Chapter

Challenges and Advances in Hemodialysis Membranes

Arash Mollahosseini, Amira Abdelrasoul and Ahmed Shoker

Abstract

Hemodialysis (HD) is a filtration vital process through which the bloods' toxins and contaminations are removed. However, several immune system activations occur during dialysis, which can result in morbidity and mortality. The efficiency of the currently available blood purification process is hindered, on one hand, by the deficient toxins and middle molecule removal, and on the other hand, with the loss of valuable blood components (such as plasma and its constituents). This chapter offers an overview of the challenges and advances in HD membranes. It includes an introduction of the end stage renal disease, concepts of dialysis, its historical background, and the path through which the configurations and materials evolved. The interactions between membrane polymeric materials with human blood is also discussed. The aspect of material modification is one of the critical areas in HD technology as it targets to solve the most immediate and prevalent HD issue of membrane bioincompatibility. High flux dialysis (HFD) and hemofiltration (HF) are introduced and discussed. This class of membranes was introduced to solve middle molecule (such as β2- microglobulin) related challenges. This chapter highlights the question of why the issue of incompatible materials still exists along with current membrane modifications.

Keywords: end-stage renal diseases, hemodialysis, hemocompatibility, membrane modification, blood purification, high flux dialysis, medium cutoff dialysis

1. Introduction

The kidneys are responsible for removing metabolic toxins created by the body's cells. Blood purification of metabolic toxins will result in an adjustment of pH and maintains the normal condition of the body. Renal systems could experience several types of complications and illnesses such as glomerular diseases or polycystic and other cyst diseases. These could result in lack of functionality to various extents. The worst extent of failure in the introduced systems is "end-stage renal diseases" (ESRD) through which patients are experiencing chronic illnesses (chronic kidney diseases (CKD)). Kidney transplant is the first option which only a small percentage of patients could get. Hemodialysis would be one of the options beside transplant. While hemodialysis therapies are proven to be life-sustaining to an extent, morbidity side effects and mortality rates for acute renal failure patients are still a huge concern despite several advances of the technology through past decades [1]. Enhancements have been attributed to many subsections of hemodialysis technology such as membrane materials, membrane configurations, pore size distributions, and cutoff and membrane modalities.

Rotational celluphone tubes in still dialysate bath (rotating drum dialyzer) were the initial configuration of dialyzers [2]. Unsubstituted and substituted cellulose materials were also chosen for the membrane fabrication. With further advances in the field, initial materials were identified as the source of hemoincompatibility, and more effort was put in developing materials with higher level of blood compatibility [3]. Synthetic polymers such as poly aryl sulfones and polyamides were the next used choice for blood purification applications [4]. These membranes also failed to perform ideally and modification resulted in next generations of hemodialysis membranes. The historical pathway of advances though which the current hollow fiber contactor modules were chosen as the best option could be found elsewhere [4]. The question of "why life-sustaining hemodialysis therapy still is not working to the best extent?" is not answered. The authors of this chapter believe the answer would be material incompatibility, and the next sections will try to cover this topic in addition to other aspects of hemodialysis.

2. Overview of dialysis process

The dialysis process is a chemical potential gradient-based separation process [5]. The process's idea was first mentioned by Graham using a semipermeable barrier for selective transport of elements in a solution [6–10]. The dialysis process contains two main streams on different sides of the membrane which is called a

