Renal Replacement Therapy

Amelioration of hemodialysis-induced oxidative stress and fatigue with a hemodialysis system employing electrolyzed water containing molecular hydrogen

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Abstract

Background: A novel hemodialysis (HD) system employing electrolyzed water containing molecular hydrogen (E-HD) has been developed to improve the bio-compatibility of HD. This study examined the impact of E-HD on changes in redox state during HD and HD-related fatigue.

Method: This single-arm, prospective observational study examined 63 patients on chronic HD (41 males; mean age, 72 ± 9 years; median duration of HD, 7 years). Redox parameters (serum myeloperoxidase [MPO], malondialdehyde-protein adduct [MDA-a], thioredoxin 1 [TRX]) during HD were compared between control HD (C-HD) and E-HD after 8 weeks. Fatigue was evaluated using a numerical rating scale (NRS) during the 8-week course.

Results: In C-HD, an increase in serum MPO accompanied increases in both oxidative products (MDA-a) and anti-oxidant molecules (TRX). In E-HD, although increases in MPO were accentuated during HD, changes in MDA-a and TRX were ameliorated as compared with C-HD. In patients who showed HD-related fatigue (47%) during C-HD, change in MDA-a by HD was a risk factor for the presence of fatigue. During the 8 weeks of observation on E-HD, those patients displayed significant decreases in fatigue scores.

Conclusion: E-HD ameliorates oxidative stress and supports anti-oxidation during HD, suggesting improved bio-compatibility of the HD system. E-HD may benefit patients with HD-related fatigue, but the mechanisms underlying changes to oxidative stress have yet to be clarified.

Keywords: Hemodialysis, Biocompatibility, Oxidative stress, Molecular hydrogen, Dialysis-fatigue

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Background

The bio-incompatibility of hemodialysis (HD) systems, such as complement activation, enhanced expression of pro-inflammatory molecules from lymphocytes, activation of platelets, and degranulation of neutrophils, has been considered to be involved with excess comorbidities including cardio-cerebrovascular disease and HD-related complications [1, 2]. Current HD systems have made improvements to dialyzer materials and purification of dialysis water [3–5], but issues of bio-incompatibility have not yet been fully resolved. For example, blood levels of myeloperoxidase (MPO) still increase during HD [6–8]. MPO is thought to mediate the generation of radical oxygen species in the presence of H_2O_2, which in turn exaggerates oxidative stress [9–13].

Fatigue is a crucial issue for patients receiving chronic dialysis in terms of patient-reported outcomes [14, 15]. Fatigue affects the quality of life and patient survival [16–19]. The pathological background of fatigue in dialysis patients is complex, including causes such as aging, anemia, malnutrition, inflammation, depression, and autonomic dysfunction [14, 15, 20, 21]. On the other hand, in patients receiving HD, the degree of fatigue can differ according to the presence or absence of HD, such as exaggerated fatigue on the days of HD, and less or even no fatigue on non-HD days [20, 22]. This unique profile may indicate a potential role of HD bio-incompatibility in the development of fatigue in HD patients and suggests that enhanced oxidative stress could be involved with the pathological mechanisms.

A novel HD system employing electrolyzed water containing molecular hydrogen (H_2) (E-HD) has been developed to improve the bio-compatibility of HD [23–26]. Oxidative stress markers have already been reported to be suppressed with this system [24–26], and better clinical outcomes have been observed in patients on E-HD than in patients on standard HD [27], including the level of fatigue [28]. The aim of this study was thus to examine the impact of E-HD on changes in redox state during HD and HD-related fatigue.

Patients and methods

Patients

Patients comprised 63 patients on HD who were treated at Yokodai Central Clinic (Yokohama, Japan) between October 2019 and May 2020. All patients had been receiving standard HD regularly 3 times a week for 3–4 h/session, using a high-performance biocompatible membrane dialyzer. As of the end of November 2019, HD therapy employing electrolyzed water containing H_2 (E-HD) as dialysis water was introduced for all patients and was provided regularly thereafter.

