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Dialysis Membranes — Physicochemical Structures and Features

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Additional information is available at the end of the chapter

1. Introduction

When functions of the living kidney decrease down to under survival level, patients are required to be treated with a system that supports kidney functions. There are several such treatment modalities available, including peritoneal dialysis (PD), hemodialysis (HD), hemofiltration (HF), hemodiafiltration (HDF), hemoadsorption (HA), and their advanced derivatives, among which the most popular treatment system is HD. The artificial kidney device used in HD is called "hemodialyzer" or more simply "dialyzer" that includes membrane to separate the waste products and excess water from blood.

Artificial kidney is also expected to correct pH that is usually acidic before treatment by balancing electrolytes in addition to removing waste products and excess water. All these functions are dependent upon the permeability of the membrane used in a dialyzer and since the quality of treatment is strongly dependent on the performance of the dialyzer, many materials have been proposed as a candidate of the membrane. We have currently several commercial materials available, including natural polymers and synthetic polymeric ones.

In this chapter, dialysis membrane and its materials are extensively discussed from the physicochemical points of view, including microscopic views taken by scanning electron microscope (SEM), mathematical expressions of membrane transport, fundamental *in vitro* experiments as well as *in vivo* trials or clinical experiences.

2. Basic principles and history of dialysis membrane

2.1. Law of diffusion

Dialysis is a phenomenon at which two different fluids (usually liquids) are separating flowing on either side of the membrane (usually counter-currently) and the solute of interest in higher concentration transports across the membrane due to concentration gradient in accordance with the Fick's 1-st law of diffusion, i.e.,

$$J_{Ax} = -D_{Ax}\frac{\partial C_A}{\partial x} \tag{1}$$

where x is the co-ordinate in the diffusion direction [m], J_{Ax} is the mass flux of solute A in x direction [kg/(s m²)], D_{Ax} is the diffusion coefficient of A in x direction [m²/s], and C_A is the concentration of A [kg/m³]. Dialysis, therefore, is one of separation techniques of the solute of interest by using the membrane and is applied elsewhere in many industrial as well as laboratory situations. Letting C_{A0} and C_{AL} to be the concentrations of A at $x=0$ and $x=L$, respectively (Figure 1), Eq.(1) is integrated in a straight-forward manner to get,

$$J_{Ax} = \left(\frac{D_{Ax}}{L}\right)(C_{A0} - C_{AL}) \equiv k_M \times (C_{A0} - C_{AL}) \tag{2}$$

where k_M is the membrane permeability [m/s] defined by (D_{Ax}/L). From Eq.(2), one would alternately mention that the rate of diffusion is proportional to the concentration difference between either side of the membrane. The value of k_M is discussed in section 4.
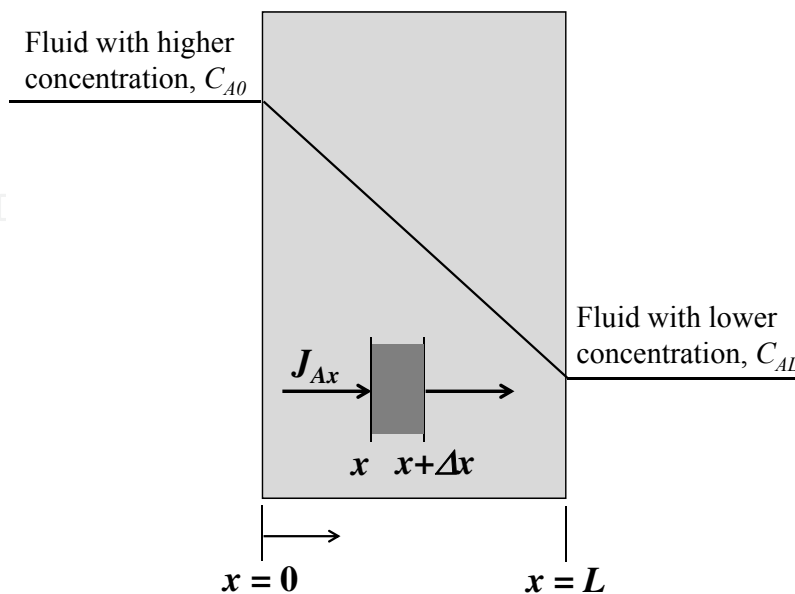

Figure 1. Diffusion across a piece of membrane assuming no existence of boundary film adjacent to either side of the membrane.

2.2. Dawn of hemodialysis

Application of dialysis to blood purification, hemodialysis (HD), was first performed for canines reported by Abel *et al.* in 1914 [1]. A chemical substance (sodium salicylate) was added to the subject as a marker prior to the experiment, mimicking the clinical situation of kidney failure in which waste products accumulate in the human body. Then the marker substance was removed by the dialyzer that included the membrane made of collodion. The dialyzer included 16 collodion tubes whose length was 40 cm that is 1.5 times longer than a currently available normal commercial model and the diameter was about 8 mm that is approximately 40 times larger than a popular hollow fiber membrane currently utilized worldwide. Since the collodion was too fragile to perform dialysis experiments, many other membranes cast from natural materials were examined whether or not they were suited as a separation membrane. Finally collodion was replaced by cellophane, and the first clinical trial was performed by Kolff *et al.* in 1943 with a rotating drum dialyzer, designed and assembled by themselves [2]. Separation performance of these dialysis membranes, however, was not discussed extensively at that time because mechanical strength of the materials was more important for performing experiments or treatments than the permeability of the membrane.

2.3. Development of commercial dialysis membranes

Cuprophan® is a registered name of the membrane made of cuprammonium rayon made from cellulose dissolved in cuprammonium solution, produced by Enka Co. in West Germany, later Membrana in Polypore Co., Germany. Another cuprammonium rayon membrane with nearly the same chemical and physical structures was developed by Asahi-Kasei Co. (Tokyo, Japan) termed Bemberg®, followed by Terumo (Tokyo, Japan). These membranes were also called regenerated cellulosic (RC) membrane since they were cast from cellulose or cotton fibers. Chemical modifications were made for RC membranes mostly because of improving their biocompatibility by replacing their hydroxyl group(s) with acetate group(s). They are called cellulose acetate (CA), cellulose diacetate (CDA), and cellulose triacetate (CTA) in accordance with the number of introduction of acetate groups to the cellulose backbone. Although RC membranes are no longer commercially available, CA, CDA, and CTA membranes still have fairly good market share since they have much higher solute and hydraulic permeabilities as well as better biocompatibility than original RC membranes.

The first synthetic polymeric membrane was developed in 1969 by Rhône-Poulenc (France) and was named AN-69®, since the main material of the membrane was acrylonitrile (AN). The brand name of the dialyzer assembled with a flat sheet AN-69® membrane was RP-6® and it was also the first dialyzer sterilized by the gamma-ray irradiation. Although the production company of AN-69® membrane has been changed over time from Rhône-Poulenc to Hospal, Gambro, and Baxter, dialyzers with AN-69® membrane are still available worldwide, especially in the field of acute kidney injury (AKI) therapy since it has strong adsorption characteristic to specific substances such as inflammatory cytokines.

The first dialyzer with a cellulosic hollow fiber membrane was developed by chemical engineers, Stuart and Lipps in 1967 [3] in Massachusetts Institute of Technology (Boston, MA, U.S.A.), and the commercial product was available in 1972 from Cordis-Dow Co. (Miami, FL,

U.S.A.). The basic structure of the hollow-fiber dialyzer is the same as the one of multi-tube heat exchanger that is compact and has large surface area. Because of these advantages, dialyzers with hollow fiber membrane have been become widely used. The first dialyzer with a synthetic polymeric hollow fiber membrane sterilized by gamma-ray was introduced by Toray Co. (Tokyo, Japan), in which polymethylmethacrylate (PMMA) was used as a main material of the membrane [4].

In order to improve solute and hydraulic permeabilities as well as biocompatibilities, many synthetic polymeric membranes have been introduced to the market since early 1980's, and currently these membranes are the main stream. Among them, polysulfone (PSf) and the like (including polyethersulfone (PES), polyarylethersulfone (PAES), etc.) have the highest market share over the world. Since these membranes are made from petroleum, they are hydrophobic in nature. Then most of these membranes include so-called hydrophilic agent that also plays a role of pore-forming agent when cast. The role of the hydrophilic agent is discussed later from the chemical (section 3), mass transport (section 4), and biological (section 5) points of view.

3. Chemical structures of dialysis membrane

3.1. Main material of the membrane

Chemical structure of the dialysis membrane usually refers to the chemical structural formula of the main material(s) of the dialysis membrane. Most chemical structural formulae of the main material of the membrane are tabulated in Table 1, including both natural and synthetic polymers. Among them AN-69®, ethylenevinylalcohol (EVAL) co-polymer, polyester polymer alloy (PEPA, Nikkiso Co., Tokyo, Japan, Figure 2) include two main materials. Actually PMMA is also a stereo complex co-polymer of two kinds of PMMA, isotactic and syndiotactic. Isotactic PMMA has acetate groups on only one side of the main chain, resulting a curled structure, whereas syndiotactic PMMA has acetate groups alternately on either side of the main chain, resulting a fairly straight structure. Combining these two polymers, membranes with low to high hydraulic permeability has been brought to realization [4].

