1. Introduction

The number of people diagnosed with end-stage renal disease (ESRD) as a result of chronic kidney disease is greatly increasing. Thus, the number of patients receiving treatment via hemodialysis is also increasing [1,2]. Hemodialysis is a process by which the blood is cleaned using a hemodialysis-membrane-based dialyzer. The most important component in this purifying process is the hemodialysis membrane, currently cellulose acetate (CA), polysulfone (PSU), polyethersulfone (PES), polymethyl methacrylate (PMMA), polyacrylonitrile (PAN), polyvinyl alcohol (PVA), polyacrylonitrile (PAN), polyvinyl alcohol (PVA), polylactic acid (PLA), polypropylene (PP), polyamide, and chitosan are the most commonly used polymers[3].

To increase the biocompatibility and purification...
ability of membranes various polymers are tested in combination with each other. In a study conducted to compare the PEG membrane with PEG/CA membrane with different concentrations of zeolite, the concentration of mordenite zeolite affected the membrane performance because its retention and large pore size decreased solute rejection but increased creatinine uptake level along with the better bio-compatibility[4]. Hemocompatibility of glutaraldehyde-crosslinked chitosan/carboxymethyl cellulose (CS/CMC-GA) was studied as a hemodialysis (HD) membrane showed that CS/CMC-GA membranes have superior properties compared to chitosan in addition to their better bio-compatibility[5]. HD membranes composed of cellulose triacetate (CTA) and polyvinylpyrrolidone: polycarlylethersulfone (PAES: PVP) were studied to assess the influence of membrane morphology and bio-compatibility on uremic blood-membrane interactions and inflammatory biomarkers, it was concluded that while CTA has a higher biocompatibility, it has a poor clearance[6].

Of the commonly used membranes polysulfone membranes are favored due to its stability under various conditions. Zhang et.al, studied a co-blending modification of PES by TA, PEG and DMAc, and the results showed that the presence of TA improved various qualities of the membrane including improved dialysis performance and hemocompatibility[7]. Zeolites were added to PES to improve the capability of the membrane to interact with creatine. The performance of the blended membrane was evaluated for selective filtration of creatine. The results showed that, in comparison with zeolites and PES, PES/zeolite showed a significantly high rejection rate for creatine and thus successfully filtered creatine[8]. The PES membrane was modified in another study with CA using imprinted zeolites to improve the selectivity of the HD membrane, the new membrane successfully demonstrated an increase in selectivity[9]. Yang et al modified HD membrane with silibinin to suppress hemodialysis induced oxidative stress, a common biomarker of chronic kidney disease. The resulting membrane successfully alleviated oxidative stress and showed potential applications in hemodialysis[10]. It is important to control the permeability of the HD membrane as loss of albumin is detrimental to the patient. In a study done to combat this challenge, two types of dialyzers were compared by assessing the albumin loss of each[11]. In this review hemodialysis membrane are divided into polysulfone and nonpolysulfone membrane.

2. Non Polysulfone Membrane

Hemodialysis is a therapy for end-stage renal disease [12]. It is done to separate uremic toxins and proteins based on their molecular weights using a semi-permeable membrane. The membrane used for this process is a cellulose acetate (CA) membrane however it lacks in terms of selectivity and hemocompatibility. This study tests a modified form of the CA membrane. The membrane was modified by the addition of polyvinyl alcohol (PVA) and polyethylene glycol (PEG) which enhance its biocompatibility and filtration capability. The structure and morphology were analyzed using FTIR and SEM, AFM, pure water flux, solute permeation, and protein retention respectively. The biocompatibility was tested using platelet adherence, hemolysis ratio, thrombus formation, and plasma recalcification time. The maximum pure water flux, BSA rejection, urea, and creatine clearance obtained was 42.4 ± 2 L/m² · h, 95 ± 1.023%, 93 ± 1.023%, and 89 ± 1.023% respectively. These results showed that PVA successfully increased the selectivity of the membrane due to its decreased pore size. It also enhanced membrane hydrophilicity. Also, there was lesser plate adhesion, lesser thrombus formation, extended plasma recalcification time, and a lower hemolysis ratio. In conclusion, this study provided a method to enhance the pre-existing method for hemodialysis.

Extended cut-off filtration by medium cut-off (MCO) membranes is safe in the maintenance of hemodialysis [13].

