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A novel bioactive haemodialysis system using dissolved dihydrogen (H_2) produced by water electrolysis: a clinical trial

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Abstract

Background. Chronic inflammation in haemodialysis (HD) patients indicates a poor prognosis. However, therapeutic approaches are limited. Hydrogen gas (H_2) ameliorates oxidative and inflammatory injuries to organs in animal models. We developed an HD system using a dialysis solution with high levels of dissolved H_2 and examined the clinical effects.

Methods. Dialysis solution with H_2 (average of 48 ppb) was produced by mixing dialysate concentrates and reverse osmosis water containing dissolved H_2 generated by a water electrolysis technique. Subjects comprised 21 stable patients on standard HD who were switched to the test HD for 6 months at three sessions a week.

Results. During the study period, no adverse clinical signs or symptoms were observed. A significant decrease in systolic blood pressure (SBP) before and after dialysis was observed during the study, and a significant number of patients achieved SBP <140 mmHg after HD (baseline, 21%; 6 months, 62%; $P < 0.05$). Changes in dialysis parameters were minimal, while significant decreases in levels of plasma monocyte chemoattractant protein 1 ($P < 0.01$) and myeloperoxidase ($P < 0.05$) were identified.

Conclusions. Adding H_2 to haemodialysis solutions ameliorated inflammatory reactions and improved BP control. This system could offer a novel therapeutic option for control of uraemia.

Keywords: electrolysed water; haemodialysis; hydrogen water; inflammation; oxidative stress

Introduction

Accumulating evidence suggests that enhanced oxidative stress and inflammation in patients on haemodialysis (HD) play crucial roles in the increased risk of cardiovascular events and infectious diseases, which result in poor prognosis for the patient [1–3]. Randomized control studies using antioxidants in HD patients suppressed cardiovascular events using high-dose vitamin E [4] and acetylcysteine [5], but conflicting results were reported for non-dialysis chronic kidney disease [6]. While inflammation significantly affects HD patients, clinically available agents to directly suppress inflammatory markers are lacking for HD patients [7].

Dihydrogen (H_2) is an inert gas with no known side effects. Recent studies have shown that administration of H_2 dissolved in water can suppress oxidative or inflammatory injury to organs in animal models, such as ischaemic reperfusion in the brain [8] and liver [9], stress-induced oxidative injury in the hippocampus [10], and inflammatory reactions in the colon induced by dextran sodium sulphate [11]. Furthermore, H_2 inhalation mitigates small intestine inflammation due to transplantation [12]. H_2 reacts with hydroxyl radicals [8,13], and thus could prevent injury caused by radical oxygen species. Applying H_2 to HD solutions, for anti-oxidative and anti-inflammatory effects, represents a unique clinical approach.

Table 1. Patient profiles at baseline

n	21
Gender (female)	15 (71%)
Age (years)	67 ± 6
Duration of HD (months)	96 ± 82
Underlying renal disease	
Non-diabetes	11 (52%)
Diabetes	10 (48%)
Previous history	
Cardiovascular disease	3 (14%)
Apoplexy	2 (10%)
Medication	
Anti-hypertensive agents	19 (90%)
Erythropoiesis-stimulating agent	21 (100%)
Iron	5 (24%)
	(Mean ± SD)

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Electrolysed water from the cathode provides unique chemical properties, such as alkalinity, low dissolved oxygen and high dissolved H_2 [14]. Thus, we developed a novel HD system using water electrolysis to provide water with high dissolved H_2 [15,16].

This report describes a 6-month clinical study of HD using solutions with dissolved H_2 to determine the feasibility and clinical effects of this approach. Results indicated that the system is safe and may provide therapeutic effects beyond those of conventional therapies.

Materials and methods

Subjects were recruited from outpatient clinics of three hospitals in Japan [Kashima Hospital (K), Iwaki; Nikko-Memorial Hospital (N), Muroran; Tokatsu Clinic Hospital (T), Matsudo]. The ethics committee of Tohoku University (no. 2006-101, no. 2007-207) and local committees of the three hospitals (K, N, T) approved all study protocols. Initially, 22 patients who provided informed consent were recruited from June 2007 to April 2009 (eight cases from K, seven from N, seven from T). One subject dropped out because of surgery unrelated to the study. Table 1 shows patient profiles for the 21 remaining subjects. All subjects were treated using standard HD, with three sessions/week (4–5 h/session), using high-performance biocompatible dialysers. Potential subjects with severe heart failure (New York Heart Association III/IV), severe liver disease, psychological problems, dementia or malignant disease within the previous 3 months were excluded from the study. After a 1-month run-in period, subjects were switched to an HD system employing the dissolved H_2 (H_2-HD). Treatment with H_2-HD was conducted for six consecutive months to observe temporal changes in clinical and laboratory parameters. The study dialysis system is composed of three basic parts: personal HD monitor systems, a personal reverse osmosis system and water electrolysis equipment (HD-24K), as shown in Figure 1. Thus, two patients could be treated simultaneously using one system. During the 2-year study period, one system was distributed to each of the three hospitals. Patients recruited were selected from those on centre HD during the daytime because the study was designed to examine the long-term clinical safety of this system. Thus, the patients enrolled were mainly female and were relatively older (average age of dialysis patients in Japan: 65.3 years; females constituted 38.4% in 2008).