Patient characteristics are shown in Table 1. The 63 patients included 41 males, mean 72 ± 9 years, and median duration of HD was 7 years. The leading cause of underlying kidney disease was diabetic kidney disease (43%), and 35% of patients had a history of cardiovascular disease. Informed consent was obtained from all participants, and the study protocol was fully approved by the ethics committee of Kanagawa Medical Association Ethics Review Committee (October 10, 2019). All methods were performed in accordance with the relevant guidelines and regulations.

Methods

Blood samples were obtained from all patients at 4 time-points, before and after a session of HD within 4 weeks before the commencement of E-HD (control HD [CHD] phase) and before and after a session of E-HD 8 weeks after commencing E-HD (E-HD phase). Blood samples were centrifuged with ethylenediamine tetra-acetic acid, and all plasma was stored at – 80 °C until needed for measurements.

Preserved plasma samples were used to measure the following parameters: MPO (Human Myeloperoxidase Quantikine ELISA Kit; R&D Systems, Minneapolis, MN, USA), thioredoxin 1 (TRX) (Human Thioredoxin Assay ELISA Kit; IBL, Fujioka, Japan), and malondialdehyde-protein adduct (MDA-adduct) (Oxi-Select™ MDA Adduct Competitive ELISA Kit; Cell Biolabs, San Diego, CA, USA).

Assessments of fatigue

Patient fatigue was evaluated using both a numerical rating scale (NRS) and our own original fatigue scale. All questionnaires were provided in written format. The NRS 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, the patient feels tired with light work; and grade 4, intense fatigue, the patient feels very tired, and falls asleep. Measurements on our original fatigue scale were made on both a dialysis day and a dialysis-free day in the CHD phase.

Cut-off NRS scores were based on analysis of the receiver operating characteristic (ROC) curve, in which fatigue with decreased activities of daily living was defined as grade ≥ 3 on our original fatigue scale. Logistic regression multivariate analysis was performed to estimate associations between risk of fatigue and redox parameters in the CHD phase.

Table 1 Patients' demographics

N	63
Age (year old)	72 ± 9
Gender: male	41 (65.1%)
HD vintage (years)	7 (1, 40)
Underlying renal disease (non-diabetic nephropathy)	36 (57.1%)
Comobidities	
Cardiovascular disease	22 (34.9%)
Malignancy	5 (7.9%)
Labolatory data	
Hemoglobin (g/dL)	10.5 ± 1.1
Creatinine (mg/dL)	10.0 ± 2.1
Albumin (g/dL)	3.8 ± 0.3
C-reactive protein (mg/dL)	0.14 (0.01, 3.40)

Overview of the E-HD system

Briefly, E-HD solutions were prepared as follows (Fig. 1): tap water was supply to the Electrolyzed Water-Hemodialysis System (Trim Medical Institute Co., Ltd., 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 target H_2 concentration. The reverse osmosis water containing H_2 (e-RO water) produced by 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, and there were no differences in terms of electrolytes levels and pH, as compared to the CHD solution, as reported elsewhere [26–28], whereas regarding H_2 levels of dialysate were in the range of 41–84 ppb.

Analysis

Variables are expressed as mean ± standard deviation (SD) or median (range), as appropriate. Statistical significance was set at the level of $P < 0.05$.

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 Bonferroni for multiple comparison procedure. All statistical analyses were performed with SPSS version 22.0 (STATA Corporation, College Station, TX, USA).

