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A new vision upon hemodialysis: A shift from synthetic to sustainable chitosan membranes

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ABSTRACT

The article provides a comprehensive review of chronic kidney disease (CKD), covering its epidemiology, pathophysiology, diagnosis, and management. It highlights CKD's increasing prevalence globally and its significant impact on public health due to its association with cardiovascular diseases and progression to end-stage kidney disease. The article delves into the diagnostic criteria, including the use of glomerular filtration rate (GFR) and albuminuria levels, and outlines the stages of CKD to facilitate early detection and management. It also discusses renal replacement therapies (RRT) such as dialysis and transplantation, comparing hemodialysis (HD) and peritoneal dialysis (PD) in terms of efficiency, complications, and quality of life impacts.

The transition towards sustainable dialysis involves the innovative integration of chitosan, a biopolymer into membrane technology. Current synthetic membranes, though functional, fall short in biocompatibility and sustainability. Chitosan's introduction aims to mitigate these issues by harnessing its advantageous biological and eco-friendly properties. Leveraging chitosan not only addresses environmental concerns by providing a sustainable alternative but also exploits the full potential of its properties to revolutionize RRT. The shift towards chitosan-enriched membranes represents a significant stride in advancing dialysis treatment, focusing on patient safety, environmental sustainability, and the effective management of CKD. This approach underscores the importance of innovation in healthcare, specifically in the development of dialysis technologies that prioritize both patient welfare and environmental sustainability.

1. Introduction

The kidneys work as the body's excretory system, responsible for the removal of metabolic waste products, toxins, and surplus fluids from the bloodstream. Impairment in kidney function, leading to the accumulation of excessive fluids and waste substances, can precipitate a spectrum of associated health complications, contributing to cardiovascular conditions, such as heart disease and stroke [1].

The CKD is marked by an ongoing decline in renal function, often persisting for months or even years [2]. Approximately 850 million people worldwide are estimated to have kidney disease and its prevalence of has been increasing over the years [3], presenting a growing public health challenge and it is expected to become the fifth leading cause of death by 2040 [4]. The aging demographic in many countries adds complexity to the CKD landscape, as older adults are particularly vulnerable to CKD-related complications. Age-related declines in kidney function increase susceptibility to CKD-related health issues [5]. As the global population continues to expand and age, the prevalence of CKD is on the rise, further underscoring its significance as a public health concern [6]. So, the urgent need for comprehensive strategies aimed at preventing and managing CKD effectively [7].

HD is an extracorporeal treatment that uses semipermeable membranes, typically prescribed three times a week for three to four hours each time, it's the most prevalent therapeutic strategy. These membranes have undergone extensive development. The design and development of these membranes have been the subject of much research to improve the dialysis operations' speed and efficiency [8]. But up until now, scientific advancements have not prioritized or given any thought to sustainability or potential reuse.

Approximately 90 % of dialysis membranes are made of polysulfone (PSu) or polyethersulfone (PES). The most popular polymers for making these membranes are now Udel® PSf and Veradel® PES [9]. However, they are made of plastic and are meant to be used only once. This environmental pressure is evident globally, as demonstrated by the

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estimated 4.1 million dialysis treatments conducted annually [10].

Switching from synthetic membranes to bio-based membranes in HD offers significant environmental benefits, primarily due to their biodegradability, renewable sourcing, and reduced reliance on petroleum-derived polymers [11]. Synthetic membranes, such as those made from PSu and PES, are non-biodegradable, contributing to long-term medical waste accumulation. Within this, the use of bio-based materials like chitosan aligns with green chemistry principles, promoting environmentally friendly manufacturing with fewer hazardous chemicals and supporting the circular economy model by repurposing several industry's byproducts [12].

Despite growing interest in alternative membrane materials, existing reviews have mostly focused on biocompatibility and mechanical performance, without fully addressing the environmental implications of synthetic polymer use. This review seeks to fill that gap by offering a comprehensive perspective on the sustainability potential of chitosan-based membranes, including their environmental advantages and functional versatility. By integrating the ecological dimension—often overlooked in previous literature—this review aims to highlight chitosan's broader relevance within the context of green medical technologies. In this context, a novel perspective on the use of natural polymers in the development of hybrid membrane systems is urgently needed. This review emphasizes chitosan and its biological and ecological benefits, highlighting its potential to revolutionize the design of sustainable HD membranes.