3.2. Hydrophilic agent

In general, cellulosic membranes are hydrophilic in nature, including original RC and its derivatives such as CA, CDA, and CTA in which hydroxyl group(s) are replaced by acetate group(s). On the contrary, since synthetic polymeric membranes are originated from petroleum, generally speaking they are hydrophobic in nature. Blood coagulation usually occurs soon after blood interacts with hydrophobic materials. Most synthetic polymeric membranes, therefore, include so-called hydrophilic agent such as polyvinylpyrrolidone (PVP) to make membrane hydrophilic. Figure 2 includes the chemical structure of PVP together with two other polymers (polyarrylate and polyethersulfone). PEPA is composed of these two polymers with or without PVP, the former shows little hydrophobicity, while the latter has strong adsorptive characteristic to various proteins due to its hydrophobicity (see section 4).
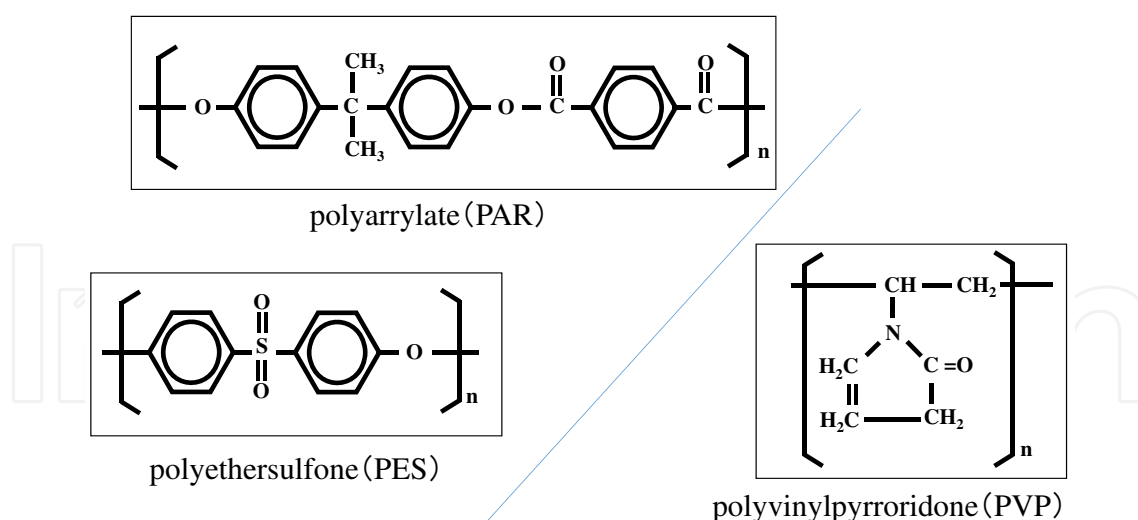
Figure 2. Chemical structures of polyester polymer alloy (PEPA) composed of PES and PAR with polyvinylpyrrori-done (PVP).

Table 1. Chemical structures of cellulosic and synthetic polymeric membranes for blood purification.

Since PVP is water-soluble, excess amount of PVP may be rinsed out from the membrane after cast that forms pores for solute and water transport. Therefore PVP is also known as a pore-forming agent. Namely, it should be understood that PVP residues in or on the membrane after rinse behave as a hydrophilic agent. Both an average and a distribution of molecular

weight of PVP are important as well as the amount of PVP used in the membrane. Moreover, PVP may be cross-linked together and to the main material of the membrane by irradiating gamma-ray in the final sterilization process. With this procedure, PVP should be tightly attached together and/or on the membrane that does not allow PVP to behave as a "cushion" (cushion effect) to the blood corpuscles [5].

Acrylic acid is specifically chosen for polyacrylonitrile (PAN, Asahi Kasei, different from AN-69®) as a hydrophilic agent, whereas no hydrophilic agent is used in PMMA, EVAL and the original PEPA in which micro-layer separation technology plays a significant role in casting procedure.

4. Physical structure of dialysis membrane

4.1. Homogeneous and asymmetry membrane

Physical structures can be demonstrated in the following two ways, i.e., microscopic view analysis and a theoretical analysis based on mathematical models. Microscopic views are usually taken by a scanning electron microscope (SEM). Recently the microscope technology has been advancing drastically and a field-emission SEM (FE-SEM) that has much higher resolutions can be utilized widely.
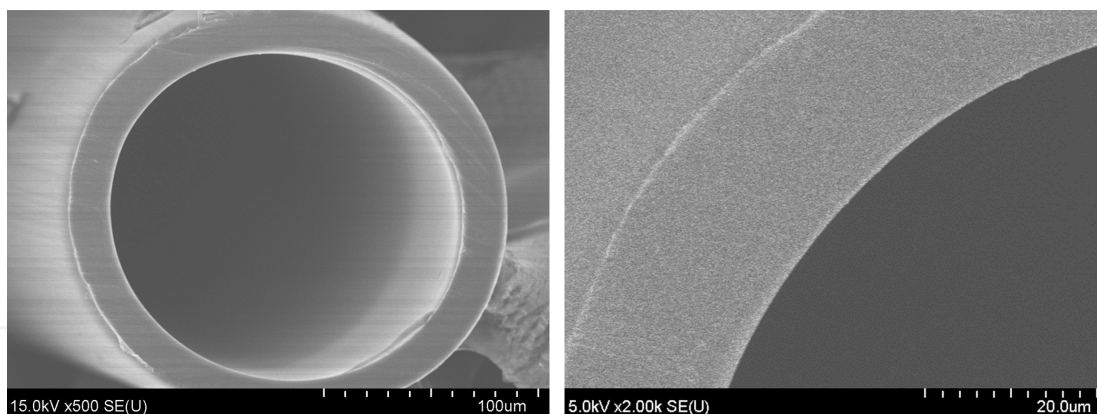

Figure 3. A cross-sectional view of EVAL hollow fiber membrane (Asahi-Kasei, Tokyo, Japan) taken by FE-SEM.

Figure 3 is a FE-SEM of intersection of EVAL membrane (Asahi-Kasei). It is entirely a dense membrane and the entire thickness contributes to the transport resistance for solutes and water. Membranes of this kind are usually called "homogeneous." Besides EVAL, PMMA, and AN-69®, most cellulosic membranes are homogeneous. Figure 4 shows a cross-sectional view of PSf membrane (Toray). One should realize that a dense thin layer exists on the inner surface of the membrane, called "skin layer" from which the density is gradually decreasing in the radial direction. Since most part excluding the skin layer is known to have little resistance for solute and water transport, it is called the "support layer" (Figure 5). The support layer, however, has an important role for the membrane to have enough mechanical strength with

little resistance for transport. Membranes of this kind are called "asymmetry." Most synthetic polymeric membranes (except for PMMA, EVAL, and AN-69®) are asymmetry. In general, although the physical thickness of synthetic polymeric membranes is thicker (approximately 35 μm) than that of cellulosic membranes (approximately 15 μm), the thickness that contributes to the separation (Δx) of the former is approximately 0.5-2 μm that is much thinner than the latter. As mentioned before, synthetic polymeric membranes are main stream these days because much higher solute and hydraulic permeabilities are achieved with the thinner Δx.
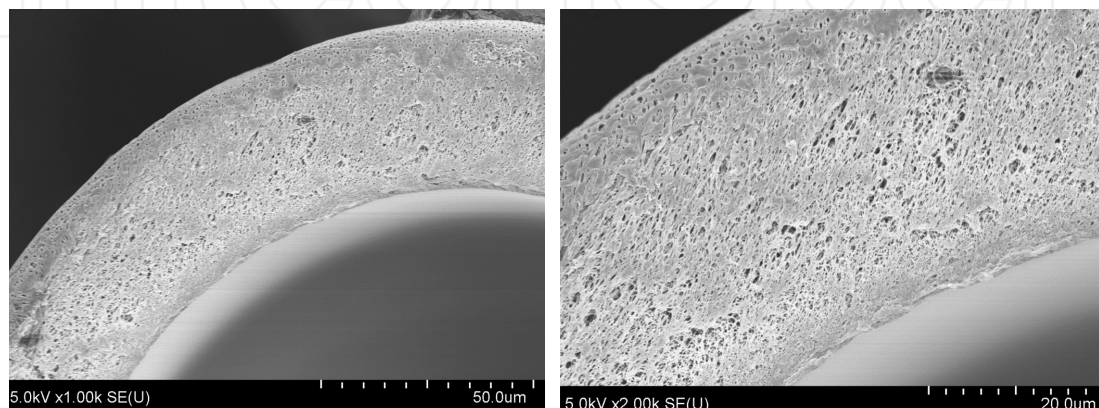