Results

Changes in parameters are summarized in Table 2. In both CHD and E-HD phases, significant increases in MPO and MDA-a and a significant decrease in TRX
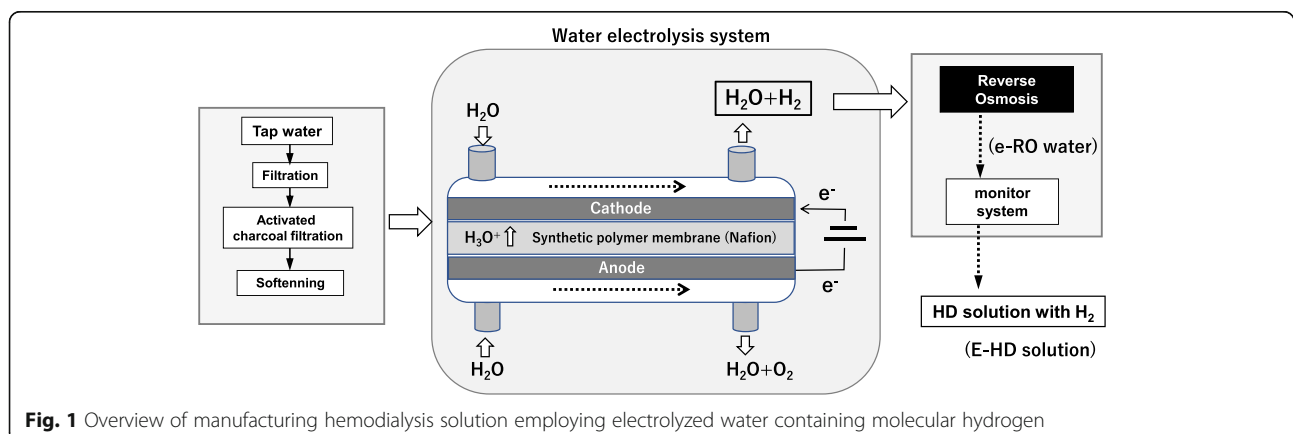

Fig. 1 Overview of manufacturing hemodialysis solution employing electrolyzed water containing molecular hydrogen

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Table 2 Changes of redox parameters by hemodialysis and comparisons between CHD and EHD phases

		CHD phase	E-HD phase	*p (CHD* vs. *E-HD)*
MPO (pg/mL)	pre-HD	427 ± 197	399 ± 205	*0.413*
	post-	656 ± 289	834 ± 432	*< 0.001*
	p (pre vs. *post)*	*< 0.001*	*< 0.001*	
TRX (ng/mL)	pre-HD	107.3 ± 36.5	114.0 ± 44.2	*0.065*
	post-	60.0 ± 34.6	76.2 ± 29.9	*< 0.001*
	p (pre vs. *post)*	*< 0.001*	*< 0.001*	
MDA-a (pmol/mL)	pre-HD	59.0 ± 21.4	61.7 ± 17.9	*0.030*
	post-	72.9 ± 21.2	67.2 ± 18.3	*< 0.001*
	p (pre vs. *post)*	*< 0.001*	*0.004*	

CHD Control HD; *EHD* HD employing electrolyzed water containing molecular hydrogen; *MPO* myeloperoxidase; *RTX* thioredoxin-1; *MDA-a* malondialdehyde-protein adduct

were seen after the session of HD, but the degrees of those changes differed significantly between CHD and E-HD phases. The increase in MDA-A was reduced, the decrease in TRX was reduced and the increase in MPO was accentuated in the E-HD phase as compared with the CHD phase.

Regarding the relationship between basal MPO level (pre-HD) and ΔMPO (post-HD - pre-HD), no relationships were observed in the CHD phase, whereas a significant positive relationship was seen between the two parameters in the E-HD phase (Fig. 2).

In the CHD phase, significant positive correlations were identified between ΔMPO and the percentage change in MDA-a between pre- and post-HD (%MDA-a) (Fig. 3A), and between ΔMPO and the percentage change in TRX between pre- and post-HD (%TRX) (Fig. 3B). In the E-HD phase, no correlation was found between ΔMPO and %MDA-a (Fig. 3C), while a significant positive correlation was observed between ΔMPO and %TRX (Fig. 3D).

In the CHD phase, NRS was 2.5±2.4 on HD day. Patient reports on fatigue were as follows: 30 cases (47.6%) in grade 1, 22 (34.9%) in grade 2, 10 (15.9%) in grade 3, and one (1.6%) in grade 4 on HD days, and 39 cases

(61.9%) in grade 1, 22 (34.9%) in grade 2, 2 (3.2%) in grade 3, and none (0.0%) in grade 4 on non-HD days.

