# AN69 Membrane in Hemodialysis Patients

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Patients undergoing hemodialysis (HD) experience serious cardiovascular complications, through malnutrition, inflammation, and atherosclerosis. Amputation for peripheral arterial disease (PAD) is more prevalent in patients undergoing HD than in the general population. In addition, revascularization procedures in dialysis patients are often associated with subsequent amputation and high mortality rates. To improve the prognosis of dialysis patients, malnutrition and inflammation must be properly treated, which necessitates a better understanding of the characteristics of dialysis membranes. Herein, the characteristics of several dialysis membranes were studied, with a special reference to the AN69 membrane, noting several similarities to low-density lipoprotein (LDL)-apheresis, which is also applicable for the treatment of PAD. Both systems (LDL-apheresis and AN69) have anti-inflammatory and anti-thrombogenic effects because they use a negatively charged surface for extracorporeal adsorptive filtration from the blood/plasma, and contact phase activation. The concomitant use of both these therapeutic systems may have additive therapeutic benefits in HD patients.

Keywords: hemodialysis ; dialysis membrane ; AN69

## 1. Burden of Chronic Hemodialysis (HD) in Japan: Epidemiological and Economic Perspectives

Japan is estimated to have the highest number of dialysis patients, and this number continues to increase every year [1]. Estimates from the Japanese Society for Dialysis Therapy indicate that currently, one out of 385.1 Japanese citizens are dialysis patients. The number of chronic dialysis patients per million in 2016 had increased to 2596.7 from 2557.0 in 2015, and at the end of 2016, 76,836 patients were undergoing hemodiafiltration (HDF) and 635 patients were treated by home hemodialysis (HD) therapy, indicating an increase of 63 patients from 2015 [2]. At the end of 2017, the number of chronic dialysis patients had reached 334,505, an increase of 4896 patients from 2016 [2]. However, the number of peritoneal dialysis (PD) patients has gradually decreased since 2014, the number of PD patients in 2015 and 2016 being 9322 and 9021, respectively. Again, 20.3% of the PD patients were on combination therapy with either HD or HDF therapy [1]. Japan is also plagued by an increase in the proportion of elderly patients (70 years and above) who remain on dialysis [3]. The financial burden of renal diseases is particularly high, with the average medical cost being 14.5 times higher in individuals with renal disease than in those without renal disease/dialysis. In Japan, the estimated medical costs incurred for treating renal diseases were approximately 1.546 trillion yen in 2016, accounting for 3.8% of the total healthcare expenditure that year [4]. In Japan, in-center dialysis, home dialysis, and transplantation are the available options for the treatment of end-stage renal disease (ESRD); however, the use of transplantation and home dialysis is generally very low [4].

## 2. Risk Factors and Complications Associated with Chronic HD

In Japan, HD is considered as a mainstream renal replacement therapy and used in 95% of patients suffering from chronic kidney disease (CKD) [5]. The most common reasons for dialysis use in Japanese patients include diabetic nephropathy (38.8%), chronic glomerulonephritis (28.8%), and nephrosclerosis (9.9%) [2]. Diabetes mellitus is a well-known risk factor for CKD. Recent estimates indicate that the cumulative survival of chronic HD patients with poor glycemic control is significantly lower than that of patients with fair or good glycemic control [6].

Cardiovascular disease (CVD) is the main cause of mortality in dialysis patients [7]. The increased cardiovascular risk in CKD patients may be attributed to hypertension that may occur due to the activation of the renin–angiotensin–aldosterone system, vascular calcification associated with abnormal metabolism of calcium and phosphorus, and the specific dyslipidemia of CKD, chronic inflammation, malnutrition, oxidative stress, and uremic factors [7][8].

Observational studies in Japanese dialysis patients have demonstrated a close relationship between dyslipidemia (hyper-low-density lipoprotein (LDL) cholesterolemia, hypo-high-density lipoprotein (HDL) cholesterolemia, hypertriglyceridemia, and/or hyper-non-HDL-cholesterolemia), the severity of atherosclerosis, and the risk of myocardial infarction. ‘The

Japanese Society for Dialysis Therapy Guidelines for Management of Cardiovascular Diseases in Patients on Chronic Hemodialysis' suggest that dyslipidemia is an independent risk factor for CVD, as it is closely associated with atherosclerosis, CVD, and myocardial infarction [9].

