decrease on HD day and VAS was significantly decreased on HD-free day, we suppose that the enhanced oxidative stress could, at least in part, be involved with the development of fatigue. Further long-term observations are needed to reach definitive conclusions regarding the effects of E-HD in this clinical type.

In non-HD subjects, the balance of sympathetic and para-sympathetic nervous system activities, as LF/HF ratio, could provide a clinical indicator of fatigue status [39]. That is, the higher the ratio, the higher the degree of fatigue. Although LF/HF is lower in HD patients than in healthy non-HD cases, autonomic nervous imbalances in chronic HD patients are reported to be closely related to lower QOL and lower performance status, indicating potential associations of autonomic imbalance with fatigue [40]. We therefore examined autonomic balance in the CHD phase and in the 8th week of the E-HD phase. No significant changes were noted in autonomic balance parameters in any groups. Interestingly, however, a positive correlation was identified between change in VAS and LF/HF ratio after E-HD in Group A, indicating a possible causative relationship between change in autonomic balance and change in fatigue for HD-responsive cases. Bio-incompatibility represents the bio-reaction between dialysis materials and peripheral blood, and myeloperoxidase release during HD could play a crucial role in the development of oxidative stress by HD [41]. Reactive oxygen species activate sympathetic activities in brain, leading to imbalances in autonomic function status [42]. E-HD could ameliorate such oxidative stress during HD and might thus influence autonomic balance. This speculation needs to be verified in a large number of patients as a next step.

Several limitations to the present study need to be kept in mind. First, the study was an observational study with a single-arm, non-blinded, and lacked a control group. In order to give concrete conclusion, it is apparent that we need randomized controlled study, with blinded style. Second, we classified patients into three groups according to a cutoff VAS of  $\geq 4$  to reflect the presence of substantial fatigue based on patient reports from our original scale. We have previously confirmed a positive correlation between results from this scale and other scales, such as VAS and fatigue scale [30]. The scale has not been fully validated, but the proposed fatigue scale from the SONG-Fatigue group is defined as the absence of fatigue according to patient-reported outcomes [3], quite similar to our original scale. Third, autonomic function testing was not performed in all patients. Those patients who

were consented to undergo testing after finishing regular dialysis were examined. Various kinds of patient bias could not be excluded. Fourth, the number of patients in Group B was too small to reach conclusions on changes to autonomic balance. To reach conclusions on the precise effects of E-HD, randomized controlled study needs to be undertaken in future.

Finally, as to the current status of E-HD penetration in Japan, it is estimated that the number of patients who are regularly treated by this system has exceeded 2000 as of April 2021 in Japan (personal communications). Until now, we have not experienced or received reports of any adverse events which might have connected with the E-HD. Therefore, we think E-HD could be safety applicable in the daily clinical practice. At present situation, cost of implementing E-HD system is higher than that of the standard RO system. But we hope that the reduced cost would be achieved through the process of E-HD becoming popular as a standard system in Japan in near future.

## Conclusion

The present results show that E-HD could substantially ameliorate fatigue in HD patients who present with subjective symptoms on HD and/or HD-free days, and could benefit from improvements in patient QOL. The influence of autonomic balance by E-HD and its impact on fatigue needs to be elucidated.

## Abbreviations

HD: Hemodialysis; H<sub>2</sub>: Molecular hydrogen; C-HD: Control hemodialysis; E-HD: Hemodialysis using electrolyzed water containing H<sub>2</sub>; VAS: Visual analog scale; LF: Low-frequency components from the 0.04- to 0.15-Hz frequency band; HF: High-frequency components from the 0.15- to 0.4-Hz frequency band.

## Acknowledgements

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## Authors' contributions

YT, SK, KS, YW, YN, and MN designed the study. DK, YW, and MN analyzed the data. MN drafted the manuscript. YT collected and entered data. DK, YW, and MN contributed to the data acquisition and interpretation. YT, SK, MM, and YN reviewed the draft. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study protocol was fully approved by the Ethics Review Committee at St. Luke's International Hospital (approval date: June 19, 2019; research number: 18-RZ013) and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants.

**Consent for publication**

Not applicable.

