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Particulates formed in dialysis fluid: effect of silica in tap water

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Abstract

Background: A fluid commonly used for dialysis in Japan is prepared from two dialysate concentrates and dialysis water. Silicon (Si) from tap water is reported in dialysis water as suspended insoluble particulate matters. We aimed to examine the source of insoluble particulate matters in the online prepared substitution fluid and to examine effects of the silica (SiO₂) of tap water on the SiO₂ of dialysis water.

Method: Based on the number of particles and particle size distribution in online prepared substitution fluid, we evaluated particle diameters and constituent elements of particles in online prepared substitution fluid. To identify sources of insoluble particulate matters in the online prepared substitution fluid, we measured particle diameters and constituent elements of particles adhering to the surface of hollow fiber of the final endotoxin-retentive filter (ETRF) and to the inner surface of the housing of the final ETRF and measured SiO₂ in tap water, dialysis water, and commercial sterile substitution fluid.

Results: Si-containing particles accounted for 83% of 30 particles detected in the final ETRF (the hollow fibers and the housing) and the online prepared substitution fluid sampled from the final ETRF. The large variability in the SiO₂ in tap water depending on the geographic regions. The SiO₂ in dialysis water was 0.4–0.7 mg/L. Si was not detected in particles in the commercial sterilized substitution fluid, and the commercial sterile substitution fluids contained SiO₂ at 0.1 mg/L.

Conclusion: We presume that insoluble particulates in online prepared substitution fluid were calcium and magnesium precipitated from dialysate and Si precipitated from dialysis water. Moreover, variation in the SiO₂ in tap water is a factor affecting the SiO₂ level in dialysis water. If the formation of silicates in the online prepared substitution fluid is considered and the target SiO₂ in dialysis water is to be set ≤ 0.1 mg/L, SiO₂ in tap water available in hospitals and dialysis centers should be known before specifications of instruments for dialysis fluid preparation are determined.

Keywords: Dialysate, Particle, Silica, Insoluble particulate matter, Online prepared substitution fluid, Online hemodiafiltration

Background

A fluid commonly used for dialysis in Japan is prepared from two dialysate concentrates (acid, A; bicarbonate, B) and dialysis water. The dilution ratio is dialysate concentrate A/dialysate concentrate B/dialysis

water = 1:1.26:32.74. Moreover, the dialysate concentrates A and B are prepared by dissolving the powdery dialysate concentrates in dialysis water. Therefore, the quality of dialysis fluid largely depends on the quality of dialysis water [1]. While the powder dialysate concentrates are manufactured in accordance with the Japanese Pharmacopoeia (JP) [2], dialysis water is primarily manufactured from tap water; therefore, the Japanese Society for Dialysis Therapy (JSDT) has proposed two sets of standards for dialysis water, standard established for

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biological contamination and water quality standard for chemical contaminants [3]. However, silicon (Si) from tap water is reported in dialysis water as suspended insoluble particulate matters [4]. Furthermore, the JSDT standards do not reference insoluble particulate matters in dialysis water or dialysis fluid.

In online hemodiafiltration (HDF) therapy, 10–100 L of online prepared substitution fluid per dialysis session is infused into the blood of a patient undergoing extracorporeal circulation [5]. An online prepared substitution fluid is produced by filtration, through an endotoxin-retentive filter (ETRF), of a dialysis fluid [6]. Based on the ETRF specifications, insoluble particulate matters $>0.1 \mu\text{m}$ are unlikely through ETRF; however, a study showed the presence of insoluble particulate matters in dialysis fluids filtered with an ETRF [4]. With the allowance that the injection volume of online prepared substitution fluid is used in a larger quantity than commercial sterile substitution fluid, even the trivial amount of insoluble particulate matters might lead to eventual health hazard.

In the present study, we first measured the number of particles and particle size distribution in online prepared substitution fluid prepared using ETRF on a bedside dialysis console of the central dialysis fluid delivery system (CDDS) [7] that is cleaned using peracetic acid, commercial sterile substitution fluid, and 5% glucose injection. Referring to the JP and a special report by the American Society for Parenteral and Enteral Nutrition [8], we assessed the number of particles per 1 mL of the sample based on the following four categories of particle diameters: $<5 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$. Based on the number of particles and particle size distribution, we evaluated the particles in online prepared substitution fluid using the highest number, the particles in commercial sterile substitution fluid, and 5% glucose injection using SEM–EDS that combines scanning electron microscopy (SEM) and energy-dispersive X-ray spectrometry (EDS). To identify sources of insoluble particulate matters in the online prepared substitution fluid, we measured particle diameters and constituent elements of particles adhering to the surface of hollow fiber of the final ETRF and to the inner surface of the housing of the final ETRF using SEM–EDS and measured silica (SiO_2) in tap water, reverse osmosis (RO) water, dialysis water, commercial sterile acidic substitution fluid, commercial sterile bicarbonate substitution fluid, and 5% glucose injection with inductively coupled plasma optical emission spectroscopy (ICP–OES). In addition, since Matsumoto et al. have reported large differences in the Si level in tap water for preparing dialysis water depending on geographical regions [9], we determined SiO_2 in tap water samples collected in various regions of Japan.

In this manner, we aimed to examine the source of insoluble particulate matters in the online prepared substitution fluid and to examine effects of the SiO_2 of tap water on the SiO_2 of dialysis water. These data are expected to establish specifications of instruments for preparing dialysis fluid in hospitals and dialysis centers to offer online prepared substitution fluid to provide the same level with the commercial sterile substitution fluid.

