Journal of Artificial Organs (2019) 22:14–28
https://doi.org/10.1007/s10047-018-1059-9

REVIEW

Artificial Kidney / Dialysis

The biocompatibility and bioactivity of hemodialysis membranes: their impact in end-stage renal disease

Michaela Kohlová[1,2] · Célia Gomes Amorim[2] · Alberto Araújo[2] · Alice Santos-Silva[3] · Petr Solich[1] · Maria Conceição B. S. M. Montenegro[2]

Received: 15 March 2018 / Accepted: 8 July 2018 / Published online: 14 July 2018

Abstract
End-stage renal disease is a growing health problem with increasing prevalence and high health care costs. Patients suffering from end-stage renal disease exhibit higher morbidity and mortality rates compared to the general population. These patients, who are treated using hemodialysis, typically suffer from anemia, inflammation, and oxidative stress. Inadequate dialyzer membrane biocompatibility exacerbates these negative side effects. Modifications of the composition of hemodialysis membranes have improved their biocompatibility and improve the patients' quality of life. Recently, the use of dialyzer membranes coated with bioactive compounds has also been proposed to further ameliorate dialysis-associated problems. Based on a survey of the current literature, application of bioactive membranes decreases the inflammation and oxidative stress of patients treated with hemodialysis.

Keywords Kidney disease · Hemodialysis membranes · Bioactive membranes · Oxidative stress · Inflammation

Introduction

End-stage renal disease (ESRD) is a severe pathological condition that results from a gradual and irreversible loss of kidney function. The clinical stages of chronic kidney disease (CKD) result from the reduction in the glomerular filtration rate (GFR) and albuminuria, which indicate the level of kidney damage and the patient's loss of kidney function. The National Kidney Foundation Clinical Practice Guidelines for Chronic Kidney Disease classifies ESRD as stage 5 of CKD that is one of the more severe stages of the disease. In this stage, the patient's GRF drops below 15 mL/min/1.73 m^2 for a minimal period of 3 months, and the patient needs renal replacement therapy via dialysis, i.e., hemodialysis and peritoneal dialysis, or via kidney transplantation [1]. The failing kidneys are no longer able to remove uremic toxins from the blood into the urine. The decrease of renal function leads to severe uremia and accumulation of potentially harmful uremic toxins such as urea, phosphorus, parathyroid hormone, β_2-microglobulin, homocysteine, leptin, protein-bound solutes, advanced glycation end products, and advanced oxidation protein products in the bloodstream [2–4]. The largest obstacle for HD removal is protein-bound solutes, requiring use of non-conventional therapy [5]. Uremia affects the biological functions of several organ tissues, induce immunological change by inhibiting or triggering immune responses, and by disruption of innate and/or adaptive immunity. Activated polymorphonuclear (PMN) neutrophils and monocytes, which are a part of innate immunity, are able to produce cytokines and to activate other inflammatory cells, leading to enhanced production of pro-inflammatory cytokines and reactive oxygen species (ROS). These then further contribute to the development of oxidative stress in ESRD patients [6, 7]. For that reason, systemic inflammation

✉ Alice Santos-Silva
assilva@ff.up.pt

✉ Maria Conceição B. S. M. Montenegro
mcbranco@ff.up.pt

1 Department of Analytical Chemistry, Faculty of Pharmacy in Hradec Králové, Charles University, Hradec Králové, Czech Republic

2 Department of Chemical Sciences, Faculty of Pharmacy, LAQV-REQUIMTE, University of Porto, Rua de Jorge Viterbo Ferreira nº. 228, 450-313 Porto, Portugal

3 Department of Biological Sciences, Faculty of Pharmacy, UCIBIO-REQUIMTE, University of Porto, Rua de Jorge Viterbo Ferreira nº. 228, 450-313 Porto, Portugal

and oxidative stress are common features in ESRD patients, and may lead to other complications such as atherosclerosis, endothelial dysfunction, malnutrition, muscle wasting, dialysis-related amyloidosis, and cachexia [8–11]. Moreover, most uremia-associated complications may further contribute to the progression of kidney disease. Actually, the correlation between low GFR/uremia and the progression of kidney disease creates a vicious circle that is very hard to disrupt (Fig. 1) [12–14].

There are considerable variations in ESRD prevalence among countries [15], including those within Europe [16]. These fluctuations indicate the varying degrees of effect of the different risk factors within populations and their dependence on several elements, such as diet, smoking, physical activity, race, and socio-economic status of the patients [16, 17].

In underdeveloped countries, the most common cause of ESRD is the progression of CKD caused by the elevated and continuous exposure to harmful toxins and drugs and by recurrent infections [17, 18]. In developed countries, the increasing aging of the population and the rise in diabetes, hypertension, and obesity, which are the main causes of CKD, has contributed to the growth of the prevalence of CKD. This has had a significant socio-economic impact and has caused a major financial burden on healthcare systems [17, 19–21]. Glomerulonephritis, glomerulosclerosis, polycystic kidney disease, autoimmune diseases, recurrent urinary tract infections, and acute kidney injuries are other risk factors associated with CKD. If not adequately treated, CKD may progress to ESRD [19, 22].

Despite the significant technological and pharmaceutical improvements in the ESRD treatment, patients survival rate remains low. The survival rate of ESRD patients during the first year of hemodialysis (HD) is around 84 and 76% in Europe and USA, respectively [23]. The type of material used for hemodialysis membrane affects significantly the surveillance rate, since use of highly biocompatible membranes can reduce inflammatory response induced during contact of blood with the artificial material [24]. The most common cause of death in ESRD patients is cardiovascular disease events, which are up to 30 times more frequent than those in the general population [25]. The high cardiovascular risk is attributed to a complex interconnection of traditional risk factors including age, obesity, lifestyle, arterial hypertension, diabetes, and dyslipidemia, and additional disease-associated risk factors, such as systemic inflammation, oxidative stress, anemia, hyperparathyroidism, hyperhomocysteinemia, left ventricular hypertrophy, endothelial dysfunction, and others [26–29].

It is noteworthy that the increase in morbidity and hospitalization rate of ESRD patients is accompanied with a significant financial burden on health systems. It is estimated that over 3 million patients worldwide have access to RRT [30] and that the expenses connected with HD treatment in developed countries represent approximately 5% of the health system budgets [31].

Hemodialysis

The inability of failing kidneys to clear small solutes such as urea with a molecular weight (MW) of less than 500 Da, of middle molecules, e.g., β_2-microglobulin and homocysteine with an MW over 500 Da, and of protein-bound uremic toxins with even higher MW has been associated with uremia co-morbidities [3] that may lead to multiple potentially life-threatening complications. Thus, replacing kidney function, through either dialysis or renal transplant, is needed for ESRD patients.

Since the 1960s, dialysis, which is an extracorporeal technique based on the movement of solutes across a semipermeable membrane, has helped to treat patients suffering from renal failure [32]. This technique utilizes a counter current flow at which the dialysis fluid flows in the opposite direction to blood flow allowing for the movement of specific solutes and water across the semipermeable membrane into

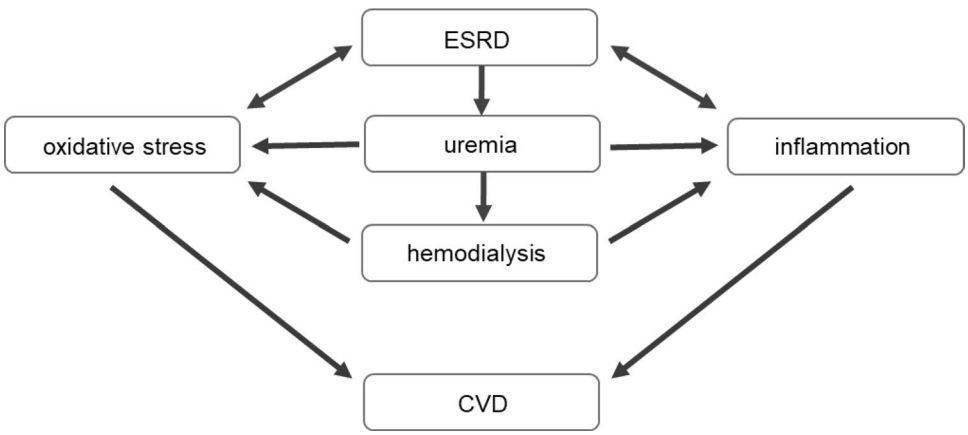

Fig. 1 Simplified scheme of the effect of hemodialysis on ESRD patients. This scheme represents vicious circle in which the presence of uremia in ESRD contributes to oxidative stress and inflammation and consequently contributes to the onset and development of CVD. The HD treatment due to long-term contact of artificial material with blood cells also affects negatively the inflammation and oxidative stress. *ESRS* end-stage renal disease, *CVD* cardiovascular disease

the dialysate [33, 34]. Three major processes control the solute exchange through the membrane: diffusion, ultrafiltration, and convection. In diffusional mass transport, the solutes move through the semipermeable membrane due to the concentration gradient. This mechanism effectively removes only small solutes (< 500 Da). Ultrafiltration enables fluid removal from the blood compartment due to a combination of the concentration gradient and higher hydrostatic pressure. Finally, convective removal, known as ''solvent drag'', combines both movements: the solute molecules are dragged across the semipermeable membrane via the movement of fluids. Since the size of the molecules removed by convection is limited only by the membrane pore size, this mechanism effectively clears both large and small molecules [35].