Figure 4. A cross-sectional view of PSf hollow fiber membrane (Toray, Tokyo, Japan) taken by FE-SEM.
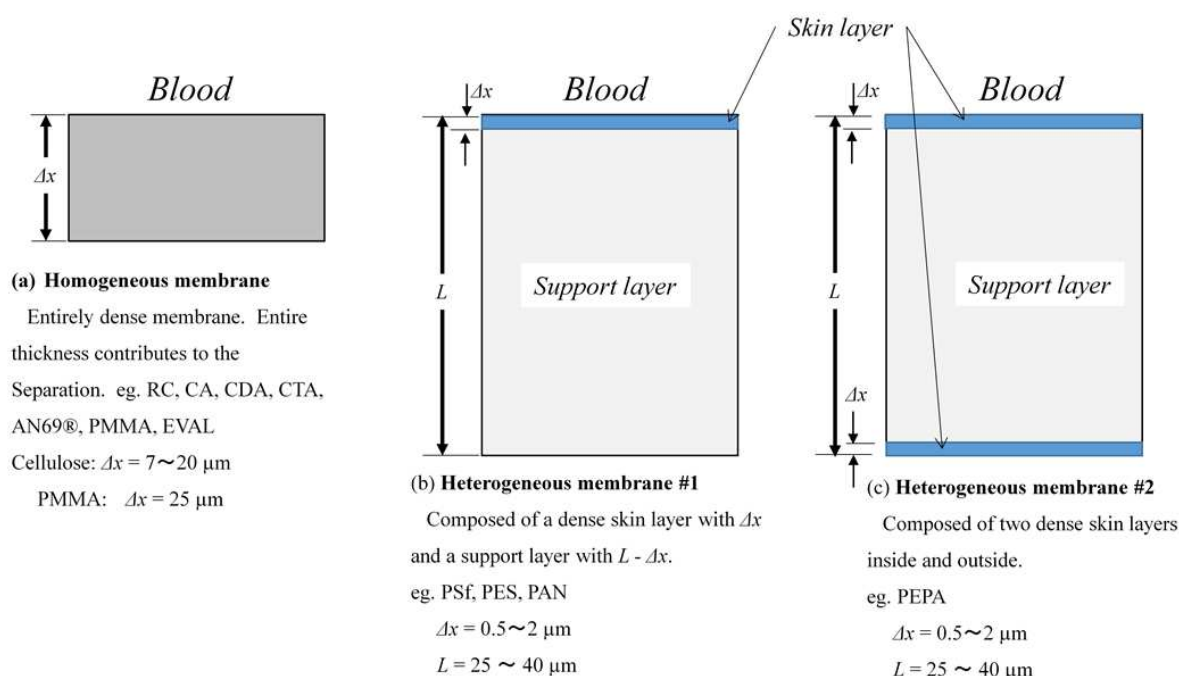

Figure 5. Cross-sectional views of dialysis membranes.

4.2. Pore theory

The pore theory is often used to analyze and to design physical structures of the membrane. The original pore theory was introduced by Pappenheimer *et al.* [6] to analyze the Glomerular filtration in the living kidney (Figure 6), and was later modified by Verniory *et al.* [7], introducing steric hindrance effect. Sakai [8] further modified the model by introducing the tortuosity for transporting across the membrane. Followings are the equations for modified pore theory.
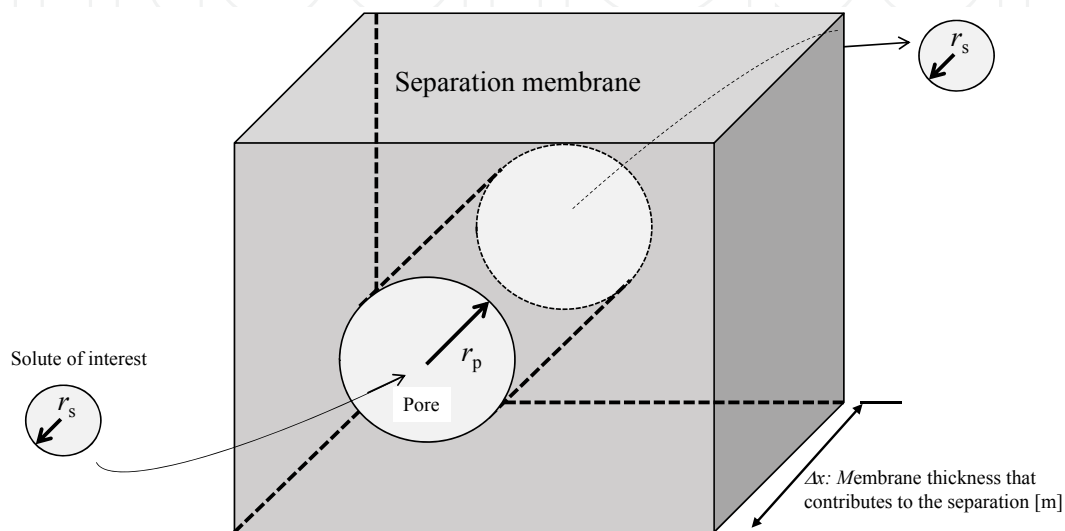

Figure 6. Pore theory (pore diffusion model). Assuming pores whose radius is uniformly r_p [m] with a membrane thickness of Δx [m], through which a solute of interest whose radius is r_s [m] is passing.

$$k_M = D_w \times f(q) \times S_D \times \left(\frac{A_k}{\tau \times \Delta x} \right) \tag{3}$$

$$L_p = \left(\frac{r_p^2}{8\mu} \right) \times \left(\frac{A_k}{\tau \times \Delta x} \right) \tag{4}$$

$$q = \frac{r_s}{r_p} \tag{5}$$

$$\sigma = 1 - g(q) \times S_F \tag{6}$$

$$S_D = (1 - q)^2 \tag{7}$$

$$S_F = 2(1 - q)^2 - (1 - q)^4 \tag{8}$$

$$f(q) = \frac{1 - 2.1050q + 2.0865q^3 - 1.7068q^5 + 0.72603q^6}{1 - 0.75857q^5} \tag{9}$$

$$g(q) = \frac{1 - (2/3)q^2 - 0.20217q^5}{1 - 0.75857q^5} \tag{10}$$

where k_M is the membrane permeability [m/s] (see also section 1), D_w is the diffusion coefficient for the solute of interest in pure water [m²/s], A_k is the surface porosity of the membrane [-], Δx is the membrane thickness that contributes to the transport resistance [m], r_s is the solute radius [m], r_p is the pore radius of the membrane [m], L_p is the hydraulic permeability of the membrane [m² s/kg], σ is the Staverman's reflection coefficient [-], τ is the tortuosity of the membrane [-], q is the ratio of r_s to r_p [-], S_D, S_F, $f(q)$, and $g(q)$ are the dimensionless stereo correction factors defined as functions of q. The pore theory can be applied to the situation in which $q < 0.8$ is satisfied.

From Eqs.(3) and (4), it is clear that $A_k/(\tau \Delta x)$ is an important factor both for solute and water transport because both k_M and L_p include this value. Figure 7 shows two examples of L [m] x L [m] portions of the membrane, i.e., membrane (A) with four pores with the same radius of a [m], and membrane (B) with one pore with a radius of $2a$. Then the surface porosity can be calculated, respectively for membranes (A) and (B) with subscripts (A) and (B), i.e.,

$$A_{k(A)} = \frac{4 \times \pi a^2}{L^2} = \frac{4\pi a^2}{L^2}$$

$$A_{k(B)} = \frac{\pi(2a)^2}{L^2} = \frac{4\pi a^2}{L^2}$$
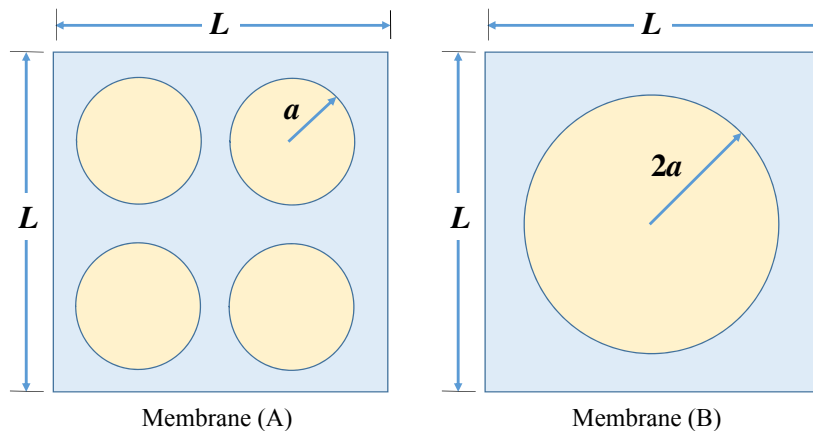
$$\therefore A_{k(B)} = A_{k(A)}$$

Figure 7. Portions of two modeled membranes with the same surface porosity.

Then one would realize that membranes (A) and (B) have the same surface porosities, although the situations are quite different in terms of the pore diameter.

Example)

Compare the two membranes (A) and (B) that have the same surface porosity (Figure 7), tortuosity and the thickness in terms of

i.   hydraulic permeability

ii.   solute permeability

         under the following two conditions

         a. r_s is negligibly small compared with a

         b. $r_s = a/3$

Solution) As stated above, A_k, τ, and Δx are the same in two membranes, $A_k/(\tau \Delta x)$ is just a constant.

i.   Recalling Eq. (4) to get,

$$L_{p(A)} = \left(\frac{a^2}{8\mu}\right) \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

$$L_{p(B)} = \left(\frac{(2a)^2}{8\mu}\right) \times \left(\frac{A_k}{\tau \times \Delta x}\right) = \left(\frac{4a^2}{8\mu}\right) \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

$$\therefore L_{p(B)} = 4 \, L_{p(A)}$$

Therefore, the membrane (B) has four times higher hydraulic permeability than the membrane (A).

ii.   Since $q=0$ may reasonably be applied in this case, recalling Eqs.(7)-(10) to get,

$S_D = S_F = f(q) = g(q) = 1$

in both membranes (A) and (B). Therefore Eq.(3) may be simplified as follows,

$$k_{M(A)} = k_{M(B)} = D_w \times (1) \times (1) \times \left(\frac{A_k}{\tau \times \Delta x}\right) = D_w \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

Consequently, there is no difference between membranes (A) and (B) in terms of transport of small solutes.

iii.   Recalling Eq.(5),

$$q_{(A)} = \frac{r_s}{r_p} = \frac{a/3}{a} = \frac{1}{3}$$

$$q_{(B)} = \frac{r_s}{r_p} = \frac{a/3}{2a} = \frac{1}{6}$$

Then recalling Eqs.(7) and (9) with q values calculated above,

$$S_{D(A)} = (1-q_{(A)})^2 = 0.8889$$

$$S_{D(B)} = (1-q_{(B)})^2 = 0.9722$$

$$f(q_{(A)}) = 0.3707$$

$$f(q_{(B)}) = 0.6587$$

Then from Eq.(3),

$$k_{M(A)} = D_w \times (0.3707) \times (0.8889) \times \left(\frac{A_k}{\tau \times \Delta x}\right) = 0.3295 \times D_w \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

$$k_{M(B)} = D_w \times (0.6587) \times (0.9722) \times \left(\frac{A_k}{\tau \times \Delta x}\right) = 0.6404 \times D_w \times \left(\frac{A_k}{\tau \times \Delta x}\right)$$

$$\therefore k_{M(B)} = 1.94 \, k_{M(A)}$$

Finally one would conclude that the membrane (B) has almost two times higher solute permeability than the membrane (A) for those solutes whose $r_s = a/3$.