Methods

Central dialysis fluid delivery system

CDDS consists of a water treatment equipment (VCR-81NF-RUHS; Daicem Membrane Systems, Tokyo, Japan), a multipatient dialysis fluid supply unit (MDSU) (DAB-20NX; NIKKISO, Tokyo, Japan), an acid powder mixing device (AHI-502; DKK-TOA, Tokyo, Japan), a bicarbonate powder mixing device (BHI-502, DKK-TOA, Tokyo, Japan), and 12 bedside dialysis consoles (DCS-100NX; NIKKISO, Tokyo, Japan). The recovery rate of the reverse osmosis unit is approximately 75%, and the mean conductivity is $4.4 \mu\text{S}/\text{cm}$. A bedside dialysis console is equipped with two ETRFs in series. The dialysis fluid piping has two systems—22 m and 15 m long—and each system has six bedside dialysis consoles connected. For the powder of dialysis fluid concentrate, Kindaly® 4E (Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) is used. The CDDS disinfection method was post-dialysis rinsing for 30 min, followed by disinfection with sodium hypochlorite including a chelating agent (DIACLEAN; Kao, Tokyo, Japan; used after 140-fold dilution) for 40 min. After 40 min of disinfection, sodium hypochlorite including a chelating agent was retained overnight. Then, pre-dialysis rinsing was performed for 60 min. This disinfection process was performed three times a week. The method for acid cleaning of CDDS was post-dialysis rinsing for 30 min, followed by disinfection with sodium hypochlorite including a chelating agent (DIACLEAN; Kao, Tokyo, Japan; used after 140-fold dilution) for 40 min. After rinsing with dialysis water for 30 min, the system was cleaned with peracetic acid (SURGITECT; Kao, Tokyo, Japan; used after 100-fold dilution) for 40 min, and the peracetic acid solution was retained overnight. Then, pre-dialysis rinsing was performed for 60 min. This process was performed three times a week. Under these conditions, there were no CDDS issues because of carbonate.

Materials

We mixed the commercial sterile acidic substitution fluid and the commercial sterile bicarbonate substitution fluid used for offline HDF (SUBPACK-Bi®; NIPRO, Osaka, Japan) and heated the mixture for 20 min in a constant temperature water bath at $80 \text{ }^\circ\text{C}$. The commercial sterile substitution fluid heated to $36 \text{ }^\circ\text{C}$ and 5% glucose

injection (OTSUKA GLUCOSE INJECTION; Otsuka Pharmaceutical, Tokyo, Japan) were the target of the study.

Measuring the number of particles

The number of particles was measured under the following conditions according to the JP standard [2]. It was confirmed that the environment for the measurement was in accordance with the JP standard before counting particles. To remove foreign substances adhering to the beaker for sampling, water for Injection (OTSUKA DISTILLED WATER; Otsuka Pharmaceutical, Tokyo, Japan) was used for cleaning. Particles were counted using a light obscuration particle counter (KL-04; RION, Tokyo, Japan) under ventilation stopped. Thresholds for particle diameter were set at 1.3, 2.0, 5.0, 10.0, 20.0, 25.0, 40.0, 50.0, and 100.0 μm . For each measurement, 5 mL of sample was used. After four measurements, the first result was excluded, and the second to the fourth were averaged. We assessed the number of particles per 1 mL of the sample based on the following four categories: particle diameters of $< 5 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$.

We randomly chose one dialysis console out of 12 consoles equipped with the final ETRF (EF-02; NIKKISO, Tokyo, Japan) with 1–6 months of use. We passed dialysis fluid through the final ETRF on the selected bedside dialysis console for 15 min (dialysis fluid flow rate of 500 mL/min). After washing beakers with the sample liquid three times, we collected 300 mL of each online prepared substitution fluid, the commercial sterile substitution fluid, and the 5% glucose injection and left the samples for 30 min to avoid the impact of gas bubbles with a size of $\geq 2 \mu\text{m}$ before counting particles [10].

Measurement of particle diameters and constituent elements in particles

At the same time as sampling of liquid for particles counting, we collected 20 mL of each online prepared substitution fluid, the commercial sterile substitution fluid, and the 5% glucose injection in 50 mL centrifuge tubes (50-mL Super Clear Centrifuge Tubes 3191–335; Labcon North America, California, USA) after rinsing three times. Particles were captured with a membrane filter (0.4 μm pore size, FJ-VKF04; Koyo Sangyo, Tokyo, Japan) under the same conditions as counting of particles. To prevent precipitation of components onto the membrane filter, 20 mL of each liquid in the centrifuge tube and 50 mL of water for Injection were placed on the membrane filter while mixing, and particles from each liquid in the centrifuge tube were captured on the membrane filter. Our targets were particles in online prepared substitution fluid with the largest number. After suction, we coated the membrane filter with particles with

osmium. We measured the particle diameter and elemental analysis of 10 particles on the coated membrane filter using SEM–EDS (accelerating voltage 8 kV) that combines SEM (Supra40; Carl Zeiss Microscopy GmbH, Jena, Germany) and EDS (XFlash 6|10; Bruker, Massachusetts, USA).

Observation of the final ETRF with SEM–EDS

After collecting the online prepared substitution fluid, we rinsed the CDDS with the dialysis water for 90 min to prevent precipitation of residual dialysis fluid components from the dialysis fluid piping. After rinsing, the final ETRF was removed from the dialysis console. This final ETRF was cut at 6 cm from the dialysis fluid inlet, and then it was air-dried until there was no remaining moisture. From six final ETRF that were treated in this manner, we selected the final ETRF that was directly connected to the sampling point for online prepared substitution fluid with the highest number of particles. We coated 10 central fibers of the selected final ETRF and 10 hollow fibers closest to the housing of the final ETRF with osmium. We analyzed the 2 cm of the osmium-coated hollow fibers on the dialysis fluid inlet side with SEM–EDS (accelerating voltage 8 kV). Referring to the result of particle numbers, we measured particle diameters and performed elemental analysis for 10 particles each. We also collected the housing of the selected final ETRF and coated it with osmium. We measured particle diameter and performed elemental analysis on the total of 10 particles adhering to the inner surface of the osmium-coated housing using SEM–EDS (accelerating voltage 8 kV) while referring to the result of particle numbers.