2. Chronic kidney disease: definition and stages

The symptoms of CKD are often vague and nonspecific, making it challenging to detect the condition in its early stages. Many individuals may not experience severe symptoms until their renal disease has progressed significantly. Common nonspecific symptoms include increased fatigue and decreased energy levels, difficulty concentrating, a diminished appetite, disrupted sleep patterns, dry and itchy skin, and increased frequency of urination, particularly at night [13].

As the renal function deteriorates, an array of supplementary symptoms may arise, contingent upon the extent and duration of CKD, such as hypertension (high blood pressure), accumulation of urea leading to uremia, elevated levels of potassium and/or phosphates in the blood (hyperkalemia and/or hyperphosphatemia), reduced production of erythropoietin (a hormone responsible for red blood cell production), fluid volume overload resulting in edema, deficiency of vitamin D and iron-deficiency anemia [14,15].

In fact, a concerning aspect of this condition is the elevated risk it presents several complications and mortality, particularly those ones related to cardiovascular health, as mentioned above [16].

CKD is characterized by a sustained reduction in GFR persisting for a duration of three months or longer, without regard to its underlying etiology [17]. The differentiation between chronic and acute kidney disease is primarily established by the requisite three-month duration [18].

CKD is typically defined and diagnosed following the criteria outlined in "Kidney Disease: Improving Global Outcomes" (KDIGO) guidelines [17]. These include either a persistent reduction in GFR below 60 mL/min/1.73 m^2 for at least three months, or evidence of kidney damage (structural or functional) with or without decreased GFR, confirmed through markers such as imaging or laboratory abnormalities [17].

Among these, GFR is considered the most comprehensive indicator of renal function in both healthy and pathological states, while albuminuria (which signifies heightened glomerular permeability) stands as the most extensively studied marker of kidney damage [19].

In one hand, GFR is more commonly used to classify the renal filtration rate, and it is defined as the flow rate of filtered fluid through the kidneys, requiring a blood test to measure the creatinine, which is usually produced at a constant rate by the body and is normally cleared from the blood by the kidneys. If the kidneys are damaged and the glomeruli are not filtering as much as normal, the level of creatinine in the blood increases [20]. Data about the GFR categories in chronic kidney disease are depicted in Table 1**,** adapted from Levin *et al* [17].

It is important to notice that direct measurement methods are complex to implement, so in clinical practice GFR is typically estimated (eGFR) using serum creatinine levels and also, that GFR categories G1 nor G2 meet the requirements to be considered CKD in the absence of damage to this organ [18].

In addition to GFR, albuminuria is a key marker for kidney damage and provides complementary information on glomerular integrity.

Albuminuria refers to the presence of albumin in urine, which normally does not occur in significant amounts due to the size exclusion properties of healthy glomeruli. Albuminuria is assessed through the albumin excretion rate (AER) over 24 hours or the albumin-to-creatinine ratio (ACR), as shown in Table 2. Values above the reference range are considered pathological and may require further investigation and clinical intervention [21].

3. Chronic kidney disease: current treatments

3.1. Renal replacement therapy and renal transplantation

The prevalence of CKD patients has also been rising not only due to life expectancy, but also due to the risk factors including obesity and diabetes mellitus have increased [22]. Up to 30 % of adults with 70 years of age and beyond may have CKD, which has a strong age correlation [14], as mentioned before. It is crucial to account for these distributions when comparing CKD prevalence due to the substantial correlation between age and the variance in the overall population age distributions throughout locations [23]. In this context, it becomes essential to consider how this growing prevalence translates into treatment demands, particularly in end-stage kidney disease (ESKD). Even though ESKD patients' mortality has decreased [24], "Global Burden of Disease" studies have revealed that CKD has risen to become a major global cause of death [25,26]. This progression highlights the growing importance of renal replacement therapies (RRT), such as dialysis and transplantation, as critical responses to the rising burden of advanced kidney disease. For patients with ESKD, RRT, either dialysis (subdivided in HD and PD) or renal transplantation, are a lifesaving but expensive treatment [27].

For almost 50 years, high-income nations have had access to it; throughout that time, the number of patients treated has rapidly increased. Due to variations in ESKD frequency, access to and availability of RRT, and population demographics, there are significant regional variations in the use of dialysis as a treatment for ESKD [28,29]. This shows the uneven access to kidney care around the world, caused not only by differences in disease rates but also by economic conditions and the strength of each country's healthcare system.