H_2-HD system

Details of the system have been reported previously [16]. Briefly, test solutions were manufactured as follows (Figure 1a): pre-filtered water was processed using activated charcoal filtration and water softening to supply the HD-24K water electrolysis system (Nihon Trim, Osaka, Japan), where water was electrolysed by direct current supply to the anode and cathode electrode plates. Water on the anode side was drained out, and water from the cathode side (electrolysed water) was collected to supply the reverse osmosis equipment (MH500CX; Japan Water System, Tokyo, Japan) at 500 mL/min. The intensity of electrolysis was adjusted to maintain pH 10.0. The reverse osmosis water made by a water electrolysis system was supplied to a personal HD monitoring system (DBB-22B; Nikkiso, Tokyo, Japan) to make the HD solution by mixing with a liquid dialysis solution concentrate. The composition of inflow H_2-HD solution was the same as a standard HD solution with the exception of the presence of dissolved H_2 in the H_2-HD. Mean dissolved H_2 levels in the manufacturing process are shown in Figure 1b.

Measurements

Blood samples were obtained just before the first HD session of the week (Monday or Tuesday). Blood was immediately centrifuged with ethylenediaminetetraacetic acid (EDTA), and the plasma was stored at −80°C until measurements were obtained.

All patients were monitored for subjective symptoms and objective signs during the study period. Blood pressure (BP) was measured using a sphygmomanometer on the upper arm with the patient in a supine position just before and after each HD session, and data were recorded into the clinical record. The following parameters were measured by enzyme-linked immunosorbent assay (ELISA): monocyte chemoattractant protein (MCP)-1 (human MCP-1 BMS281INST; Bender MedSystems, Vienna, Austria); myeloperoxidase (MPO) (human serum myeloperoxidase ELISA; Immunodiagnostik, Augsburg, Germany); and 8-hydroxy-2'-deoxyguanosine (8-OHdG) (New 8-OHdG Check ELISA; Nikken Seil, Shizuoka, Japan). N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured using the electrochemiluminescence assay (Elecsys 2010; Roche Diagnostics, Mannheim, Germany). Highly sensitive C-reactive protein (hsCRP) was measured by nephrometry (N High Sensitive CRP; Dade Behring, Marburg, Germany).

Skin temperature was measured by thermography (Handy Thermo TVS-200EX; Japan Abionics, Tokyo, Japan), displaying every 0.2°C, and the area for study was examined using the following equation: thermal product = area (%) × temperature. Dissolved H_2 in solution was measured using a DH Meter (DH-35A; DKK-TOA, Tokyo, Japan), and H_2 in expired air was measured using a gas analyser (BGA-1000D breath gas

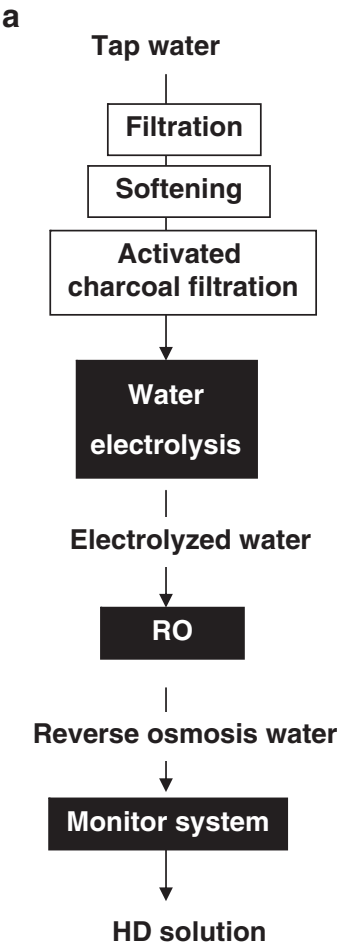

Fig. 1. (**a**) Manufacturing process of haemodialysis solution in the H_2-HD system (RO: reverse osmosis). (**b**) Dissolved H_2 (DH) levels in solutions of the H_2-HD system (TW: tap water; EW: electrolysed water; RO: reverse osmosis water; HD1: 1 h of haemodialysis; HD2: 2 h of haemodialysis; HD3: 3 h of haemodialysis; HD4: 4 h of haemodialysis). (**c**) H_2 levels in expired air during haemodialysis utilizing the H_2-HD system (HD1: 1 h of haemodialysis; HD2: 2 h of haemodialysis; HD3: 3 h of haemodialysis; HD4: 4 h of haemodialysis; Post-HD: 30 min after completion of haemodialysis). (**d**) Intercurrent change in dissolved H_2 (DH) levels in haemodialysis solution and saline in blood line. Sham haemodialysis (HD) was performed using the HD solution and saline instead of blood, with 500 mL/min flow for the HD solution, 200 mL/min for saline, with dialyser: 1.5 m^2 (circles: HD solution; triangles: saline solution; data are expressed as mean ± SD).

