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NIPRO

The 63rd Annual Meeting of the Japanese Society for Dialysis Therapy

Luncheon Seminar

Contributions and Life Prognosis Made by Super High-Flux Dialyzers

- July 1, 2018, 12:40 ～ 13:40
- Kobe International Conference Center
  International Conference Room(3F)

Chairman **Ikuto Masakane** Seieikai Medical Corporation

Career

2012 Vice President, Yabuki Hospital
2018 Department of Nephrology

Associations

Japanese Society of Nephrology; The Japanese Society for Dialysis Therapy; Japanese Society for Hemodiafiltrasion; Japanese Society for Peritoneal Dialysis; Japanese Society for Home Hemodialysis

Contributions Made by Super High-Flux Dialyzers Based on Biocompatibility and Prognosis

Speaker

Masanori Abe

Nihon University School of Medicine

Effects on Dialysis Patients According to the Choice of Dialysis Membrane and BPA

Speaker

Gonzalez-Parra Emilio

Universidad Autónoma de Madrid

Co-sponsored by the 63rd Annual Meeting of the JSDT and Nipro Corporation

Luncheon Seminar

Contributions Made by Super High-Flux Dialyzers Based on Biocompatibility and Prognosis

Speaker **Masanori Abe**

Professor and Chairman, Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine

Career

1997 Graduated from the Faculty of Medicine, Nihon University; Department of Second Internal Medicine, Nihon University School of Medicine
1999 Sagamihara Kyodo Hospital, Kanagawa Prefectural Welfare Federation of Agricultural Cooperatives
2003 Medical Director, Department of Nephrology and Blood Purification, Yokohama Central Hospital, Yokohama, Japan
2005 Doctorate degree in Medicine, Nihon University School of Medicine
2007 Head of the Department of Internal Medicine, Chairman of the Blood Purification Center, Nihon University, Nerima Hikarigaoka Hospital
2007 Assistant Professor, Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine
2014 Associate Professor, Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine
2016-Present Professor and Chairman, Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine

Associations

Board-Certified Member and Fellow of the Japanese Society of Internal Medicine; Specialist, Trainer, Councilor, and Director of the Japanese Society for Dialysis Therapy; Member of the "Best practice for diabetic patients on hemodialysis 2012"; Specialist, Trainer, and Councilor of the Japanese Society of Nephrology; Specialist of the Japanese Circulation Society; Councilor, Survey Committee Member, and Journal Editorial Committee Member of the Japan Society for Blood Purification in Critical Care; Japan Diabetes Society; Executive Director of the Japan Diabetic Nephropathy Study Group; Japanese Society for Apheresis; Japanese Society of Hypertension; Japan Atherosclerosis Society; Tokyo DMAT Member

More than 90% of dialyzers in Japan are high or super-high flux dialyzers

Internationally, dialyzers are classified into four categories—low flux, mid flux, high flux, and super-high flux—based on ultrafiltration rate, urea clearance, β_2-microglobulin (β_2MG) clearance, and amount of albumin leakage. In Japan, until 2013, dialyzers were classified into five categories —types I-V—based primarily on β_2MG clearance. According to annual nationwide surveys of patients on dialysis conducted by the Japanese Society for Dialysis Therapy (JSDT), 93.8% of all dialyzers used were type IV or V, which in terms of the international classification system means that most dialysis patients in Japan were treated with high-flux or super-high flux dialyzers. Nowadays, we classify dialyzers in Japan as type Ia or Ib, which range from low to super-high flux dialyzers, or type IIa or IIb, which are super-high flux dialyzers (Table 1).[1]

Various dialyzers have been developed to remove β_2MG, the causative agent of dialysis-related amyloidosis. As a result, the incidence of carpal tunnel syndrome is now more strongly associated with the duration of dialysis than with serum β_2MG levels. At the same time, reports of worsening prognosis in hemodialysis patients with increasing serum β_2MG levels is now shifting the focus from the elimination of uremic toxins to prognosis-related factors (Figure 1).[2]