Hypertension in HD patients plays an important role in the development of CVD. Because of the variability of blood pressure within a week, weekly averaged blood pressure (WAB) is a useful prognostic marker for evaluating hypertension in HD patients [10].

Peripheral arterial disease (PAD), defined as obstructive atherosclerosis of the lower extremities, is associated with an increased risk of cardiovascular events, and an increased mortality rate in HD patients [11]. Moreover, PAD is characterized by a high morbidity rate in dialysis patients related to vascular calcification and a high mortality rate related to lower limb amputation. Vascular calcification is induced by PAD, and is difficult to treat [12][13]. Vascular calcification reportedly increases with a decline of glomerular filtration ratio (GFR) [14]. Both the prevalence and severity of PAD in HD patients are closely associated with arterial calcification in the lower limbs [15]. Arterial abnormalities may be caused by rheological abnormalities [16]. Compared to those in healthy individuals, leukocyte aggregates are increased in HD patients. Increased platelet/leukocyte aggregates are associated with atherosclerosis in these patients [16].

Moreover, patients undergoing dialysis often complain of uncomfortable symptoms such as pruritus, irritability, depression, insomnia, and intradialytic hypotension. The common pathogenesis of these dialysis-related complications could be explained by the uremic retention of solutes and bio-incompatibility of dialysis therapy, which may in turn lead to microinflammation [17]. With respect to these complications, malnutrition, inflammation, and atherosclerosis are the most important aspects to consider, as they cause the highest morbidity and mortality among dialysis patients [18].

## 3. Unique Biocompatibility and Selective Adsorptive Properties of the AN69 Membrane

**Introduction and History of the AN69 Membrane**

The development of a synthetic membrane for use in dialysis was initiated in 1969 by a company named Rhône-Poulenc, following a request from the French government. This led to the development of the AN69 membrane. A copolymer of sodium methallyl sulfonate and acrylonitrile was used to manufacture an AN69 membrane. The unique feature of the AN69 membrane is that it is hydrophilic in nature compared with other synthetic membranes. This is because of the presence of sulfonate groups that create a hydrogel structure by attracting water, thereby providing hydraulic permeability with highly diffusive properties [19]. The AN69 membrane was first produced as a flat sheet; however, since 1980, it has been developed as a hollow fiber. The AN69 membrane has evolved continuously since its development in the early 1970s to meet the challenges and requirements of dialysis therapy. Its continuous advancement in thickness and internal diameter has led to improved performance. In the 1980s, the dialyzer manufacturing process was modified to allow sterilization by γ-radiation, instead of ethylene oxide [19]. The use of the AN69 membrane has been found to be associated with improved efficiency, reduced treatment duration, reduced risk of peripheral neuropathy, and improved clinical outcomes and quality of life. This paved the way for the initiation of volume-controlled, high-flux dialysis [19].

## 4. Key Features of the AN69 Membrane

**Adsorptive Features**

The microstructure and chemical composition of the AN69 membrane facilitate the bulk absorption of low-molecular-weight proteins, such as basic proteins and inflammatory mediators. The adsorptive property of the AN69 membrane, specifically for basic medium-sized proteins, distinguishes it from other adsorptive membranes and synthetic high-flux dialysis membranes [19]. A study demonstrated that low-molecular-weight acidic proteins can be eliminated by filtration on negatively charged membranes (such as AN69) or uncharged membranes. Conversely, basic low-molecular-weight proteins can be removed by specific ionic interactions on the AN69 membrane [20]. The superior biocompatibility of the AN69 membrane is due to its unique adsorptive capacity for anaphylatoxin and inflammatory complement factors [19].

The hallmark features of the AN69 membrane are its high permeability to fluids, including a broad range of uremic retention products, and its excellent biocompatibility, measured using either novel or conventional indicators [19].

## 5. Effect on Inflammatory Response

During HD, exposure of the blood to foreign surfaces activates various defense mechanisms, including coagulation, fibrinolysis, and complement activation, via an alternative pathway. In turn, complement activation leads to impairment of the host defense, as a result of increased consumption of complement proteins [21]. It has been observed that the intensity of complement activation varies with the type of membrane used: for example, with cellulose (CU), a much more marked activation is observed when compared to synthetic PAN membrane [22].