Conventional HD treatment takes place in hospitals and dialysis centers, and is usually carried out three time a week for 3–5 h each session. More recently, HD is carried out at home during day or night. The number and duration of sessions depend on prescription of the physician. This option for HD treatment has some benefits compared to the conventional HD as it can improve the patients' both social and professional quality of life [36].

Peritoneal dialysis (PD) is another type of dialysis that allows ESRD patients to have a more flexible treatment schedule, as it can be carried out at home or in any other clean location. Due to its flexibility, PD treatment is frequently preferred for pediatric patients, since it improves school attendance and the quality of the child's family life [37]. In addition, fewer dietary and fluid intake restrictions apply in PD treatment compared with conventional HD. PD has also been associated with a lower mortality rate, especially in the first 3 years of treatment, compared to HD, probably due to the better preservation of the residual renal function. Other PD benefit is the lower cost related to the treatment. Adequate training and education of the patients and/or the care providers are required to safely provide dialysis at home. The long-term assessment of PD is much shorter compared to HD. However, as PD has been associated with some complications, namely, sudden death, cardiovascular events, peritonitis and/or sepsis, progressive malnutrition, and inadequate dialysis, some patients may have to change to conventional HD due to these limiting factors [38–41].

Side effects of hemodialysis

HD treatment is a lifesaving procedure for ESRD patients. However, despite the technological improvements made that have led to a significant increase in hemodialysis benefits, the HD procedure per se may still contribute to the development of some side effects. The most common are hypotension, fatigue, pruritus, nausea and vomiting, headache, and muscular cramps [42, 43]. The rapid solute and extracellular fluid exchange have been proposed as the main triggers for those side effects [44]. However, the mechanisms underpinning these complications are still poorly clarified.

Chronic inflammation and oxidative stress are also common features in ESRD patients undergoing HD [45, 46]. Several factors have been proposed as the potential triggers, specifically the HD membrane bioincompatibility, uremia, bacterial contamination of the dialysate, and infection at the vascular access. The latter is more frequent when a central venous catheter is used [45, 47]. The long-term intradialytic contact of blood with large-sized artificial materials can lead to continuous leukocyte and complement system activation, as well as to the release of pro-inflammatory cytokines [48, 49]. These disturbances in the immune system then greatly contribute to the long-term co-morbidities of ESRD patients [50].

The search for new improvements related to the biocompatibility and bioactivity of HD membranes is ongoing. Despite these technical innovations, inflammatory stimuli/response is always observed in some patients.

Inflammation

The inflammatory status of ESRD patients undergoing hemodialysis is clearly shown by the elevated levels of C-reactive protein (CRP), interleukin 6 (IL-6), and hepcidin, which are well-known inflammatory markers. The hepatic synthesis of CRP is triggered by IL-6 released from activated inflammatory cells that also induce hepcidin production in liver. The enhanced levels of circulating hepcidin contribute to worsening of anemia by altering iron metabolism [51]. Anemia is commonly present in ESRD patients and is mainly due to the inability of failing kidneys to produce an adequate amount of erythropoietin to trigger erythropoiesis [52], and consequently, to correct the anemia. The enhanced inflammation in ESRD patients has also been associated with hyporesponsiveness to erythropoiesis-stimulating agents used for treatment of anemia [53, 54]. Moreover, several pro-inflammatory cytokines that are enhanced in ESRD patients, such as IL-1, tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ), are able to inhibit erythropoiesis thus contributing to worsening of anemia [55].

Some studies have reported an increase in CRP and in neutrophil elastase (NE) levels after HD sessions suggesting that the HD procedure per se triggers the activation of neutrophils and enhances inflammation (Fig. 1) [56]. The contact between neutrophils and the priming agent triggers the translocation of intracellular granules to the cell surface and the subsequent release of their content into the extracellular space. The secretion of several pro-inflammatory substances, such as NE, myeloperoxidase,

lactoferrin, cathepsins, defensins, cytokines (IL-1, IL-6, -12, TGF-β, TNF-α), and chemokines (IL-8, CCL2, CCL3) can further activate more neutrophils and other inflammatory cells. Thus, these released substances modulate/enhance the inflammatory response [45, 57–62]. The release of NE following PMN activation has recently gained interest, because it has been associated with the promotion of inflammation and with a negative impact on the outcome of ESRD patients using HD [63, 64]. NE is able to degrade extracellular matrix proteins including collagen, elastin, and fibronectin, favoring neutrophil migration into or through the tissues. This then can regulate inflammatory functions [65]. These mechanisms of regulating the inflammatory response by NE include cytokine activation/inactivation by proteolytic cleavage, as well as the regulation of chemokine and cytokine bioactivity by shedding or activating cell surface receptors [66]. Under physiological conditions, the proteolytic activity of NE is regulated by endogenous inhibitors [67, 68]. An imbalance between NE and its inhibitors results in excessive tissue breakdown, which leads to organ dysfunction and to worsening of the patients' inflammatory state [69–72].

Increased levels of NE have been reported in HD patients, and it is particularly enhanced in HD patients exhibiting a decreased response or resistance to recombinant human erythropoietin treatment [45]. The high NE levels in HD patients have also been associated with changes in erythrocyte membrane proteins that destabilize membrane structure and lead to the premature removal of erythrocytes, thereby worsening the anemia [73].

The increase in neutrophil activation biomarkers following an HD procedure seems to result from the interplay of several factors and depends on the material used for the production of HD membranes. According to Table 1, membranes based on unmodified cellulose initiate a higher PMN cell activation compared to modified cellulose and synthetic polymer membranes [74, 75]. Moreover, an improvement in PMN cell activation has been observed even among different synthetic polymer HD membranes. The impact of polymer composition on inflammation will be discussed in the "Hemodialysis membranes" section.

Changes in monocyte number and function have also been reported in HD patients. The number of pro-inflammatory CD14+ and CD16+ cells increases in peripheral blood and contributes to an increase in cytokine production, chronic inflammation, and endothelial cell damage [76]. Monocytes and macrophages also decrease phagocytic function and present defective antigens [50]. Lymphopenia and several alterations in T cells and B cells have also been reported in ESRD patients [77, 78].

Oxidative stress

ESRD is associated with an increase in incidence of inflammation and oxidative stress-based complications. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the capacity of the endogenous antioxidant defense mechanisms [79].

The HD procedure contributes to exacerbate oxidative stress in ESRD patients (Fig. 1) by triggering the activation of inflammatory cells and by allowing the loss of water-soluble antioxidants such as vitamin C through the semipermeable HD membrane [47, 80]. Moreover, the dietary restrictions and malnutrition of ESRD patients also contribute to depletion of antioxidant defense system. It has been well documented that even a single HD session significantly increases oxidative degradation products and decreases the quantity of antioxidants [81].

The overproduction of ROS by activated neutrophils and monocytes occurs via nicotinamide adenine dinucleotide phosphate oxidase [7] and leads to oxidative stress via triggering a chain of oxidative reactions. This process induces oxidative modifications in several blood components and oxidative damage of nucleic acids, membrane lipids, and proteins occurs while reducing blood cell viability and contributing to development of anemia [82, 83]. ROS is also able to increase inflammation via activation of the transcription factor NF-kB pathway, which regulates the transcription of pro-inflammatory cytokines, such as TNF-a, IL-1b, IL-2, IL-6, IL-12, CRP, and leukocyte adhesion molecules. In addition, pro-inflammatory cytokines can lead to the overproduction of ROS by activating other inflammatory cells, establishing a vicious cycle between oxidative stress and pro-inflammatory cytokine overproduction [48, 84, 85]. Some studies have reported a positive correlation between serum CRP levels and lipid peroxidation in ESRD patients, further strengthening the correlation between inflammation and oxidative stress [86, 87]. Strong evidence exists that oxidative stress along with inflammation is the key factors in the development and progression of CVD, increasing morbidity and mortality risk in ESRD patients [88, 89]. Therefore, the control of oxidative stress and inflammation in ESRD patients emerges as the crucial step reducing ESRD-related complications and should start at the early stages of the disease.

Different strategies have been addressed enabling control of the oxidative stress and inflammatory processes such as administration of pharmaceutical drugs. However, this approach appears to be a low efficient due to the lack of selectivity of the drugs. Indeed, some pharmaceuticals such as statins used to control dyslipidemia and some