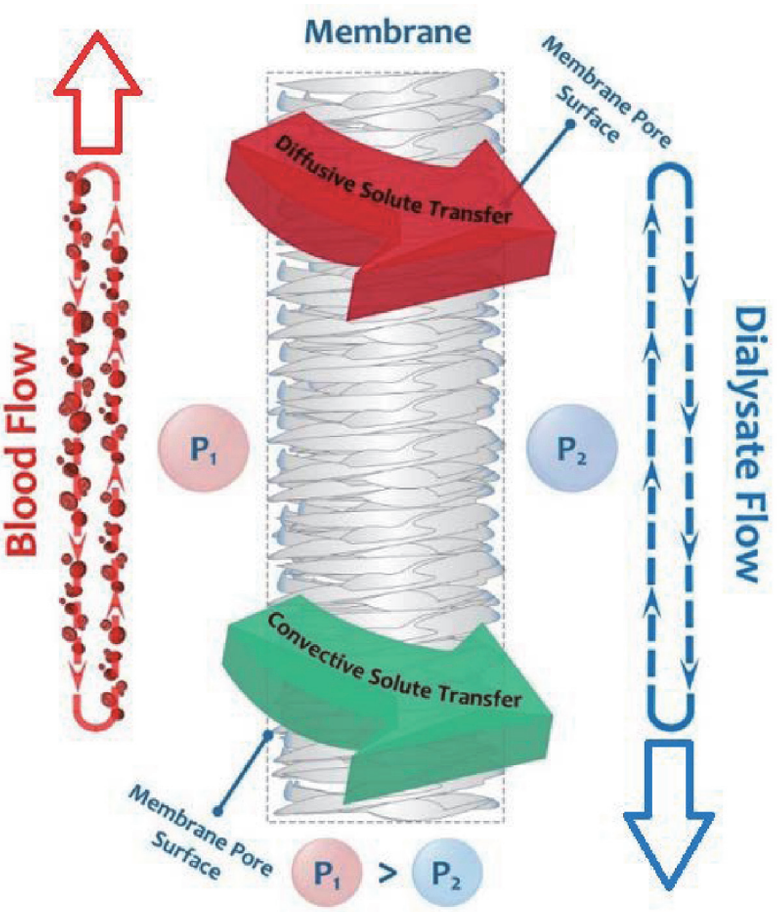

Figure 1.
Schematic diagram of a membrane in hemodialysis process: The left side describes the blood side of the membrane and the right side shows the dialysate side of the process. P_1 and P_2 describe pressure within the blood and dialysate side, respectively. Due to the difference in chemical potential, solutes in blood move through the membrane to the dialysate side.

dialyzer, one containing higher amount of targeted chemicals (blood from chronic kidney diseases (CKD) or ESRD patient) and one with zero or lower concentrations (dialyzing fluid or dialysate), as shown in **Figure 1**. The Uremic and metabolic-resulted substances (which were commonly removed from blood by the kidney), are passed through the membrane, from the bloodstream side to the dialyzer side due to the difference in chemical potential.

Hemodialysis aims to remove toxins and extra water from human bodies with renal failure diseases. Based on the controlling mechanism of solute removal from the main bloodstream, diffusion, convection, or adsorption, the renal replacement modality could be categorized into three main subsections [11]: in case diffusion is controlling the process, the method is called "hemodialysis"; if convection is predominant, the method would be known as "hemofiltration"; and finally when diffusion happens simultaneously with significant convection, the method is named as "hemodiafiltration." It is worth mentioning that adsorption occurs all the time, however there are specific devices that use this as the main separation method in an adsorptive column [12, 13].

3. Classification of different dialysis membranes and modalities

There are different classes based on which dialysis processes are classified. An old classification divides membranes into cellulosic and synthetic-based hemodialyzers. Based on the ability to remove small molecules (urea is chosen as the reference with the molecular weight of 60 kDa), dialyzer membranes are categorized to high-performance and low-performance membranes [14]. Another classification is based on the ability of the membranes to remove middle size molecules (β_2 macroglobulin with the molecular weight of 11,800 Da is chosen as the reference) which divides dialyzers into high-flux and low-flux membranes. Based on US Food and Drug Administration (FDA), hemodialysis membranes are divided into high-permeability and conventional membranes [14]. Modalities of hemodialysis also divide the process into center or hospital dialysis, home dialysis (performed by the patients), and limited care dialysis (performed out of hospitals and homes, in a designated center, where patients perform their own dialyses and a technician is responsible for the upkeep of the instruments) [15]. Going through each type and modality of the hemodialysis therapy is strongly related to the patient's condition and the practitioner's prescription [14].

4. Current Issues of hemodialysis membranes

Since the emergence of the technology, several aspects of hemodialysis have been enhanced. Yet based on the reports, mortality rate in patients are still high. More importantly patients are suffering from inter- and post-dialysis health complications such as cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease. A significant share of the current hemodialysis membranes are made out of poly aryl sulfone (with distribution of 22% PES and 77% PSF) [16]. A research observing more than 139,000 patients revealed that most mortality rate is attributed to PSF membranes (comparison was made between cellulose triacetate (CTA), polyester polymer alloy, poly (methyl methacrylate) (PMMA), PSF, PES, ethylene vinyl alcohol (EVAL), and PAN [17]). The research announced PMMA membranes to have the lowest hazard ratio (HR) (the factor that they defined for comparing membranes).