Chemical characteristic determines the hydrophilicity and hydrophobicity of the material, whereas physical structure determines the pore sizes as well as the thickness that contributes to the transport resistance. Therefore, both chemical and physical features are important for designing dialysis membrane.

5. Performance of dialysis membrane

In this section, we discuss the performances under *in vitro* ultrafiltration experiments and those under on-line HDF in clinical situations because the former is suited for evaluation of maximal performance of the membrane and the latter takes a responsibility of the real performance under advanced clinical situations.

5.1. Aqueous *in vitro* ultrafiltration experiment

Six filters (dialyzers), one with PSf (PS-1.6UW, Fresenius-Kawasumi Co., Tokyo, Japan) and other five with PEPA (Nikkiso Co., Tokyo, Japan) were investigated (Table 2). Since both PSf and PEPA are hydrophobic in nature, these membranes include PVP for anti-thrombosis purpose, except for one dialyzer that includes PEPA membrane with no additives (FLX). Amount of PVP used in the membrane is semi-quantitatively shown as (+++), (++), (+), and (-), respectively for "most", "much", "small" and "none".

#	name of products	abbreviated names	Surface area [m²]	membrane materials	hydrophilic agent	pore size info	membrane make
1	PS-1.6UW	PS	1.6	PSf	PVP (+++)	(Not available)	Fresenius Medical Care, Badhonburg, Germany
2	FLX-15GW	FLX	1.5	PEPA	PVP (-)	standard	Nikkiso Co., Tokyo, Japan
3	FDX-15GW	FDX	1.5	PEPA	PVP (+)	standard	Nikkiso Co., Tokyo, Japan
4	FDY-15GW	FDY	1.5	PEPA	PVP (+)	larger	Nikkiso Co., Tokyo, Japan
5	FDX-150GW	new FDX	1.5	PEPA	PVP (++)	standard	Nikkiso Co., Tokyo, Japan
6	FDY-150GW	new FDY	1.5	PEPA	PVP (++)	larger	Nikkiso Co., Tokyo, Japan

Table 2. Technical specification of investigated ultrafilters

The time courses of the sieving coefficient ($s.c._4$) [9, 10] for albumin of PS-1.6UW dialyzer were shown in Figure 8. Strong time-dependent patterns were found with peak values approximately at 10 minutes after starting experiments. The lower the albumin concentration, the higher the $s.c._4$ values was found with longer time for achieving steady-state.
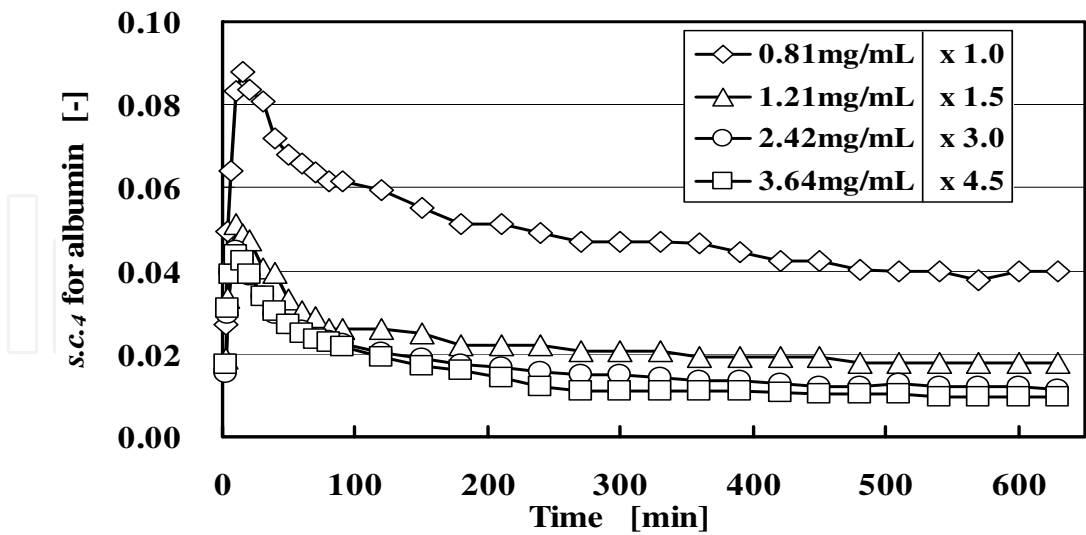

Figure 8. Time courses of the sieving coefficient for albumin under various concentrations of albumin in PS-1.6UW (PSf membrane) Q_{Bi}=200 mL/min, Q_F=10 mL/min, Volume of test sol'n=2.0 L.

The time courses of $s.c._4$ for albumin of three PEPA filters with albumin concentration of 3.64 mg/mL are shown in Figure 9. The $s.c._4$ gradually increased in these PEPA with PVP(-) or

PVP(+) and never took peak values. Membranes used in FLX and FDX basically have the same pore sizes and the only difference is that the latter contained PVP, which concludes that PVP directly influences the membrane transport of albumin. By enlarging the pore diameter by approximately 5 % in FDY with the same PVP content, the $s.c._4$ increased with the enlargement accordingly.
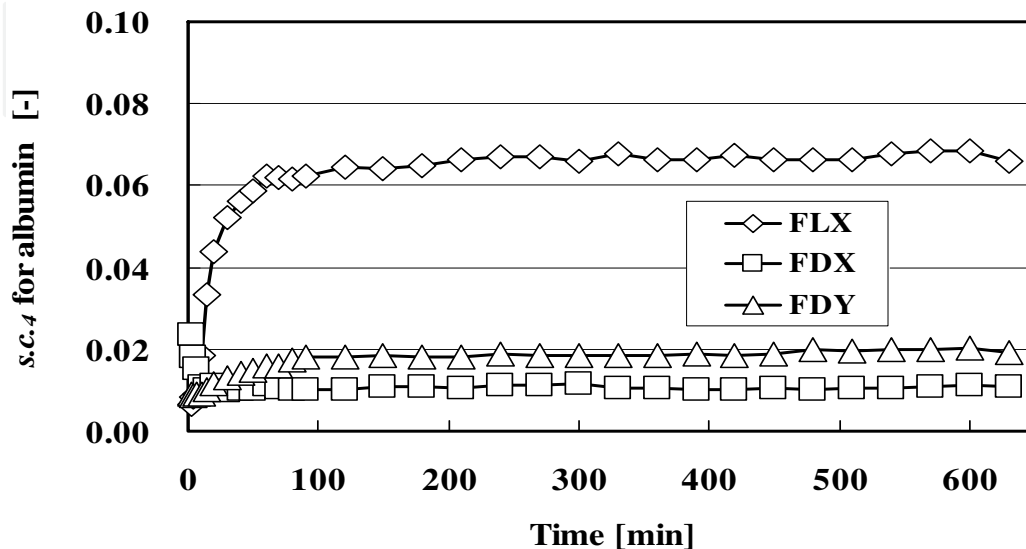

Figure 9. Time courses of the sieving coefficient for albumin under a fixed albumin concentration (3.64 mg/mL) in three PEPA membrane dialyzers Curves are different from the ones found with PSf membrane. Q_{Bi}=200 mL/min, Q_F=10 mL/min, Volume of test sol'n=2.0 L.

The time courses of $s.c._4$ for albumin of the latest version of PEPA dialyzers are depicted in Figure 10 for albumin concentration of 3.64 mg/mL. It should be noted that the peak values were found in new PEPA membranes that included increased amount of PVP at 6 minutes after starting the experiments. Moreover, time dependent pattern of these curves are different from the ones shown in Figure 9 and are similar to those found with PSf membrane in Figure 8. Then it may be concluded that the time course of $s.c._4$ for albumin is strongly dependent on the amount of PVP included in the membrane and not on the main material of the membrane.

Since the albumin concentrations of the test solutions were lower by the factor of 1/30-1/10 to the standard albumin concentration in human blood (3.6 – 4.0 g/dL), $s.c._4$ values for albumin shown above do not directly correspond to the clinical results. One should, however, need to consider that the membrane separation characteristics depend on the pore diameter, amount of hydrophilic agent as well as experimental conditions [11].