Based on ROC curves, we determined the cut-off level for fatigue as NRS ≥ 3 in the present study. According to basal levels in the CHD phase, 36 cases (57.1%) were classified to the non-fatigue group and 27 cases (42.9%) to the fatigue group. Clinical characteristics of the two groups are shown in Table 3. A faint but significant difference in serum albumin level was found between the two groups in the CHD phase (Table 3), and change in MDA-a due to HD was higher in the CHD phase (Table 4).

Logistic regression analysis was used to analyze associations between risk of fatigue (NRS ≥3) and changes in redox parameters (ΔMPO, %TRX, %MDA-a) for the CHD phase, after adjusting for serum albumin. Serum albumin and %MDA-a were identified as independent factors for fatigue in the CHD phase (Table 5). While in E-HD phase, %TRX was identified as independent factor for fatigue at 8 weeks (Table 6).

During the 8 weeks of observation as compared with basal NRS in the CHD phase, no changes were seen in the non-fatigue group, whereas significant decreases were observed at 2, 4, and 8 weeks, respectively (Fig. 4).
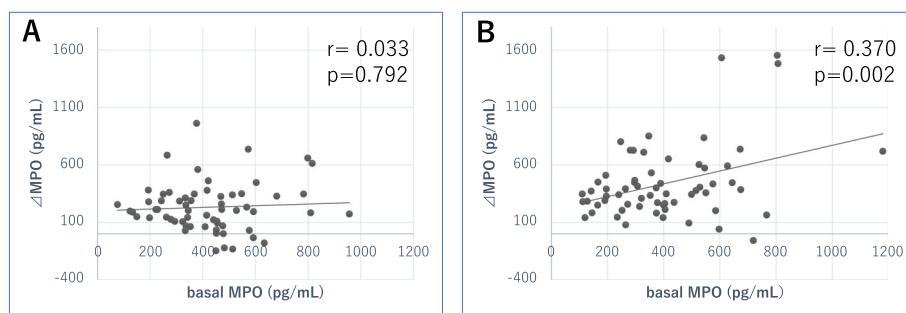

Fig. 2 Relationship between basal MPO levels (pre-HD) and ΔMPO by HD. **A** Control HD. **B** HD employing electrolyzed water (8th week). ΔMPO: post-HD level − pre-HD level. HD, hemodialysis; MPO, myeloperoxidase

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Table 3 Comparisons of patients basal background between the non-fatigue group and fatigue group

	Non-fatigue group (NRS < 3)	Fatigue group (3 < =NRS)	p
N	36 (57.1%)	27 (42.9%)	
Age (year old)	71.7 ± 9.4	73.1 ± 9.3	0.581
Male (%)	25 (69.4%)	16 (59.2%)	0.410
HD vintage (years)	9.5 ± 7.0	10.0 ± 10.0	0.843
Dry weight (kg)	60.6 ± 14.9	56.8 ± 13.4	0.313
Pre-HD BP: SBP/DBP (mmHg)	163 ± 23/84 ± 14	161 ± 23/79 ± 14	0.754/0.282
Post-HD BP: SBP/DBP (mmHg)	146 ± 21/83 ± 14	152 ± 28/76 ± 12	0.347/0.876
Pre-HD HR (/min)	74 ± 9	74 ± 11	0.809
Post-HD HR (/min)	74 ± 13	69 ± 10	0.313
Presence of Diabetes mellitus	17 (47.2%)	10 (37.0%)	0.430
History CVD	15 (41.6%)	7 (25.9%)	0.210
Current cancer	2 (5.5%)	3 (11.1%)	0.428
Creatinine (mg/dL)	10.3 ± 2.3	9.7 ± 1.7	0.261
Hemoglobin (g/dL)	10.6 ± 1.2	10.3 ± 0.8	0.299
Albumin (g/dL)	3.87 ± 0.22	3.70 ± 0.37	0.026
CRP (mg/dL)	0.37 ± 0.52	0.53 ± 0.82	0.377