Table 1.Definition of 'Super high-flux'

Parameter		Low-flux	Mid-flux	High-flux	Super-flux
UF	mL/mmHg/h	< 20	20-30	30-50	> 50
Urea	Kd (mL/min)	< 180	180-200	200-220	> 220
	KoA (mL/min)	< 500	500-600	600-700	> 700
	eKt/V	< 1.2	1.2-1.4	1.4-1.6	> 1.6
β_2MG	Kd (mL/min)	< 20	20-40	40-60	> 60
	KoA (mL/min)	< 30	30-50	50-100	> 100
Albumin leakage	g/session	0	0	< 2	2-5

Classification in Japan~2013	I	II	III	IV	V
β_2MG clearance (mL/min)	< 10	10-30	30-50	50-70	≧70
Classification	Low	Low	High	Super high	Super high

Hemodialyzer 2013~	Type I		Type II	
	Ia	Ib	IIa	IIb
Urea clearance (mL/min)	125 ≦		185 ≦	
β_2MG clearance (mL/min)	< 70		70 ≦	
Albumin permebility	< 0.03	0.03 ≦	< 0.03	0.03 ≦
Classification	Low ~ Super high		Super high	

＊ QB=200mL/min、membrance surface area1.5㎡

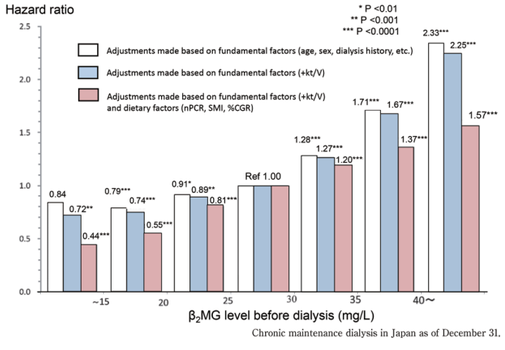

Figure1:Shift from focusing on "uremic toxin to eliminate" to "prognosis-related elements"

Guidelines recommend HPM dialyzers

JSDT's "Guidelines for Maintenance Hemodialysis: Hemodialysis Prescriptions" recommend the use of high-performance membrane (HPM) dialyzers. In 2005, HPM dialyzers were defined by a β_2MG clearance of at least 10 mL/min; in 2013, the albumin sieving coefficient and specific functions such as the β_2MG absorption capability were added alongside β_2MG clearance. The guidelines recommend achieving a maximum predialysis serum β_2MG concentration of less than 30 mg/L. The rate of β_2MG reduction per dialysis session is reported to be 60% or more with a blood flow rate of 200 mL/min when using an HPM dialyzer with a β_2MG clearance of more than 50 mL/min. Almost all dialyzers used in Japan currently meet these criteria. Outside Japan, the KDOQI guidelines discourage the use of poorly biocompatible cellulose membranes. The European Best Practice Guidelines (EBPG) recommend the use of highly biocompatible high-flux membranes with large pores to improve morbidity and mortality rates.[3] The EBPG also recommend avoiding dialysis membranes that trigger the activation of complement and white blood cells or the inflammatory response, as these factors correlate with biocompatibility.

PVP and BPA are also associated with biocompatibility

In relation to biocompatibility during hemodialysis, dialyzers are the main consideration in terms of biological response because of their relatively large surface area in contact with the blood. Acetate and endotoxins in dialysis fluid are also considered to be factors that affect biocompatibility. With respect to dialyzer biocompatibility specifically, of the need to consider the use of PVP (polyvinylpyrrolidone or povidone) and BPA (bisphenol A) has recently been highlighted, in addition to the activation of complement and granulocytes and platelet aggregation.

While PVP is essential in the hydrophilization of the polysulfone (PS) membrane and the polyethersulfone (PES) membrane and enhances biocompatibility by preventing protein and platelet adhesion, it also poses risks of anaphylaxis and allergic reactions. Indeed, recent studies have pointed to PVP as the likely causative factor of some skin reactions and cases of anaphylaxis when using the PS membrane. For example, povidone iodine is used to disinfect the skin when a catheter is inserted for vascular access and could cause sensitization to PVP. Subsequent dialysis with a PS membrane containing PVP could result in anaphylaxis in rare instances.