5.2. Clinical performance of super-high flux dialyzers/diafilters

According to the Japanese reimbursement system, all the commercial dialyzers are classified into five categories in accordance with the clearances for β2-microglobulin (β2-MG, MW 11800) under Q_B=200 mL/min, Q_D=500 mL/min for dialyzers with surface area of 1.5 m² (Table 3). Classes IV and V dialyzers, clearances for β2-MG greater or equal to 50 and 70 mL/min,
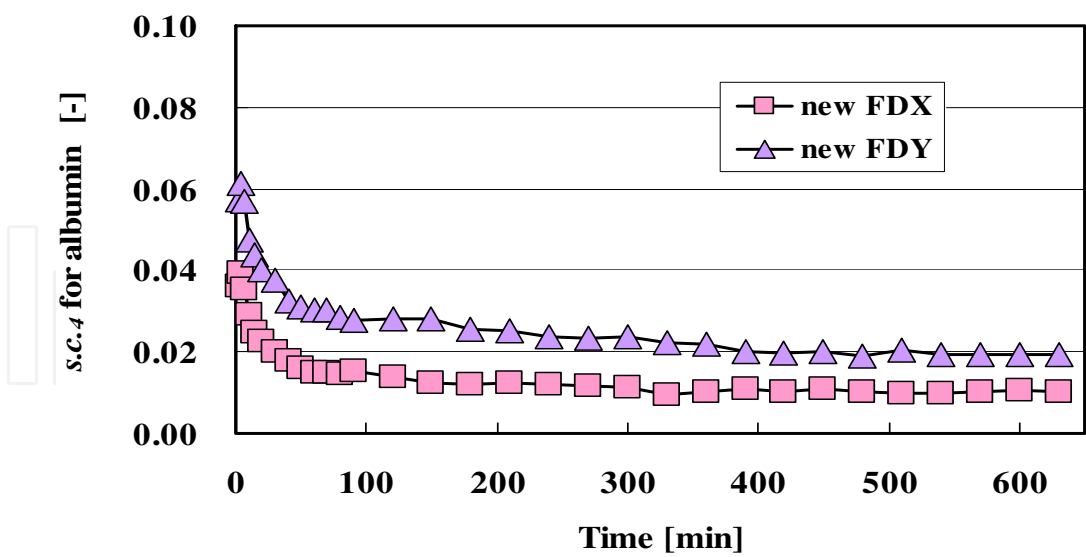
Figure 10. Time courses of the sieving coefficient for albumin under a fixed albumin concentration (3.64 mg/mL) in two new PEPA membrane dialyzers Curves are similar to the ones found with PSf membrane. Q_{Bi}=200 mL/min, Q_F=10 mL/min, Volume of test sol'n=2.0 L.

respectively, are the "super-high flux" models and more than 95 % of Japanese dialysis patients are treated with dialyzers of this kind [12]. These dialyzers had been used also for on-line hemodiafiltration (HDF) with considerable amount of albumin removal (> 3 g/treatment) until 2010 before on-line HDF has been officially announced to be included in the reimbursement system.

Class	β_2-MG clearance [mL/min]	Reimbursement
I	< 10	low
II	>=10～< 30	
III	>=30～< 50	
IV	>=50～< 70	
V	>= 70	high

1. Flow conditions: Q_B=200 mL/min, Q_D=500 mL/min, Q_F=10 mL/min/m².

2. A_0=1.5 m²

3. If A_0 is NOT1.5 m², use of the closest model is recommended. Clearance for β_2-MG under A_0=1.5 m² may be estimated by using the performance evaluation equations with K_oA as a constant.

Table 3. Classification of dialyzers in Japanese reimbursement system

Although 99 uremic toxins are compiled by Vanholder [13], clinicians and researchers have different opinions on which solutes to be removed or up to how much albumin may be leaked out. Figure 11 shows the relationship between the reduction rate of β2-MG and albumin loss taken with various dialyzers in different modalities. Only a limited increase in β2-MG reduction was found with the increase of albumin removal. Therefore β2-MG removal may not be directly related to convection transport when super-high flux dialyzers are used. In other words, super high-flux dialyzers are the ones in which β2-MG removal does not correlate with the amount of albumin loss or the convection transport.
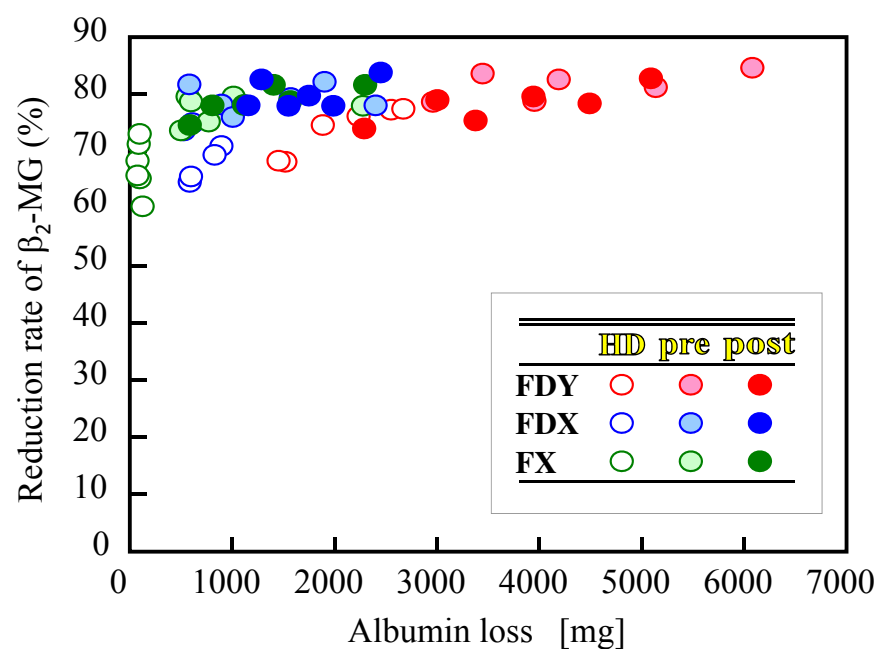

Figure 11. Relationship between the reduction rate of β2-microglobulin (MW: 11,800) and albumin loss.

Figure 12 shows the same relationship between the reduction rate of α_1-microglobulin (α_1-MG, MW 33,000) and albumin loss. Up to albumin loss of 3 g/session, almost linear relationship was observed, meaning that it may not be possible to remove α_1-MG without removing albumin, although the molecular weight of albumin is twice as large as that of α_1-MG. There is no such article that reports α_1-MG is toxic; moreover, α_1-MG is not even included in Vanholder's list [13]. We, however, experienced fairly good number of patients who have become better with albumin loss of 3 g or more for bone pain, shoulder pain, and improvement of fingertip power, and 5 g or more for finger numbness, restless legs syndrome. Therefore α_1-MG may be a possible surrogate marker of HDF treatment for those who have symptoms with normal HD therapy. Relief of clinical symptoms with various treatment modalities is summarized in Figure 13.
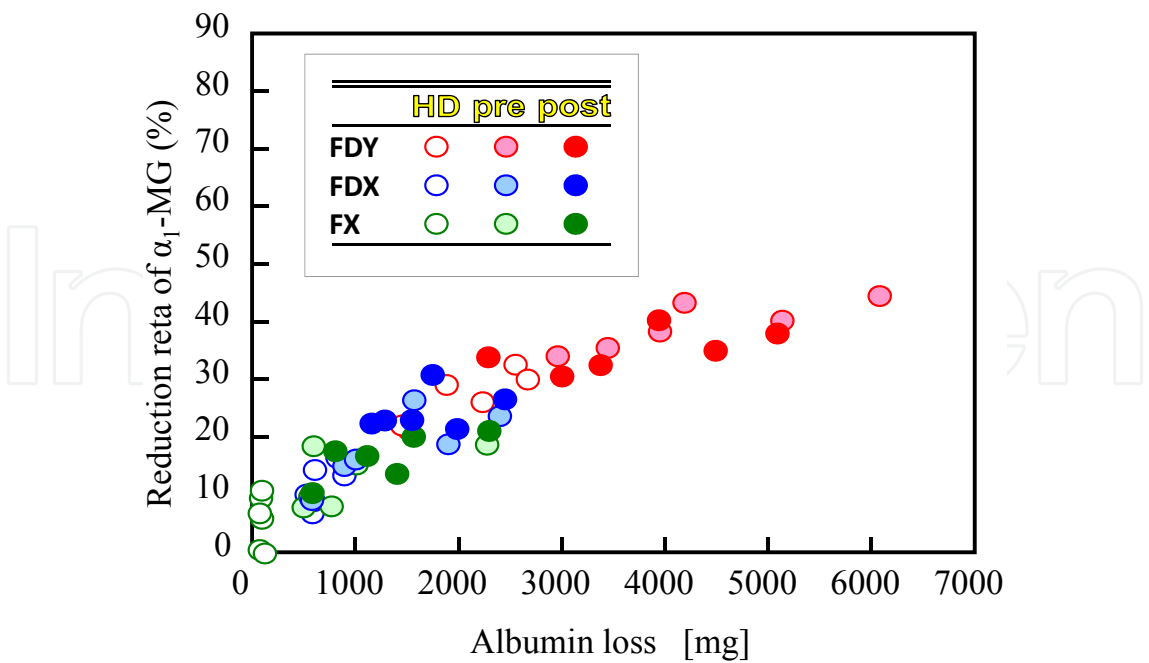
Figure 12. Relationship between the reduction rate of α1-microglobulin (MW: 33,000) and albumin loss.
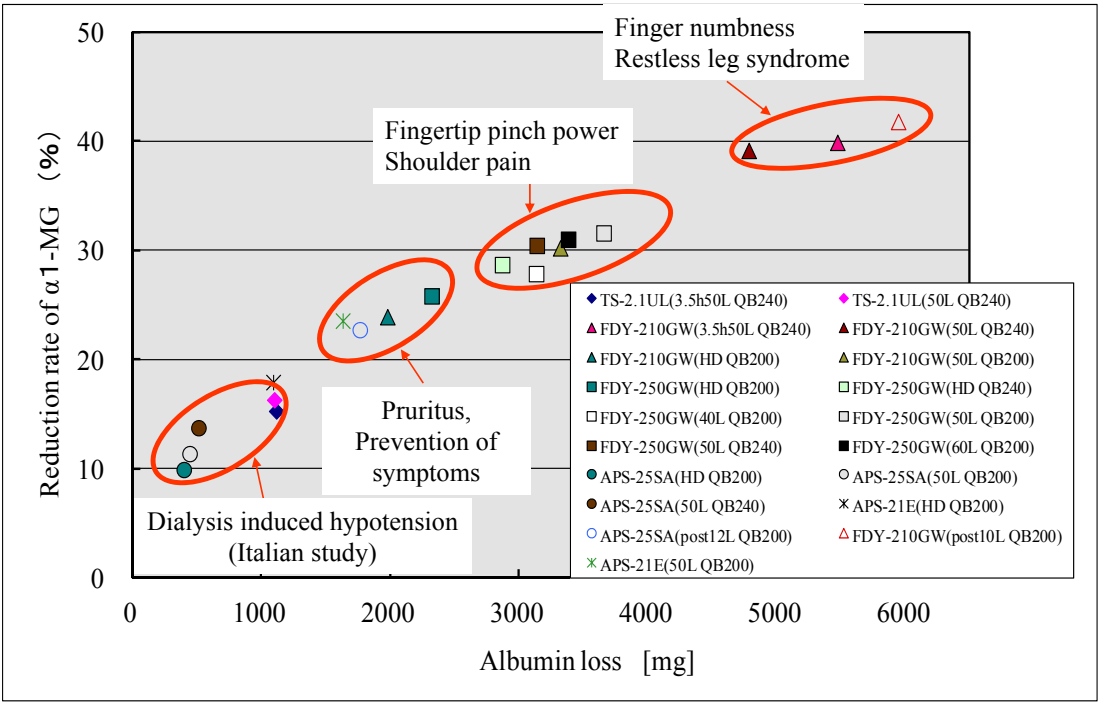