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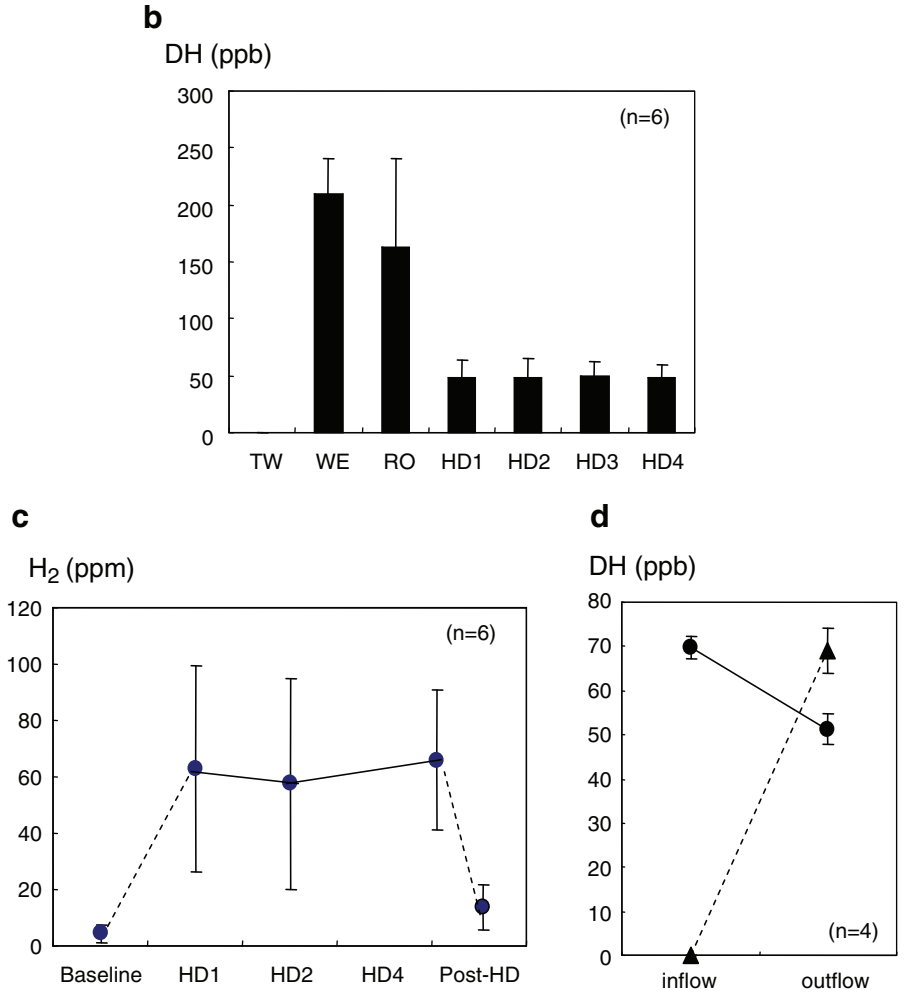

Fig. 1. *(continued).*

analyser; Laboratory for Expiration Biochemistry Nourishment Metabolism, Nara, Japan).

All values are expressed as mean ± standard deviation (SD), or median (range) as indicated. One-way repeated measures analysis of variance was used for statistical analysis, with values of $P < 0.05$ considered statistically significant. For a skewed distribution, those data were transformed to a normal distribution and were subjected to statistical analysis.

Results

Average H_2 levels of the test water were: 210 ppb in electrolysed water, 163 ppb in reverse osmosis water and 48 ppb in HD solution (sampled at 1, 2, 3 and 4 h) (Figure 1b). The H_2 levels in reverse osmosis water tended to decrease in comparison to electrolysed water. No significant changes were found in the H_2 levels in HD solution during treatment. Significant increases occurred in the H_2 in expired air during H_2-HD (average 62 ppm) (Figure 1c).

Sham HD was performed using HD solution with H_2 and a saline solution instead of blood. As shown in Figure 1D, the H_2 levels in the outflow HD solution were lower than those of the inflow, whereas there was a sharp increase in H_2 levels in the outflow saline solution in the blood line.