BPA, which is an endocrine disruptor, is reported at high levels of exposure to increase the risks of cardiovascular disease and diabetes. BPA levels also increase with decreasing estimated glomerular filtration rate, because BPA is metabolized by the liver and excreted through the kidneys (Figure 2).[4] A clinical study conducted in 2015 found that serum BPA levels increased after a hemodialysis session with the PS membrane containing BPA but remained unchanged with the PES membrane, which does not contain BPA (Figure 3).[5]

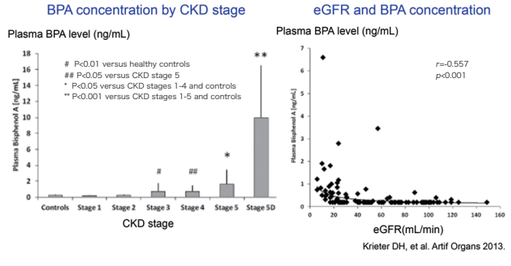

Figure2:Bisphenol A and kidney functions

PES and PMMA membranes are associated with good prognosis

In JSDT's nationwide surveys in 2008 and 2010 on the type of dialyzers being used in Japan, the prognosis of patients treated with type V dialyzers was reported to be excellent in 2008. Although the number of patients differed for the various types of dialyzer membrane materials used, survival rate was significantly higher in patients treated with the PES or PMMA membrane than in those treated with the PS membrane. In 2010,

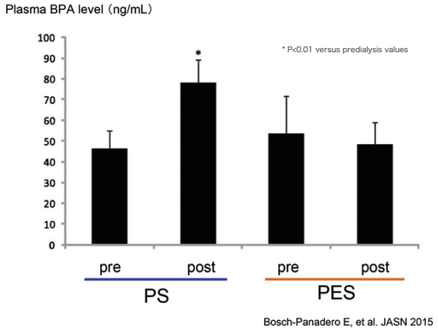

Figure3:Plasma BPA concentration before and after HD

the survival rate was compared between seven types of dialyzers used in approximately 136,000 cases. Hemodialysis was performed with the PS membrane in over half of the patients (57.0%), followed by PES in 15.1%, cellulose triacetate (CTA) in 14.3%, polyether-polyamide copolymer (PEPA) in 7.4%, PMMA in 3.8%, polyacrylonitrile (PAN) in 1.5%, and ethylene-vinyl alcohol copolymer (EVOH) in 0.9%. Many of the patients' background characteristics differed significantly among the types of dialyzer membrane materials used (Table 2).[5] For example, more younger patients and more male patients were dialyzed using the PES membrane. Higher percentages of older patients and women were dialyzed using the EVOH membrane. The proportion of diabetic patients was high among patients dialyzed using the PAN membrane. After adjusting for basic factors such as age, sex, and duration of dialysis, prognosis turned out to be significantly better with the PES membrane than with the PS membrane. Further analysis was performed after adjusting for dialysis dose (Kt/V) and β_2MG as well as basic factors. The hazard ratio was slightly decreased with the EVOH or PAN membrane, but the PES membrane was not affected by dialysis dose. Finally, after adjusting for nutrition- and inflammation-related factors such as serum albumin, normalized protein catabolic rate, creatinine generation rate, and C-reactive protein (CRP) in addition to basic factors and dialysis dose, the hazard ratios of the PES group persisted (Figure 4).[6] Additionally, after propensity score matching, the PES and PMMA membranes were associated with a better prognosis than the PS membrane (Figure 5).[6] The effect of BPA is also implied, given that the PES and PMMA membranes do not contain BPA.