The demographic shift causing this increase is anticipated to happen more in poorer nations than in developed ones, which will put financial pressure on many of them to treat more patients with ESKD using RRT [30–32].

Around the world, 2.6 million people were undergoing RRT in 2020. However, it is estimated that a similar number may have died that same year due to limited access to dialysis and transplantation [33]. While

Table 1
Glomerular filtration rate categories in chronic kidney disease.

Category	GFR (ml/min/1.73 m^2)	Description
G1	≥ 90	Normal or high
G2	60 - 89	Mildly decreased
G3a	45 - 59	Mildly to moderately decreased
G3b	30 - 44	Moderately to severely decreased
G4	15 - 29	Severely decreased
G5	< 15	Kidney failure

Table 2
Albuminuria categories in chronic kidney disease.

Category	AER (mg/24 h)	ACR (mg/g)	Description
A1	< 30	< 30	Normal to mildly increased
A2	30 – 300	30 – 300	Moderately increased
A3	> 300	> 300	Severely increased

significant progress has been made in reducing mortality from other major chronic diseases, such as cardiovascular and respiratory conditions [34], the global burden of kidney disease remains disproportionately high, particularly in settings with limited healthcare access. To better understand these disparities, it is useful to examine regional data that reflect how this burden is distributed and addressed in different health systems.

According EDTA-ERTA report in 2021, the 3 countries or regions with the highest prevalence of patients on RRT were Portugal, with 2003 *per million population* (*pmp*), Spain – Canary Islands region with 1556 *pmp* and Spain – Catalonia with 1525 *pmp* [35].

The data depicted in Fig. 1 clearly illustrates these disparities, showing that Southern and Western European regions tend to have higher RRT prevalence rates compared to Eastern and Northern areas. This suggests that access to treatment, early detection, healthcare infrastructure, and population age profiles vary significantly across Europe.

Such visual data reinforce the need for region-specific strategies in managing CKD and ESKD, as a one-size-fits-all approach may not effectively address each population's reality. These insights are invaluable for policymakers, healthcare providers, and researchers in the field of nephrology, facilitating targeted interventions and improved patient care [36]. To contextualize this figure, it is important to examine the demographic profile of RRT patients in these regions.

The patient population receiving RRT in 2021 had a number of significant clinical and demographic characteristics. These important numbers are outlined in this scientific explanation, which emphasizes their importance in the field of renal medicine and, according to EDTA-ERTA, in the same year, 62 % of the prevalent patients receiving RRT in 2021 were of the male gender, indicating a noticeable gender disparity within this patient population [35]. Also, 47% of prevalent RRT patients were aged 65 years or older [35], signifying that a substantial proportion of individuals requiring RRT were in the geriatric age group. This observation underscores the importance of tailoring renal care and treatment protocols to accommodate the unique needs of elderly patients [37]. Moreover, understanding the underlying causes of kidney