SiO₂ measurement

After the CDDS was rinsed with dialysis water for at least 90 min, water samples were collected in polyethylene bottles from the following three points: tap water used for the CDDS, the water treatment equipment (RO permeate), and the substitution fluid sampling point (dialysis water) (100 mL each) (location of collection, Bunkyo-ku, Tokyo; collection period, April–September 2017). To compare SiO₂ in tap water, RO permeate, and dialysis water samples with SiO₂ in commercial drugs, commercial sterile acidic substitution fluid, commercial sterile bicarbonate substitution fluid, and 5% glucose solution (100 mL each) were collected in polyethylene bottles. Furthermore, to compare tap water in various geographic regions of Japan, tap water samples were collected in polyethylene bottles at Kita-ku, Sapporo; Aoba-ku, Sendai; Bunkyo-ku, Tokyo; Nakamura-ku, Nagoya; Yodogawa-ku, Osaka; Naka-ku, Hiroshima; and Hakata-ku, Fukuoka (100 mL each) (collection period, the first week of April 2017). Polyethylene bottles cleaned with purified water

were washed in advance with the solution to be collected three times. SiO₂ in the tap water, RO permeate, dialysis water, commercial sterile acidic substitution fluid, commercial sterile bicarbonate substitution fluid, and 5% glucose solution collected as above were measured by ICP-OES (730-ES; Agilent Technologies, CA, USA) according to the Standard Methods for the Examination of Water of the Japan Water Works Association [11].

Results

Number of particles

Table 1 shows particle counts in the online prepared substitution fluid, commercial sterilized substitution fluid, and 5% glucose solution samples. Particles whose diameter ≥ 5 μm were detected in all samples. The largest number of particles was detected in the commercial sterilized substitution fluid. Among the online prepared

substitution fluid samples, the largest number of particles was reported in the sample from the final ETRF tested after 3 months of use.

Particle diameter and elemental analysis

Figure 1 shows SEM images and EDS mapping results for particles in the online prepared substitution fluid sample collected from the final ETRF after 3 months of use, the commercial sterilized substitution fluid sample, and the 5% glucose solution sample. Oxygen (O) and Si were detected in particles in the online prepared substitution fluid collected from the final ETRF after 3 months of use. Carbon (C) and O were detected in particles in the commercial sterilized substitution fluid and 5% glucose solution samples. Table 2 shows the particle diameter measurement and constituent element analysis results for 10 particles in the online

Table 1 Number of particles

Particle size (μm)	Number of particles (/mL)						Commercial sterile substitution fluid	5% glucose injection
	Online prepared substitution fluid							
	Final ETRF use time (month or months)							
	1	2	3	4	5	6		
<5	2.7	2.5	2.0	1.7	1.0	0.7	488.0	4.3
5 ≤	0.7	0.1	1.7	0.6	0.8	0.2	9.5	0.2
10 ≤	0.1	0.0	0.7	0.2	0.2	0.1	0.5	0.0
25 ≤	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0

The number of particles in online prepared substitution fluid, commercial sterile substitution fluid, and 5% glucose injection. ETRF stands for endotoxin-retentive filters