Table 1 Hemodialysis membranes: advantages and limitations

Type of membrane	Designation	Advantages	Limitations
Unmodified cellulose	Cuprophan®	Good small solute removal [97] Higher HD treatment adequacy compared to modified cellulose and PS membranes [97]	Higher complement and PMN cells activation, compared to modified cellulose and synthetic membranes [74, 75] Penetration of bacterial products from dialysate into blood [98] Does not remove medium-sized molecules from blood [98]
Modified cellulose	Cellulose acetate (CA) (hydroxyl groups replaced by acetate groups)	Lower complement activation in comparison with unmodified cellulose membranes [151]	Higher neutrophils apoptosis compared to PS membrane [152] Higher complement activation in comparison with synthetic membranes [153]
	Hemophan® (several hydroxyl groups replaced by tertiary amine)	Lower complement activation compared to unmodified cellulose [106]	Higher pro-inflammatory cytokine production compared to PAM membranes [154]
	Synthetically modified cellulose (SMC) (hydroxyl groups party replaced by benzyl groups)	Lower complement activation then unmodified cellulose membranes [107]	Lower β_2-microglobulin removal compared to synthetic membranes [97]
	Cuprammonium rayon	Lower complement activation than Hemophan® and unmodified cellulose membranes [49]	Albumin loss higher then with PS, PAM membranes [155]
Synthetic	Polycarbonate (PC)	Naturally hydrophilic character [75] Lower complement activation compared to unmodified cellulose membranes [156]	Higher production of inflammatory markers compared to PAM membranes [157] Higher complement activation compared to PAN and PS membranes [158]
	Polysulfone (PS)	Good removal of β_2-microglobulin [159] Lower mortality rate compared to cellulose membranes [154]	Causes neutrophil activation [160] Higher neutrophil activation compare to EVAL membranes [161] Increases pro-inflammatory cytokine production [162]
	Polyamide (PAM)	Good removal of β_2-microglobulin [163]	Risk of anaphylactic reaction [164] Persistence of slight complement activation [165]
	Polyethersulfone (PES)	Great removal of middle-MW molecules [166]	Protein adsorption on its surface [166] Persistence of immune system activation [166]
	Polyacrylonitrile (PAN)	Adsorption of pro-inflammatory, low-/medium- sized proteins and bacterial products [167] Lower neutrophil activation compared to PMMA membranes [168]	Production of bradykinin [169] High risk of anaphylactic reaction compared to other synthetic membranes [164] Persistence of slight complement activation [170]
	Poly(methyl methacrylate) (PMMA)	Great removal of middle-MW proteins [171, 172] Lower pro-inflammatory cytokine production compared to PS membranes [154] Positive effect on anemia [154]	Persistence of slight complement activation [173] Causes mild leukopenia [173]
	Polyester polymer alloy (PEPA)	Low albumin permeation [174] Good β_2-microglobulin removal [174]	Persistence of low complement activation [175]
	Ethylene-vinyl alcohol copolymer (EVAL)	Naturally hydrophilic character [75] with low protein adsorption [116] Removes high MW molecules [117] Better oxidative stress reduction compared to CA membranes [117] Lower neutrophil activation compared to PS membranes [115]	Not described. Discussed in "Synthetic membranes" section

Table 1 (continued)

Type of membrane	Designation	Advantages	Limitations
Bioactive membrane	Vitamin E coated	Decreases oxidative stress [134] Improves inflammatory status [132, 135] and anemia [147]	Persistence of complement activation [135]

angiotensin-converting-enzyme inhibitors administered to control hypertension are known to inhibit inflammation and the development of oxidative stress [90]. Antioxidant enriched diet and food supplements can also have a beneficial preventive effect.

Hemodialysis membranes

Hemodialysis membranes have developed through several stages to improve their biocompatibility and HD adequacy, increase their ability to reduce oxidative stress and inflammation, and to better clear uremic toxins. These advances in HD membrane characteristics have led to an overall improvement of patients' well-being and quality of life.

The ability of HD membranes to remove solutes from blood depends on their pore size. Membranes are classified either as high-efficiency or low efficiency depending on their ability to remove small solutes. High-flux and low-flux membranes are divided based on their ability to remove large solutes. High-flux membranes have larger pores than low-flux membranes, thus allowing the diffusion of a larger quantity of medium-sized molecules such as β_2-microglobuline, which is an independent risk factor for all-cause mortality [91–93]. Several studies have demonstrated that the use of high-flux membranes is associated with improved clearance of medium-sized molecules [94]. Compared to low-flux membranes, high-flux membranes also have other advantages, namely, weaker procoagulant activity and activation of the complement system, reduced inflammatory response with a lower secretion of cytokines and acute phase proteins (IL-6, CRP), an improved lipid profile, a reduced risk of infection, and a better-preserved renal function. These advantages explain the more frequent use of high-flux membranes that improve patients' outcomes and survival rates.

Small molecules with MW of less than 500 Da are easily removed by HD procedure using low-flux membranes. However, advanced dialysis techniques including high-flux, online hemodiafiltration and prolonged conventional hemodialysis sessions have to be used to remove medium-sized molecules and protein-bound solutes from the blood stream.

In recent years, the HD strategy has moved forward to the use of ultra-high-flux protein-leaking dialyzers and techniques using protein adsorption on membrane surface. Such methods combine direct removal of large solutes via their adsorption [5, 9, 95].

Table 1 shows that the HD membranes can be prepared from natural and synthetic polymers regardless the low/high-flux type [96].

Cellulose-based membranes

The first HD Cuprophan® membranes were based on cellulose derived from cotton. This type of membrane enabled a good removal of small solutes [97], but was not able to remove medium-sized molecules [98] and featured reduced biocompatibility [74, 75]. This contributed to a poor outcome of the patients, as presented in Table 1, and therefore, its use for HD treatment was discontinued. The reduced biocompatibility of cellulose membranes was related to the presence of free hydroxyl groups in its composition that led to complement activation by the alternative pathway [99, 100], and to the activation of mononuclear leukocytes followed by the release of pro-inflammatory cytokines [101]. Activated cells are more prone to undergo apoptosis, which may ultimately lead to leukopenia [102]. Indeed, leukopenia was often observed in patients treated with HD cellulose membranes [103]. The use of Cuprophan® membranes leading to poor outcomes for HD patients triggered further research aimed at improvements in their biocompatibility [104, 105]. Cellulose membranes were enhanced through the chemical masking of the hydroxyl groups such as by their acylation with acetate groups. These modified membranes, also referred to as substituted membranes, include cellulose acetate, cellulose diacetate (CDA), and cellulose triacetate (CTA), in accordance with the number of acetate groups introduced in the individual monomeric cellulose units. These structural modifications eliminate the majority (up to 80%) of free hydroxyl groups presented on the membrane surface that enabled binding to complement receptor C3b. Thus, the density of unsubstituted hydroxyl groups is the main factor determining the extent of complement activation and is responsible for the adverse effects [105]. The CTA dialysis membrane is now the most biocompatible of all cellulosic membranes that causes the lowest rate of complement activation [106] (Table 1). The replacement of hydroxyl groups by acetates leads to an increase in membrane pore size and has the most pronounced impact on water and small solute molecule permeability [105].

Another type of synthetically modified cellulose HD membrane contains aromatic benzyl groups that are

covalently bound onto the cellulosic chains via ether bonds. These functionalities create hydrophobic domains. They compensate the overall hydrophilic character of the native cellulose surface [107, 108]. The balance between hydrophilicity and hydrophobicity results in improved biocompatibility through the ratio between the hydrophilic domain that have a negligible effect on platelet activation while activating complement, and the hydrophobic domain responsible for platelet activation with a minimal activation of complement [107].

A cellulosynthetic membrane such as Hemophan® is another type of improved cellulose-based membrane. Compounds such as functional tertiary amines are added to the liquefied cellulose during the membrane preparation process. The hydroxyl groups of the membrane surface are modified with a bulky diethylaminoethyl group, which sterically inhibits the contact between the membrane and blood cells and improve the biocompatibility [105, 109].

Several studies [107, 108, 110] carried out with cellulose and cellulose acetate membranes have confirmed that replacing hydroxyl groups reduces complement activation, and have suggested that the degree of hydroxyl group substitution, rather than the substituents themselves, was the most important factor (Table 1).

Synthetic polymer membranes

These membranes are fabricated from polymers such as polysulfone (PS), polyethersulfone (PES), poly(methyl methacrylate) (PMMA), polyester polymer alloy (PEPA), polyacrylonitrile (PAN), polycarbonate (PC), polyamide (PAM), and poly(ethylene-co-vinyl alcohol) (EVAL) (Fig. 2) [96]. Several studies comparing their physical and biocompatibility characteristics have been carried out. Table 1 presents a description of the most relevant information concerning the biocompatibility of these membranes.

Compared to cellulosic membranes, the synthetic polymer types present more physical–chemical advantages in their structure, namely, larger pore size, better hydraulic permeability, and higher filtration capacity, thus, a greater ability to remove solutes [105]. The improved performance of these membranes is also due to their asymmetric structure, consisting of a denser surface layer responsible for the molecular weight cut-off (MWCO) and for their mechanical strength compared to symmetric cellulose membranes.

The synthetic polymer membranes used in dialyzers are almost exclusively hollow fibers [111], which tremendously increase the surface area available for blood purification. Since the introduction of these membranes in dialyzers, a vast number of studies have been focused on evaluating their biocompatibility and separation ability, as well as on their impact on the mortality and morbidity of patients undergoing HD treatment treated with them. Hakim et al. [112]