This study investigates the use of MCO for the control of chronic low-grade inflammation and its influ-
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**Fig. 1.** (A–C) Report mean and 95% CI intervals for leukocytes, lymphocytes and CD3+ cells as reported above stratified by timepoint and treatment (MCO vs. high flux dialysis). *P* values were obtained from linear mixed effect models with subject ID (nested in sequence) with treatment (MCO = 1), period and sequence as main effects. A *P* value of < 0.05 was considered statistically significant. For CD3+ cells as well as (B) and (C) flow cytometric analysis was performed on re-thawed cryopreserved PBMCs which had been collected before the dialysis session (0 h) at all four study visits. Cells were then either left untreated (B) or stimulated with PMA + Ionomycin (C)—viability was generally > 85%. (Reproduced with permission from Lorenz et al.[13], Copyright 2022, Nature Research).

**Fig. 2.** Cross over design, timepoints and sample acquisition (Reproduced with permission from Lorenz et al.[13], Copyright 2022, Nature Research).
ence on cellular membrane aberrations. An open table, multicentre, randomised, 90-day 2-phase cross-over clinical trial was conducted to arrive at a conclusion; 34 of the 46 patients completed the trial. Pre- and post-dialysis serum inflammatory mediators were assayed for each study visit and Ex vivo T cell activation was assessed from cryopreserved leukocytes by flow cytometry and, the treatment models were compared using linear mixed models. Most mediators' filtration/dialysate concentrations, including MCP-1 (mean ± SD: 10.5 ± 5.9 vs. 5.1 ± 3.8 pg/ml, P < 0.001), rose significantly during MCO-1 compared to high flux-HD. However, there were no benefits for the largest mediator, YKL-40. Although there was no sustained reduction for any of the mediators the significant long-term reduction of CD69+ (P = 0.01) and PD1+ (P = 0.02) activated CD4+ T cells must be noted. In conclusion, MCO membranes do not reduce serum inflammation significantly but they do cause long-term reduction of peripheral T cell hyperactivation.

Hemodialysis blood-membrane incompatibility is one of the major reasons for post-hemodialysis complications that occur as it can lead to the activation of different cascades due to interactions between essential human serum proteins and HD membranes[14]. This study assesses the interaction energy between common hemodialysis polymer structures in a zwitterionized state and human serum proteins (HSPs), such as Human serum albumin (HSA), fibrinogen (FB), and transferrin (TRF), using molecular dynamics (MD) simulation to understand significant interactions as a reference for HD material development. The binding energies and hydrophilicity of the membrane models and the binding energies of the selected proteins were assessed. The study concluded that there is no correlation between surface hydrophilicity and hemocompatibility. Furthermore, FB attachments could be eliminated by comparing all FB-membrane model interactions’ modification with a natural biopolymer even though each protein exhibits a distinct trend when interacting with various base polymers and modifying layers. Also, high functionalization of the membrane surface may not always result in an increase in hemocompatibility since although it can lower albumin and transferrin attachment it can also activate the fibrinogens. To conclude, the MD approach was useful to observe the interaction between protein-membrane pairs and can be further utilized to study HD biocompatibility enhancement.

Hemoincompatibility is a critical issue for hemodialysis since interactions between various human blood elements and polymeric structures of HD membranes result in the activation of immune system cascades [15]. This study conducts MD simulations to understand the interactions between HSPs -fibrinogen (FB), human serum albumin, and transferrin- and common HD membranes. PAES and cellulose triacetate were used as the common dialyzer membranes and membrane modifications were performed with HEMA and PMEA using polydopamine-assisted co-deposition. For FB the PDA coating resulted in the lowest binding energy with the CTA membrane model and the PDA-HEMA coating showed the lowest binding energy with the PAES membrane model. For HSA both the PDA and PDA-PMEA layers showed a decrease in the binding energy with the CTA membrane. For all three coatings –PDA, PDA-HEMA, and PDA-PMEA– the binding energy is lowered with the PMEA membrane. Finally, for TRF PDA-PMEA and PDA-HEMA resulted in lower binding energy. Due to the above results, it was concluded that PMEA is superior to HEMA due to its ability to absorb intermediary water molecules and the advantageous chemical moiety of its methyl group as opposed to HEMA’s hydroxyl group.