HD hemodialysis; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *HR* heart rate; *CVD* cardiovascular disease; *CRP* C-reactive protein
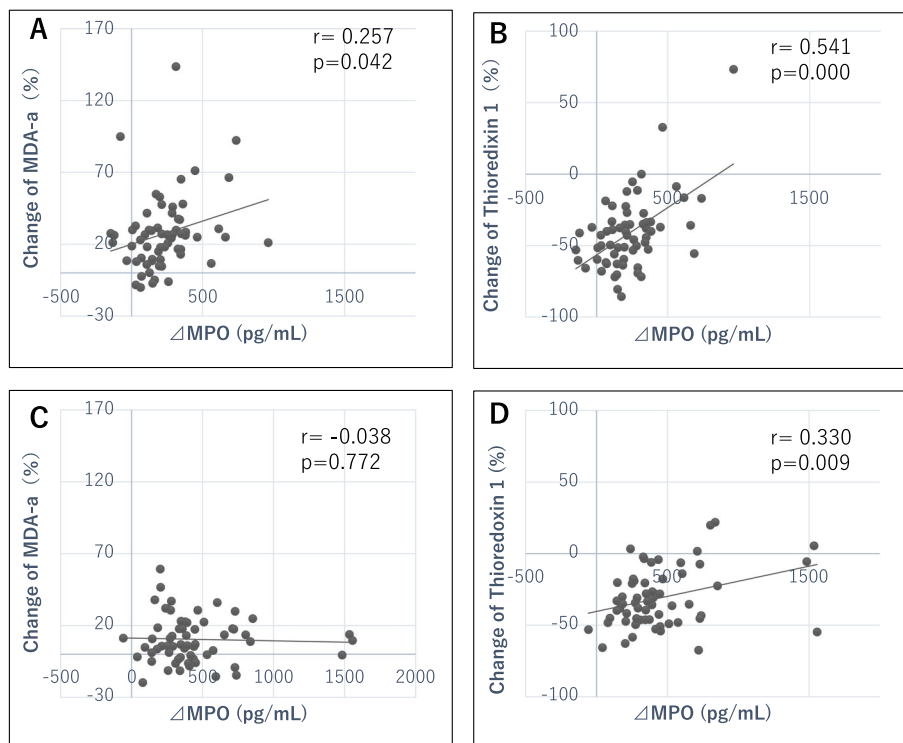

Fig. 3 Relationship between ΔMPO by HD and percentage changes in redox molecules (%) by HD. **A**, **B** Control HD (CHD phase). **C**, **D** E-HD (E-HD phase). Percentage change in molecule (%): (post-HD level − pre-HD level)/pre-HD level × 100. ΔMPO: post-HD level − pre-HD level. HD, hemodialysis; MPO, myeloperoxidase; MDA-a, malondialdehyde-protein adduct

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Table 4 Comparisons of change of redox parameters by hemodyalysis between CHD and E-HD phases, and between the non-fatigue group and fatigue group

	All	Non-fatigue group	Fatigue group	*p*
	(*n* = 63)	(*n* = 36)	(*n* = 27)	*Non-Fatigue* vs. *Fatigue*
CHD	+ 233.1 ± 206.2	+ 245.0 ± 196.5	+ 216.1 ± 230.2	*0.602*
EHD	+ 434.2 ± 312.4	+ 480.1 ± 330.1	+ 379.2 ± 294.2	*0.206*
p	*< 0.001*	*< 0.001*	*0.002*	
CHD	−41.7 ± 25.3	−37.3 ± 29.5	−43.5 ± 19.1	*0.626*
EHD	−31.1 ± 20.3	−29.5 ± 22.4	−33.1 ± 17.4	*0.509*
p	*0.004*	*0.058*	*0.017*	
CHD	+ 27.4 ± 26.3	+ 22.1 ± 16.6	+ 34.5 ± 34.5	*0.063*
EHD	+ 10.2 ± 15.8	+ 8.4 ± 15.7	+ 12.7 ± 16.0	*0.297*
p	*< 0.001*	*< 0.001*	*0.001*	

In the E-HD phase, both groups showed similar changes in redox parameters (Table 4).