The current hemodialysis membranes create inflammation responses due to their bioincompatibility during the blood interaction with synthesized polymeric structures. This was reported for membranes with natural-based or synthetic-based polymers [3, 4]. Each specific interaction (contact of blood proteins with membrane surface which initiates different cascade reactions and results in immune system response), is considered as an issue for dialysis membranes. Furthermore, beside four main interactions (surface activation (coagulation), platelet, complement, and leukocyte activation), infections, allergic reactions, complete disinfection of dialysate, and finally backflow of contaminated compounds could be all mentioned as other hemodialysis barriers [18]. It should be noted that these are all general aspects of the hemodialysis therapies and each modality might have its own specific problems in addition to previously mentioned ones. Another barrier to consider is the deficient removal for middle size molecular products and uremic toxins.

Fouling and protein adsorption, the examples of the blood-polymer interaction related reactions, are barriers for dialysis process. This might not be considered as important as in other UF processes; however the reduction of performance, especially for common dialysis session with duration no longer as 5 hours, could affect patients' wellness and results in mortality. Moreover, higher extent of fouling means more intense immune response of the body. Accordingly antifouling behavior (lower protein adsorption) of the polymeric dialysis membranes owns a great deal of importance to eliminate initial protein-polymer surface interaction and consequently patients' physiological response.

Hemocompatibility levels are slightly modified as not as much complement activation is reported for current membrane, as compared with regenerated cellulose membranes used back in the 1960s [19]. Clearance factors were also improved since the 1970s with the introduction of hollow fiber configurations for dialysis and using countercurrent hollow fiber membrane modules [20, 21]. Currently, instrumental progresses with higher control over dialysate temperature, plasma osmolality and sodium profiling, ultrafiltration rates, and blood volume balance have led to a more enhanced level hemodialysis [22, 23]. This is while there are still intensive ongoing researches over reducing mortality rate and morbidity due to incompatibility issues.

5. Membrane-blood interaction and biological responses

The body's immune systems are activated along with blood protein adsorption to the surface (which is a complicated phenomena). Protein attachment to the surface is commonly studied under the title of displacement processes (Vroman effect) which might initiate the coagulation cascade [24, 25]. Any adhered cell (or triggered cells by the surface) could be activated, which consequently results in cascade activation (autocatalytic enzymatic processes) of other cells through production of mediators (with various purposes ranging from hindering interfacial cell adherence to defensive system activation) [26]. Defensive system activation in hemodialysis reflects hemoincompatibility of the used polymeric membrane. Despite the fact that membranes are only one element of the whole extracorporeal circuit and there are other surfaces which blood contacts to reach to the membrane module and to return to the body, as the filters have the highest surface area and the highest share of contact with blood, they are considered as the primary culprit for hemoincompatibilty of blood purification systems.

The reactions resulting in incompatibility are complex, and there are many unknown regions still to be covered; however, platelets, leukocytes, the complement, and the coagulation system are proven to be role players of this concept [26].

5.1 Thrombogenesis

Platelet activation which is commonly known as one of its resultants, blood clotting, could be initiated from either extrinsic or intrinsic pathway (with or without injury respectfully). Due to the lack of endothelium functionality of the membranes, polymeric surfaces are identified as a foreign threat to the body, and a series of reactions involving numerous enzymes and proteins occurs to protect the body. Activation of fibrinogen leads to their transformation to fibrin. Fibrins are turned into fibrin clots with a crosslinked and steady structure as a result of factor XIII (fibrin stabilizing factor) secretion which is activated by thrombin. Transformation of inactive zymogenes into its activated form also assists the process. Platelets will be activated and aggregated, boosting a continuous interaction which leads to blood clotting. Furthermore, other blood cells are attracted to the clot and contribute in more fibrin formation through enzymatic reactions. The formed biological layer or "protein cake" contains plasma proteins like factor XII, fibrinogen, vitronectin, kininogens, etc., which could result in further thrombogenesis [4, 27, 28].

5.2 Complement activation

Complement activation is a human immune system's inflammatory response as a result of foreign threats. It starts by local inflammatory mediator production (C5a, C4a, and C3a). The elements of the complement cascade are mainly enzymes or binding proteins. Along with the first 15 minutes of hemodialysis, C3 is produced and cleaved into C3a, C3b, etc. The cascade continues into production of C5a and C5b-9 during the next stages of dialysis. As reported by Poppelaars et al. [26] during a single session of hemodialysis, the level designated to C5b-9 and C3d/C3 ratios in plasma (measures of complement system activation) reaches up to 70%. However this has been interpreted as an underestimation of the measures values as they are only calculated for fluid phase, while solid phase (deposited complement system's element on the surface) is not considered. Considering all the efforts to clarify the pathway of complement activation, it could be summarized that the base mechanism is known to be the attachment of binding proteins (mannose-binding lectin (MBL) and ficolin-2) to the membrane surface which leads to lectin pathway (LP) activation. The same procedure also encounters for properdin and C3b which results in alternative pathway (AP) activation.