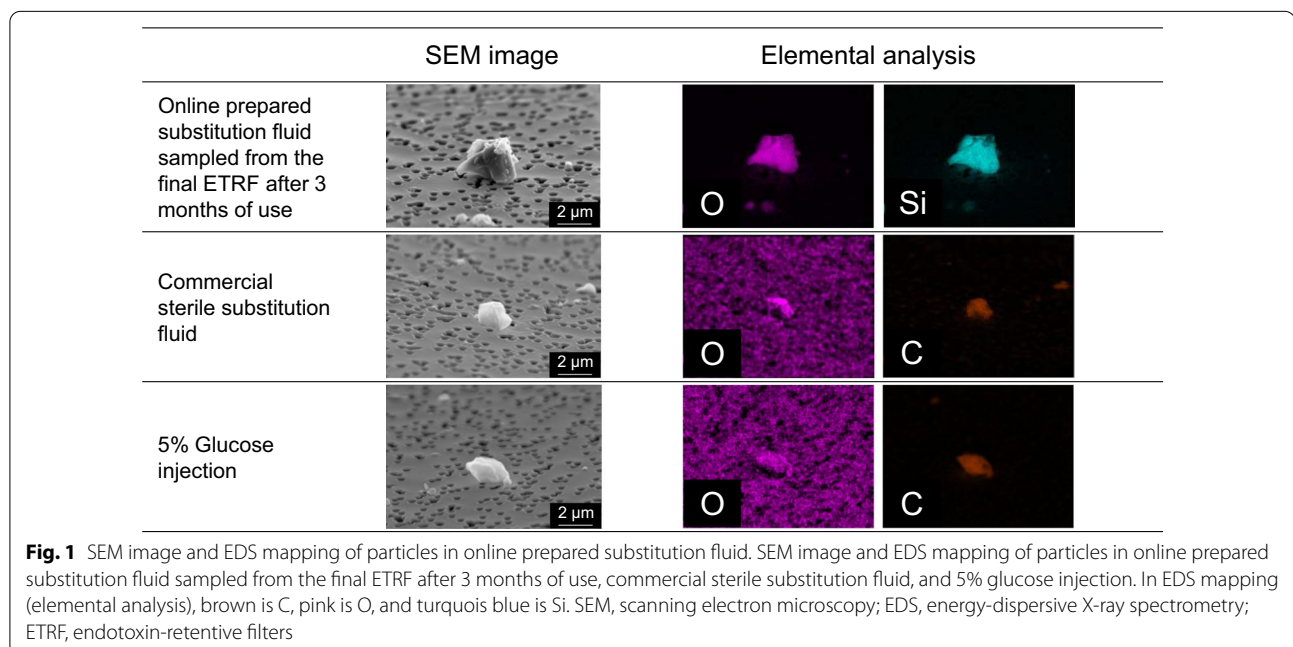


Table 2 Particle diameter and constituent elements analysis

Online prepared substitution fluid sampled from the final ETRF after 3 months of use		Commercial sterile substitution fluid		5% glucose injection	
Particle size (µm)	Element	Particle size (µm)	Element	Particle size (µm)	Element
0.705	O Si	1.306	C O	1.051	C O
1.026	C O Ca	1.337	C O	1.661	C O
1.137	C O Ca	1.537	C O	1.787	C O
1.588	O Mg Si	1.590	C O	1.836	C O
1.749	C O Ca	1.738	C O	1.924	C O
1.939	O Mg Si	1.917	C O	1.986	C O
2.190	O Mg Si	1.988	C O	2.605	C O
2.613	O Si	2.810	C O	2.904	C O
3.724	O Si	4.913	C O	3.228	C O
10.700	O Mg Si	7.043	C O	5.000	C O

Particle diameter and constituent elements for 10 particles each from online prepared substitution fluid sampled from the final ETRF after 3 months of use, commercial sterile substitution fluid, and 5% glucose injection. In constituent elements, C is carbon, O is oxygen, Mg is magnesium, Si is silicon, and Ca is calcium. ETRF stands for endotoxin-retentive filters

prepared substitution fluid sampled from the final ETRF after 3 months of use, the commercial sterilized substitution fluid, and the 5% glucose solution. Of the particles in the online prepared substitution fluid sample collected from the final ETRF used for 3 months, three particles were composed of C, O, and calcium (Ca), three particles were composed of O and Si, and four particles were composed of O, magnesium (Mg), and Si. All ten particles in the commercial sterilized substitution fluid sample or the 5% glucose solution sample were composed of C and O.

Diameter and constituent elements of particles adhering to the final ETRF

Figure 2 shows SEM images and EDS mapping results for the surface of central fibers from the final ETRF used for 3 months, the surface of hollow fibers closest to the housing of the final ETRF, and the inner surface of the housing of the final ETRF. No particles were found on the surface of central fibers in the final ETRF. O, Mg, and Si were detected in the particles on the surface of the hollow fibers closest to the housing of the final ETRF. O and Si were detected in the particles on the inner surface of the housing of the final ETRF.

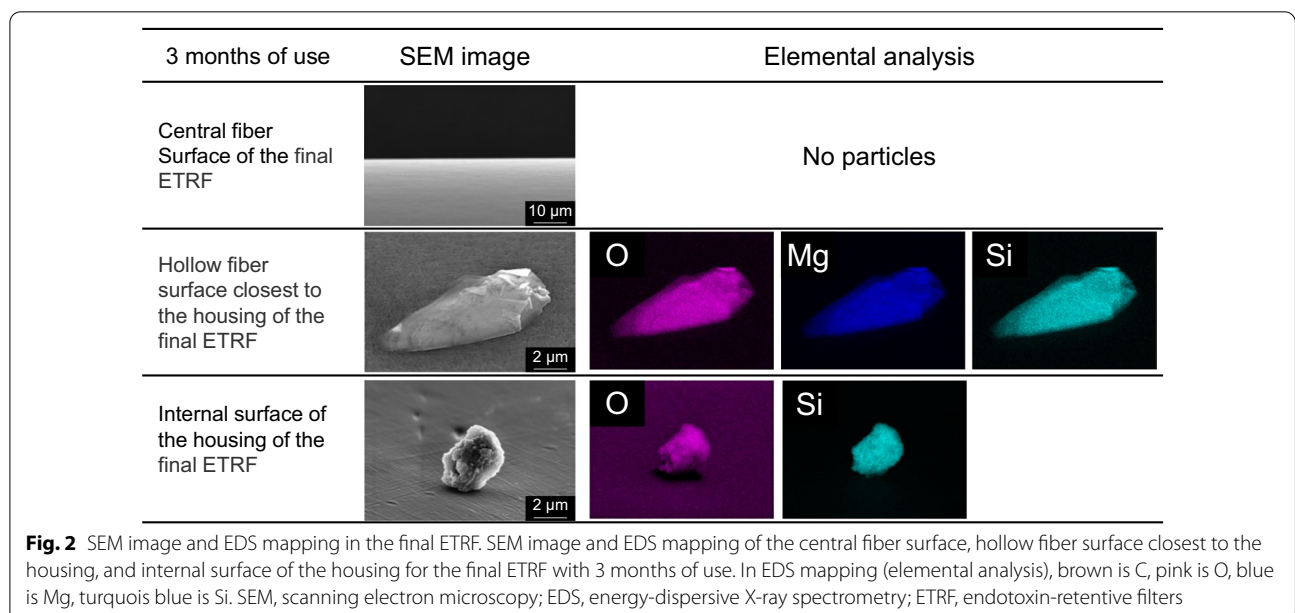


Table 3 Particle diameter and constituent of particles adhering to the final ETRF