No specific adverse signs or symptoms were noted during the study. No changes were observed in the fluid removed by dialysis session, dry weight, cardiothoracic ratio (%) after HD or thermography (Table 2). The dry weight of the patients was determined based on being free of: fluid retention (no peripheral oedema or pleural or pericardial effusion), severe muscle cramps, symptomatic hypotension during as well as after dialysis and severe fatigue after dialysis. Determination of whether the dry weight of the patients was within a clinically acceptable range was made by the attending physician. Significant differences were found in pre- and post-dialysis systolic BP (SBP) values by one-way repeated measures ANOVA (Figure 2). A significant change in pulse pressure was found at the post-dialysis session. A substantial number of patients achieved SBP <140 mmHg by the end of H_2-HD (baseline, 21%; 6 months, 62%; Figure 3).

During the course of study, no changes were found in the number of anti-hypertensive agents prescribed. At the study entry, anti-hypertensive agents were used for 19 subjects, and an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) was administered for 14 patients. During the study course, one

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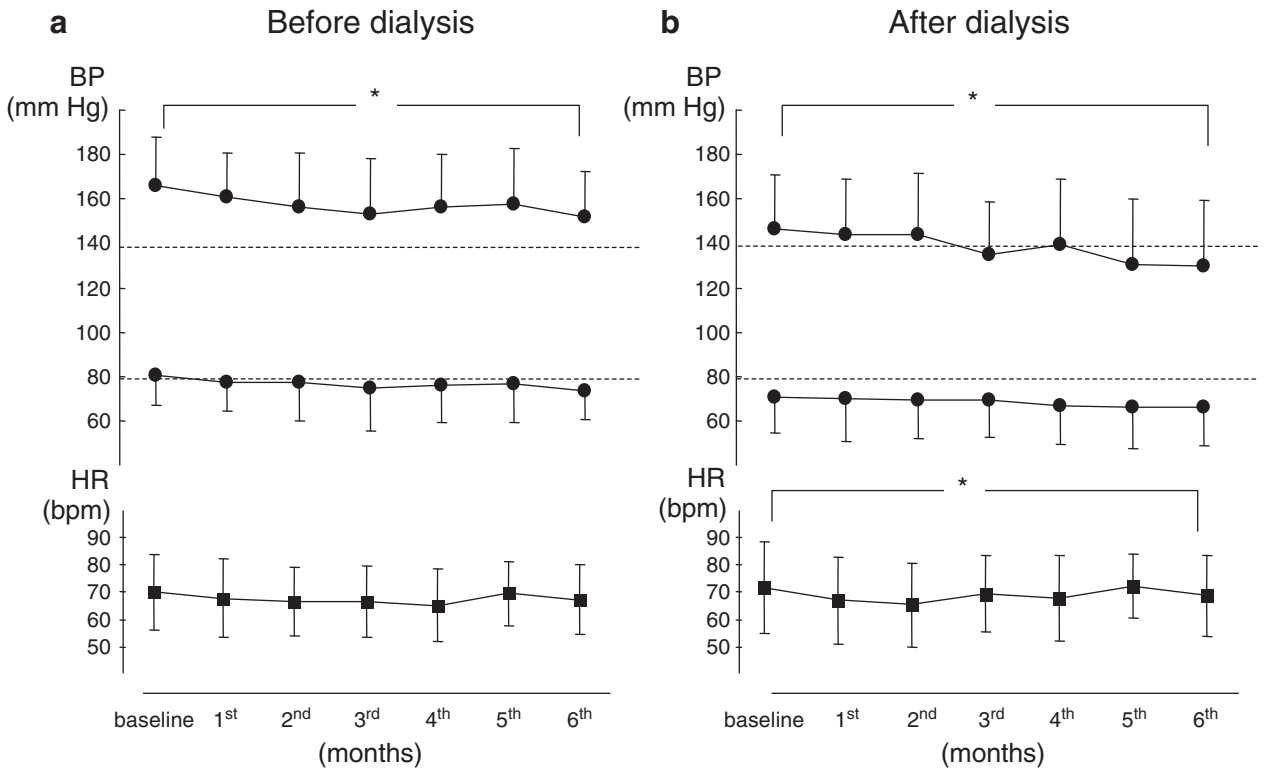

Fig. 2. Changes in blood pressure and heart rate over time at pre- (**a**) and post-HD (**b**) sessions. All measurements were obtained at the first HD session of the week. Significant changes were found for systolic blood pressure both (a) before and (b) after dialysis over the course of the study [$*P < 0.05$, by repeated measures ANOVA; *post hoc* analysis: (a) baseline *vs*. sixth month; $P < 0.05$, (b) baseline *vs*. fifth and sixth month]. Significant changes were found in heart rate after dialysis sessions (b) during the course of the study [$*P < 0.05$, by repeated measures ANOVA; *post hoc* analysis: (b) baseline *vs*. first and second month; data are expressed as mean ± SD].

subject stopped taking anti-hypertensive agents, but 14 subjects remained on an ACEI or ARB until the end of the study. Twelve patients received iron supplements as needed, and erythropoiesis-stimulating agents were used in all subjects, adjusted according to the target level of haemoglobin (10-12 g/dL); the dose was increased in four subjects, remained unchanged in 13 subjects and decreased in four subjects compared to baseline.