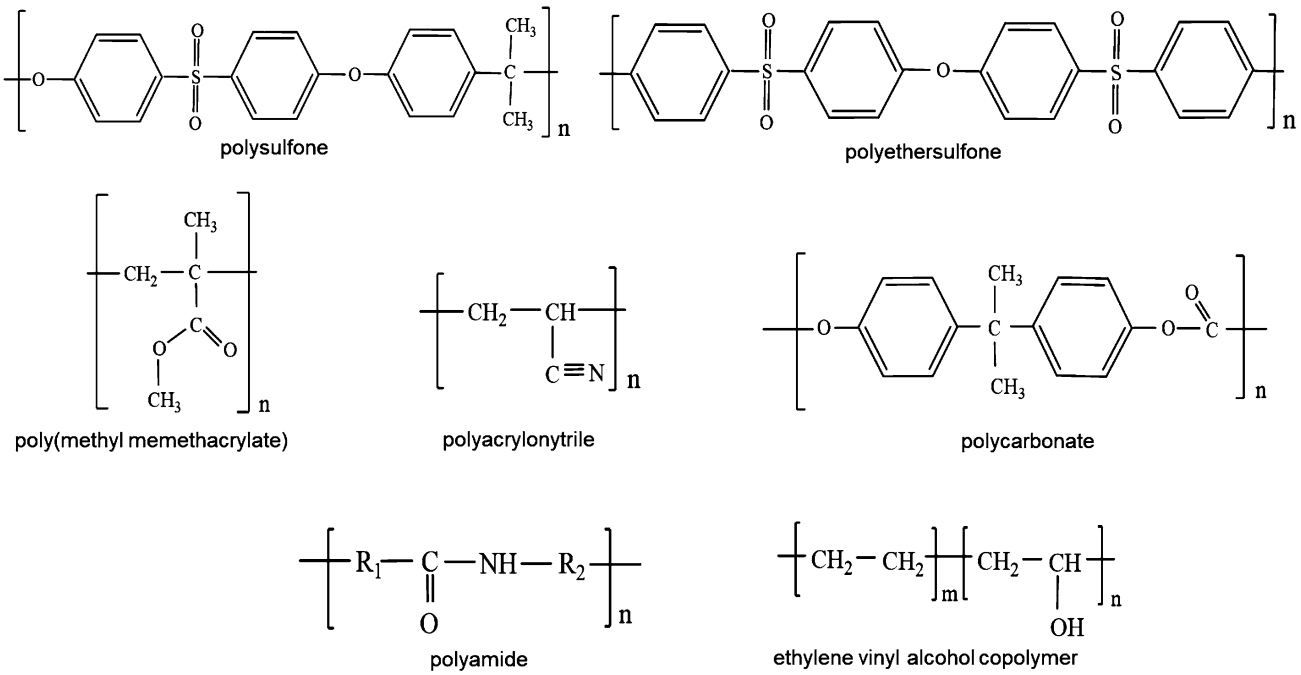

Fig. 2 Chemical structure of synthetic polymers used for hemodialysis membrane

compared the effect of HD treatment using unsubstituted cellulose, modified cellulose, and synthetic polymer membranes on the mortality of ESRD patients. They reported that after adjusting the dose of dialysis and controlling the comorbid factors, the risk of mortality of the patients dialyzed with modified cellulose and synthetic polymer membranes was at least 25% lower than that of patients treated with unsubstituted cellulose membranes. 6 years later, MacLeod et al. [97] compared data from 27 studies assessing the effects of cellulose, modified cellulose, and synthetic polymer HD membranes used in the treatment of ESRD patients. These authors reported no significant improvement in mortality rate with the use of synthetic polymer membranes compared to cellulose membranes. However, the use of synthetic polymer membranes led to a decrease in loss of serum albumin and a higher reduction of β2-microglobulin. Similar beneficial changes were also found in a meta-analysis described by Jaber et al. [113]. They reported an improvement in the mortality rate of patients treated with HD synthetic polymer membranes. Other studies focusing on the inflammatory state of HD patients treated with these types of HD membranes proved positive effects of the last type membranes, namely, a reduction in neutrophil priming and activation [60, 114]. Unfortunately, both studies included only a small number of patients and further studies are needed to evaluate the impact of the synthetic polymer membranes on inflammation.

EVAL, another type of polymer for membrane fabrication exhibited important hydrophilic characteristics, reduced protein adsorption, and decreased complement and blood cell activation compared to PS and PMMA [115], CDA and PS [116], and CTA [117]. Despite all these biological advantages, no further studies focusing on its potential value for clinical HD treatment have been reported. This is likely due to the fact that the mechanical strength of EVAL is not sufficient to withstand the pressures experienced during HD procedure.

PMMA and PAN membranes have been used to produce protein-leaking dialysis with additional mechanism of adsorption. Owing to their hydrophobic character, the membranes exhibited increased ability for removal of some large solutes, cytokines, and middle-MW molecules, such as β2-microglobulin [9, 95].

PS is a polymer with exceptional filtering and biocompatibility characteristics, thermal stability, mechanical strength, and chemical inertness. It is one of the few biomaterials that can withstand all sterilization techniques. Despite these important characteristics, the hydrophobic nature of PS can cause difficulties during HD. The adsorption of serum proteins onto PS membranes can lead to serious or even life-threatening complications due to activation of the complement alternative pathway. To overcome this problem, PS is blended with a hydrophilic polymer, polyvinylpyrrolidone, which has excellent biocompatibility. Compared to cellulosic membranes, these PS membranes stand out for their better biocompatibility, their improved clearance of medium-sized molecules, and for their larger surface area. PS allows a higher and more rapid reduction of uremia [118] and the enhanced biocompatibility of PS membranes also reduces oxidative stress in HD patients [119]. Overall, the long-term use of PS membranes brings an important improvement in the outcome of HD patients [119]. Nevertheless, according to Gastaldello et al. [120], only a few studies have proven the better outcome of PS membranes compared to modified cellulose membranes.

A recent cohort study, involving almost 137,000 patients undergoing HD for at least 2 years and being treated with different types of membranes including CTA, EVAL, PAN, PEPA, PES, PMMA, and PS, was carried out by Abe et al. [121]. They estimated the association between baseline dialyzers and all-cause 2-year mortality. Using PS as the reference group, they found that the hazard ratio was significantly higher for patients treated with CTA, PMMA, PAN, and EVAL membranes. Adjusting for nutrition and inflammation, the hazard ratio was significantly reduced for patients treated with PES and PMMA membranes. This study suggests that the type of membrane used in hemodialysis may affect mortality risk and that long-term studies are needed to clarify the impact of hemodialysis membranes on the outcome of the patients.

According to the literature, PS membranes have demonstrated better performance concerning solute removal and biocompatibility than other synthetic types. Therefore, they are widely used for hemodialysis treatment [118]. However, even the most biocompatible membranes were not able to exclude an inflammatory response linked to release of pro-inflammatory cytokines and ROS, during the long-term intradialytic contact with blood. Thus, new ideas are desired for developing advanced approaches including the production of bioactive membranes [122].

Bioactive membranes

To overcome the previously discussed disease complications encountered during HD treatments, new strategies have been considered in the development of HD membranes. The main focus is to improve biocompatibility and also to introduce antioxidant protection to blood cells and circulating proteins and lipoproteins using bioactive compounds [89, 123]. Antioxidants, such as vitamin E, C, and glutathione, have been used as oral supplements to correct the progressive decrease of blood antioxidants and to alleviate the exacerbated generation of ROS in HD patients [89]. Moreover, other active compounds besides antioxidants have been considered, as

they could potentially help to reduce CVD morbidity and mortality.

Vitamin E-modified membrane

Vitamin E, the most important lipophilic antioxidant in humans, is known to be a potent ROS scavenger. During HD treatment, the circulating levels of vitamin E are probably inadequate to face the increased free radical production, and are probably reduced due to its overconsumption [124]. Several studies have evaluated the effect of the oral administration of 200–800 mg/day vitamin E on oxidative stress in HD patients. The majority of these studies reported a decrease in oxidative stress. One clinical outcome trial with 196 patients found that vitamin E protected against secondary CVD [124]. Orally administered vitamin E in HD patients has also been associated with reduced inflammation manifested in fewer pro-inflammatory cytokines [125], an improved lipid profile [126], and in lipid peroxidation [127, 128]. However, there are still no guidelines for dosage, intake frequency, and intake time for oral vitamin E supplements in ESRD patients on hemodialysis.

The ability of vitamin E to scavenge ROS and thus reduce oxidative stress in HD patients explained the research that led to the production of a novel bioactive hemodialysis membrane. The linkage between vitamin E directly reducing the production of ROS at the site of contact between blood cells and the dialysis membrane could provide antioxidant protection in the time and location targeted manner. Moreover, ROS scavenging by vitamin E attached to the bioactive membrane could also contribute to reduction of the prevalence of CVD events in ERDS patients treated with HD [129, 130].

A cellulose-based vitamin E-coated membrane (VEM) was first introduced on the market in the late 90s as Excebrane® dialyzer. The antioxidant effects were confirmed by Galli et al. who demonstrated reduced lipid peroxidation after using a cellulose-based VEM compared to a non-coated cuprammonim rayon membrane [129]. Takouli et al. also reported an increase in total antioxidant capacity, as well as a significant decrease in the content of inflammatory markers, CRP, and IL-6 while using cellulose acetate VEM compared to common cellulose acetate membranes [131].

Later, PS-based VEMs were introduced on the market for clinical use after their biocompatibility was confirmed [132, 133]. Nowadays, several commercial types of modified cellulose/PS/PES-based low/high-flux membranes coated with vitamin E such as VitabranE®, CL-13, EE12 Terumo, and Clirans®E are available. Since the introduction of VEM into clinical dialysis practice, many studies summarized in the meta-analysis carried out by Yang et al. [132]. They reported the site-specific ROS scavenging antioxidant effect of vitamin E immobilized in the membrane, as shown by the reduction in pro-inflammatory cytokines and acute phase reactants, such as CRP and IL-6 [132–135]. The recent meta-analysis of D´Arrigo et al. [123], which included sixty studies, compared the effect of VEM and conventional HD membranes on anemia, inflammation, oxidative stress, and dialysis adequacy, as the main endpoints of interest. Their findings were consistent with meta-analysis by Yang et al. [132] confirming the positive effect of the use of VEM on reduction of oxidative stress and inflammation biomarkers, namely, a significant decrease in IL-6 levels. However, the use of VEM did not have positive impact on anemia. The study also confirmed no increase in benefits for VEM usage on other HD associated parameters, such as dialysis adequacy, lipid profile, and serum albumin. Clermont et al. [136] reported that the use of VEM contributed to reduction of neutrophil activation given the decrease in NE levels.