**Competing interests**

SK is an employee of Nihon Trim Co., Ltd., and SK, MM, and MN are belonging to the Research Division of Tohoku University (cooperative research division with Nihon Trim Co., Ltd.).

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**References**

- Jhamb M, Weisbord SD, Steel JL, et al. Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. *Am J Kidney Dis*. 2008;52:353–65.
- Ju A, Unruh ML, Davison SN, et al. Patient-reported outcome measures for fatigue in patients on hemodialysis: a systematic review. *Am J Kidney Dis*. 2018;71:327–43.
- Ju A, Teixeira-Pinto A, Tong A, Smith AC, Unruh M, Davison SN, Daputo J, Dew MA, Fluck R, Germain MJ, Jassal SV, Obrador GT, O'Donoghue D, Viecelli AK, Strippoli G, Ruospo M, Timofte D, Sharma A, Au E, Howell M, Costa DSJ, Anumudu S, Craig JC, Rutherford C. Validation of a core patient-reported outcome measure for fatigue in patients receiving hemodialysis: the SONG-HD fatigue instrument. *Clin J Am Soc Nephrol*. 2020;15(11):1614–21. <https://doi.org/10.2215/CJN.05880420>.
- Jhamb M, Pike F, Ramer S, et al. Impact of fatigue on outcomes in the hemodialysis (HEMO) study. *Am J Nephrol*. 2011;33:515–23.
- Bossola M, Di Stasio E, Antocicco M, et al. Fatigue is associated with increased risk of mortality in patients on chronic hemodialysis. *Nephron*. 2015;130:113–8.
- Koyama H, Fukuda S, Shoji T, et al. Fatigue is a predictor for cardiovascular outcomes in patients undergoing hemodialysis. *Clin J Am Soc Nephrol*. 2010;5:659–66.
- Jhamb M, Argyropoulos C, Steel JL, et al. Correlates and outcomes of fatigue among incident dialysis patients. *Clin J Am Soc Nephrol*. 2009;4:1779–86.
- Bossola M, Marzetti E, Di Stasio E, Monteburini T, Cenerelli S, Mazzoli K, Parodi E, Siroli V, Santarelli S, Ippoliti F, Nebiolo PE, Bonomini M, Melatti R, Vulpio C. Prevalence and associated variables of post-dialysis fatigue: results of a prospective multicentre study. *Nephrology (Carlton)*. 2018;23(6):552–8. <https://doi.org/10.1111/nep.13059>.
- Debnath S, Lorenzo C, Bansal S, Morales J, Rueda RO, Kasinath BS, Sharma K, O'Connor JC. Branched-chain amino acids depletion during hemodialysis is associated with fatigue. *Am J Nephrol*. 2020;51(7):565–71. <https://doi.org/10.1159/000507839>.
- Bossola M, Di Stasio E, Siroli V, Ippoliti F, Cenerelli S, Monteburini T, Parodi E, Santarelli S, Nebiolo PE, Bonomini M, Picca A, Calvani R, Marzetti E. Prevalence and severity of postdialysis fatigue are higher in patients on chronic hemodialysis with functional disability. *Ther Apher Dial*. 2018;22(6):635–40. <https://doi.org/10.1111/1744-9987.12705>.
- Tangvoraphonkhai K, Davenport A. Extracellular water excess and increased self-reported fatigue in chronic hemodialysis patients. *Ther Apher Dial*. 2018;22(2):152–9. <https://doi.org/10.1111/1744-9987.12648>.
- Bossola M, Luciani G, Tazza L. Fatigue and its correlates in chronic hemodialysis patients. *Blood Purif*. 2009;28(3):245–52. <https://doi.org/10.1159/000231985>.
- Johansen KL, Finkelstein FO, Revicki DA, Evans C, Wan S, Gitlin M, Agodoa IL. Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients. *Nephrol Dial Transplant*. 2012;27(6):2418–25. <https://doi.org/10.1093/ndt/gfr697>.
- Fukuda S, Koyama H, Kondo K, Fujii H, Hirayama Y, Tabata T, Okamura M, Yamakawa T, Okada S, Hirata S, Kiyama H, Kajimoto O, Watanabe Y, Inaba M, Nishizawa Y. Effects of nutritional supplementation on fatigue, and autonomic and immune dysfunction in patients with end-stage renal disease: a randomized, double-blind, placebo-controlled, multicenter trial. *PLoS ONE*. 2015;10(3):e0119578. <https://doi.org/10.1371/journal.pone.0119578> (eCollection 2015).