5.3 Leukocyte activation

One result of complement activation in hemodialysis patients is the induced expression of adhesion molecules on leukocytes (white blood cell) [29]. Activation of neutrophils and other leukocytes results in activation of inflammatory mediators. This could consequently improve the adhesion to endothelial cells, chemoattraction for leukocytes, an additional activation of leukocytes or platelets on one hand, and oxidization of monocytes and neutrophils to release oxidants on the other hand [4, 29, 30].

Blood-membrane interactions could directly activate blood cells such as leukocytes, platelets, and red blood cells or indirectly activate them through the pathway that activates the complement system or coagulation factors.

5.4 Coagulation cascade

Contact activation of proteins could be initiated by factor XII conversion into active enzyme state (factor XIIa) which leads to activation of prekallikrein (PK)).

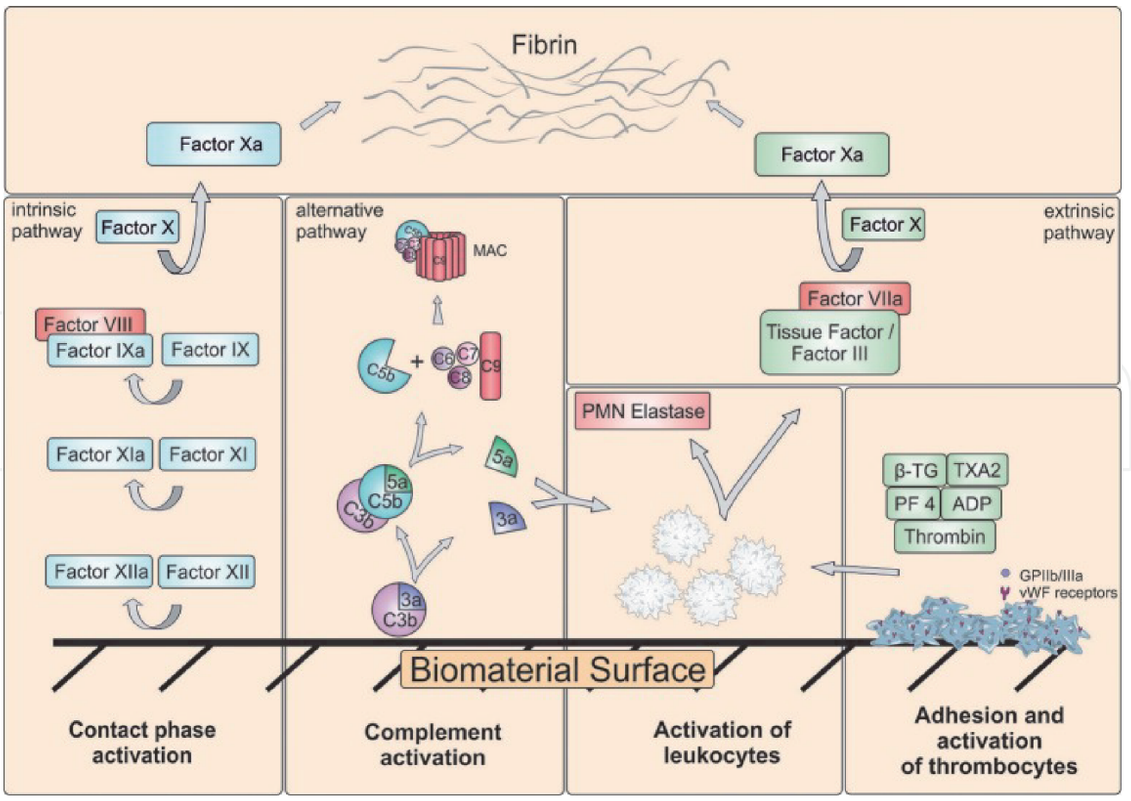

Figure 2.
Blood biological reactions including complement system activation, intrinsic and extrinsic coagulation activation, fibrin network formation, platelet attachment to the surface, and leukocyte activation [34].