Table 2. Demographic, clinical, and laboratory values in hemodialysis patients according to types of dialyzer membranes

	CTA	EVOH	PAN	PEPA	PES	PMMA	PS	P value
Age(Years)	68.1 ± 12.2	75.1 ± 10.6	70.0 ± 11.6	69.2 ± 11.9	63.2 ± 12.1	69.1 ± 11.8	64.5 ± 11.8	< 0.0001
Sex(% woman)	40.1	56.3	45.7	41.6	33.0	44.5	38.4	< 0.0001
dialysis history(year)	6 [4-11]	5 [3-10]	7 [4-12]	6 [4-12]	8 [5-13]	7 [4-12]	8 [4-14]	< 0.0001
Diabetes (%)	37.2	34.0	38.8	34.9	31.3	33.9	31.6	< 0.0001
CVD history (%)	28.2	35.7	32.4	26.6	23.2	28.9	27.0	< 0.0001
Coronary artery disease	8.5	9.1	9.5	8.5	7.0	8.4	8.2	
Cerebral infarction	16.7	24.0	19.0	15.3	13.1	18.0	15.0	
Cerebral hemorrhage	5.4	7.2	4.4	5.4	4.7	5.1	5.3	
Limb amputation	3.2	4.0	5.9	2.9	2.7	3.2	3.0	
BMI(kg/m2)	21.1 ± 3.7	19.5 ± 3.5	20.7 ± 3.5	21.0 ± 3.5	21.6 ± 3.7	20.6 ± 3.2	21.2 ± 3.5	< 0.0001
Hb(g/dL)	10.5 ± 1.2	10.2 ± 1.4	10.3 ± 1.2	10.5 ± 1.2	10.6 ± 1.2	10.4 ± 1.2	10.6 ± 1.2	< 0.0001
Alb(g/dL)	3.6 ± 0.4	3.4 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	3.5 ± 0.4	3.7 ± 0.4	< 0.0001

Abe M et al. Am J Nephrol 2017

Conclusion

Even though Japan does not use the term "super-high flux dialyzer" as is used internationally, more than 90% of dialysis patients in Japan are currently being treated using super-high flux dialyzers. With respect to the biocompatibility of super-high flux dialyzers, greater use of high-performance dialyzers should be recommended while, at the same time, the effects of PVP and BPA should be investigated. Also, further long-term prospective studies are needed to clarify these findings, including whether the PES and PMMA membranes can improve prognosis.

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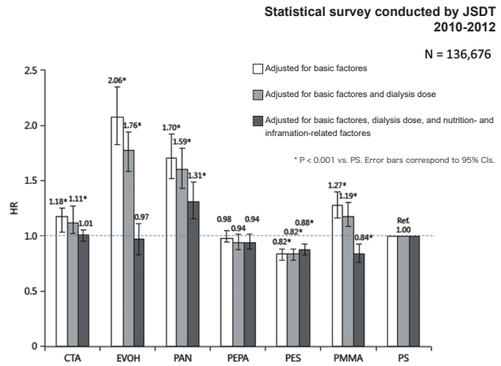

Figure4: Hazard ratios of all-cause motality amoung 7 types of dialyzer membranes using Cox proportional hazards regression

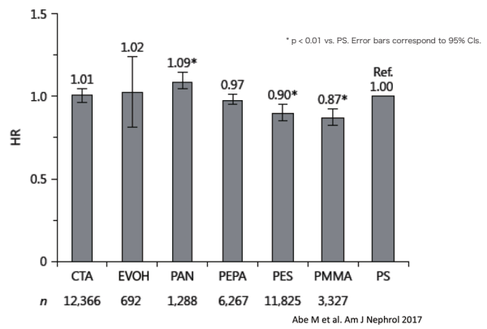

Figure5: Hazard ratios of all-cause mortality after propensity score matching for 6 types of dialyzer groups compared to the PS group

Luncheon Seminar

Effects on Dialysis Patients According to the Choice of Dialysis Membrane and BPA