Changes in laboratory parameters are shown in Table 3. No significant changes were found in laboratory parameters, except for small but significant increases in blood urea nitrogen (BUN) and creatinine levels. In terms of plasma oxidative and inflammatory markers, no changes in 8-OHdG were noted, but significant decreases in MCP-1 and MPO were found. Sub-analysis revealed that the third tertile group (high-level group) had significant decreases in both parameters (Figure 4). Plasma NT-proBNP levels also tended to decrease ($P = 0.078$).

Discussion

A clinical study of HD solution with dissolved H_2 (H_2-HD) was conducted to test the feasibility and clinical effects of the approach. During a 6-month trial, patients received H_2-HD with no adverse effects. While changes in dialysis parameters and medications were minimal, the high BP seen at baseline (before H_2-HD) decreased significantly after commencement of H_2-HD, with a corresponding decrease in NT-proBNP levels. The number of patients who achieved normotensive status increased throughout the study and exhibited significant decreases in pulse pressure by the end of the study. Plasma inflammatory markers MCP-1 and MPO decreased significantly during the test period.

The system presented suppresses oxidative stress and inflammation by delivering H_2 as an antioxidant [8–12]. In the system, average H_2 level in EW was 210 ppb, and average H_2 in the HD solution before use was 48 ppb (Figure 1b). A sharp increase was seen in expiratory H_2 at the start of each HD session, but this parameter returned to basal levels by the end of the session (Figure 1c), which suggests delivery of H_2 from the dialysis solution to the body, supporting the result of sham H_2-HD (Figure 1d).

A previous short-term (1 month) study of H_2-HD showed no adverse effects or changes in dialysis parameters such as urea reduction rate [16]. In the present 6-month study, no specific adverse signs or symptoms were observed, although a small number of patients experienced non-symptomatic decreases in BP (SBP < 100 mmHg) after HD sessions. Clinically minimal changes were observed in dialysis-related laboratory parameters, such as increases in BUN and creatinine, which could be attributed to the increased protein intake and associated creatinine generation in some patients with an increased appetite. No deterioration was seen

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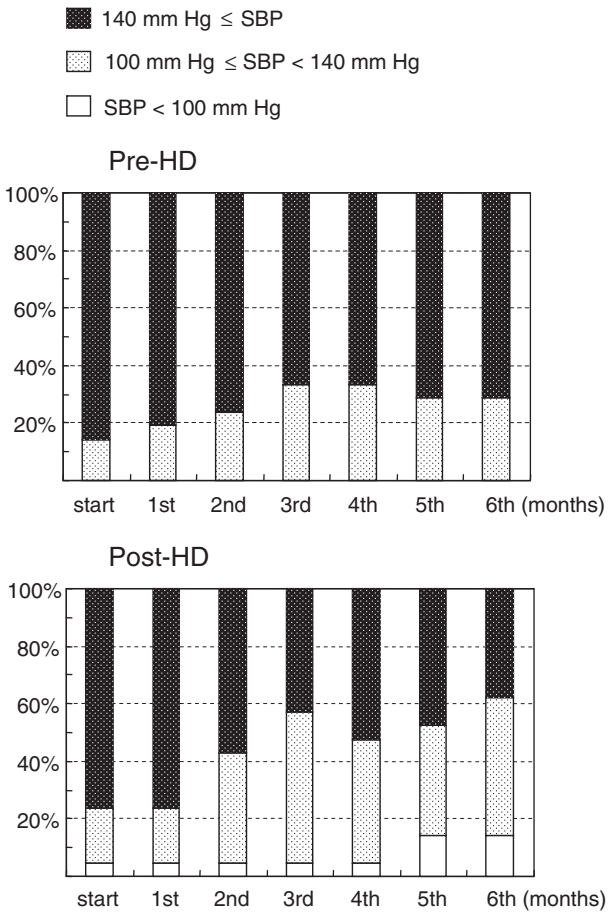

Fig. 3. Distribution of systolic blood pressure (SBP) during the study period at (**a**) pre- and (**b**) post-HD sessions (black: SBP ≥140 mmHg; grey: 100≤ SBP <140 mmHg; white: SBP <100 mmHg).

in nutrition parameters or anaemia control. These results indicate the clinical feasibility of H_2-HD as a maintenance dialysis modality.