Activated factor XIIa also turns high molecular weight kallikrein (HMWK) continuously into bradykinin. Contact activation to this extent also results in inflammation promotion as interleukins and tumor necrosis factors (TNFs) would be produced along with stimulation of nitric oxide release [31–33]. A series of various factors' activation continues till factor Xa is generated from which thrombin and fibrin production is stimulated. This is where clot formation happens. Factor Xa is the common step that all intrinsic and extrinsic cascades reach, before clot formation [34]. **Figure 2** shows activation cascades process after blood-membrane contact.

6. Current progress in hemodialysis membranes technology

6.1 Middle molecule removal: introduction to high flux hemodialysis

Despite all the advances in compatibility of blood purification membranes, mortality rates are still reported to be high. Hemodialysis-related complications such as headache, fatigue, lack of functionality and concentration, anemia, mineral and bone metabolism disorder, and inadequate nutrition result in patients' lower quality of life. This reflects the fact that even conventional hemodialysis has contributed in longer life span of patients, it fails to maintain full quality of life [35].

Humoral mediators including cytokines of inflammatory system and other high molecular weight molecular structures of protein bonded toxins were identified as probable responsible structures for deficient dialysis [36]. Systematic inflammatory response syndrome (SIRS or sepsis) is the side effect of inflammatory activation products. This includes several cytokines which are protein or pleiotropic

polypeptides structures (hormone-like substances) secreted by the human body's immune system. There exist several types of cytokines, namely, chemokine, interferon (IFN), interleukin (IL), lymphokines, colony-stimulating factors (CSF), and tumor necrosis factor (TNF) with different molecular weights. SIRS will result in coagulation, fibrinolytic, and complement activations which are all parts of plasma protein cascade system. In a normal condition, there are other cytokines and proteins secreted to mediate the condition, but in a SIRS, regulatory system's element fails to control the condition [37].

Middle and large molecular structures (with average molecular weights higher than 500 Dalton) and excess water accumulation are mentioned to impose concentration-dependent toxicity and, accordingly, higher mortality [35, 36]. These molecular structures range from smaller ones such as phosphorus and uremia with molecular weight less than 0.6 kDa to cytokines such as interleukin with molecular weight equal to 26 kDa. Molecular structures such as urea, creatinine, and similar structures with a molecular weight less than 500 Da are efficiently being removed by HD. Higher molecular weight cutoff membranes are created for removal of larger molecular weight toxins and toxin-bonded proteins. Modalities involving higher fluxes use convection transport phenomena which are entitled as hemofiltration membranes (HF). These methods are capable of eliminating molecular substances with molecular weight equal to or higher than 40,000 Da. The region between diffusive and convective membranes covers hemodiafiltration membranes (HDF) [38, 39].

Convective dialysis is parallel to albumin and nutrient loss of the bloodstream. Currently, hemodiafiltration blood purification membranes are recommended to be more efficient in comparison with high-flux dialysis due to less intradialytic hypotension and less nutrient loss [40]. Cutoff adjustment of new MCO membranes is due to advances in membrane manufacturing technologies (high-tech fabrication equipment, improved packing densities, enhanced spinning techniques, fiber undulation, decreased internal filtration as a result of fiber diameter control) [41]. MCOs have permeability values between protein-leaking dialyzers and high cutoff membranes with $ß_2$-microglobulin and albumin sieving coefficients equal to 1.0 and 0.2, respectively [41]. Accordingly, efficient middle toxin removal would also not solve the hemodialysis-related complications, and the solution to this problem should be found in compatibility of the membrane materials.

6.2 Hemocompatibility enhancements

Since the two concepts of "biocompatibility" and "hemocompatibility" are frequently being used instead of each other, there has to be a clear definition of these two terms. While biocompatibility, as a more general concept, targets higher liquid and solid parts of living tissues' endurance to foreign items, hemocompatibility focuses on eliminating blood's interactions with non-blood surfaces and materials [42]. There is also a defined framework for hemocompatibility assessment of a material. The International Organization for Standardization (ISO) has issued guideline over hemocompatibility measures in medical device evaluations (ISO 10993-4) [34, 43]. Accordingly, modified bio-hemocompatible hemodialysis membrane should pass thrombosis, coagulation, platelet adhesion resistance, immunology (complement systems and leukocytes), and hematology tests [34].