Discussion

The present study aimed to examine the primary mechanisms underlying the anti-oxidative actions of E-HD, and their possible effects in ameliorating HD-related fatigue. The study used a single-arm, prospective, observational design, and the main findings are summarized as follows. In the CHD phase, increases in serum MPO accompanied increases in oxidative product (MDA-a) and anti-oxidant molecules (TRX), whereas in the E-HD phase, increases in MPO were accentuated during HD, but changes in MDA-a and TRX were both ameliorated as compared with the CHD phase. During the 8 weeks of observation, patients with HD-related fatigue displayed significant decreases in fatigue score.

Enhanced oxidative stress in HD patients could lead to the development of micro-inflammation, which would potentially play a role in cardio-cerebrovascular events and dialysis-related complications [11]. Among factors exacerbating oxidative stress, bio-incompatibility of the HD system could be a substantial contributor. With the current E-HD system, greater increases in MPO during HD were noted. MPO is involved in the generation of ROS in the presence of H_2O_2 [10, 13], and thus may be associated with exaggerated oxidative stress when viewed in isolation.

The significant positive correlation between ΔMPO and increased oxidative products in the CHD phase may well support this notion. Interestingly, concentrations of the anti-oxidant molecule TRX (molecular weight, 12 kDa) decreased significantly with HD, probably due to partial loss during the HD process, while a positive correlation between ΔMPO and %TRX was apparent in the CHD phase. This suggests a biological response counter-regulating the enhanced creation of reactive oxygen species (ROS). We speculate that increased levels of MPO would induce oxidative processes due to activation of nuclear factor-κB (NFκB), but oxidative stress would simultaneously activate the Nrf2 (nuclear factor erythroid 2 (NF-E2)-related factor 2)-Keap1 (Kelch-like ECH-associated protein 1) signaling to generate anti-oxidants [29]. The exact profiles of Nrf2 and NFkB activation during HD need to be clarified.

Unexpectedly, MPO levels during HD were even more elevated in E-HD than in CHD. Several mechanisms could be involved with MPO release during HD, such as the physiological responses of neutrophils with decreased ionic Ca in the cell [30], removal of degranulation suppressors, angiogenin from blood during HD [31], and non-physiological neutrophil bursts, such as with mechanical damage from HD [8]. We have previously reported that the respiratory burst function of neutrophils is much better preserved in electrolyzed water-treated human neutrophils as compared with controls [23]. Taking these observations together, enhanced MPO release may reflect better neutrophil viability with the use of electrolyzed water-based dialysis solution.

Table 5 Multiple logistic regression analysis for the presence of fatigue at the CHD-phase

Variable	Odd ratio	95%CI	*p value*
⏢MPO	0.998	(0.995–1.002)	*0.296*
⏢TRX%	1.001	(0.974–1.029)	*0.998*
⏢MDA-a%	1.028	(1.001–1.056)	*0.038*
Albumin	0.075	(0.008–0.695)	*0.023*

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Table 6 Multiple logistic regression analysis for the presence of fatigue at the EHD-phase