In contrast, Panichi et al. [134] reported improvements in hemoglobin levels and a better response to ESA treatment with the use of VEM in HD patients. Studies by other authors [137, 138] also reported a decrease in ESA dose requirements in HD patients treated with VEM. However, these studies have some limitations either being carried out only in one HD center or did not assure equal conditions for VEM and conventional HD treatment of patients. As already outlined by Locatelli et al. [138], the improvement in anemia is usually accompanied with a decrease in IL-6 level suggesting that the use of VEM may improve anemia. This is happening by protecting erythrocyte membranes against peroxidation, and thereby increasing erythrocyte survival, and also indirectly by reducing the pro-inflammatory cytokines and hepcidin levels that inhibit erythropoiesis and/or alter iron availability for erythropoiesis.

Nevertheless, few studies did not find such clear improvements in the outcome of ESRD patients on HD treatment with VEM [139, 140].

By recognizing the importance of the bioactivity of HD membranes, a new field of research has emerged that is focused on making other structural modifications and/or using other bioactive compounds to reduce inflammation and oxidative stress [122].

Lipoic acid-modified membrane

Fat-soluble antioxidant lipoic acid was also used as an oral antioxidant supplement in HD patients to reduce oxidative stress-associated complications. Two different studies have shown that the oral administration of lipoic acid reduces inflammation and oxidative stress, although not as well as with a VEM [125, 141]. A new bioactive membrane model using lipoic acid was designed by Mahlicli et al. [142], where the antioxidant was chemically immobilized at the

PS membrane. The ability to reduce oxidative stress was confirmed in vitro.

Ahmadi et al. [125] combined vitamin E and lipoic acid in an oral supplement and this demonstrated even better results in suppressing oxidative stress compared to the approach when both antioxidants were administrated separately. The results of this study revealed that a combination of lipoic acid and vitamin E can be a modulator of inflammatory and malnutrition status in hemodialysis patients. Thus, new therapeutic strategies like that are needed to reduce CVD mortality and morbidity. The combination of these antioxidants could be a new approach in bioactive membrane development.

Neutrophil elastase inhibitor-modified membrane

Another approach is to reduce the negative effect of elevated levels of NE. Although therapy consisting oral administration of an NE inhibitor has not been tested on HD patients, its ability to ameliorate the negative proteolytic effects of NE has been studied in patients with various lung disorders, showing positive outcomes [143, 144]. Hence, the immobilization of an NE inhibitor on an HD membrane has been proposed by Grano et al. [145]. The in vitro tests using NE inhibitor-coated membranes proved to be effective against the proteolytic activity of NE, and therefore, the authors proposed that this new bioactive membrane could be applied as a new therapeutic tool to treat HD patients [145]. However, to the best of our knowledge, this membrane model has not yet been tested in vivo.

Conclusions

ESRD imposes a heavy worldwide socio-economic burden due to its increasing prevalence and the high morbidity and hospitalization rates incurred by these patients. The prevention and improved control of diabetes and hypertension, the main causes of chronic kidney disease in developed countries, has stabilized the incidence of ESRD over the past decade [146].

ESRD is associated with severe complications caused by uremic toxins as well as by the long-term contact between blood and artificial hemodialysis membranes, which, despite improvements in geometry and materials, still present biocompatible limitations. Chronic inflammation and oxidative stress are major side effects of uremia and of HD therapy per se and both are CVD risk factors that may contribute to the high morbidity and mortality rates of ESRD patients.

The correlation between the use of cellulose membranes in the HD treatment of ESRD patients and the associated activation, inflammation, oxidative stress, and poor outcome of the patients drove research studies to focus on modified cellulose and synthetic polymer membranes with better biocompatibility. The use of these HD membranes to treat ESRD patients confirmed that they are still associated with inflammation and oxidative stress, although to a much lower degree. To overcome these complications, research has focused on structural modifications of HD membranes and on the use of bioactive compounds to reduce inflammation and oxidative stress. Based on the positive effect of oral antioxidant supplements on oxidative stress, VEM were developed, and the majority of clinical studies have shown that this type of bioactive membrane plays an important role in reducing the inflammatory response and oxidative stress. A decrease in inflammation could further contribute to improve anemia in ESRD patients on HD. Moreover, the reduction of oxidative stress and its negative effect on erythrocyte membranes could also contribute to improve anemia [147].

Despite the noticed improvements brought using VEM, the overall impact on CVD associated morbidity and mortality still requires longer follow-up on patients.

The incorporation of other types of antioxidants and bioactive compounds, such as lipoic acid and neutrophil elastase inhibitors, is still under development [142, 145].

Considering that the MWCO of the membranes may play an important role in improving a patient's outcome, certain high MWCO membranes that are able to remove uremic toxins and inflammatory products without a loss of albumin are currently studied and have the potential to be used in the dialysis treatment of ESRD patients [148–150].

In summary, the beneficial effects reported with the HD treatment of ESRD patients using VEM membranes has shifted the focus of research onto other types of bioactive membranes to achieve the best HD performance.

Acknowledgements The author, Michaela Kohlová, is grateful to the Charles University Grant Agency for GAUK Grant No. 860216 and would like to acknowledge the financial support of the specific research project, No. SVV 260 412. This work was also financially supported by the STARSS project (Reg. No. CZ.02.1.01/0.0/0.0/15_003/0000465) co-funded by the ERDF. FCT/MEC co-financed by the FEDER, under Partnership Agreement PT2020 (UID/MULTI/04378/2013—POCI/01/0145/FEDER/007728) together with Norte Portugal Regional Coordination and Development Commission (CCDR-N)/NORTE2020/Portugal 2020 (Norte-01-0145-FEDER-000024) and POCI-01-0145-FEDER-031322 also supported this study.

References

1. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:1–266.
2. Glorieux G, Schepers E, Vanholder RC. Uremic toxins in chronic renal failure. Prilozi. 2007;28:173–204.

3. Karkar A. Modalities of hemodialysis: quality improvement. Saudi J Kidney Dis Transplant. 2012;23:1145–61.
4. Vanholder R, De Smet R, Glorieux G, Argiles A, Baurmeister U, Brunet P, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63:1934–43.
5. Piroddi M, Bartolini D, Ciffolilli S, Galli F. Nondialyzable uremic toxins. Blood Purif. 2013;35:30–41.
6. Libetta C, Sepe V, Esposito P, Galli F, Dal Canton A. Oxidative stress and inflammation: implications in uremia and hemodialysis. Clin Biochem. 2011;44:1189–98.
7. Morena M, Delbosc S, Dupuy AM, Canaud B, Cristol JP. Overproduction of reactive oxygen species in end-stage renal disease patients: a potential component of hemodialysis-associated inflammation. Hemodial Int. 2005;9:37–46.
8. Cohen G, Horl WH. Immune dysfunction in uremia—an update. Toxins (Basel). 2012;4:962–90.
9. Galli F. Protein damage and inflammation in uraemia and dialysis patients. Nephrol Dial Transplant. 2007;22:v20–36.
10. Himmelfarb J. Oxidative stress in hemodialysis. Contrib Nephrol. 2008;161:132–7.
11. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004;65:1009–16.
12. Yao Q, Pecoits-Filho R, Lindholm B, Stenvinkel P. Traditional and non-traditional risk factors as contributors to atherosclerotic cardiovascular disease in end-stage renal disease. Scand J Urol Nephrol. 2004;38:405–16.
13. Thomas R, Kanso A, Sedor JR. Chronic kidney disease and its complications. Prim Care. 2008;35:329–44 **(vii)**.
14. Pendse S, Singh AK. Complications of chronic kidney disease: anemia, mineral metabolism, and cardiovascular disease. Med Clin N Am. 2005;89:549–61.
15. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88:950–7.
16. Bruck K, Stel VS, Gambaro G, Hallan S, Volzke H, Arnlov J, et al. CKD prevalence varies across the European general population. J Am Soc Nephrol. 2016;27:2135–47.
17. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379:165–80.
18. Barsoum RS. Chronic kidney disease in the developing world. N Engl J Med. 2006;354:997–9.
19. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382:260–72.
20. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158:825–30.
21. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLoS One. 2016;11:e0158765.
22. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med. 2009;169:342–50.
23. Hedgeman E, Lipworth L, Lowe K, Saran R, Do T, Fryzek J. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. Int J Nephrol. 2015;2015:184321.
24. Abe M, Hamano T, Wada A, Nakai S, Masakane I, Renal Data Registry Committee JSfDT. Effect of dialyzer membrane materials on survival in chronic hemodialysis patients: results from the annual survey of the Japanese Nationwide Dialysis Registry. PLoS One. 2017;12:e0184424.
25. Dasgupta I, Shroff R, Bennett-Jones D, McVeigh G, Group NHGD. Management of hyperphosphataemia in chronic kidney disease: summary of National Institute for Health and Clinical Excellence (NICE) guideline. Nephron Clin Pract. 2013;124:1–9.
26. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimburger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3:505–21.
27. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA. 2005;293:1737–45.
28. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med. 2004;140:9–17.
29. Zoccali C. Cardiovascular risk in uraemic patients—is it fully explained by classical risk factors? Nephrol Dial Transplant. 2000;15:454–7.
30. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385:1975–82.
31. Chang YK, Hsu CC, Chen PC, Chen YS, Hwang SJ, Li TC, et al. Trends of cost and mortality of patients on haemodialysis with end stage renal disease. Nephrology (Carlton). 2015;20:243–9.
32. Scribner BH. A personalized history of chronic hemodialysis. Am J Kidney Dis. 1990;16:511–9.
33. Karkar A. Advances in hemodialysis techniques, vol. 20. INTECH Open Access Publisher; 2013. p. 409–37. https://doi.org/10.5772/52444.
34. Misra M. Basic mechanisms governing solute and fluid transport in hemodialysis. Hemodial Int. 2008;12:25–8.
35. Ronco C, Ghezzi PM, Brendolan A, Crepaldi C, La Greca G. The haemodialysis system: basic mechanisms of water and solute transport in extracorporeal renal replacement therapies. Nephrol Dial Transplant. 1998;13:3–9.
36. Yang A, Lee WY, Hocking K. Survival comparison of daily home hemodialysis vs. conventional in the nursing home setting. Nephrol News Issues. 2015;29:25–7, 30–1.
37. Kaur A, Davenport A. Hemodialysis for infants, children, and adolescents. Hemodial Int. 2014;18:573–82.
38. Chaudhary K, Sangha H, Khanna R. Peritoneal dialysis first: rationale. Clin J Am Soc Nephrol. 2011;6:447–56.
39. Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS, et al. Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. Ann Intern Med. 2005;143:174–83.
40. Kendrick J, Teitelbaum I. Strategies for improving long-term survival in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2010;5:1123–31.
41. Genovesi S, Porcu L, Luise MC, Riva H, Nava E, Contaldo G, et al. Sudden death in end stage renal disease: comparing hemodialysis versus peritoneal dialysis. Blood Purif. 2017;44:77–88.
42. Himmelfarb J. Hemodialysis complications. Am J Kidney Dis. 2005;45:1122–31.
43. Moledina DG, Perry Wilson F. Pharmacologic treatment of common symptoms in dialysis patients: a narrative review. Semin Dial. 2015;28:377–83.
44. Vanholder R, De Smet R. Pathophysiologic effects of uremic retention solutes. J Am Soc Nephrol. 1999;10:1815–23.
45. Costa E, Pereira BJ, Rocha-Pereira P, Rocha S, Reis F, Castro E, et al. Role of prohepcidin, inflammatory markers and iron status