Figure 13. Relief of clinical symptoms by employing various protein-losing treatment modes.

5.3. Consideration of on-line HDF

On-line HDF is mostly performed in post-dilution mode with high Q_B (400 mL/min) in European countries, whereas that is mostly performed in pre-dilution mode with limited Q_B (250 mL/min) in Japan. Diafilters preferred in post-dilution and pre-dilution HDF must be designed under different concepts. Membrane for the post-dilution HDF requires a limited permeability for albumin, otherwise unexpected large amount of albumin may be leaked out. Therefore relatively large surface area is preferred for achieving large amount of fluid exchange (20 L/session). Since usually higher clearances are expected with post-dilution HDF, membrane for the pre-dilution HDF prefers higher solute permeability that may allow much albumin to penetrate across the membrane. Amount of albumin loss, however, may be relatively easily controlled by changing the amount of ultrafiltration that is usually around 60 L/session. In the recent market, since diafilters specifically designed for either post-dilution or pre-dilution are available, choice of diafilters must be paid much attention not only for effective treatment but also for safety. Moreover, a proposal of technical specifications for the future diafilters is also reported [14].

Many randomized control studies have been done in order to verify superiority or better outcomes of on-line HDF [15-[19]; however, we have not yet come into a conclusion that states on-line HDF is better than other treatment modalities. These studies showed that on-line HDF was at least better than low-flux HD; however, the difference between on-line HDF and high-flux HD was ambiguous [18, 19], in terms of survival rate within a study period of three years or so. Post–hoc analyses and sub-analyses of those studies showed superiority of on-line HDF with large amount of fluid exchange (at least > 15 L) to other treatment modalities in terms of dialysis-induced hypotension, reaction to ESR medications, as well as survival rate. Among them, the ESHOL study [20] greatly encouraged patients on dialysis as well as medical staffs in which on-line HDF showed better clinical outcomes in all the end points than high-flux HD. Many debates, however, still continues also elsewhere including in Japan where the number of patients on on-line HDF is rapidly growing and exceeded 10 % of the total patients [21].

6. Biological consideration of dialysis membrane

Biological consideration of the dialysis membrane is often referred to biocompatibility. Since dialyzers are repeatedly used four hours a session, three times a week, even a small event that repeatedly would occur each time may cause undesired side effects such as chronic inflammation.

6.1. Improvement of biocompatibility of the regenerated cellulosic membrane

Up until 1970s, RC membrane dominated over the market, and it was gradually replaced by synthetic polymeric membranes. Transient leukopenia that is an abrupt decease of leukocytes occurs at 15 to 30 minutes after starting the treatment has been one of the best known bio-incompatible events [22]. Reprocessing dialyzers was common in 1970's and since bio-

incompatible events were often found when a dialyzer was used for the first time, this was called the "first use syndrome" [23].

Craddock *et al.* reported that complement activation under the use of RC membrane induced transient accumulation of leukocytes in the blood vessels and in the lung [24]. As shown in section 2, RC has three hydroxyl groups in its backbone, and these hydroxyl groups have been realized to be closely related to undesired complement activation. Then acetate groups was introduced to the one, two, or all three of hydroxyl group(s) to produce cellulose acetate (CA), cellulose diacetate (CDA), and cellulose triacetate (CTA), respectively. Since these semi-synthesized cellulosic membranes have not only better biocompatibility but also higher permeabilities for solutes and water transport, they are still on the market.

6.2. Improvement of biocompatibility of synthetic polymeric membrane

It is well known that the Glomerular basement membrane (GBM) in human kidney is nega-tively charged. Although AN-69® is also a negatively charged membrane, one must pay much attention for the use of this membrane because it may cause anaphylaxy shock soon after starting the treatment [25]. Strong negative charge (-70 mV) would activate Hageman (XII) factor to XIIa that eventually produces bradykinin from kininogen as a substrate. Under normal situation bradykinin may be deactivated by kininase II; however, if the patient takes angiotensin-converting enzyme (ACE) inhibitor, it deactivates kininase II. This would induce the cascade reaction with bradykinin, including NO generation, increased vascular permea-bility, expansion of blood vessels, suppressing blood pressure, and ending up with shock during the treatment. This is often called "negative charge syndrome" (NCS, Figure 14). Although all dialysis membranes are negatively charged, it is usually a contraindication to prescribe ACE inhibitor to a patient under the use of AN69®.
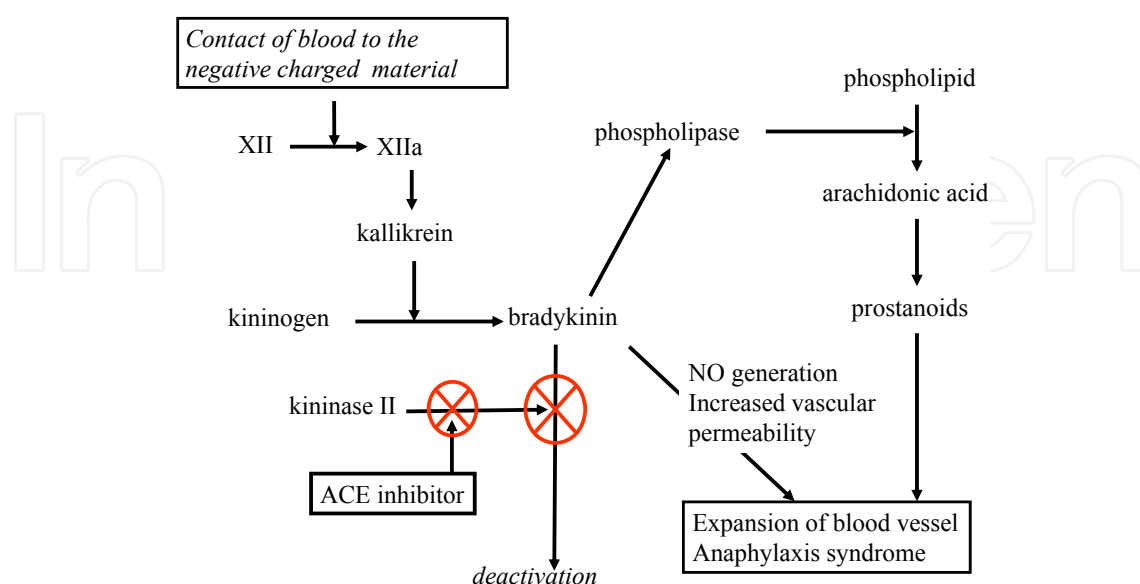

Figure 14. Mechanisms of negative charge syndrome (NCS).

6.3. Surface improvement technique

Hemophan® was developed by introducing a positively charged substance, diethylaminoethyl (DEAE), to RC membrane in order to improve its surface character (Membrana, Germany). Although only a limited amount of DEAE was introduced relative to entire amount of cellulose, complement activation was greatly suppressed. Hemophan®, however, adsorbed heparin, which induced blood coagulation. Because of this fact, the production of this membrane was ceased. Another trial was made by coating the membrane surface with vitamin E in order to make the RC membrane antioxydative (Terumo, Tokyo, Japan). Later, this technique was applied to PSf membrane and the commercial model is still available (Asahi Kasei Medical Co., Tokyo, Japan).