Different modification approaches were presented throughout the past few decades which targeted hemocompatibility enhancement of blood-contacting membranes. These efforts resulted in various generations of hemodialysis membranes. First-generation hemodialysis membranes were commonly made out of hydroxyl methacrylate or cellulose polymers without any specific surface treatment

or modification. Poor hemocompatibility of the materials used led to poly(ethylene glycol) (PEG) surface immobilization (second generation). PEG brushes enhanced membranes to an extent, but instability and cleavage along with low hemocompatibility was still an issue. Beside PEG, several hydrophilic structures, such as poly(vinyl pyrrolidone) (PVP) [34] and poly(vinyl alcohol) (PVA) [44], sulfonated structures [45], and nanomaterials [46, 47] were used for modification of dialysis membranes. Currently, researchers are targeting third generation, including zwitterionic polymeric surfaces which are believed to be better than second generation due to better performance of the PEG immobilizations due to higher hemocompatibility and stability [48–51].

Zwitterionic structures (ZW) are in fact the amino acid-mimicking structures initially synthesized based on inner structures of specific human cells [52, 53]. Zwitterions have several applications in live cell imaging [54, 55], antibacterial surfaces [56] and wound dressings [57], dental applications [58], separative membrane coatings [59], and most importantly blood purification [51]. Academic efforts over immobilization of ZWs on hemodialysis membranes have been reported over different membrane materials (cellulose acetate (CA) [60], poly(ether sulfone) (PES) [61–63], poly(sulfone) (PSF) [64], poly(dimethyl siloxane) (PDMS) [65], poly(vinylidene fluoride) (PVDF) [66], etc.) using various chemical immobilization approaches.

Three main types of ZW structures are sulfobetaine, phosphobetaine, and carboxybetaine. Application of ZWs was initially introduced by phosphobetaine derivatives as mimicking the structure of human blood cells; however the two other types were more frequently used due to their less production cost and ease of processing. As explained by Chapman et al., ZWs must have dual positive-negative charged functional groups and own at least the following properties: electric charge neutrality, lack of H-bond donation sites, and possess of H-bond acceptors [67]. Pseudo-zwitterionic materials (or mixed charged polymers), as newer classes of biomedical surface modifiers, are enhanced semi-ZW structures with positively dual charged structures that are not affected by other chemical functional groups due to higher stability. Accordingly, they have been introduced as better candidates for improving hemodialysis membranes by surface immobilization or forming hydrogels [68–70].

Table 1 offers some of the most recent efforts focused on zwitterionization of membrane surfaces. Researches presented in the table offer various polymeric membranes zwitterionized with sulfobetaine (SBMA) and sodium polystyrene sulfonate (SSNa). Common indexes of hemocompatibility measurements, including clotting times, complement activation factors, and coagulation and hemolysis percentage, are reflected for each research in case of availability in the related literature.

Different surface immobilization techniques were used to enhance membranes' surface with various types of zwitterionic materials. An important factor to consider is the efficiency of grafting techniques which could be expressed by surface grafting density of zwitterionics on the membranes. Moreover, hydrophilicity and surface roughness are the other factors affecting the adsorption of proteins and consequently initiation of cascade reactions. PVDF-SBMA membranes with in situ polymerization technique resulted in highest grafting density and one of the highest hydrophilicity degrees. Yet the modified structure did not resist to platelet and protein adhesion significantly. This could probably be due to the deficient surface roughness of the enhanced hemodialysis membrane. PSF, PVDF, and PDMS membranes with SBMA modification have more frequently resulted in zero platelet adhesion [64, 71, 72, 76]. Among the three aforesaid membranes, PSF- and PDMS-carboxy-terminated SBMA membranes showed zero protein adsorption [76].