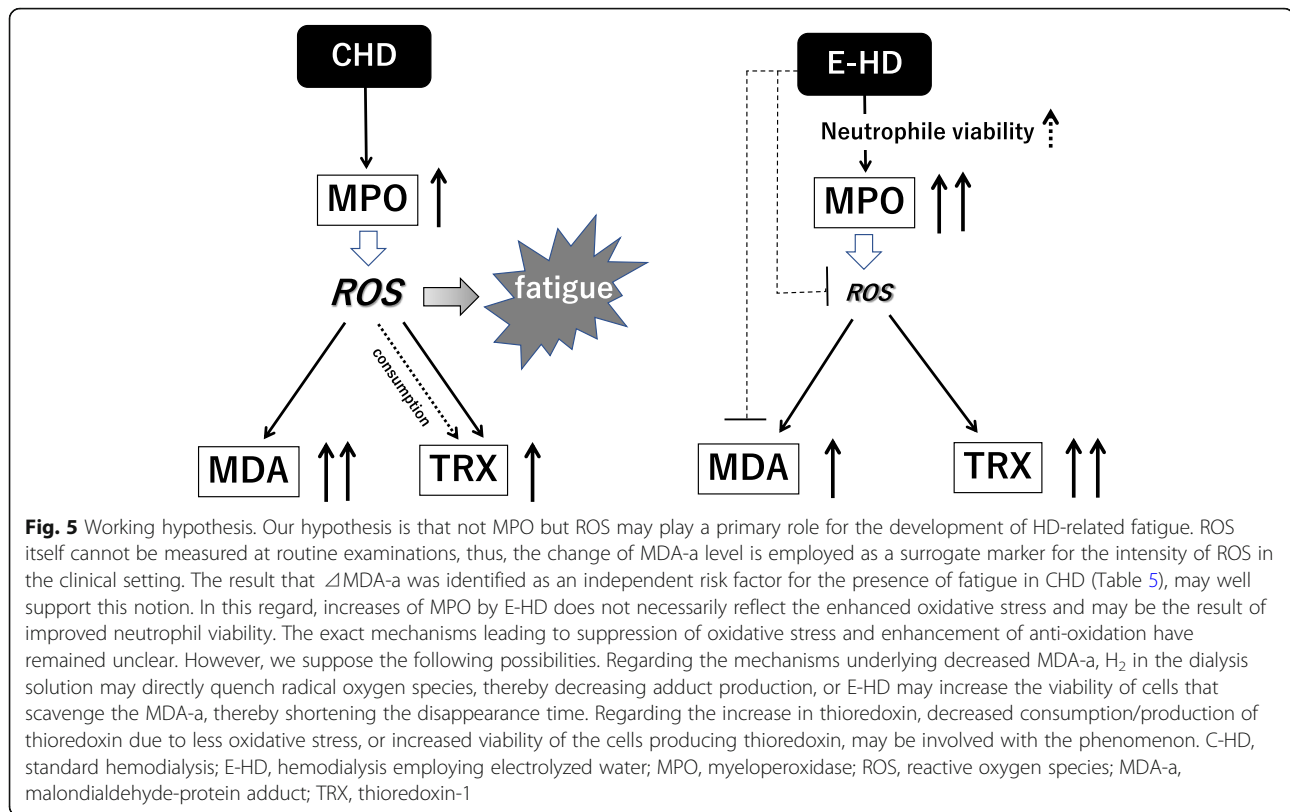| Variable	Odd ratio	95%CI	*p value*
⊿MPO	0.998	(0.995–1.001)	*0.140*
⊿TRX%	1.036	(1.003–1.069)	*0.030*
⊿MDA-a%	0.991	(0.956–1.027)	*0.613*
Albumin	0.545	(0.094–3.151)	*0.498*

Regarding the changes of redox parameters during HD, there were significant increases in MPO and MDA-a, and decreases in TRX in CHD and E-HD phases. Interestingly, increases of MDA-a in the E-HD were significantly lower than those of CHD, while decreases in TRX in E-HD were significantly higher than those of CHD (Table 2), although increases of MPO by HD, which is supposed to be a surrogate marker for oxidative stress, were significantly higher in E-HD than those in CHD. Upon those changes of MDA-a and TRX, it seems that E-HD may directly or indirectly suppress ROS and activate or preserve anti-oxidant system during HD. Nevertheless, as compared with those of the CHD phase, the marginal but significant increases of MDA-a in the pre-HD levels at the E-HD phase (8th week), may indicate the exaggerated oxidative stress by E-HD, whereas the higher TRX of the pre-HD levels at the E-HD phase may indicate the potentiation of anti-oxidative system by E-HD (Table 2). At present, we cannot explain the mechanism of this intriguing finding clearly. Instead, our working hypothesis over the post-HD fatigue and the therapeutic contribution by E-HD are shown in Fig. 5.