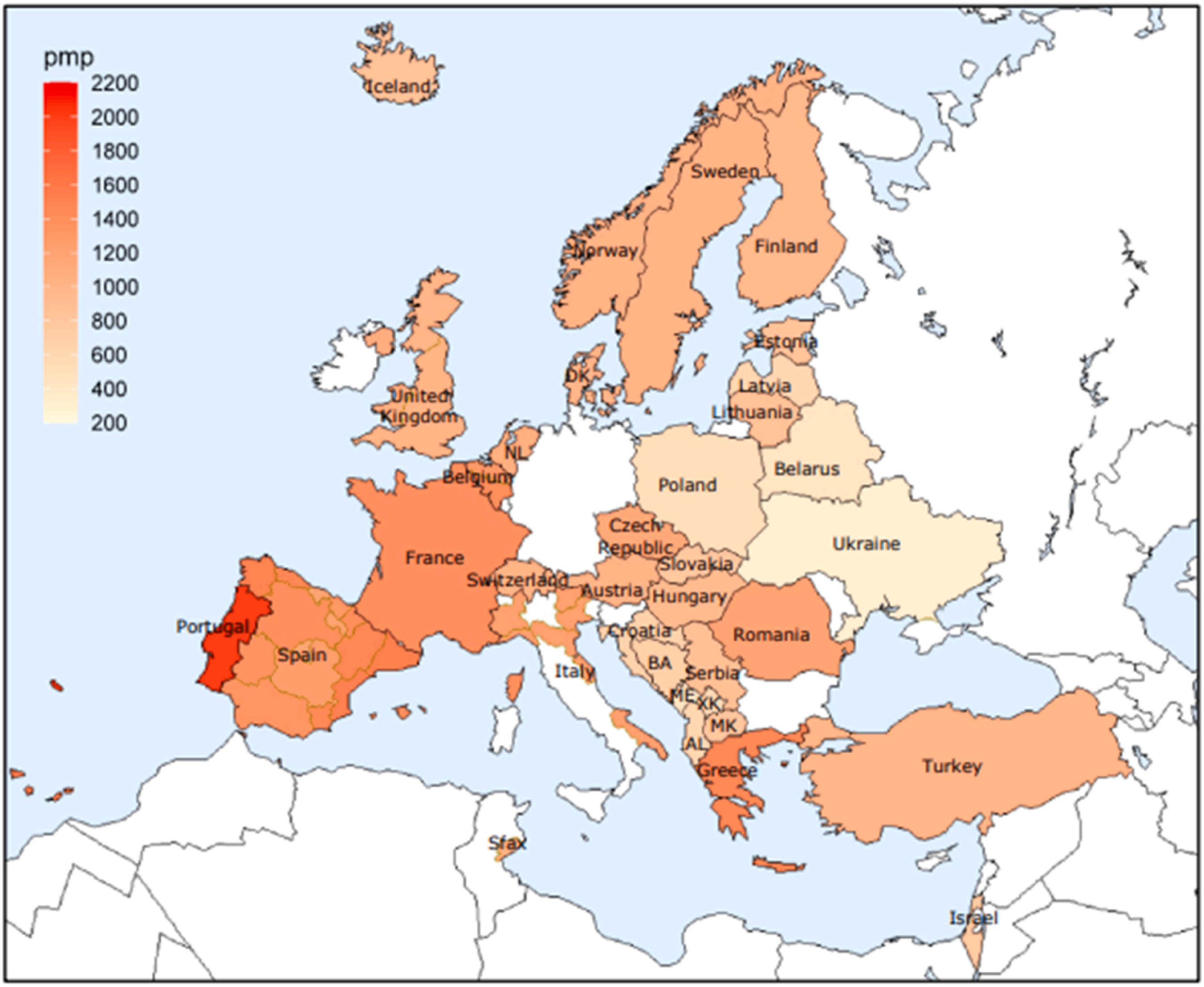

Fig. 1. Regional disparities in RRT Prevalence (2021) [35]. This figure and its data highlighted portrays the regional disparities in the prevalence of patients on RRT during the year 2021, highlighting regions where CKD management appears more advanced or where disease burden may be higher.

disease in these populations is crucial for guiding prevention and treatment efforts. In this group of RRT patients, the main cause of kidney disease was glomerulonephritis or sclerosis, showing how important these conditions are in leading to the need for treatment like dialysis or transplantation [35].

Kidney transplantation remains the most effective treatment for end-stage renal disease, offering better survival rates and quality of life compared to dialysis [38].

However, it is still faced with several significant challenges. The most critical limitation is the persistent shortage of eligible donor organs, largely due to the stringent compatibility requirements, including matching tissue and blood types, which create a considerable gap between supply and demand [39].

As a result, many patients face extended waiting periods, during which they must continue dialysis, often for years, while coping with the physical and emotional burden of the disease [39,40].

Even when a suitable organ becomes available, the risk of immune rejection remains a constant concern. Despite remarkable progress in immunosuppressive therapies, the recipient's immune system may still recognize the transplanted kidney as foreign, initiating the rejection process [41]. Balancing immune suppression to prevent rejection while minimizing side effects such as infections, cardiovascular complications, and malignancies remains a delicate and ongoing challenge [42,43]. Immunosuppressive regimens also require strict patient adherence, as even minor lapses can compromise graft survival [44]. In addition to medical concerns, the transplantation process itself carries surgical risks. Complications may arise before, during, or after surgery, including bleeding, infection, and site-specific issues, despite advances in surgical techniques. Moreover, the ethical complexities of organ allocation continue to raise important questions [45].