Membrane-ZW	Immobilization method	ZW Density (mg/cm^2)	Clotting time (sec)			Hemolysis (%)[*5]	Protein adhesion	Platelet adhesion	WCA (degree)	Ref.
			APTT[*2]	TT[*3]	PT[*4]					
PDMS-GMA-SBMA		N/A	N/A	N/A	N/A	N/A	90% fibrinogen adhesion reduction	60% reduction	79	[65]
PVDF-SBMA	Interfacial atmospheric plasma-induced surface copolymerization	0.7	N/A	N/A	N/A	0.3	88% fibrinogen adhesion reduction	Zero adhesion	18	[71]
PVDF-SBMA	In situ immobilization	5	Plasma clotting time was reported to be 15 min			2	90% fibrinogen adhesion reduction	500 cells per mm^2	10	[66]
PSF-SBMA-r-SSNa	Surface-initiated atom transfer radical polymerization	0.95	78	18	N/A	N/A	4 $\mu g_{BSA}/cm^2$ and 2 $\mu g_{BFG}/cm^2$	Zero adhesion	12.3	[72]
PSF-SBMA-b-SSNa	Surface-initiated atom transfer radical polymerization	0.88	85	23	N/A	N/A	16 $\mu g_{BSA}/cm^2$ and 13 $\mu g_{BFG}/cm^2$	87×10^5 cells/cm^2	17.2	[72]
PSF-SBMA	Surface-initiated atom transfer radical polymerization	N/A	58	19	N/A	0.9	2.5 $\mu g_{BSA\ or\ BFG}/cm^2$	Zero adhesion	30	[64]
PSF-DEPAS	Surface-initiated atom transfer radical polymerization	N/A	N/A	N/A	N/A	N/A	32.5 $\mu g_{BSA}/cm^2$	Qualitative reduction	38	[73]
PSF-SBMA	Surface-initiated atom transfer radical polymerization	0.171	52.5	22	11	N/A	2.70 $\mu g_{BSA}/cm^2$ and 2.51 $\mu g_{BFG}/cm^2$	0.34×10^5 cells/cm^2	31.35	[74]
PSF-SSNa	Surface-initiated atom transfer radical polymerization	0.110	73.1	22	11	N/A	13.02 $\mu g_{BSA}/cm^2$ and 10.07 $\mu g_{BFG}/cm^2$	6.94×10^5 cells/cm^2	20.80	[74]
PES-SBMA	In situ polymerization	N/A	75	19	N/A	N/A	8 $\mu g_{BSA}/cm^2$ and 10 $\mu g_{BFG}/cm^2$	10×10^5 cells/cm^2	11.1	[61]
PES-SSNa	In situ polymerization	N/A	115	18	N/A	N/A	12.5 $\mu g_{BSA}/cm^2$ and 12 $\mu g_{BFG}/cm^2$	40×10^5 cells/cm^2	57	[62]
PES-SBMA-SSNa	In situ polymerization	N/A	85	18	N/A	N/A	8 $\mu g_{BSA}/cm^2$ and 7 $\mu g_{BFG}/cm^2$	60×10^5 cells/cm^2	45	[62]
PES-SSNa-SBMA	Radical graft polymerization	0.2	55	30	10	N/A	6.5 $\mu g_{BSA}/cm^2$ and 4.2 $\mu g_{BFG}/cm^2$	3×10^5 cells/cm^2	55	[63]

Membrane-ZW	Immobilization method	ZW Density (mg/cm^2)	Clotting time (sec)			Hemolysis (%)[*5]	Protein adhesion	Platelet adhesion	WCA (degree)	Ref.
			APTT[*2]	TT[*3]	PT[*4]					
PES-SBMA	Radical graft polymerization	0.22	51	30	10	N/A	5 $\mu g_{BSA}/cm^2$ and 4 $\mu g_{BFG}/cm^2$	3×10^5 cells/cm^2	54	[63]
PES-SSNa	Radical graft polymerization	0.14	90.10	30	10	N/A	10 $\mu g_{BSA}/cm^2$ and 7 $\mu g_{BFG}/cm^2$	37×10^5 cells/cm^2	53	[63]
PSF-carboxyl-terminated SBMA	Carbodiimide-free radical polymerization	N/A	N/A	N/A	N/A	N/A	Zero fibrinogen adsorption	Zero adhesion	32.8	[75]
PDMS-carboxyl-terminated SBMA	Carbodiimide-free radical polymerization	N/A	N/A	N/A	N/A	N/A	Zero fibrinogen adsorption	Zero adhesion	10	[76]
PDMS-SBMA-co-AA	Carbodiimide-free radical polymerization	N/A	N/A	N/A	N/A	N/A	N/A	0.1×10^5 cells/$cm^2$90% adhesion reduction	N/A	[77]
PU-SBMA-co-AA	Carbodiimide-free radical polymerization	N/A	N/A	N/A	N/A	N/A	N/A	0.2×10^5 cells/$cm^2$80% adhesion reduction	N/A	[77]
PLA-SBMA[*6]	Atom transfer radical polymerization	1.3	N/A	N/A	N/A	N/A	N/A	3.2×10^5 cells/cm^2	9	[78]

*[*1]None of the papers reported values for C3a, C5a, TAT, or PF4.*
*[*2]Activated partial thromboplastin time.*
*[*3]Thrombin time.*
*[*4]Prothrombin time.*
*[*5]Hemolysis ranges: 0–2% of hemolysis, non-hemolytic; 2–5% of hemolysis, slightly hemolytic; more than 5% of hemolysis, hemolytic.*
*[*6]Toxin clearance was reported as 66% urea and 60% creatinine.*
*[*7]In case there are flux recovery ratio measurements more than one cycle, the first cycle is reported.*

Table 1.
Zwitterionized hemodialysis membrane's hemocompatibility assessment.