Significant decreases in plasma MPO and MCP-1 were noted during the study, particularly among patients with high basal levels. MPO, an enzyme secreted by neutrophils and monocytes, is a catalyst for the production of hypochlorous acid (HOCl), a potent pro-oxidant that generates reactive oxygen species and consumes nitric oxide (NO) [17]. MCP-1 is a chemokine that acts as a key mediator for monocyte trafficking to the site of injured endothelium [19] and is responsible for acute and chronic inflammation [18]. Increased levels of MPO correlate with risk of mortality among chronic HD patients [19], and a strong correlation exists between MCP-1 levels and cardiovascular events in HD patients [20,21]. Thus, the present results may reflect the suppression of inflammatory processes and reduced neutrophil injury in patients, suggesting a possible therapeutic role for this system in patients with enhanced inflammation.

However, oxidative markers did not show uniform changes during H_2-HD; no changes in plasma 8-OHdG levels occurred. Monocytes can be activated during HD, and they may be the major cell types directly exposed to the HD solution. This may explain the significant influence found on monocyte markers. Iron overload in dialysis patients can cause an increase in plasma levels of 8-OHdG, reflecting oxidative injury to DNA by iron [22,23]. We found a significant positive correlation between levels of plasma ferritin and 8-OHdG in the subjects at entry (data not shown). However, iron storage in the patients was not excessive at entry as reflected by relatively low serum ferritin levels, and nine of 21 subjects never received iron supplementation during the study period. These factors may be related to the study results. It is an issue of interest whether H_2-HD could suppress 8-OHdG levels in patients with excess iron storage as represented by high ferritin levels, and provide some benefit to those patients in respect to iron utilization. This should be examined in the future.

Table 2. Clinical parameters

	Baseline	1 month	3 months	6 months	*P*
Body weight/dry weight (kg)	51.9 ± 9.5	51.9 ± 9.5	51.8 ± 9.5	51.8 ± 9.6	NS
Cardiothoracic ratio (%)	51.2 ± 3.1	50.7 ± 3.2	50.0 ± 3.1	50.4 ± 2.8	NS
Fluid removed by HD session (kg)	2.8 ± 1.0	2.6 ± 1.0	2.8 ± 0.9	2.7 ± 0.8	NS
Pre-dialysis					
Systolic blood pressure (mmHg)	166 ± 22	161 ± 20	153 ± 25	152 ± 21	<0.05
Diastolic blood pressure (mmHg)	81 ± 13	77 ± 13	75 ± 19	73 ± 13	NS
Pulse pressure (mmHg)	85 ± 16	83 ± 17	79 ± 16	78 ± 16	NS
Heart rate (beats/min)	70 ± 14	68 ± 14	66 ± 13	67 ± 13	NS
Post-dialysis					
Systolic blood pressure (mmHg)	148 ± 24	145 ± 25	136 ± 24	131 ± 30	<0.01
Diastolic blood pressure (mmHg)	71 ± 16	71 ± 20	70 ± 17	67 ± 18	NS
Pulse pressure (mmHg)	76 ± 19	74 ± 17	66 ± 21	64 ± 18	<0.05
Heart rate (beats/min)	72 ± 17	67 ± 16	70 ± 14	69 ± 15	NS
Thermo index					
Hand (non-access side)	3142 ± 236	3201 ± 189	3217 ± 180	3181 ± 186	NS
Foot (right side)	3143 ± 175	3144 ± 202	3171 ± 186	3145 ± 245	NS
Foot (left side)	3113 ± 198	3124 ± 206	3175 ± 214	3143 ± 233	NS
Anti-hypertensive agents/person	1.9 ± 1.3	2.0 ± 1.3	2.2 ± 1.4	2.0 ± 1.4 (Mean ± SD)	NS

One-way repeated measures ANOVA was used for statistical analysis.

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Table 3. Laboratory parameters

	Baseline	1 month	3 months	6 months	*P*
White blood cell (per μL)	5134 ± 1944	5267 ± 1922	5064 ± 1788	4975 ± 1529	NS
Blood haemoglobin (g/dL)	10.4 ± 0.7	10.5 ± 1.0	10.4 ± 1.0	10.5 ± 1.0	NS
Blood urea (mg/dL)	61.5 ± 13.0	62.9 ± 13.6	67.1 ± 13.9	69.2 ± 12.9	<0.01
Creatinine (mg/dL)	9.5 ± 2.3	9.7 ± 2.3	9.9 ± 2.1	10.0 ± 2.1	<0.05
Phosphate (mg/dL)	5.4 ± 1.5	5.2 ± 1.3	5.4 ± 1.5	5.4 ± 1.3	NS
Uric acid (mg/dL)	7.6 ± 1.4	7.5 ± 1.3	7.7 ± 1.5	7.8 ± 1.4	NS
Albumin (g/dL)	3.7±0.3	3.7 ± 0.2	3.7 ± 0.3	3.7 ± 0.3	NS
Total cholesterol (mg/dL)	164 ± 44	162 ± 43	166 ± 40	162 ± 42	NS
hsCRP (mg/L)	7.56 (050-59.90)	4.93 (0.50-80.40)	5.86 (0.50-80.10)	8.26 (0.50-75.00)	NS[a]
Fe (μg/dL)	50.5 ± 21.5	54.7 ± 15.6	52.1 ± 34.1	53.1 ± 19.9	NS
TIBC (μg/dL)	253 ± 72	253 ± 72	268 ± 51	255 ± 73	NS
Ferritin (ng/mL)	49.3 (6.2-394.0)	49.9 (6.5-515.0)	34.9 (5.4-664.0)	28.7 (5.9-267.0)	NS[a]
Plasma 8OHdG (ng/mL)	0.57 ± 0.30	0.57 ± 0.31	0.54 ± 0.20	0.54 ± 0.27	NS
Plasma MCP-1 (pg/mL)	333 ± 163	291 ± 146	322 ± 147	301 ± 130	<0.01
Plasma MPO (ng/mL)	45.0 ± 31.3	40.2 ± 22.8	35.5 ± 17.5	41.3 ± 23.1	<0.05
Plasma NT-proBNP (pg/mL)	4360 (542-21 200)	4395 (514-35 000)	3705 (564-22 900)	3185 (743-32 100) Mean ± SD, median (range)	NS[a]