in resistance to rhEPO therapy in hemodialysis patients. Am J Nephrol. 2008;28:677–83.
46. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial. 2002;15:329–37.
47. Kaysen GA. The microinflammatory state in uremia: causes and potential consequences. J Am Soc Nephrol. 2001;12:1549–57.
48. Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg? Semin Dial. 2004;17:449–54.
49. Varela MP, Kimmel PL, Phillips TM, Mishkin GJ, Lew SQ, Bosch JP. Biocompatibility of hemodialysis membranes: interrelations between plasma complement and cytokine levels. Blood Purif. 2001;19:370–9.
50. Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. J Ren Nutr. 2012;22:149–56.
51. Ganz T, Nemeth E. Iron balance and the role of hepcidin in chronic kidney disease. Semin Nephrol. 2016;36:87–93.
52. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23:1631–4.
53. Malyszko J, Malyszko JS, Mysliwiec M. Hyporesponsiveness to erythropoietin therapy in hemodialyzed patients: potential role of prohepcidin, hepcidin, and inflammation. Ren Fail. 2009;31:544–8.
54. Costa E, Swinkels DW, Laarakkers CM, Rocha-Pereira P, Rocha S, Reis F, et al. Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in haemodialysis patients. Acta Haematol. 2009;122:226–9.
55. Stenvinkel P. The role of inflammation in the anaemia of end-stage renal disease. Nephrol Dial Transplant. 2001;16:36–40.
56. Korevaar JC, van Manen JG, Dekker FW, de Waart DR, Boeschoten EW, Krediet RT, et al. Effect of an increase in C-reactive protein level during a hemodialysis session on mortality. J Am Soc Nephrol. 2004;15:2916–22.
57. Blidberg K, Palmberg L, Dahlen B, Lantz AS, Larsson K. Chemokine release by neutrophils in chronic obstructive pulmonary disease. Innate Immun. 2012;18:503–10.
58. Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. Rheumatology. 2010;49:1618–31.
59. Cohen G, Raupachova J, Horl WH. The uraemic toxin phenylacetic acid contributes to inflammation by priming polymorphonuclear leucocytes. Nephrol Dial Transplant. 2013;28:421–9.
60. Hernandez MR, Galan AM, Cases A, Lopez-Pedret J, Pereira A, Tonda R, et al. Biocompatibility of cellulosic and synthetic membranes assessed by leukocyte activation. Am J Nephrol. 2004;24:235–41.
61. Sela S, Shurtz-Swirski R, Cohen-Mazor M, Mazor R, Chezar J, Shapiro G, et al. Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. J Am Soc Nephrol. 2005;16:2431–8.
62. Witko-Sarsat V, Gausson V, Nguyen AT, Touam M, Drueke T, Santangelo F, et al. AOPP-induced activation of human neutrophil and monocyte oxidative metabolism: a potential target for *N*-acetylcysteine treatment in dialysis patients. Kidney Int. 2003;64:82–91.
63. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G, Cholesterol, et al. Biomarkers of inflammation and progression of chronic kidney disease. Kidney Int. 2005;68:237–45.
64. Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. Pediatr Nephrol. 2009;24:1445–52.
65. Pham CT. Neutrophil serine proteases: specific regulators of inflammation. Nat Rev Immunol. 2006;6:541–50.
66. Pham CT. Neutrophil serine proteases fine-tune the inflammatory response. Int J Biochem Cell Biol. 2008;40:1317–33.
67. Korkmaz B, Horwitz MS, Jenne DE, Gauthier F. Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human diseases. Pharmacol Rev. 2010;62:726–59.
68. Groutas WC, Dou D, Alliston KR. Neutrophil elastase inhibitors. Expert Opin Ther Pat. 2011;21:339–54.
69. Sandhaus RA, Turino G. Neutrophil elastase-mediated lung disease. Copd. 2013;10:60–3.
70. Polanska B, Augustyniak D, Makulska I, Niemczuk M, Zwolinska D, Jankowski A. Elastase, alpha1-proteinase inhibitor, and interleukin-8 in pre-dialyzed and hemodialyzed patients with chronic kidney disease. Pediatr Int. 2010;52:735–43.
71. Fournier BM, Parkos CA. The role of neutrophils during intestinal inflammation. Mucosal Immunol. 2012;5:354–66.
72. Abboud RT, Vimalanathan S. Pathogenesis of COPD. Part I. The role of protease-antiprotease imbalance in emphysema. Int J Tuberc Lung Dis. 2008;12:361–7.
73. Pereira R, Rocha S, Borges A, Nascimento H, Reis F, Miranda V, et al. Elastase release during the hemodialysis procedure seems to induce changes in red blood cell membrane proteins. Hemodial Int. 2011;15:429–31.
74. Girndt M, Heisel O, Kohler H. Influence of dialysis with polyamide vs haemophan haemodialysers on monokines and complement activation during a 4-month long-term study. Nephrol Dial Transplant. 1999;14:676–82.
75. Hakim RM. Clinical implications of hemodialysis membrane biocompatibility. Kidney Int. 1993;44:484–94.
76. Lee JW, Cho E, Kim MG, Jo SK, Cho WY, Kim HK. Proinflammatory CD14(+)CD16(+) monocytes are associated with vascular stiffness in predialysis patients with chronic kidney disease. Kidney Res Clin Pract. 2013;32:147–52.
77. Pahl MV, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. Nephrol Dial Transplant. 2010;25:205–12.
78. Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Naive and central memory T-cell lymphopenia in end-stage renal disease. Kidney Int. 2006;70:371–6.
79. Massy ZA, Stenvinkel P, Drueke TB. The role of oxidative stress in chronic kidney disease. Semin Dial. 2009;22:405–8.
80. Koenig JS, Fischer M, Bulant E, Tiran B, Elmadfa I, Druml W. Antioxidant status in patients on chronic hemodialysis therapy: impact of parenteral selenium supplementation. Wiener Klinische Wochenschrift. 1997;109:13–9.
81. Daschner M, Lenhartz H, Botticher D, Schaefer F, Wollschlager M, Mehls O, et al. Influence of dialysis on plasma lipid peroxidation products and antioxidant levels. Kidney Int. 1996;50:1268–72.
82. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. Erythrocyte damage in mild and severe psoriasis. Br J Dermatol. 2004;150:232–44.
83. Sung CC, Hsu YC, Chen CC, Lin YF, Wu CC. Oxidative stress and nucleic acid oxidation in patients with chronic kidney disease. Oxid Med Cell Longev. 2013;2013:301982.
84. Pedruzzi LM, Stockler-Pinto MB, Leite M Jr, Mafra D. Nrf2-keap1 system versus NF-kappaB: the good and the evil in chronic kidney disease? Biochimie. 2012;94:2461–6.
85. Sanz AB, Sanchez-Nino MD, Ramos AM, Moreno JA, Santamaria B, Ruiz-Ortega M, et al. NF-kappaB in renal inflammation. J Am Soc Nephrol. 2010;21:1254–62.
86. Annuk M, Soveri I, Zilmer M, Lind L, Hulthe J, Fellstrom B. Endothelial function, CRP and oxidative stress in chronic kidney disease. J Nephrol. 2005;18:721–6.
87. Cachofeiro V, Goicochea M, de Vinuesa SG, Oubina P, Lahera V, Luno J. Oxidative stress and inflammation, a link between