Speaker **Gonzalez-Parra Emilio**

Universidad Autónoma de Madrid

Career

1986	Graduated from the Faculty of Medicine, University of Valladolid
1987-1988	Joined the Medical Affairs Department, Military Hospital
1989-1993	Obtained doctorate degree, Ph. D in medicine, Autonoma University
1994-2003	Associate Professor, Internal Medicine Department, Complutense University
1995-2002	Director, Nephrology Department, Military Hospital
2003-2009	Deputy Director, Nephrology Department, Gomez Ulla Military Hospital
2003 to date	Director, Hemodialysis Department, Complutense University
2007-2010	Professor, Department of Pathology, San Pablo University
2010 to date	Professor, Autonoma University
2010 to date	Director, Hemodialysis Department, Jimenez Diaz Foundation Hospital

Associations

Vice Chairman, Director and Co-Founder, Society of Nephrology of Madrid
Director and Treatment Guideline Coordinator, Spanish Society of Nephrology
Committee Chairman, Spain CKD-MBD Guidelines
Member of the Hispanic American MBD Foundation
Member of the International Society of Nephrology

Clarification of the effects of bisphenol A, the new uremic toxin, is urgently needed

Bisphenol A (BPA) is an environmental hormone whose chemical structure is similar to that of phenols, which are protein-bound uremic toxins. Even in very low concentrations, BPA is capable of altering cell function. Exposure to BPA has been associated with the development of obesity, insulin resistance, metabolic syndrome, diabetes, and atherosclerosis. BPA is a new uremic toxin whose mechanism of action needs to be urgently investigated (Figure 1).
Used in a variety of materials such as polycarbonates and resin, more than two million tons of BPA are produced annually. The chemical is also used in the synthesis of polysulfones and polyether ketones, in addition to plastic bottles, toothpaste, and packaging materials, and as an antioxidant for plasticizers. Furthermore, we are exposed to BPA on a daily basis given that epoxy resins containing the chemical are used in almost all food and beverage cans.
The use of BPA in baby products has been restricted internationally. For example, in 2011, the European Union banned the use of plastic baby bottles containing BPA. And, in 2012, the U.S. Food and Drug Administration announced that it would prohibit the use of BPA in baby bottles and cups (Figure 1).

Verification of BPA toxicity

When taken orally, BPA is excreted in urine after absorption into the intestines and metabolism in the liver. When entering the body through a non-oral route, BPA is incorporated directly into the blood in its unconjugated form. As a result, it will not be metabolized and will not undergo glucuronidation to the water-soluble BPA glucuronide. The water-soluble form is easier to remove with dialysis. Given that BPA is used in many types of dialysis equipment, including dialyzers, I believed it was necessary to investigate whether BPA was toxic or not in order to improve the management of patients with kidney disease. So, we conducted a study of oral administration of high concentrations of BPA (20 μg/kg/day) in mice. The kidneys, testes, and bladder showed signs of BPA exposure leading to urethral obstruction. This indicates that the ingestion of BPA has adverse effects on the body.

Choice of hemodialysis membrane affects serum BPA levels

We conducted a clinical study on how the choice of hemodialysis membrane affects serum BPA


F.D.A. Makes It Official: BPA Can't Be Used in Baby Bottles and Cups
By SABRINA TAVERNISE
Published: July 17, 2012

- **European Union prohibits baby bottles with BPA from 2011**
  - The European Union will ban the use of organic compound Bisphenol A (BPA) in plastic baby bottles from 2011 with the backing of a majority of EU governments, the EU's executive Commission said on Thursday (25 November).

Figure1: BPA Can't Be Used in Baby Bottles and Cups

levels. BPA concentration in the blood of 69 dialysis patients after treatment was compared after alternate use of the PS and PES membranes.[1] First, through blood sampling before treatment, we found that dialysis patients had higher serum and intracellular BPA concentrations than healthy controls.

The patients were separated into two groups: 28 were dialyzed using the PS membrane and 41 using the PES membrane. Dialysis was continued for 3 months with one membrane, then followed by 3 months of treatment with the other membrane. The group that used the PS membrane saw an increase in BPA concentration (from 48.8±6.8 to 69.1±10.1 ng/mL) but a decrease after switching to the PES membrane (from 70.6±8.4 to 47.1±7.5 ng/mL). Conversely, the group that initially used the PES membrane saw a decrease in BPA concentration but an increase after switching to the PS membrane (Figure 2). The results suggest that BPA concentrations in blood can be lowered with the use of dialyzers with a BPA-free PES membrane.