6.4. Membranes with polyvinylpyrrolidone

PSf and the ones whose chemical structures are similar to PSf have the highest market share among all dialysis membranes. They usually include polyvinylpyrrolidone (PVP) as a hydrophilic agent since they are hydrophobic in nature. PVP was once used as a supplement of plasma in medicine. Anaphylaxy shock, however, was reported, the cause of which was strongly doubted to be the PVP included in the membrane. Then we performed the following clinical investigation by using dialyzers with PSf and the ones with PEPA membrane with different amount of PVP [11].
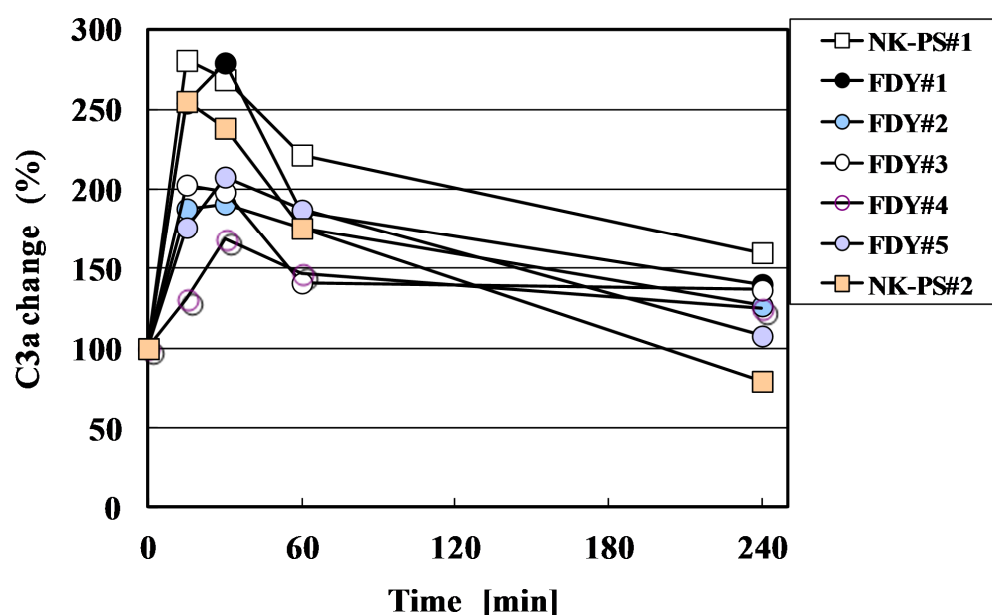

Figure 15. Time course of C3a change during four hr treatment. The same PSf dialyzers with PVP(+++) were used in the 1-st and last (7-th) weeks. The same FDY dialyzers with PVP(+) were used from the 2nd to the 6th weeks.

The time course of C3a concentration profile in clinical study is shown in Figure 15. PSf with PVP(+++) showed three times higher concentration 15 minutes after the start of treatment. The C3a elevation was slightly lower at the first use of PEPA with PVP(+) and the peak concen-

trations were approximately halved or even less from the second to the fifth week. The peak concentration, however, returned back to three folds in the first use of PSf after five-week use of PEPA with PVP(+).

According to another clinical data shown in Figure 16, PSf with PVP(+++) showed highest C3a elevation, followed by PEPA with PVP(++), PVP(+), and PVP(-). The degree of C3a elevation was a function of amount of PVP included in the membrane regardless of the main material of the membrane.
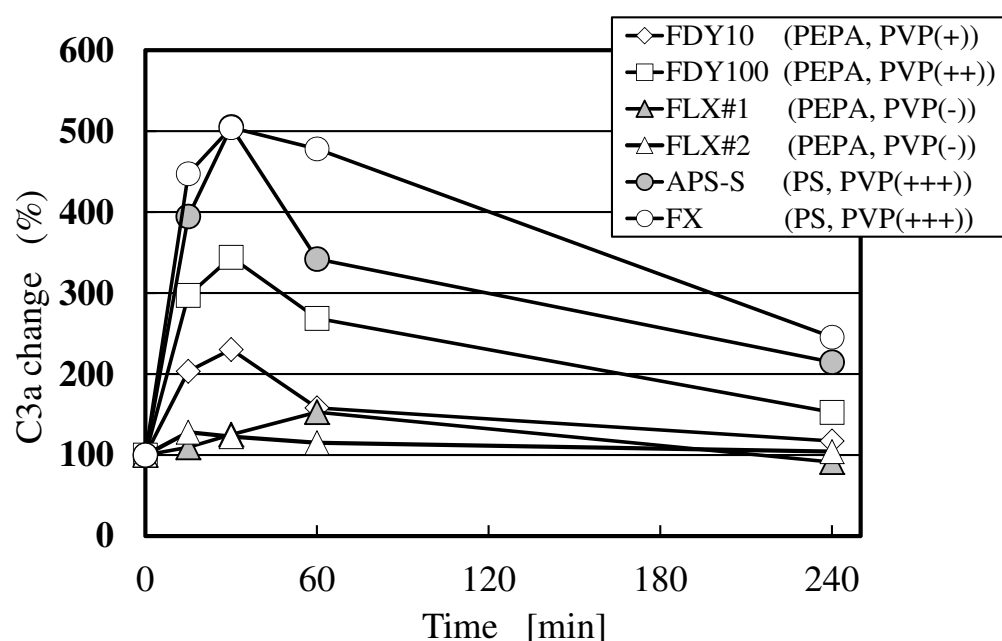

Figure 16. Time course of C3a change during four hr treatment in 1 patient. Symbols are arranged in the chronological order from the top to the bottom.

From these results, we learned that PVP may not be the best choice as a hydrophilic agent in terms of blood compatibility.

7. Future perspectives of dialysis membrane

With above mentioned technique, we will be able to expect an even better dialysis membrane to come into the market. Several futuristic functions desired for dialysis membrane is also introduced, expecting a new era to come. Followings are the problems to be solved in the future perspectives of dialysis membrane.

7.1. Solute removal performance

Since on-line HDF has been gaining popularity in European countries as well as in Japan, HDF with much larger amount of fluid exchange has to be more easily performed for the further success of this modality. Standard on-line HDF in European countries is performed in post-dilution system with Q_B=400 mL/min, Q_D=700 mL/min, Q_F=90 mL/min, Q_S=80 mL/min=19.2 L/4hr in single patient dialysis machine (SPDM) system, whereas that in Japan is performed in pre-dilution system with Q_B=250 mL/min, Q_D=500 mL/min, Q_F=260 mL/min, Q_S=250 mL/min=60 L/4hr in central dialysis fluid delivery system (CDDS) [26] (Figure 17). In terms of solute removal, the difference between these two methods is the largest target solute to be removed, i.e., "European HDF" is targeted to remove β2-MG (MW 11,800) with little loss of albumin (some ten mg/treatment), whereas "Japanese HDF" is targeted to remove α1-MG (MW 33,000) or even greater ones with albumin "removal" less than 4 g/treatment because enough removal of α1-MG cannot be possible without removing considerable amount of albumin (Figure 13). Although ultra-"super-high flux" dialyzers are commercially available in Japan, termed class V in Japanese reimbursement system, which remove α1-MG to achieve clinically effective reduction rate (> 30 %) [26], they also remove considerable amount of albumin (> 5 g/treatment) as well as amino acids, important small solutes from the nutritional point of view. Therefore when more precise prescriptions are necessary, on-line pre-dilution HDF is preferred because it removes α1-MG more than 30 % with albumin loss of 4 g/treatment or less and with considerably reduced clearance for small solutes, including amino acids, due to reduced net dialysis fluid flow rate (net Q_D=500-250=250 mL/min).
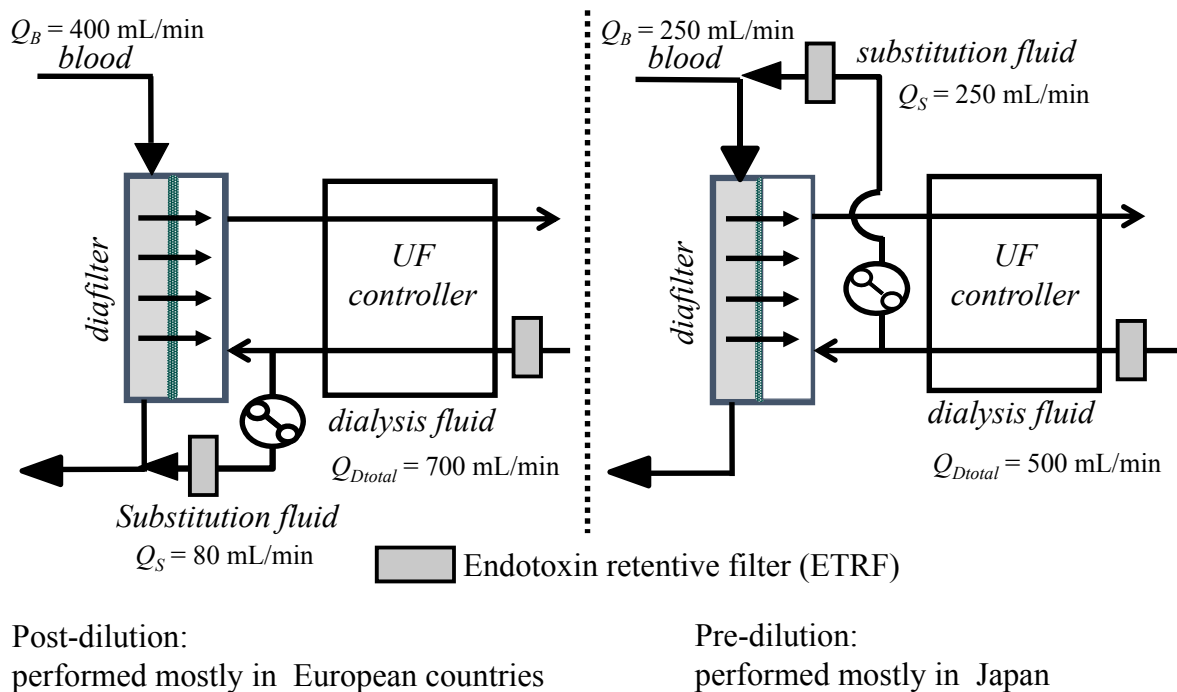

Figure 17. Comparison of post-dilution and pre-dilution on-line HDF with typical European and Japanese flow rates, respectively.