- Morfin JA, Fluck RJ, Weinhandl ED, Kansal S, McCullough PA, Komenda P. Intensive hemodialysis and treatment complications and tolerability. *Am J Kidney Dis*. 2016;68(5S1):S43–50. <https://doi.org/10.1053/j.ajkd.2016.05.021>.
- Salehi F, Dehghan M, Mangolian Shahrababaki P, Ebadzadeh MR. Effectiveness of exercise on fatigue in hemodialysis patients: a randomized controlled trial. *BMC Sports Sci Med Rehabil*. 2020;12:19. <https://doi.org/10.1186/s13102-020-00165-0> (eCollection 2020).
- Grigoriou SS, Krase AA, Karatzaferi C, Giannaki CD, Lavdas E, Mitrou GI, Bloxham S, Stefanidis I, Sakkas GK. Long-term intradialytic hybrid exercise training on fatigue symptoms in patients receiving hemodialysis therapy. *Int Urol Nephrol*. 2021;6:66. <https://doi.org/10.1007/s11255-020-02711-8>.
- Singh NP, Bansal R, Thakur A, Kohli R, Bansal RC, Agarwal SK. Effect of membrane composition on cytokine production and clinical symptoms during hemodialysis: a crossover study. *Ren Fail*. 2003;25(3):419–30. <https://doi.org/10.1081/jdi-120021154>.
- Brys ADH, Di Stasio E, Lenaert B, Sanguinetti M, Picca A, Calvani R, Marzetti E, Gambaro G, Bossola M. Serum interleukin-6 and endotoxin levels and their relationship with fatigue and depressive symptoms in patients on chronic haemodialysis. *Cytokine*. 2020;125: 154823. <https://doi.org/10.1016/j.cyto.2019.154823>.
- Tamada S, Ebisu K, Yasuda S, Kato M, Ninomiya N, Yamasaki T, Iguchi T, Nakatani T, Watanabe Y. Kamikihito improves cancer-related fatigue by restoring balance between the sympathetic and parasympathetic nervous systems. *Prostate Int*. 2018;6(2):55–60. <https://doi.org/10.1016/j.pnrl.2017.11.002>.
- Lai S, Bagordo D, Perrotta AM, Gigante A, Gasperini ML, Muscaritoli M, Mazzaferro S, Cianci R. Autonomic dysfunction in kidney diseases. *Eur Rev Med Pharmacol Sci*. 2020;24(16):8458–68. [https://doi.org/10.26355/eurrev\\_202008\\_22643](https://doi.org/10.26355/eurrev_202008_22643).
- Nakayama Masaaki, Shigeru Kabayama and Sadayoshi Ito The hydrogen molecule as antioxidant therapy: clinical application in hemodialysis and perspectives. *Renal Replacement Ther*. 2016;2:23.
- Nakayama M, Kabayama S, Terawaki H, et al. Less-oxidative hemodialysis solution rendered by cathode-side application of electrolyzed water. *Hemodial Int*. 2007;11:322–7.
- Nakayama M, Kabayama S, Nakano H, et al. Biological effects of electrolyzed water in hemodialysis. *Nephron Clin Pract*. 2009;112:c9–15.
- Nakayama M, Nakano H, Hamada H, et al. A novel bioactive haemodialysis system using dissolved dihydrogen (H<sub>2</sub>) produced by water electrolysis: a clinical trial. *Nephrol Dial Transplant*. 2010;25:3026–33.
- Namayama M, Itami N, Suzuki H, et al. Novel haemodialysis (HD) treatment employing molecular hydrogen (H<sub>2</sub>)-enriched dialysis solution improves prognosis of chronic dialysis patients: a prospective observational study. *Sci Rep*. 2018;8:254.
- Terawaki H, Zhu WJ, Matsuyama Y, et al. Effect of a hydrogen (H<sub>2</sub>)-enriched solution on the albumin redox of hemodialysis patients. *Hemodial Int*. 2014;18:459–66.
- Maeda K, Yoshizaki S, Iida T, Terada T, Era S, Sakashita K, Arikawa H. Improvement of the fraction of human mercaptalbumin on hemodialysis treatment using hydrogen-dissolved hemodialysis fluid: a prospective observational study. *Renal Replacement Ther*. 2016;2:42.
- Nakayama M, Itami N, Suzuki H, et al. Possible clinical effects of molecular hydrogen (H<sub>2</sub>) delivery during hemodialysis in chronic dialysis patients: Interim analysis in a 12 month observation. *PLoS ONE*. 2017;12:e0184535.