Hollow fiber surface closest to the housing of the final ETRF after 3 months of use		Inner surface of the housing of the final ETRF after 3 months of use	
Particle size (µm)	Element	Particle size (µm)	Element
0.543	O Mg Si	1.607	O Si
1.550	O Mg Si	1.645	O Si
2.598	O Mg Si	1.727	C O Ca
3.943	O Mg Si	2.455	O Si
4.797	O Mg Si	2.696	C O Ca
5.304	O Mg Si	5.942	O Mg Si
5.419	O Mg Si	7.607	O Mg Si
11.290	O Mg Si	7.914	O Si
17.230	O Mg Si	12.800	O Si
22.590	O Mg Si	29.770	O Mg Si

Particle diameter and constituent elements for 10 particles each from particles on the hollow fiber surface closest to the housing of the final ETRF and particles on the inner surface of the housing of the final ETRF after 3 months of use. In constituent elements, C is carbon, O is oxygen, Mg is magnesium, Si is silicon, and Ca is calcium. ETRF stands for endotoxin-retentive filters

Table 3 shows the particle diameter measurement and constituent element analysis results for ten particles on the surface of the hollow fibers closest to the housing of the final ETRF used for 3 months and ten particles on the inner surface of the housing of the final ETRF. All of the ten particles on the surface of the hollow fibers closest to the housing of the final ETRF used for 3 months were composed of O, Mg, and Si. Of the ten particles on the inner surface of the housing of the final ETRF, five particles were composed of O and Si, two particles were composed of C, O, and Ca, and three particles were composed of O, Mg, and Si.

SiO₂

Table 4 shows SiO₂ in tap water used for CDDS, RO permeate, dialysis water, commercial sterile acidic and bicarbonate substitution fluids, and 5% glucose solution. The lower limit of quantification of SiO₂ was 0.1 mg/L. The SiO₂ in tap water and RO permeate was 5.8–7.7 and 0.4–0.7 mg/L, respectively. The SiO₂ in dialysis water samples collected from the substitution fluid sampling point once a month until 6 months after the use of the final ETRF was started was 0.4–0.7 mg/L. Both the commercial sterile acidic and bicarbonate substitution fluids contained SiO₂ at 0.1 mg/L. The SiO₂ in the 5% glucose solution was below the lower limit of quantification. Figure 3 shows the SiO₂ in tap water samples collected in various regions of Japan. The tap water samples from Sapporo, Sendai, Tokyo, and Fukuoka tended to contain higher levels of SiO₂, and the tap water samples from Nagoya, Osaka, and Hiroshima tended to contain lower levels of SiO₂.

Discussion

Formation mechanism of insoluble particulate matters in the final ETRF

Among the online prepared substitution fluid samples, the largest number of particles was detected in the online prepared substitution fluid sample collected from the final ETRF after 3 months of use. 1.7 particles with a diameter of 5 µm or larger were detected per 1 mL of the online prepared substitution fluid sampled from the final ETRF used for 3 months. Single-use filters, used for infusion therapy in critically ill patients, are effective in preventing particulates from entering the body and reduce the incidence of systemic inflammatory response syndrome (SIRS) [12]. However, ETRFs for preparing ultrapure dialysis fluid are reused in various countries [13].

Table 4 SiO₂ concentration in various portions of CDDS and in commercial sterile solutions

	SiO ₂ (mg/L)					
	Final ETRF use time (month or months)					
	1	2	3	4	5	6
CDDS						
Tap water	6.1	5.8	6.1	7.7	7.2	6.7
RO permeate	0.5	0.4	0.5	0.7	0.7	0.7
Dialysis water (substitution fluid sampling point)	0.5	0.4	0.5	0.7	0.7	0.7
Commercial sterile acidic substitution fluid	0.1					
Commercial sterile bicarbonate substitution fluid	0.1					
5% glucose injection	Below the lower limit of quantification					

SiO₂ in tap water used for CDDS, RO permeate, dialysis water, commercial sterile acidic substitution fluid and commercial sterile bicarbonate substitution fluid, and 5% glucose injection. CDDS central dialysis fluid delivery system, ETRF endotoxin-retentive filters, SiO₂ silica