Factors such as medical urgency, waiting time, and donor availability must be carefully weighed to ensure fairness and equity in distribution. Ultimately, even with immunosuppression, the risk of rejection remains, and some patients may require a repeat transplant or return to dialysis [46].

Within this, a sizable portion of ESKD patients might not be a good fit for transplantation due to medical contraindications, making dialysis (i.e. HD and PD) the appropriate approach in those situations.

3.2. Hemodialysis versus peritoneal dialysis

HD and PD are the two primary modalities employed for RRT, each offering distinct clinical, social, and economic pros and cons.

HD is a widely used RRT characterized by efficient toxin removal. It provides an effective clearance of waste products and excess fluids from the bloodstream [47].

Within this, patients receive HD under the professional oversight of healthcare providers in dialysis centers. However, this treatment demands a significant time commitment. This schedule can disrupt patients' routines [48]. Additionally, the use of vascular access may lead to access-related complications, infections and thrombosis being the leading ones [49].

Moreover, HD membranes are mostly synthetic, non-biodegradable, and single use, contributing significantly to medical waste. This raises concerns regarding their environmental impact, especially considering the volume of treatments worldwide [12,50,51]. Conversely, PD provides ongoing elimination of toxins, possibly maintaining residual kidney function [52]. It is a home-based therapy that gives patients more freedom and adaptability hence the treatment takes place at the patient's home [53].

The fact that PD does not require invasive vascular access reduces related problems, which is a considerable benefit [54], still, it demands strong patient involvement since they must undergo proper training before initiating PD, ensuring they can manage the equipment and follow hygienic protocols at home [55] including the care to avoid complications like peritonitis [56]. It also allows gentler fluid removal over longer periods, which may be better tolerated [57]. Additionally, PD places a strong focus on psychological preparedness [58].

Having in mind social considerations, human interactions are encouraged by in-center HD, which presents the opportunity for a positive dialysis community [59], but, in contrast, patients' financial well-being may be impacted by losing employment opportunities and expenses associated with travelling to dialysis facilities [60]. which is not an issue for PD, since this one is home-based [61].

It is immediately accessible and can be initiated without delay and any patients and physicians prefer the professional supervision offered by in-center HD [62].

4. Hemodialysis treatment

In the evaluation of patient outcomes, it was revealed that a 2-year survival rate was comparable between patients' receiving PD and those on HD, however, HD remains the dominant modality, making up around 89 % of dialysis and over 69 % of all RRT [63]. The HD treatment is usually administered three times a week for three to four hours each time [64]. Some patients require longer sessions to achieve adequate waste removal and fluid balance. Treatment frequency varies as well; most patients receive treatment three times a week, but some may require more frequent sessions [65].

Blood is circulated through a device known as a dialyzer during HD, which removes extra fluid and solutes from the patient [66]. A blood circuit, a dialysate, a dialyzer, a dialysis machine, and a vascular access are the requests for this treatment (Fig. 2) [67].

For the blood to enter the HD circuit, vascular access (Fig. 3) is required. Currently, the options are Arteriovenous (AVFs), which are formed by joining a patient's artery to a vein. Also, arteriovenous grafts (AVGs), which are created by joining a patient's artery to a vein using a hollow tube, and central nervous catheters, which are catheters inserted into the femoral, jugular, or subclavian vein [68].

The process of cannulation, initiating the blood flow, involves the insertion of two needles by healthcare professionals. The "arterial" needle removes blood from the patient, while the "venous" needle returns cleaned blood. Proper needle placement and site rotation are crucial to ensure efficient blood flow and prevent complications [69].

In fact, the HD machine is the heart of the process, including the blood pump to control blood flow through the dialyzer, being this one the epicenter of this therapeutic intervention, being colloquially denominated as the “artificial kidney”. This apparatus is the principal site where the sanguineous purification transpires, mirroring the filtration functionality characteristic of a healthy nephron [70].

Fig. 2. Real-time image of a HD machine / process.

Fig. 3. Real-life image of a patient's AVF.

As the HD machinery propels blood through the dialyzer, its intricate configuration is operationalized. The dialyzer's design incorporates a semi-permeable membrane constituted of multifarious hollow fibers, which orchestrate the selective transmembrane movement of solutes. This membrane facilitates the diffusion of toxins and the osmotic flux of excess fluids from the blood, effectuating a purification process that is pivotal in the maintenance of the patient's electrolytic and metabolic equilibrium [71].