A similar study was also conducted for online hemodiafiltration (HDF).[2] Although the significant decrease seen in BPA concentration after changing from the PS membrane to the PES membrane was the same as that seen in the hemodialysis study, the concentration did not change considerably after switching from the PES membrane to the PS membrane. The differences between the two membranes after 3 months of online usage were not observed in the HDF study. However, it is notable that BPA concentration was considerably increased among patients using the PS membrane after 6 months of usage (Figure 3).

PS membranes increase oxidative stress

Next, a study on oxidative stress markers according to the type of membrane used in dialyzers compared the expression levels of oxidative stress proteins in peripheral blood mononuclear cells collected from patients dialyzed with the PS and PES membranes.

The expression levels of peroxiredoxin-1, transcription factor Nrf2, and heme oxygenase-1 (HO-1) were significantly higher with the PS membrane. The results were similar for oxidative stress proteins in peripheral blood mononuclear cells, with quinone oxidoreductase-1 and superoxide dismutase-1 as well as HO-1 and Nrf2 also increasing with the PS membrane. On the other hand, no significant changes were observed with the PES membrane (Figure 4).

Comparative research using inflammatory biomarkers in plasma for CRP and interleukin-6 (IL-6) was also conducted with the PS and PES membranes. Patients were dialyzed using the two types of membranes alternately for 3 months each, which resulted in increased levels of both CRP and IL-6 after dialysis with the PS membrane and decreased levels with the PES membrane.

Inflammatory reactions were also observed after culturing peripheral blood mononuclear cells with different concentrations of BPA for 24 hours. Expression levels of tumor necrosis factor mRNA and IL-6 increased with increasing BPA concentrations, thereby accelerating the inflammatory reaction. The PS and PES membranes were also compared. While the PS membrane containing BPA increased inflammatory reaction, no reaction was observed for the PES membrane.

PES membranes with high biocompatibility

Lastly, I would like to discuss the biocompatibility of the PES membrane. In a clinical study conducted in Spain by Dr. Patricia Martinez-Miguel and colleagues, the CD14+CD16+ count in dialysis patients who were previously dialyzed with the PA membrane and underwent 4 months of treatment with the PES membrane decreased compared with the count in dialysis patients who were dialyzed with the PS and PA membranes (Figure 5).[3] This suggests a better profile regarding activation of the inflammatory response, and that the PES membrane has better biocompatibility or contributes to increased removal of medium-sized toxic molecules.

A clinical study conducted in Germany in 2010 comparatively evaluated NIPRO's PES membrane and two reference filters.[4] Using the PES membrane resulted in the smallest increase in thrombin-antithrombin-III complex during dialysis and demonstrated exceptionally effective elimination of β2-macroglobulin and myoglobin.

Another study of the PES membrane, by Locatelli in 2009, compared the impact of two synthetic high-flux dialyzers on renal anemia. After 6 months of continual dialysis treatment using the respective membranes, the hemoglobin concentration of patients dialyzed with the PES membrane significantly increased. Furthermore, the erythropoietin dosage for patients dialyzed with the PS membrane increased but decreased for those dialyzed with the PES membrane. These results imply that anemia will improve if the PES membrane is used (Figure 6).[5]

Conclusion

BPA is an endocrine disruptor with multiple biological effects that is metabolized in the liver and eliminated by the kidneys. It must be removed in patients with chronic kidney disease because its accumulation causes systemic effects. Like p-cresol, BPA causes an increase in inflammation and oxidative stress in dialysis patients. The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) recommends avoiding BPA in materials used in dialysis.

For these reasons, BPA is an exogenous uremic toxin to which exposure should be avoided in dialysis patients. There are a few membranes that do not contain BPA, such as the PES membrane. The need to reduce inflammation and oxidation has been shown in multiple studies, and BPA may be associated with these toxic effects.