Several studies have demonstrated that the AN69 membrane has a lower ability to activate the complement system because of its adsorptive properties when compared to other membranes, such as CA dialyzers and CU membranes [22][23][24][25].

Adverse effects of dialysis, such as fever, hypotension, and acute-phase inflammatory reactions, are linked to the production of activated monocytes and macrophages. These were IL-1, tumor necrosis factor (TNF)-α, and IL-6. Compared to the other membranes such as CU, the AN69 membrane neither induces cytokine production nor causes the activation of mononuclear cells [26][27]. Moreover, no changes in neutrophil and monocyte counts occur during HD with the AN69 membrane, unlike with the CU membrane [28].

Since high-flux dialysis membranes, such as the AN69 membrane, are highly permeable, concerns regarding their potential to permit the passage of cytokine-inducing residues across these membranes, either through back-diffusion or back-filtration, have been raised. However, in vitro studies have shown that the AN69 membrane is not permeable to specific types of bacterial endotoxins compared with the permeability of other membranes [29][30].

Recent advances in the manufacturing technique of dialysis membranes enabled the development of a new hemofilter with an AN69 surface-treated membrane (Oxiris) [31]. It provides high absorbance of endotoxin (negatively charged) and cytokines and excellent anti-thrombogenicity because of its positively charged surface [32][33]. Case series and studies have reported the hemofilter's validity in reducing cytokine concentrations in COVID-19 patients [34][35][36].

## 6. Effect on Oxidative Stress and Carbonyl Stress

In addition to increased inflammation, HD is often associated with oxidative stress due to the activation of white blood cells, which triggers the generation of reactive oxygen species (ROS) and the loss of antioxidants during dialysis. Oxidative stress increases the risk of morbidity and mortality in this patient population and could be measured as advanced oxidation protein products in the plasma of uremic patients [37][38].

Evidence indicates that the AN69 membrane provides more protection from oxidative stress in HD patients than other membranes such as CDA [39]. Carbonyl stress is also implicated in long-term complications, such as atherosclerosis or dialysis-related amyloidosis, in ESRD patients [40][41]. Increased levels of advanced glycation end products (AGEs), which contribute to uremic toxicity, result from the accumulation of carbonyl AGE precursors in uremic plasma [42]. The effect of the AN69 membrane on carbonyl stress marker levels was similar to those of other membranes in a single HD session. However, in patients who were switched from PSu to the AN69 membrane, the carbonyl stress marker levels reduced to the control level [42].

## 7. Hemocompatibility

A high fibrinogen concentration is associated with increased cardiovascular risk and accelerated atherosclerosis. The AN69 membrane has good hemocompatibility, as it induces a lower thrombotic response, and fibrinogen and erythrocyte sedimentation rates are higher in non-biocompatible membranes [42].

## 8. Negative Charge

During the 1990s, the incidence of hypersensitivity reactions in HD patients, especially in those using electronegatively charged PAN membranes (AN69), increased significantly. This was due to the widespread use of antihypertensive drugs, such as angiotensin-I-converting enzyme inhibitors (ACEi) [43]. These inhibitors prevented the normal breakdown of bradykinin, the chief mediator of hypersensitivity reactions that occur during HD [44][45]. Similar reactions have also been reported with the use of PSu and other synthetic membranes during dialysis. The Evaluation of the Losartan in Hemodialysis (ELHE) study, which assessed the efficacy of an alternative antihypertensive drug, losartan, for HD patients, indicated a lower prevalence of anaphylactoid reactions compared to the use of ACEi when used in combination with the AN69 membrane [46]. To neutralize the electronegativity of the AN69 membrane and lower the generation of kinins, a

membrane was developed with a coating of polyethyleneimine, called the AN69-ST (ST for surface treated) membrane [19]. They demonstrated lower adsorption of high-molecular–weight kininogen and contact-phase activation than the regular AN69 membrane [47].

## 9. Functional Similarities of AN69 with LDL-Apheresis

LDL-Apheresis is the process of removing LDLs from the plasma and was originally used for familial hyperlipidemia patients. Recommendations for initiation of LDL-apheresis in patients affected by hypercholesterolemia are controvercial, as no study demonstrated definitively improved survival with LDL-apheresis. International guidelines and systematic review recommend to consider LDL-apheresis in homozygotes or those with analogous phenotypes if the patient has already been treated with diet and pharmacotherapy and LDL cholesterol levels still remain higher than cut-off values based on age and cardiovascular state [48][49].