One-way repeated measures ANOVA was used for statistical analysis. hsCRP, high-sensitive C-reactive protein; 8OHdG, 8-hydroxy-2'-deoxyguanosine; MCP-1, monocyte chemoattractant protein-1; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a]Data of log transformation were analysed by one-way repeated measures ANOVA.

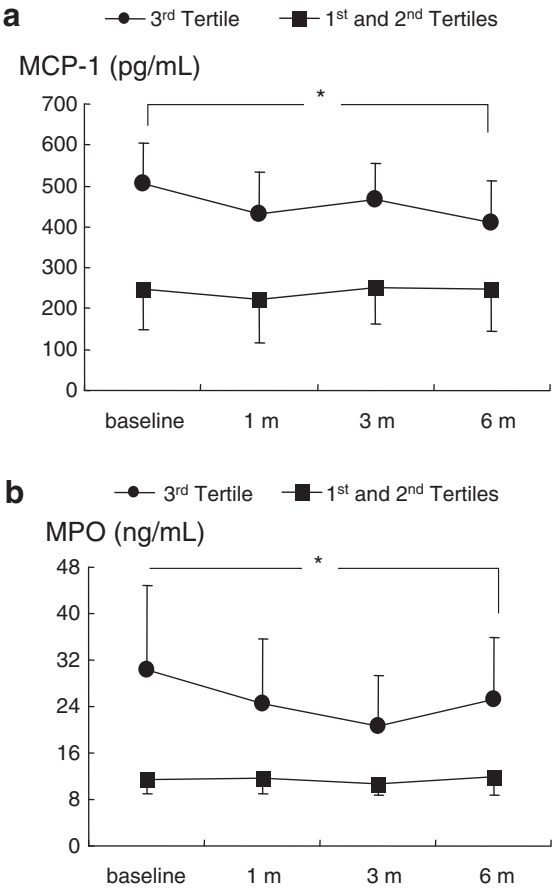

Fig. 4. Changes in plasma levels of (**a**) MCP-1 and (**b**) MPO. Significant decreases were identified in the third tertile groups in plasma levels of (a) MCP-1 ($P < 0.001$) and (b) MPO ($P < 0.05$) [by repeated measure ANOVA, *post hoc* test; (a) baseline *vs*. first and sixth month: $P < 0.05$ and $P < 0.01$, respectively; (b) baseline *vs*. third month: $P < 0.01$; closed circles: third tertile ($n = 7$); closed squares: first and second tertiles ($n = 14$); data are expressed as mean ± SD].

Significant decreases in BP occurred following H_2-HD induction, supporting the previous observation in a short H_2-HD trial [16]. Notably, substantial correction of high BP was observed in the 6-month study period, with an accompanying trend towards reduction in the cardiac risk marker NT-proBNP [24]. Since no changes were noted in the use of anti-hypertensive agents, fluid removed by HD, and dry weights, changes in BP control could have contributed to the effects of H_2-HD. Two recent meta-analyses on anti-hypertensive treatments in HD patients [25,26] demonstrated the clinical significance of hypertensive control for patient outcomes. Presently, the main therapeutic strategies for hypertension include administration of anti-hypertensive agents, reduction in dry weight (extracellular fluid volume) [27], and therapies such as short-daily HD [28], or nocturnal HD [29]. The present H_2-HD system represents a novel therapy to achieve better BP control.