According to the Italian study [17], on-line HDF/HF is a useful tool for treating patients with dialysis induced hypotension. Then diafilters with higher hydraulic permeability with little albumin loss that do not aim to achieve higher solute removal may be useful for those patients. Not to mention, design specifications of dialyzer/diafilter is as important as the membrane permeability in terms of solute removal under given therapeutic conditions.

7.2. Biocompatibility

Many classic problems with biocompatibility in the past such as transient leukopenia, complement activation, negative charge syndrome, etc., have already been dissolved by modifying physical and chemical structures of the dialysis membrane. Most currently available synthetic polymeric membranes, however, employ PVP as a hydrophilic agent as well as a pore-forming agent. Study shows that many symptoms including abrupt decrease of blood pressure or shock right after starting treatments could be induced most probably due to PVP included in the membrane, and it is sometimes called "PVP intolerance". Novel hydrophilic agents may be studied for the purpose of replacing PVP. Alternately, novel casting technique in which no hydrophilic agent is necessary has to be studied, knowing that PMMA, EVAL, and PEPA are cast with no additives although they are also originated from petroleum.

7.3. Surface modification and adsorption

Surface modification with the third substances is another way to obtain membranes with preferred permeability as well as biocompatibility. For example, PSf membrane coated with vitamin E showed a great success for reducing reactive oxygen species (ROS) as well as free radicals that also showed preferable clinical results (Terumo, Asahi-Kasei). Toray introduced a novel technique with NV polymer to their PSf membrane to reduce adsorption of cells as well as protein molecules on the membrane. Although both two membranes work well clinically, they still utilize PVP in the same amount as previously included before. Then it should be noted since surface modification is closely related to solute transport as well as biocompatibility, biomimicry situations under dialysis must be further taken into consideration.

8. Conclusions

Since hemodialysis experiments with canines were first reported, many membranes, either natural or synthetic polymeric ones, have been developed and the latter have been the main stream due to higher solute and hydraulic permeabilities as well as better biocompatibility. The mass transport mechanism across the membrane can be expressed by the Fick's 1-st law of diffusion; however, not only the membrane permeability but also the design specifications are important for assembling dialyzers with better performances.

The chemical structure of the dialysis membrane determines the hydrophilicity and hydrophobicity of the membrane. Since all synthetic polymeric membranes are made from petroleum, they are hydrophobic in nature. Most of these membranes include a hydrophilic agent

such as PVP for anti-thrombosis purpose. According to the in vitro experiments and clinical observations, it was proved that PVP was closely related to the sieving coefficient for albumin and had big influence on the complement activation. Then we must pay much attention on additives in addition to the main material(s) of the membrane.

Physical structure of the dialysis membrane can be discussed in two ways, i.e., direct observations by taking microscopic views (SEM) and the theoretical analysis by using a mathematical model. There are two kind of dialysis membranes, "homogeneous" and "asymmetry", among which the latter is gaining popularity because of the much smaller thickness that contributes to the resistance of solute and water transport. The pore theory is a useful tool for analyzing mass and water transport across the membrane and for designing a physical structure of the membrane.

Since the number of on-line hemodiafiltration (HDF) is growing these days not only from the solute removal point of view but also from the improvement of dialysis-induced hypotension during the treatment, membranes specifically designed for performing HDF has to be more extensively studied both clinically and fundamentally. Importance of biocompatibility of the membrane should be more carefully taken into account for selecting a device, considering membrane characteristic such as adsorption, especially in the field of acute kidney injury (AKI).

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References

[1] Abel JJ, Rowntree, LG, Turner BB: On the removal of dissosible substances from the circulation blood of living animals by dialysis. *J Pharmcol Exp Ther* 1914; 5: 275-316.

[2] Kolff W J, Watschinger B: Further development of a coil kidney: disposable artificial kidney. *J Lab and Clin Med* 1956; 47: 969–77.

[3] Lipps BJ, Stewart RD, Perkins HA, Holmes GW, McLain EA, Rolfs MR, Oja PD: The hollow fiber artificial kidney, *Trans ASAIO* 1967; 13: 200-7.

[4] Sakai Y, Tsukamoto H, Fujii Y, Tanzawa H: Formation of poly(methyl methacrylate) membranes utilizing stereocomplex phenomenon. New York: Plenum Press: Ultrafiltration Membranes and Applications Plenum; 99–107, 1980.

[5] Hayama M, Yamamoto K, Kohori F, Sakai K: How polysulfone dialysis membranes containing polyvinylpyrrolidone achieve excellent biocompatibility?, *J Membrane Sci* 2004; 234: 41–9.

[6] Pappenheimer JR, Renkin EM, Borrero, LM: Filtration, diffusion and molecular sieving through peripheral capillary membranes – a contribution to the pore theory of capillary permeability, *Am J Physiol* 1951; 167: 166.

[7] Verniory A, Dubois R, Decoodt P, Gassee JP, Lambert PP: Measurement of the permeability of biological membranes – Application to the glomerular wall, *J Gen Physiol* 1973; 62: 489-507.

[8] Sakai K: Technical determination of optimal dimensions of hollow fiber membranes for clinical dialysis, *Nephrol Dial Transplant* 1989; 4 (Suppl): 79.

[9] Yamashita AC, Sakiyama R, Hamada H, Tojo K: Two new definitive equations of the sieving coefficient, *Kidney and Dialysis* (*JIN TO TOSEKI*) 1998; 45: S36-8. (in Japanese)

[10] Yamashita AC: New dialysis membrane for removal of middle molecule uremic toxins, *Amer J Kid Dis* 2001; 38 suppl.1: S217-9,.

[11] Yamashita AC, Tomisawa N, Takezawa A, Sakurai K, Sakai T: Blood compatibility and filtration: characteristics of newly developed polyester polymer alloy membrane, Hemodial Int 2004; 8: 99 – 100.

[12] Japanese Society for Dialysis Therapy (JSDT): An overview of regular dialysis treatment in Japan, Table 1913, as of Dec. 31, 2012, JSDT, 2012.

[13] Vanholder R, De Smet R, Glorieux G, *et al.*, European Uremic Toxin Work Group (EUTox): Review on uremic toxins: classification, concentration, and interindividual variability, *Kidney Int* 2003; 63: 1934-43.

[14] Yamashita AC: Diafilters for predilution and postdillution on-line hemodiafiltration, *Blood Purif* 2013; 35 (suppl 1): 29-33.

[15] Panichi V, Rizza GM, Paoletti S, *et al.* (RISCAVID Study Group): Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study, *Nephrol Dial Transplant* 2008; 23: 2337-43.

[16] Canaud B, Bragg-Gresham JL, Marshall MR, *et al.*: Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS, *Kidney Int* 2006; 69: 2087-93.

[17] Locatelli F, Altieri P, Andrulli S, *et al.*: Hemofiltration and Hemodiafiltration Reduce Intradialytic Hypotension in ESRD, *J Am Soc Nephrol* 2010; 21: 1798–807.

[18] Penne EL, Blankestijn PJ, Bots ML, *et al.* (the CONTRAST study group): Effect of in‐creased convective clearance by on-line hemodiafiltration on all cause and cardiovas‐cular mortality in chronic hemodialysis patients-the Dutch CONvective TRAnsport STudy (CONTRAST): rationale and design of a randomised controlled trial, *Curr Control Trials Cardiovasc Med* 2005; 6: 8.

[19] Ok E, Asci G, Toz H, et al. (Turkish Online Haemodiafiltration Study): Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study, *Nephrol Dial Transplant* 2013; 28: 192-202.

[20] Maduell F, Moreso F, Pons M, et al. (ESHOL Study Group): High-efficiency postdilu‐tion online hemodiafiltration reduces all-cause mortality in hemodialysis patients, *J Am Soc Nephrol* 2013; 24: 487-97.

[21] Japanese Society for Dialysis Therapy (JSDT): An overview of regular dialysis treat‐ment in Japan, Table 34, P.38, as of Dec. 31, 2013, JSDT, 2014.

[22] Kaplow LS, Goffiret JA: Profound neutropenia during the early phase of hemodialy‐sis, *JAMA* 1968; 203: 1135-7.

[23] Villarroel F: First-use syndrome in patients treated with hollow-fiber dialyzers, *Blood Purif* 1987; 5: 112-4.

[24] Craddock PR, Fehr J, Dalmasso AP *et al.*: Hemodialysis leukopenia. Pulmonary vas‐cular leukostasis resulting from complement activation by dialyzer cellophane mem‐branes, *J Clin Inves* 1977; 59: 879-88.

[25] Tielemans C, Madhoun P, Lenaers M, *et al.*: Anaphylactoid reactions during hemo‐dialysis on AN69 membranes in patients receiving ACE inhibitors, *Kidney Int* 1990; 38; 982-4.

[26] Yamashita AC, Sato T: Central online hemodiafiltration in Japan: Management of water quality and practice, *Blood Purif* 2009; 27 (suppl 1): 50-5.