chronic kidney disease and cardiovascular disease. Kidney Int Suppl. 2008:S4–S9.
88. Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative stress in hemodialysis patients: a review of the literature. Oxid Med Cell Longev. 2017;2017:3081856.
89. Galli F, Piroddi M, Annetti C, Aisa C, Floridi E, Floridi A. Oxidative stress and reactive oxygen species. Contrib Nephrol. 2005;149:240–60.
90. Cattaneo D, Remuzzi G. Lipid oxidative stress and the anti-inflammatory properties of statins and ACE inhibitors. J Ren Nutr. 2005;15:71–6.
91. Merello Godino JI, Rentero R, Orlandini G, Marcelli D, Ronco C. Results from EuCliD (European Clinical Dialysis Database): impact of shifting treatment modality. Int J Artif Organs. 2002;25:1049–60.
92. Oshvandi K, Kavyannejad R, Borzuo SR, Gholyaf M. High-flux and low-flux membranes: efficacy in hemodialysis. Nurs Midwifery Stud. 2014;3:e21764.
93. Ward RA. Do clinical outcomes in chronic hemodialysis depend on the choice of a dialyzer? Semin Dial. 2011;24:65–71.
94. Debska-Slizien A, Malgorzewicz S, Dudziak M, Ksiazek A, Sulowicz W, Grzeszczak W, et al. Cardiovascular risk in patients undergoing maintenance hemodialysis with Helixone(R) membrane: a multicenter randomized study. Pol Arch Med Wewn. 2014;124:593–8.
95. Aucella F, Gesuete A, Vigilante M, Prencipe M. Adsorption dialysis: from physical principles to clinical applications. Blood Purif. 2013;35:42–7.
96. Sakai K, Matsuda M. Solute removal efficiency and biocompatibility of the high-performance membrane—from engineering points of view. Contrib Nephrol. 2011;173:11–22.
97. MacLeod A, Daly C, Khan I, Vale L, Campbell M, Wallace S, et al. Comparison of cellulose, modified cellulose and synthetic membranes in the haemodialysis of patients with end-stage renal disease. Cochrane Database Syst Rev. 2005;20:CD003234.
98. Boure T, Vanholder R. Which dialyser membrane to choose? Nephrol Dial Transplant. 2004;19:293–6.
99. Horl WH. Hemodialysis membranes: interleukins, biocompatibility, and middle molecules. J Am Soc Nephrol. 2002;13:62–71.
100. Cheung AK, Parker CJ, Wilcox L, Janatova J. Activation of the alternative pathway of complement by cellulosic hemodialysis membranes. Kidney Int. 1989;36:257–65.
101. Jaber BL, Cendoroglo M, Balakrishnan VS, Perianayagam MC, Karsou SA, Ruthazer R, et al. Impact of dialyzer membrane selection on cellular responses in acute renal failure: a crossover study. Kidney Int. 2000;57:2107–16.
102. Jacob AI, Gavellas G, Zarco R, Perez G, Bourgoignie JJ. Leukopenia, hypoxia, and complement function with different hemodialysis membranes. Kidney Int. 1980;18:505–9.
103. Chenoweth DE. Complement activation during hemodialysis: clinical observations, proposed mechanisms, and theoretical implications. Artif Organs. 1984;8:281–90.
104. Carracedo J, Ramirez R, Madueno JA, Soriano S, Rodriguez-Benot A, Rodriguez M, et al. Cell apoptosis and hemodialysis-induced inflammation. Kidney Int Suppl. 2002;61:89–93.
105. Clark WR, Hamburger RJ, Lysaght MJ. Effect of membrane composition and structure on solute removal and biocompatibility in hemodialysis. Kidney Int. 1999;56:2005–15.
106. Schaefer RM, Horl WH, Kokot K, Heidland A. Enhanced biocompatibility with a new cellulosic membrane: cuprophan versus hemophan. Blood Purif. 1987;5:262–7.
107. Hoenich NA, Woffindin C, Stamp S, Roberts SJ, Turnbull J. Synthetically modified cellulose: an alternative to synthetic membranes for use in haemodialysis? Biomaterials. 1997;18:1299–303.
108. Bowry SK, Rintelen TH. Synthetically modified cellulose (SMC): a cellulosic hemodialysis membrane with minimized complement activation. ASAIO J. 1998;44:M579-83.
109. Subramanian S, Venkataraman R, Kellum JA. Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. Kidney Int. 2002;62:1819–23.
110. DeAngelis RA, Reis ES, Ricklin D, Lambris JD. Targeted complement inhibition as a promising strategy for preventing inflammatory complications in hemodialysis. Immunobiology. 2012;217:1097–105.
111. Sakai K. Dialysis membranes for blood purification. Front Med Biol Eng. 2000;10:117–29.
112. Hakim RM, Held PJ, Stannard DC, Wolfe RA, Port FK, Daugirdas JT, et al. Effect of the dialysis membrane on mortality of chronic hemodialysis patients. Kidney Int. 1996;50:566–70.
113. Jaber BL, Lau J, Schmid CH, Karsou SA, Levey AS, Pereira BJ. Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: a meta-analysis. Clin Nephrol. 2002;57:274–82.
114. Linnenweber S, Lonnemann G. Effects of dialyzer membrane on interleukin-1beta (IL-1beta) and IL-1beta-converting enzyme in mononuclear cells. Kidney Int Suppl. 2001;78:282-5.
115. Itoh S, Susuki C, Tsuji T. Platelet activation through interaction with hemodialysis membranes induces neutrophils to produce reactive oxygen species. J Biomed Mater Res A. 2006;77:294–303.
116. Nakano A. Ethylene vinyl alcohol co-polymer as a high-performance membrane: an EVOH membrane with excellent biocompatibility. Contrib Nephrol. 2011;173:164–71.
117. Matsumoto Y, Mukai M, Arihara K, Saito T, Kumagai H. Ethylene-vinyl alcohol copolymer dialyzer membrane reduces protein oxidation in hemodialysis patients. Ren Fail. 2011;33:382–7.
118. Bowry SK, Gatti E, Vienken J. Contribution of polysulfone membranes to the success of convective dialysis therapies. Contrib Nephrol. 2011;173:110–8.
119. Walker RJ, Sutherland WH, De Jong SA. Effect of changing from a cellulose acetate to a polysulphone dialysis membrane on protein oxidation and inflammation markers. Clin Nephrol. 2004;61:198–206.
120. Gastaldello K, Melot C, Kahn RJ, Vanherweghem JL, Vincent JL, Tielemans C. Comparison of cellulose diacetate and polysulfone membranes in the outcome of acute renal failure. A prospective randomized study. Nephrol Dial Transplant. 2000;15:224–30.
121. Abe M, Hamano T, Wada A, Nakai S, Masakane I. High-performance membrane dialyzers and mortality in hemodialysis patients: a 2-year cohort study from the annual survey of the Japanese renal data registry. Am J Nephrol. 2017;46:82–92.
122. Piroddi M, Pilolli F, Aritomi M, Galli F. Vitamin E as a functional and biocompatibility modifier of synthetic hemodialyzer membranes: an overview of the literature on vitamin E-modified hemodialyzer membranes. Am J Nephrol. 2012;35:559–72.
123. D'Arrigo G, Baggetta R, Tripepi G, Galli F, Bolignano D. Effects of vitamin E-coated versus conventional membranes in chronic hemodialysis patients: a systematic review and meta-analysis. Blood Purif. 2017;43:101–22.
124. Coombes JS, Fassett RG. Antioxidant therapy in hemodialysis patients: a systematic review. Kidney Int. 2012;81:233–46.
125. Ahmadi A, Mazooji N, Roozbeh J, Mazloom Z, Hasanzade J. Effect of alpha-lipoic acid and vitamin E supplementation on oxidative stress, inflammation, and malnutrition in hemodialysis patients. Iran J Kidney Dis. 2013;7:461–7.
126. Daud ZA, Tubie B, Sheyman M, Osia R, Adams J, Tubie S, et al. Vitamin E tocotrienol supplementation improves lipid profiles in chronic hemodialysis patients. Vasc Health Risk Manag. 2013;9:747–61.