The present study assessed the extent of fatigue using patient reports. We defined "clinically relevant fatigue" as subjective symptoms reflecting reduced activities of daily living. Based on data from the CHD phase, 27 of the 63 patients (42.9%) were classified to the fatigue group. Lower serum albumin and higher MAD-a elevation during HD were identified as risk factors for the presence of fatigue in the CHD phase. During the 8-week observation, NRS scores in the fatigue group were significantly improved from 2 weeks after the introduction of E-HD, whereas no clinically significant changes were observed in the non-fatigue group. Regarding redox profiles between fatigue and non-fatigue groups, no differences were observed between groups in the E-HD phase. These results may indicate a pathological role of enhanced oxidative stress in the development of fatigue after HD, and E-HD may be of particular benefit in ameliorating subjective symptoms of fatigue among patients affected in this manner.

Several limitations to the present study need to be considered when interpreting the results. First, we did not correct for measured test molecules, and levels in the post-HD period may thus have been overestimated. Post-HD levels have been speculated to be nearly 10% lower if the fluid were not removed. Nevertheless, the significant differences between the CHD and E-HD phases at the respective time-points appear likely to be robust. Second, we only measured redox parameters at two time-points, pre- and post-HD, and the temporal course of changes after HD were unclear. Although MPO levels post-HD were significantly higher in the E-HD phase than in the CHD phase, this result does not confirm a larger AUC of MPO during the periods after HD. This crucial issue regarding peak MPO levels and the AUC after HD needs to be clarified. Third, the present single-arm observational study was unable to answer

Fig. 4 Temporal course of changes in NRS for subjective fatigue. Pre: control hemodialysis at 2–4 weeks before commencement of E-HD. E-HD: hemodialysis employing electrolyzed water. Non-fatigue (*n* = 36): NRS < 3 at control HD (Pre). Fatigue (*n* = 27): NRS ≥ 3 at control HD (Pre). *p < 0.05 vs. pre. **p < 0.01 vs. pre

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Fig. 5 Working hypothesis. Our hypothesis is that not MPO but ROS may play a primary role for the development of HD-related fatigue. ROS itself cannot be measured at routine examinations, thus, the change of MDA-a level is employed as a surrogate marker for the intensity of ROS in the clinical setting. The result that △MDA-a was identified as an independent risk factor for the presence of fatigue in CHD (Table 5), may well support this notion. In this regard, increases of MPO by E-HD does not necessarily reflect the enhanced oxidative stress and may be the result of improved neutrophil viability. The exact mechanisms leading to suppression of oxidative stress and enhancement of anti-oxidation have remained unclear. However, we suppose the following possibilities. Regarding the mechanisms underlying decreased MDA-a, H_2 in the dialysis solution may directly quench radical oxygen species, thereby decreasing adduct production, or E-HD may increase the viability of cells that scavenge the MDA-a, thereby shortening the disappearance time. Regarding the increase in thioredoxin, decreased consumption/production of thioredoxin due to less oxidative stress, or increased viability of the cells producing thioredoxin, may be involved with the phenomenon. C-HD, standard hemodialysis; E-HD, hemodialysis employing electrolyzed water; MPO, myeloperoxidase; ROS, reactive oxygen species; MDA-a, malondialdehyde-protein adduct; TRX, thioredoxin-1

whether E-HD can suppress subjective fatigue, or whether the oxidative stress from HD plays a role in the development of HD-related clinical fatigue. In the future, randomized control studies are needed to clarify these issues. Last, evaluation on fatigue used a subjective, patient-reported method, and thus lacks consistency. The development of novel parameters based on objective systems is expected.

Conclusion
E-HD appears to ameliorate oxidative stress and increase anti-oxidant systems during HD, suggesting improved bio-compatibility of the HD system. E-HD could benefit patients with HD-related fatigue, but the mechanisms in relation to oxidative stress remain to be elucidated.

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