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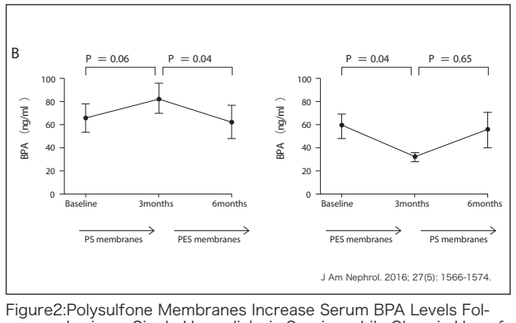

Figure2:Polysulfone Membranes Increase Serum BPA Levels Following a Single Hemodialysis Session while Chronic Use of PES Membranes for 3 Months Decreases Serum BPA

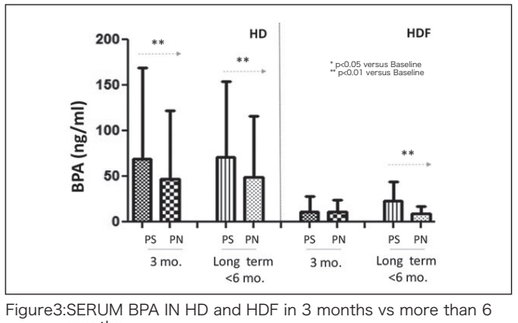

Figure3:SERUM BPA IN HD and HDF in 3 months vs more than 6 months

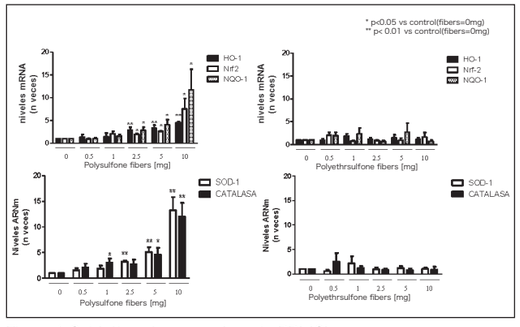

Figure4: Oxidative stress markers in PBMC's

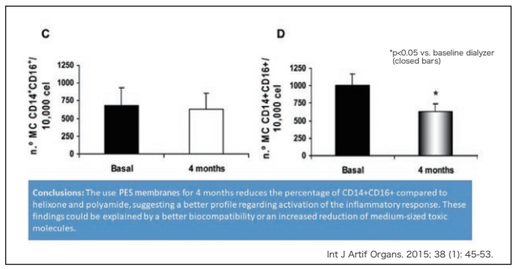

Figure5:C) Percentage of activated monocytes in the control group after 4 months of treatment with the same baseline dialyzer,polyamide or helixone(open bars). D) Percentage of activated monocytes in the control group after 4 months of treatment with polynephrone(grey bars). The data are expressed as mean and standard error of the mean.

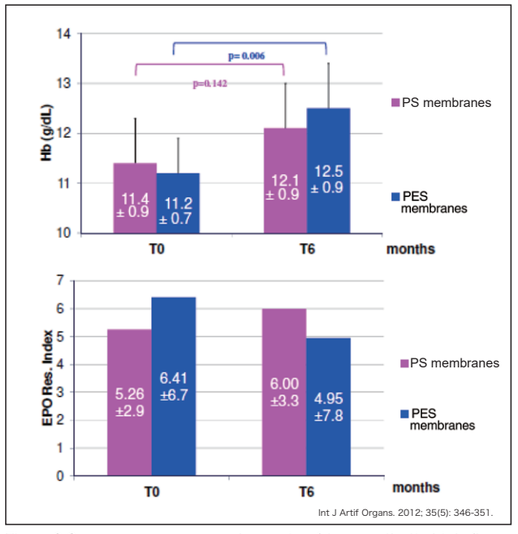

Figure6:Consequences on renal anemia of two synthetic high-flux dialyzers