There are several methods to remove LDL cholesterol from the blood. These include heparin-induced extracorpoeral LDL cholesterol precipitation, immunoadsorption, double filtration plasma pheresis of lipoproteins, and liposorber system. Through selective adsorption, liposorber system LDL-apheresis removes LDL from plasma using negatively charged dextran beads [50]. In addition to the lipid-lowering function, several other beneficial effects of LDL-apheresis have been reported, including anti-inflammatory, anti-atherogenic, and anti-thrombotic effects [50][51]. Owing to its pleotropic benefits, LDL-apheresis is effective against PAD in HD patients, through the reduction of LDL, coagulation factors, and ROS production [52]. In this context, it is important to note that LDL-apheresis has several functional similarities with the AN69 membrane. Both of these systems use a negatively charged surface for extracorporeal adsorptive filtration from the blood/plasma, and contact phase activation has been associated with both these systems [53]. Similar to AN69, LDL-apheresis therapy leads to a reduced generation of cytokines and CRP and improved macrophage function, thereby eliciting its anti-inflammatory role. Similar to the protective role of AN69 in oxidative stress, LDL-apheresis lowers the ROS generation by leukocytes. As observed in the case of AN69, LDL-apheresis also improves hemorheology by increasing blood viscosity and lowering coagulant and fibrinogen levels [50].

In addition to the beneficial effects of AN69, it is associated with fewer complications in HD patients, even those with PAD, as compared to those associated with other common membranes [54]. LDL-apheresis has also been successfully used in HD patients with complications such as PAD, owing to its pleitropic benefits other than lipid-lowering effects [50][54]. Therefore, the concomitant use of both these therapeutic systems in specific patients, such as those with PAD, may provide additive therapeutic benefits in such HD patients.

## 10. Clinical Evidence of AN69 Membrane Use in Chronic HD Patients

The AN69 membrane is one such membrane that has favorable effects on dialysis because of its well-balanced removal of low-molecular–weight proteins and small solutes [10].

## 11. Other Benefits of the AN69 Membrane in HD Patients

### 11.1. Effect on Serum Hepcidin Levels

CKD patients have a dysregulated iron metabolism, leading to anemia of chronic disease (ACD). Liver hormone hepcidin controls iron homeostasis. Hepcidin is a negative regulator of intestinal iron absorption and iron release from macrophages. Hepcidin induces degradation of the iron exporter ferroportin to reduce iron entry into plasma from dietary sources and body stores. Iron deficiency and erythropoietic drive suppress hepcidin production to provide adequate iron for erythropoiesis [55]. Hepcidin excess, as a consequence of inflammation, decreased renal clearance, and reduced erythropoietin production, is suspected to cause the dysregulation of iron metabolism, resulting in ACD.

#### 11.1.1. Ex Vivo Study

An ex vivo study [56] was performed using 50 mL of whole blood collected from healthy volunteers circulated for 2 h in a microcircuit with mini-dialyzers (acrylonitrile-co-methallyl sulfonate [AN69] or PSu without ultrafiltration). The levels of hepcidin-25 were measured in the blood samples at 0, 60, and 120 min. The study demonstrated that although serum hepcidin 25 levels increased after the ex vivo session with PS, they significantly decreased with AN69 after one and two hours (mean change ratio: −68 ± 39%).

### 11.1.2. In Vivo Study

An in vivo study included the collection of blood samples with 28 MHD patients at the start and end of HD sessions with the PS or AN69 membrane. The serum levels of hepcidin 20, 22, and 25 were measured using liquid chromatography tandem mass spectrometry. The serum levels of urea nitrogen and β2-microglobulin were also measured. The study findings indicated that the reduction of β2-microglobulin was significantly higher for PSu (62.4 ± 6.5%) than for the AN69 membrane (29.2 ± 8.2%). However, the reduction ratios of hepcidin 20, 22, and 25 did not significantly differ between the PS and AN69 membranes [56].

The study thus demonstrated that the AN69 membrane had the potential to remove hepcidin because of its high adsorptive capacity, whereas PSu removed serum hepcidin because of its high solute-removing potential. In consideration of the high adsorptive capacity of the AN69 membrane for hepcidin, HD patients treated with AN69 membrane might need less quality of intravenous iron administration.

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