127. Bhogade RB, Suryakar AN, Joshi NG, Patil RY. Effect of vitamin E supplementation on oxidative stress in hemodialysis patients. Indian J Clin Biochem. 2008;23:233–7.
128. Roob JM, Khoschsorur G, Tiran A, Horina JH, Holzer H, Winklhofer-Roob BM. Vitamin E attenuates oxidative stress induced by intravenous iron in patients on hemodialysis. J Am Soc Nephrol. 2000;11:539–49.
129. Galli F, Varga Z, Balla J, Ferraro B, Canestrari F, Floridi A, et al. Vitamin E, lipid profile, and peroxidation in hemodialysis patients. Kidney Int Suppl. 2001;78:148-54.
130. Mafra D, Santos FR, Lobo JC, de Mattos Grosso D, Barreira AL, Velarde LG, et al. Alpha-tocopherol supplementation decreases electronegative low-density lipoprotein concentration [LDL(-)] in haemodialysis patients. Nephrol Dial Transplant. 2009;24:1587–92.
131. Takouli L, Hadjiyannakos D, Metaxaki P, Sideris V, Filiopoulos V, Anogiati A, et al. Vitamin E-coated cellulose acetate dialysis membrane: long-term effect on inflammation and oxidative stress. Ren Fail. 2010;32:287–93.
132. Yang SK, Xiao L, Xu B, Xu XX, Liu FY, Sun L. Effects of vitamin E-coated dialyzer on oxidative stress and inflammation status in hemodialysis patients: a systematic review and meta-analysis. Ren Fail. 2014;36:722–31.
133. Kirmizis D, Papagianni A, Belechri AM, Memmos D. Effects of vitamin E-coated membrane dialyser on markers of oxidative stress and inflammation in patients on chronic haemodialysis. Nephrol Dial Transplant. 2011;26:2296–301.
134. Panichi V, Rosati A, Paoletti S, Ferrandello P, Migliori M, Beati S, et al. A vitamin E-coated polysulfone membrane reduces serum levels of inflammatory markers and resistance to erythropoietin-stimulating agents in hemodialysis patients: results of a randomized cross-over multicenter trial. Blood Purif. 2011;32:7–14.
135. Sasaki M. Development of vitamin E-modified polysulfone membrane dialyzers. J Artif Organs. 2006;9:50–60.
136. Clermont G, Lecour S, Cabanne JF, Motte G, Guilland JC, Chevet D, et al. Vitamin E-coated dialyzer reduces oxidative stress in hemodialysis patients. Free Radic Biol Med. 2001;31:233–41.
137. Mandolfo S, Corradi B, Bucci R, Farina M, Pilolli F, Galli F. Evaluation of the impact of a new synthetic vitamin E-bonded membrane on anemia and rHuEPO requirement in ESRD patients with central venous catheters: a pilot study. Int Urol Nephrol. 2012;44:1493–500.
138. Locatelli F, Andrulli S, Vigano SM, Concetti M, Urbini S, Giacchino F, et al. Evaluation of the impact of a new synthetic vitamin E-bonded membrane on the hypo-responsiveness to the erythropoietin therapy in hemodialysis patients: a multicenter study. Blood Purif. 2017;43:338–45.
139. Sanaka T, Mochizuki T, Kinugasa E, Kusano E, Ohwada S, Kuno T, et al. Randomized controlled open-label trial of vitamin E-bonded polysulfone dialyzer and erythropoiesis-stimulating agent response. Clin J Am Soc Nephrol. 2013;8:969–78.
140. Morena M, Gausson V, Mothu N, Bouchet JL, Chanas M, Grandvuillemin M, et al. Regional variations of low-density lipoprotein oxidizability in hemodialysis patients may explain discrepancies in interventional therapy on oxidative profile. Blood Purif. 2008;26:300–10.
141. Khabbazi T, Mahdavi R, Safa J, Pour-Abdollahi P. Effects of alpha-lipoic acid supplementation on inflammation, oxidative stress, and serum lipid profile levels in patients with end-stage renal disease on hemodialysis. J Ren Nutr. 2012;22:244–50.
142. Mahlicli FY, Altinkaya SA. Immobilization of alpha lipoic acid onto polysulfone membranes to suppress hemodialysis induced oxidative stress. J Membr Sci. 2014;449:27–37.
143. Kohira S, Oka N, Inoue N, Itatani K, Hanayama N, Kitamura T, et al. Effect of the neutrophil elastase inhibitor sivelestat on perioperative inflammatory response after pediatric heart surgery with cardiopulmonary bypass: a prospective randomized study. Artif Organs. 2013;37:1027–33.
144. Stockley R, De Soyza A, Gunawardena K, Perrett J, Forsman-Semb K, Entwistle N, et al. Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. Respir Med. 2013;107:524–33.
145. Grano V, Tasco G, Casadio R, Diano N, Portaccio M, Rossi S, et al. Reduction of active elastase concentration by means of immobilized inhibitors: a novel therapeutic approach. Biotechnol Prog. 2004;20:968–74.
146. Wetmore JB, Gilbertson DT, Liu J, Collins AJ. Improving outcomes in patients receiving dialysis: the peer kidney care initiative. Clin J Am Soc Nephrol. 2016;11:1297–304.
147. Nakatan T, Takemoto Y, Tsuchida AK. The effect of vitamin E-bonded dialyzer membrane on red blood cell survival in hemodialyzed patients. Artif Organs. 2003;27:214–7.
148. Girndt M, Fiedler R, Martus P, Pawlak M, Storr M, Bohler T, et al. High cut-off dialysis in chronic haemodialysis patients. Eur J Clin Investig. 2015;45:1333–40.
149. Kneis C, Beck W, Boenisch O, Klefisch F, Deppisch R, Zickler D, et al. Elimination of middle-sized uremic solutes with high-flux and high-cut-off membranes: a randomized in vivo study. Blood Purif. 2013;36:287–94.
150. Zickler D, Schindler R, Willy K, Martus P, Pawlak M, Storr M, et al. Medium cut-off (MCO) membranes reduce inflammation in chronic dialysis patients-a randomized controlled clinical trial. PLoS One. 2017;12:e0169024.
151. Uda S, Mizobuchi M, Akizawa T. Biocompatible characteristics of high-performance membranes. Contrib Nephrol. 2011;173:23–9.
152. Nahar N, Shah H, Siu J, Colvin R, Bhaskaran M, Ranjan R, et al. Dialysis membrane-induced neutrophil apoptosis is mediated through free radicals. Clin Nephrol. 2001;56:52–9.
153. Grooteman MP, Nube MJ, van Limbeek J, van Houte AJ, Daha MR, van Geelen JA. Biocompatibility and performance of a modified cellulosic and a synthetic high flux dialyzer. A randomized crossover comparison between cellulose triacetate and polysulphon. ASAIO J. 1995;41:215–20.
154. Kreusser W, Reiermann S, Vogelbusch G, Bartual J, Schulze-Lohoff E. Effect of different synthetic membranes on laboratory parameters and survival in chronic haemodialysis patients. NDT Plus. 2010;3:i12–9.
155. Nensel U, Rockel A, Hillenbrand T, Bartel J. Dialyzer permeability for low-molecular-weight proteins. Comparison between polysulfone, polyamide and cuprammonium-rayon dialyzers. Blood Purif. 1994;12:128–34.
156. Horl WH, Riegel W, Schollmeyer P. Plasma levels of main granulocyte components in patients dialyzed with polycarbonate and cuprophan membranes. Nephron. 1987;45:272–6.
157. Schindler R, Boenisch O, Fischer C, Frei U. Effect of the hemodialysis membrane on the inflammatory reaction in vivo. Clin Nephrol. 2000;53:452–9.
158. Henderson LW, Chenoweth D. Biocompatibility of artificial organs: an overview. Blood Purif. 1987;5:100–11.
159. Lornoy W, Becaus I, Billiouw JM, Sierens L, van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18:105–8.
160. Ward RA, Ouseph R, McLeish KR. Effects of high-flux hemodialysis on oxidant stress. Kidney Int. 2003;63:353–9.
161. Sirolli V, Ballone E, Di Stante S, Amoroso L, Bonomini M. Cell activation and cellular-cellular interactions during hemodialysis: effect of dialyzer membrane. Int J Artif Organs. 2002;25:529–37.
162. Singh NP, Bansal R, Thakur A, Kohli R, Bansal RC, Agarwal SK. Effect of membrane composition on cytokine production and

clinical symptoms during hemodialysis: a crossover study. Ren Fail. 2003;25:419–30.
163. Schaefer RM, Gilge U, Goehl H, Heidland A. Evaluation of a new polyamide membrane (Polyflux 130) in high-flux dialysis. Blood Purif. 1990;8:23–31.
164. Ebo DG, Bosmans JL, Couttenye MM, Stevens WJ. Haemodialysis-associated anaphylactic and anaphylactoid reactions. Allergy. 2006;61:211–20.
165. Cheung AK, Henderson LW. Effects of complement activation by hemodialysis membranes. Am J Nephrol. 1986;6:81–91.
166. Irfan M, Idris A. Overview of PES biocompatible/hemodialysis membranes: PES-blood interactions and modification techniques. Mater Sci Eng C Mater Biol Appl. 2015;56:574–92.
167. Thomas M, Moriyama K, Ledebo I. AN69: Evolution of the world's first high permeability membrane. Contrib Nephrol. 2011;173:119–29.
168. Horl WH, Steinhauer HB, Schollmeyer P. Plasma levels of granulocyte elastase during hemodialysis: effects of different dialyzer membranes. Kidney Int. 1985;28:791–6.
169. Tielemans C, Madhoun P, Lenaers M, Schandene L, Goldman M, Vanherweghem JL. Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. Kidney Int. 1990;38:982–4.
170. Chenoweth DE, Henderson LW. Complement activation during hemodialysis: laboratory evaluation of hemodialyzers. Artif Organs. 1987;11:155–62.
171. Campistol JM, Torregrosa JV, Ponz E, Fenollosa B. Beta(2)-microglobulin removal by hemodialysis with polymethylmethacrylate membranes. Contrib Nephrol. 1999;125:76–85.
172. Aoike I. Long-term clinical experience with PMMA membrane. Contrib Nephrol. 1999;125:205–12.
173. Wegmuller E, Montandon A, Nydegger U, Descoeudres C. Biocompatibility of different hemodialysis membranes: activation of complement and leukopenia. Int J Artif Organs. 1986;9:85–92.
174. Igoshi T, Tomisawa N, Hori Y, Jinbo Y. Polyester polymer alloy as a high-performance membrane. Contrib Nephrol. 2011;173:148–55.
175. Stein G, Gunther K, Sperschneider H, Carlsohn H, Huller M, Schubert K, et al. Clinical evaluation of a new dialyzer, FLX-12 GW, with a polyester-polymer alloy membrane. Artif Organs. 1993;17:339–45.