Hemolysis percentage, which shows the extent of blood cell damage when it touches the membrane surface, was reported to be the lowest for PVDF-SMBA membranes with plasma-induced surface copolymerization as modification technique [71]. Different clotting time parameters were also observed, and despite other parameters which were better for SBMA-modified surfaces, SSNa-zwitterionized membranes showed higher clotting time in general [53, 63]. The higher anticoagulant characteristics of SSNa-modified membranes could be interpreted into higher extent of coagulation cascade-resulted enzyme blockages (factor XII, factor XIIa, etc.).

Rather than ZW structures, other biomimetic surface modification approaches have been assessed by researchers for hemodialysis hemocompatibility improvements [5–7]. These bioinspired structures are mainly patterned from anticoagulants which are commonly used during a dialysis session. One of the most frequent reported structures from this class is heparin. Heparin and heparin-mimicking structures have been reported to be efficient in controlling the blood clotting process on the membrane and accordingly increasing its hemocompatibility. Due to high content of carboxyl and sulfate functional groups, heparin and heparin-mimicking structures are known as good candidate for both anticoagulation facilitator and membrane hydrophilicity's enhancer [79]. Just like ZW, heparin is also reported to be effective as attached to different membrane materials such as poly (acrylonitrile) (PAN) [80], poly(lactic acid) (PLA) [81], PSF [82], etc.

The main hemocompatibility mechanisms of previous and current generations of hemodialysis membranes are described to be related to hydrophilicity improvements (thicker hydration layer and less resistance to blood particle movements (higher degree of hemolysis)). Another class of modification which results in similar characteristics of surfaces is hydrogel. Several advantages of hydrogels in biomedical fields have been noted such as their living tissue resemblance or their 3D porous structures [75, 83]. Since hydrogels are polymeric networks, almost all possible polymeric modifications could be considered. This means adsorptive nanoparticles, ZWs, and biomimetic structures could all be used within this technique to have advantages of hybrid approaches [84]. A sample of such an approach is using graphene oxide-based heparin-mimicking hydrogel structures [85]. Interestingly, in comparison with common hemocompatibility approaches, hydrogel-based techniques could be significantly efficient. A support for such a hypothesis is a research reported by [86] who immobilized a heparin-mimicking thin film hydrogel on PES hemodialysis membrane which resulted in three times higher clotting time than best modified blood purification membranes (activated partial thromboplastin time value of 600 sec).

7. Conclusion and outlook

Several hemodialysis membranes' enhancements for higher hemocompatibility characteristics have been achieved experimentally as reported by various studies. Nevertheless, there are many questions which are not answered nor assessed. As an instance, several immobilization techniques have been introduced, but there is no clear comparison that could recommend a final better method for surface modification. More importantly, not all the membrane hemocompatibility studies consider all standard aspects of hemocompatibility assessment. In other words, available papers are reporting few factors of hemocompatibility assessment. Accordingly, no accurate comparison between different immobilization techniques and enhancer materials such as zwitterions or anticoagulants could truly be made based on the literatures.

Several aspects of hemodialysis have been improved since the emergence of technology. Material improvement along with pore size adjustment and different modalities of blood purification systems have resulted in higher hemocompatibility of the membranes and wider range of products for hospital and home dialysis sessions. Despite the improvements in different aspects of hemodialysis, the patient's quality of life is still not acceptable. Accordingly, there have to be more efforts put on incompatibility issues of the membranes.

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List of abbreviations

HD	hemodialysis
ESRD	end-stage renal disease
HFD	high-flux dialysis
HF	hemofiltrations
CKD	chronic kidney disease
LP	lectin pathway
AP	alternative pathway
MBL	mannose-binding lectin
HDF	hemodiafiltration
kDa	kilodalton
ISO	International Standardization Organization
PEG	poly(ethylene glycol)
PVP	poly(vinyl pyrrolidone)
PVA	poly(vinyl alcohol)
ZW	zwitterionic structures
CA	cellulose acetate
PES	poly(ether sulfone)
PSF	poly(sulfone)
PDMS	poly(dimethyl siloxane)
PVDF	poly(vinylidene fluoride)
PAN	poly(acrylonitrile)
PLA	poly(lactic acid)

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