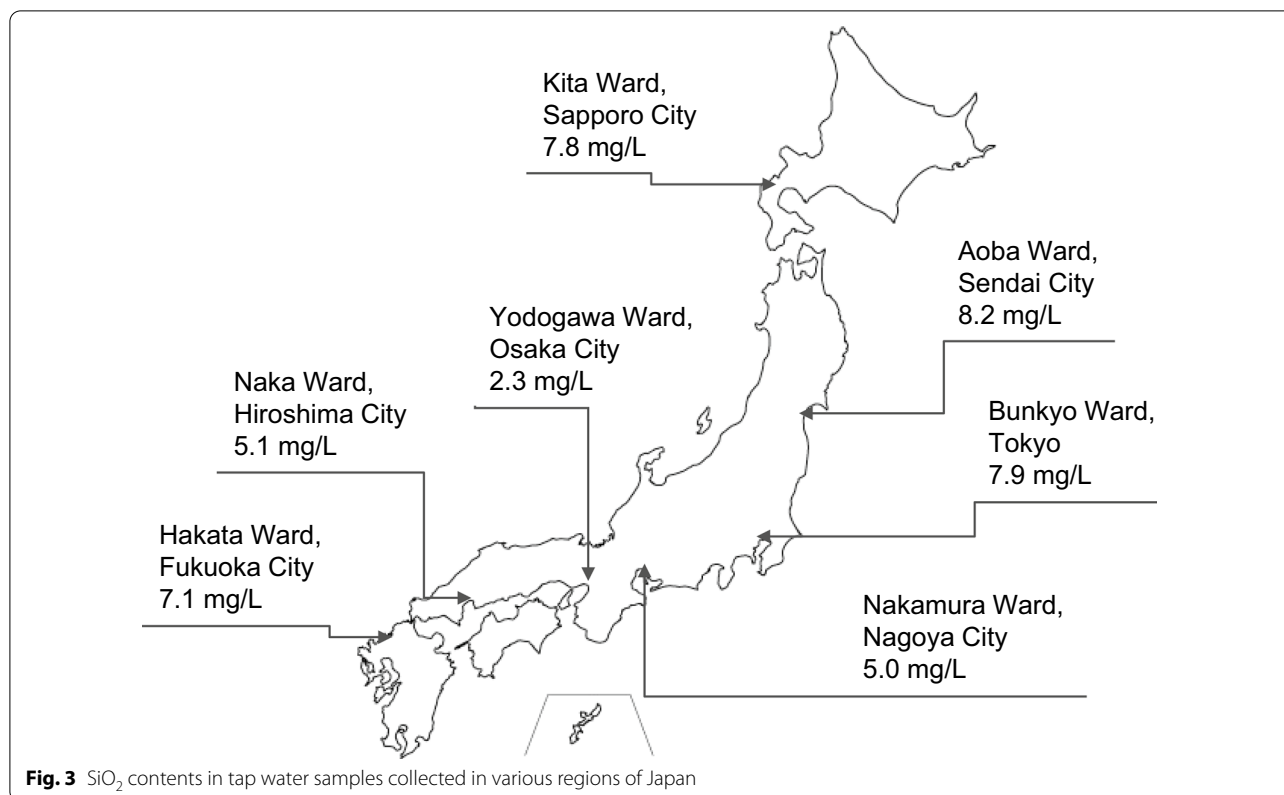
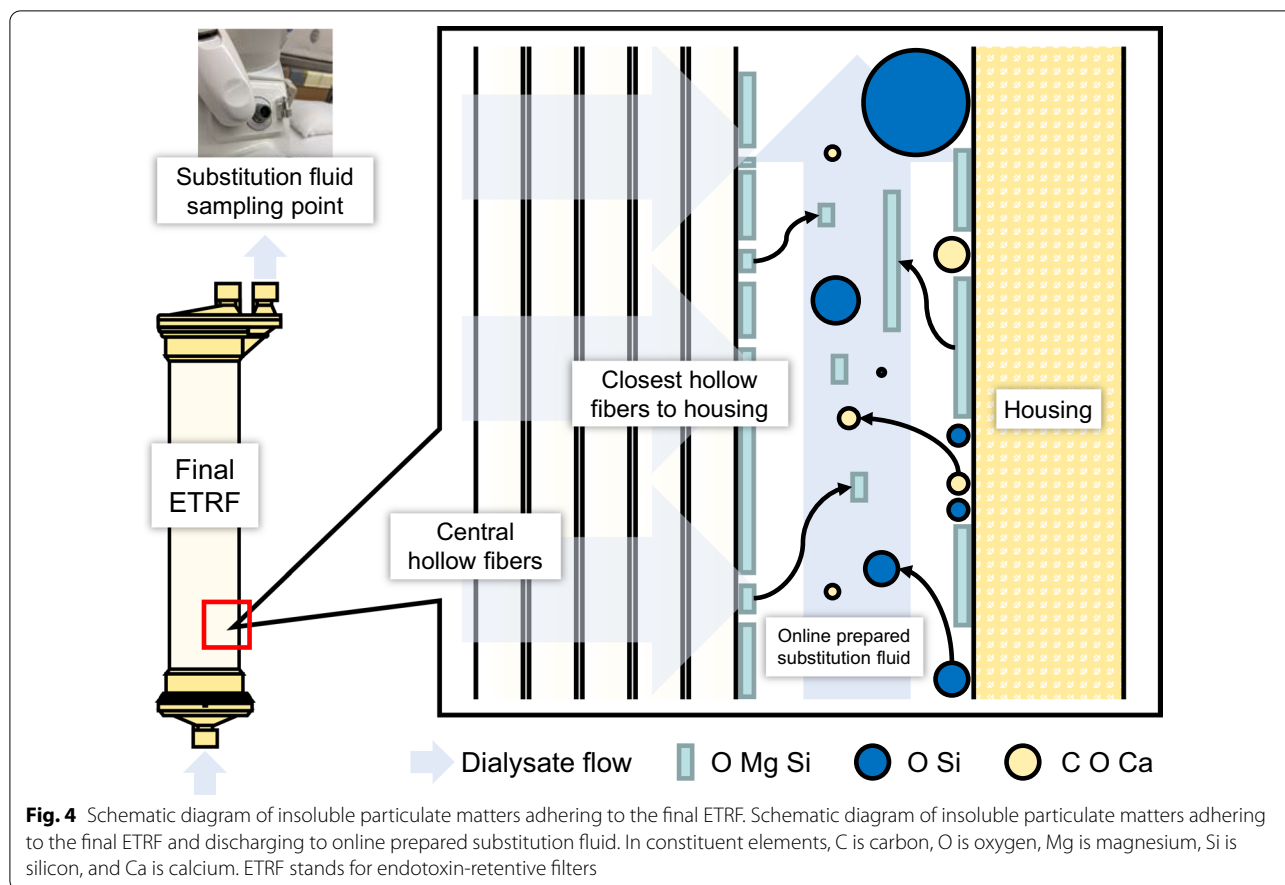


Figure 4 shows a schematic of insoluble particulate matters adherence to the final ETRF and discharge into the online prepared substitution fluid. In the final ETRF, filtration was made from inside the hollow fibers to the outside. No particles on the surface of the central fibers in the final ETRF were observed. In the rinse, peracetic acid cleaning, and disinfection processes, the fluids from a central fiber in the final ETRF rinse, peracetic acid-clean, and disinfect the surface of other central hollow fibers, and insoluble particulate matters are possibly prevented from adhering to the surface of the central hollow fibers. Furthermore, no particles were observed in the central part of the final ETRF because, even if insoluble particulate matters are formed, they flow out from the center to the housing during each process.