Protein carbonylation is a common irreversible oxidative damage during chronic kidney disease[16]. In this study, Carbazate groups were grafted on the commercial cellulose membrane (CM) to find carbonylated proteins for hemodialysis. The CM membrane was prepared by the activation of CDI in DMSO proceeded by a reaction with hydrazine. The physical and chemical properties of the membrane were unchanged and strong stability over the pH range of 2.5 to 7.4 was seen. The membrane also successfully carried out the scavenging characteristic that it was supposed to show. A piece of
CM with a substitution degree upwards of 10 could scavenge 37.68% of the carbonylated proteins from a sample of 4 mg acrolein BSA. And 50.81% from 12 mg of a patient’s blood serum. This modified membrane showed effective results, making it a promising material for hemodialysis.

3. Polysulfone Membrane

Hemodialysis membranes are commonly made with the polymer PES- polyethersulphone- due to its high stability under various conditions[17]. However, its hydrophobic nature causes membrane fouling. This study uses a mixed matrix membrane (MMM) made of PES and graphene oxide (GO) -graphene is an allotrope of carbon- to enhance the hemodialysis membrane performance. GO was synthesized from tartaric acid and the membrane was fabricated using a casting solution. The MMM showed better mechanical strength properties and hydrophilicity. The tensile stress and strain values were 5.55 MPa and 0.039 m respectively. The solution flux value was 2.94 L m⁻² h⁻¹ and the clearance of creatinine was 78.3%. The results obtained show that the mixed matrix membrane is a good candidate for hemodialysis membranes.

Usually, a PES polymer is used as the hemodialysis membrane, this study uses a short chain length polymer i.e PVP-k25 as an additive to improve the biocompatibility and toxic solute removal performance of the PES membrane[18]. Noncovalent electrostatic interaction between amide nitrogen and carbonyl carbon of the PVP-k25 was developed with in-house carboxylic oxidized multiwall carbon nanotubes (MWCNT) and then blended with PES. This integration produced a surface-modified HD membrane that has fingerlike channels in composite membranes. An FTIR spectrum was used to study the bonding nature and the functionalization of the MWCNT. FESEM imaging confirmed the improved capillary system, the leaching behavior of PVP-k25, and the dispersion properties of O-MWCNT. There was a 24% improvement in hydrophilic behavior, the leaching ratio reduced by 1.89%, and BSA and lysozyme-based antifouling showed a 25% improvement. Thus, there was an overall improvement in the membrane’s biocompatibility and its clearance ratio of toxic substances.

Cell activation upon exposure of blood to hemodialysis membranes is an important factor in determining membrane biocompatibility[19]. This study observed different cell activation among different polysulfone (Psf) hemodialysis membranes. It shows that the number of platelets adherent to their surface and reactive oxygen species (ROS) production by neutrophils differs from membrane to membrane. CX-U, a conventional psf membrane, induced adhesion of platelets to its surface, increasing the surface expression of CD11b, and production of ROS by neutrophils. NV-U, a hydrophilic polymer-immobilized psf membrane, had negligible effect on platelets and neutrophils. On studying the two membranes, GPIIb/IIIa mediated the adhesion of platelet and ROS production on platelets and Mac-1 and 3 on neutrophils. The number of adherent platelets and ROS production was directly proportional to the amount of fibrinogen absorbed on the membranes. Thus, a membrane with low fibrinogen absorption may reduce cell activation during dialysis and hence improve biocompatibility.

The formation of microaggregates is associated with complications of hemodialysis therapy[20]. The formation of the aggregates involves interactions between blood cells and HD membranes and specifically HD membrane-induced platelet activation. This study analyses the effects of two polysulfone membranes–CX-U and NV-U– with different abilities to activate blood cells, on the formation of the microaggregates. Human blood was circulated through a mini-module dialyzer using the membranes in vitro, and the platelet-neutrophil complexes in blood were determined by flow cytometry. CX-U is a standard membrane that induced the formation of neutrophil complexes however NV-U– a new hydrophilic polysulfone membrane–did not; this is due to a difference in cell activation ability, CX-U has a significant cell activation. Additionally, CX-U induced
reactive oxygen species production and the increased expression of CD II b expression on neutrophils was enhanced by platelets. Conversely, NV-U has little to no effect on neutrophil activation regardless of the

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Fig. 3. Schematic mechanism of GO formation (Reproduced with permission from Fahmi et al.[17], Copyright 2018, Royal Society of Chemistry).

Fig. 4. Cross sectional image of (A) the PES membrane and (B) the PES/GO350 membrane. The figures on the right show a higher magnification of a particular area (brown square) (Reproduced with permission from Fahmi et al.[17], Copyright 2018, Royal Society of Chemistry).
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