The mechanism of anti-hypertensive effect of H_2-HD is likely due to the significant anti-oxidative capacity of H_2, which suppresses radical oxygen species (ROS) and peroxynitrite in patients. A pathological interaction exists between oxidative stress and inflammation. Oxidative stress activates nuclear factor kappa B to produce chemokines and cytokines, leading to macrophage activation. This increases ROS production, reduces the availability of antioxidants and increases oxidative stress [30]. A causal link exists between oxidative stress and hypertension in experimental renal failure models [31,32], upregulation of NADPH oxidase in cardiovascular tissues, and reduced nitric oxide (NO) availability by oxidative stress, which includes decreased NO production and enhanced NO inactivation accompanying production of peroxynitrite, a potent vasoconstrictor. This NO deficiency increases sympathetic activity, decreases vasodilatory tone and promotes remodelling of the arterial walls, leading to uraemic hypertension [30]. In the H_2-HD system, H_2 acts as an antioxidant and is delivered in the HD solution where it reacts

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with hydroxyl radicals to produce H_2O and hydrogen atoms, which may further suppress ROS activation. Thus, these results, along with the possible mechanism underlying development of hypertension by oxidative stress, suggest that changes in bioavailability of NO may be involved in the improvement of hypertension in patients on H_2-HD.

Some issues remain to be clarified. Firstly, previous animal studies [8–10] have described H_2 levels dissolved in EW ca 800 ppb, while the present study exposed patients to H_2 at average levels of 48 ppb. The levels of H_2 that are adequate and safe for clinical use need to be determined based on dose–response effects. Secondly, the idea of applying water electrolysis technology to HD treatment was first introduced by Huang *et al*. [33], and we employed this technology to deliver H_2 to the HD solution. The H_2 is generated on the cathode side, as bubbles with nanoscale diameters [34], which is likely different from those produced by the simple bubbling methods used in previous studies [8,9,10]. Furthermore, this technology gives electrolysed water unique features, such as superoxide dismutase as well as catalase-like activities [14]. Therefore, the effects of H_2-HD may not be identical to that produced by H_2 bubbling in water. Finally, the inflammatory conditions of the subjects were not clinically prominent, and the study period was short. Thus, studies are needed to clarify the impact of H_2-HD on patients with more severe inflammation.

In conclusion, H_2 application to HD solutions appears to ameliorate inflammatory reactions and improve BP control. This bioactive system could provide a novel therapeutic option for uraemia control.

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Conflict of interest statement. Tohoku University received a research grant from Nihon Trim Co. Ltd., but otherwise, the authors have nothing to declare.

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Relation between serum fibroblast growth factor-23 level and mortality in incident dialysis patients: are gender and cardiovascular disease confounding the relationship?

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Abstract

Background. Circulating fibroblast growth factor-23 (FGF23) promotes renal phosphate excretion and is markedly increased in patients with chronic kidney disease. High serum FGF23 is associated with cardiovascular risk factors and was recently identified as a predictor of total mortality in haemodialysis patients. Herein, our aim was to evaluate the relation between FGF23 and mortality, including the impact of gender and cardiovascular disease (CVD), in a Swedish cohort of 'incident' dialysis patients.
Methods. Two hundred and twenty-nine incident dialysis patients (149 males; mean age 55 years) were included. Serum intact FGF23, calcium, phosphate, S-albumin, parathyroid hormone, high-sensitivity C-reactive protein and interleukin-6 were measured at baseline. Cardiovascular disease was defined as clinical symptoms and/or a history of CVD.
Results. During a median follow-up time of 23 months, 66 patients (29%) died. FGF23 levels positively correlated to calcium ($r = 0.27$, $P < 0.0001$), phosphate ($r = 0.40$, $P < 0.0001$), calcium × phosphate product ($r = 0.52$, $P < 0.0001$) and creatinine ($r = 0.18$, $P = 0.007$). In Cox proportional hazard models, FGF23 was not associated with increased mortality risk, neither in crude nor in multivariate adjusted models. However, in a subgroup analysis of men with prevalent CVD, FGF23 level above median was associated with higher mortality risk in crude models [hazard ratio 2.19, 95% confidence interval 1.04–4.60, $P = 0.04$].
Conclusions. In primary analysis, serum FGF23 was not associated with increased mortality risk in this cohort of 'incident' dialysis patients. Our data support that the impact of FGF23 on mortality may be modified by gender and CVD and, as previously shown, is blunted in the setting of pronounced hyperphosphatemia.

Keywords: chronic kidney disease; CKD; FGF23; FGF-23; mortality

Introduction

Fibroblast growth factor-23 (FGF23) is a circulating factor that has become a central player in chronic kidney disease–mineral and bone disorder (CKD–MBD) [1]. The physiological function of FGF23 is to decrease serum levels of inorganic phosphate (Pi) and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) by direct actions on the kidney [2–4]. Additionally, FGF23 was recently shown to suppress synthesis and secretion of parathyroid hormone (PTH) [5,6]. Circulating FGF23 levels rise with declining renal function [7], presumably as a compensatory mechanism to counteract Pi retention and development of secondary hyperparathyroidism.

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