Particles composed of O, Mg, and Si were detected on the surface of the hollow fibers closest to the housing of the final ETRF. In the presence of ionic Mg, SiO₂ precipitates as an Mg-containing silicate (magnesium silicate) even at low SiO₂ concentrations [14]. Table 4 shows that the SiO₂ in the dialysis water is 4–7 times higher than that in the commercial sterile acidic or bicarbonate substitution fluid, while 89–93% of SiO₂ in tap water is removed by the water treatment equipment. The SiO₂ in the 5% glucose solution was below the lower limit of quantification. These results suggest that magnesium

silicate is prone to be formed in the online prepared substitution fluid. Moreover, only insoluble magnesium silicate [15] was attached to the hollow fibers closest to the housing of the final ETRF because these hollow fibers undergo less effective rinse, peracetic acid cleaning, and disinfection from the housing side compared with the central part of the final ETRF.

Particles composed of O and Si, C, O, and Ca, or O, Mg, and Si were detected on the inner surface of the housing of the final ETRF. Particles composed of O and Si are possibly amorphous SiO₂, which is formed by independent precipitation of SiO₂ in water [15]. Particles composed of C, O, and Ca are possibly CaCO₃ because the formation of Ca-containing carbonate (CaCO₃) overrides the formation of Ca-containing silicate [16]. The detection of only magnesium silicate on the surface of the hollow fibers closest to the housing of the final ETRF suggests that the inner surface of the housing undergoes less effective rinse, peracetic acid cleaning, and disinfection compared with the central part of the final ETRF and thus is prone to the formation of particles. Moreover, it is possible that insoluble particulate matters formed on the surface of the central fibers or the hollow fibers closest to the housing of the final ETRF were discharged during rinse, peracetic acid cleaning, and disinfection processes and attached to the inner surface of the housing.



The substitution fluid sampling point where online prepared substitution fluid was collected is directly connected to the final ETRF; therefore, entrance of particles of CaCO_3 , amorphous SiO_2 , and magnesium silicates to the body of a patient undergoing online HDF is unavoidable, as long as the online prepared substitution fluid is prepared using reused ETRF.

Particles in the commercial sterile substitution fluid and 5% glucose injection, and Si-containing particles in online prepared substitution fluid

The largest number of particles was detected in the commercial sterilized substitution fluid. Given a relatively low ionization degree of sodium hydrogen carbonate in commercial sterilized substitution fluids (0.88 at 36 °C), sodium hydrogen carbonate presumably existed as an insoluble salt [17]. Only particles entirely composed of C and O were detected in the commercial sterilized substitution fluid and 5% glucose solution. The data shown in Fig. 1 suggest that glucose, which was not completely dissolved, was collected by the membrane filter and measured by SEM-EDS. Therefore, particles in the commercial sterilized substitution fluid and 5% glucose

solution were considered to be derived from glucose. Because the average diameter of human pulmonary capillaries is 5 μm [18], particles greater than 5 μm in diameter can obstruct blood flow in the pulmonary capillaries and have a risk of causing complications such as pulmonary embolism [8]. However, glucose is soluble and is not able to obstruct blood flow in the pulmonary capillaries.

Si-containing particles accounted for 83% of 30 particles detected in the final ETRF used for 3 months (the hollow fibers and the housing) and the online prepared substitution fluid sampled from the final ETRF used for 3 months. Si was not detected in particles in the commercial sterilized substitution fluid and 5% glucose solution. Both the commercial sterile acidic and bicarbonate substitution fluids contained SiO_2 at 0.1 mg/L. The SiO_2 in the 5% glucose solution was below the lower limit of quantification. That information on Si and SiO_2 is not included in the commercial sterilized substitution fluid and 5% glucose solution package inserts or Medicine Interview Forms. Therefore, we presume that insoluble particulates in online prepared substitution fluid were Ca and Mg precipitated from dialysate and Si precipitated from dialysis water.

The concordant fluctuation in the SiO₂ level of dialysis water and tap water samples shown in Table 4 indicates that variation in the SiO₂ in tap water is a factor affecting the SiO₂ level in dialysis water. Figure 3 shows the large variability in the SiO₂ in tap water depending on the geographic regions. In Japan, sources of tap water include river water and ground water [19]. Water in regions with many volcanoes, such as Hokkaido and Kanto regions, have been known to contain high levels of SiO₂ [20]. Moreover, river water in the Chubu region tends to contain low levels of SiO₂, that in the Chugoku region contains low levels of SiO₂, and that in the Kyushu region contains the highest levels of SiO₂ [21]. The SiO₂ in tap water sampled in the city of Osaka was the lowest; this is presumably attributable to sediment removal and spring diatom blooms in Lake Biwa, the source of the Yodo River flowing through Osaka City [19, 22]. As shown in Table 4, ETRFs cannot remove SiO₂ from the dialysis water and the water treatment equipment removed 89–93% of SiO₂ from tap water with a mean removal rate of 91%. Table 5 shows SiO₂ in dialysis water estimated with an assumed SiO₂ removal rate of 91% from tap water in various geographic regions of Japan. The lowest SiO₂ level in dialysis water with an assumed removal rate of 91% from tap water in various geographical regions of Japan was 0.2 mg/L, which is twice as high as the SiO₂ in the commercial sterilized substitution fluid. With online HDF necessitates the same (or even higher) quality as that of injectable agents manufactured by pharmaceutical companies [23] because the amount of infusion is much greater in online HDF than in a normal injection. If the target SiO₂ in dialysis water is to be set ≤ 0.1 mg/L, the water treatment equipment can be used to reduce SiO₂, and additional effective removal of SiO₂ can be achieved by combining the water treatment equipment with an electrodeionization (EDI) pure water production system [24].