30. Maruyama Y, Nakayama M, Ueda A, Miyazaki M, Yokoo T. Comparisons of fatigue between dialysis modalities: a cross-sectional study. *PLoS ONE*. 2021;16(2):e0246890.
31. Mizuno K, Ojio D, Tanaka T, Minusa S, Kuriyama H, Yamano E, et al. Relationship between truck driver fatigue and rear-end collision risk. *PLoS ONE*. 2020;15(9):e0238738.
32. Satta H, Iwamoto T, Kawai Y, Koguchi N, Shibata K, Kobayashi N, Yoshida M, Nakayama M. Amelioration of hemodialysis-induced oxidative stress and fatigue with a hemodialysis system employing electrolyzed water containing molecular hydrogen. *Renal Replacement Ther*. 2021;7:37. <https://doi.org/10.1186/s41100-021-00353-9>.
33. Davenport A, Guirguis A, Almond M, et al. Postdialysis recovery time is extended in patients with greater self-reported depression screening questionnaire scores. *Hemodial Int*. 2018;22:369–76.
34. Alvarez L, Brown D, Hu D, et al. Intradialytic symptoms and recovery time in patients on thrice-weekly in-center hemodialysis: a cross-sectional online survey. *Kidney Med*. 2019;2:125–30.
35. Horigan AE, Barroso JV. A comparison of temporal patterns of fatigue in patients on hemodialysis. *Nephrol Nurs J*. 2016;43(2):129–38 (**quiz 139**).
36. Bossola M, Di Stasio E, Monteburini T, Parodi E, Ippoliti F, Bonomini M, Santarelli S, Eugenio Nebiolo P, Sirolli V, Cenerelli S. Intensity, duration, and frequency of post-dialysis fatigue in patients on chronic haemodialysis. *J Ren Care*. 2020;46(2):115–23. <https://doi.org/10.1111/jorc.12315>.
37. Sondergaard H. Fatigue while undergoing long-term hemodialysis. *Clin J Am Soc Nephrol*. 2020;15:1539–40. <https://doi.org/10.2215/CJN.14870920>.
38. Horigan AE. Fatigue in hemodialysis patients: a review of current knowledge. *J Pain Symp Manag*. 2012;44(5):715–24.
39. Mizuno K, Tanaka M, Yamaguti K, Kajimoto O, Kuratsune H, Watanabe Y. Mental fatigue caused by prolonged cognitive load associated with sympathetic hyperactivity. *Behav Brain Funct*. 2011;7:17. <https://doi.org/10.1186/1744-9081-7-17>.
40. Fujii H, Koyama H, Fukuda S, Tokai H, Tajima S, Koizumi J, Yamaguti K, Kuratsune H, Watanabe Y, Hirayama Y, Shoji T, Inaba M, Nishizawa Y. Autonomic function is associated with health-related quality of life in patients with end-stage renal disease: a case-control study. *J Ren Nutr*. 2013;23(5):340–7. <https://doi.org/10.1053/j.jrn.2012.12.008>.
41. Fukushi T, Yamamoto T, Yoshida M, Fujikura E, Miyazaki M, Nakayama M. Enhanced neutrophil apoptosis accompanying myeloperoxidase release during hemodialysis. *Sci Rep*. 2020;10(1):21747. <https://doi.org/10.1038/s41598-020-78742-z>.
42. Cruz JC, Flör AFL, França-Silva MS, Balarini CM, Braga VA. Reactive oxygen species in the paraventricular nucleus of the hypothalamus alter sympathetic activity during metabolic syndrome. *Front Physiol*. 2015;6:384. <https://doi.org/10.3389/fphys.2015.00384>.

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