This study is not enough since the relation between patients' health and Si-containing particles needs to be deeply considered by in vivo study such as using patients' samples. Si ingested by eating and drinking is excreted in urine, but in patients with renal failure, Si is not excreted in urine and is thought to accumulate [25, 26]. Therefore, serum Si concentrations in hemodialysis patients (64 ± 12 µg/dl) are higher than those in healthy subjects (< 20 µg/dl) [27]. In particular, serum Si concentrations of hemodialysis patients with bone diseases (76 ± 18 µg/dl) and hemodialysis patients with neurological disorders (86 ± 15 µg/dl) are significantly higher than those of hemodialysis patients without complications (64 ± 12 µg/dl), suggesting that high serum Si concentrations in hemodialysis patients are one of the causes of bone diseases and neurological disorders [27]. Atomic spectrometry methods used in the analysis of plasma Si concentrations evaluate the identification and concentration of the element [28]. This analytical method can evaluate the identification and concentration of Si, but it cannot distinguish the form of Si. Multiple forms of Si in water need to be considered, including soluble silica, ionic silica, soluble silicates, colloidal silica, silicates, inorganic and organic substances containing Si, and biological materials containing Si [29–31]. Removal of these Si-containing substances also requires consideration of the method of removal depending on the form of Si, such as removal with ion exchange resins if the Si is in ionic form, or removal with membrane devices such as reverse osmosis membranes if the Si is in colloidal form [32]. In addition, when silica is taken into the body other than by ingestion through food or drink (e.g., by inhalation or intravenous injection), it invariably shows some toxicity [33]. Based on these literature findings, the effects on hemodialysis patients regarding Si should be considered comprehensively, including serum Si concentration, the form of Si taken into the hemodialysis

Table 5 SiO₂ in dialysis water estimated with an assumed removal efficiency of 91%

Date	Sampling Ward	Locations City	SiO ₂ (mg/L)		
			Tap water (measured)	SiO ₂ removal (%)	Dialysis water (calculated)
Mar. 2017	Kita	Sapporo	7.8	91	0.7
	Aoba	Sendai	8.2		0.7
	Bunkyo	Tokyo	7.9		0.7
	Nakamura	Nagoya	5.0		0.5
	Yodogawa	Osaka	2.3		0.2
	Naka	Hiroshima	5.1		0.5
	Hakata	Fukuoka	7.1		0.6

SiO₂ in dialysis water estimated with an assumed removal efficiency of 91% for SiO₂ in tap water in various geographic regions of Japan. SiO₂, silica

patient's body, and the uptake pathway of silica taken into the hemodialysis patient's body. Based on the results of the current study, magnesium silicates (particles consisting of Mg and Si) are present in the online prepared substitution fluid and may serve as a trigger of the thrombus formation [34]. SiO₂ in the commercial sterilized substitution fluid and 5% glucose solution are ≤ 0.1 mg/L, and Ca, Mg, and Si were not detected in particles in commercial sterile substitution fluid and 5% glucose solution. Therefore, even if two ETRFs are connected in series, additional caution should be exercised for the online prepared substitution fluid because it contains insoluble particulate matters of CaCO₃, amorphous SiO₂, and magnesium silicates.

Conclusion

We evaluated particles in online prepared substitution fluid obtained from a peracetic acid-cleaned CDDS and particles attached to the final ETRF (hollow fibers and the housing) using SEM/EDS. We also measured SiO₂ contained in tap water collected from various regions of Japan, the commercial sterilized substitution fluid, and 5% glucose solution. The measurement results with particles in the online prepared substitution fluid and particles attached to the final ETRF revealed that Si-containing particles accounted for 83% of 30 particles detected in the online prepared substitution fluid and the final ETRF. The SiO₂ in tap water for producing dialysis water varied among the geographical regions from which the samples were collected. The commercial sterile substitution fluids contained SiO₂ at 0.1 mg/L. The SiO₂ in the 5% glucose solution was below the lower limit of quantification.

That information on Si and SiO₂ is not included in the powdery dialysate concentrates package inserts or Medicine Interview Forms. Therefore, we presume that insoluble particulate matters in online prepared substitution fluid were Ca and Mg precipitated from dialysate and Si precipitated from dialysis water. Moreover, variation in the SiO₂ in tap water is a factor affecting the SiO₂ level in dialysis water. If the formation of silicates in the online prepared substitution fluid is considered and the target SiO₂ in dialysis water is to be set ≤ 0.1 mg/L, SiO₂ in tap water available in hospitals and dialysis centers should be known before specifications of instruments for dialysis fluid preparation are determined.

Abbreviations

A: Acid; B: Bicarbonate; JP: Japanese Pharmacopoeia; JSDT: Japanese Society for Dialysis Therapy; Si: Silicon; HDF: Hemodiafiltration; ETRF: Endotoxin-retentive filter; CDDS: Central dialysis fluid delivery system; SEM: Scanning electron microscopy; EDS: Energy-dispersive X-ray spectrometry; SiO₂: Silica; RO: Reverse osmosis; ICP-OES: Inductively coupled plasma optical emission

spectroscopy; O: Oxygen; C: Carbon; Ca: Calcium; Mg: Magnesium; SIRS: Systemic inflammatory response syndrome; EDI: Electrodeionization.

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Author contributions

MI and KT designed the study. MI and MY contributed to data collection. MI performed the analysis. MI and AY wrote the original draft. All authors reviewed and approved the final draft of the 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

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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