4.1. Dialyzers in hemodialysis treatment

In the dialyzer, as is an example of a real one in Fig. 4, both blood and dialysate are pumped counter currently to enhance the concentration difference of the solutes and facilitate the removal of uremic toxins [72].

Fig. 4. FX® CorDiax dialyzer by Fresenius Medical Care.

The dialysate fluid dialysate is a carefully formulated fluid that helps remove waste products from the blood and maintain the body's electrolyte balance (Table 3) and is prepared through a series of water detoxifications using activated carbon filter, reverse osmosis and distillation [73]. It is relevant to note that the constituents' concentrations can vary based on individual patient needs and the specific prescriptions of their healthcare providers. This table gives a general idea of the dialysate composition used in standard HD treatments [74].

During HD, the dialysate fluid's solute content is carefully controlled to maintain physiological homeostasis [75]. In adults, dialysate flow rate is normally set to 500 mL/min primarily to achieve adequate removal of small solutes (e.g. urea, creatinine, and phosphate) [76].

As mentioned, the purpose of the dialyzers is to balance the electrolyte content of the patient's blood and eliminate uremic poisons and extra water from it. In HD, the molecular weight of solutes is integral to their selective transmembrane transport [77]. Low molecular weight compounds such as urea (60 Da), creatinine (125 Da), and phosphate (134 Da) are efficiently cleared from the bloodstream, given their facile diffusivity through the semipermeable dialysis membrane. Conversely, macromolecules like albumin (68 kDa) and transferrin (90 kDa) are retained due to their substantial molecular dimensions, which exceed the membrane's pore size threshold. This selective permeability is pivotal, as it ensures the removal of metabolic waste while preserving critical plasma proteins essential for homeostatic functions.

In an HD system, the interaction between the dialysate and blood occurs through the semi-permeable membrane within the dialyzer, based on the principles of diffusion and osmosis. This process is crucial for effectively cleansing the blood of patients with kidney failure [78].

The patient's blood, containing waste products (urea, creatinine, and phosphate) flows inside the hollow fibre membranes of the dialyzer. Surrounding these fibers is the dialysate, a specially formulated fluid that flows outside the fibers in a counter-current direction to the blood flow. This setup is essential for maximizing the efficiency of waste removal [79].

Once the exchange is complete, the cleansed blood is returned to the patient's body, and the dialysate, now containing the removed waste and excess fluid, is discarded. This interaction within the dialyzer is critical for the effective and safe treatment of patients undergoing HD [80].

4.2. Dialyzers' membranes over the time

The composition of the membrane in a dialyzer is a critical determinant of its performance in facilitating the removal of waste products during the dialysis process [81].

Table 3
Quantitative composition and therapeutic applications of dialysate constituents in HD regimen.

Quantitative Composition	Concentration (mmol/L)	Therapeutic applications
Sodium	135-145	Regulates osmotic balance; Fluid removal.
Potassium	0-4	Management of the serum potassium; Crucial for cardiac function.
Calcium	1.25-1.75	Essential for neuromuscular activity; Vascular activity.
Magnesium	0.5-1	Required for various biochemical reactions; Blood pressure regulation.
Chloride	100-108	Balances cationic charges to prevent electrolyte disturbances
Bicarbonate	32-40	Corrects metabolic acidosis; Maintains acid-base balance.
Glucose	0-5.5	Provides caloric substrate; Aids in osmotic fluid removal.

Historically, cellulose-based membranes were extensively utilized in dialyzers' making. Among these, cellulose acetate and cellulose triacetate were common choices. These materials offered a natural and porous structure, facilitating the effective removal of waste products from the blood. The inherent porosity of cellulose-based membranes played a crucial role in separating toxins while preserving essential blood components. Modifications to cellulose membranes, such as acetate-free biofiltration (AFB) membranes, have improved their biocompatibility. However, they generally do not match the performance metrics of their synthetic counterparts [82]. As technology progressed, there was a notable shift towards synthetic alternatives [83].

In modern dialyzer designs, there is a prevalent adoption of synthetic membranes made from materials such as PSu or PES. These synthetic alternatives bring several improvements to the area [84]. Firstly, they provide enhanced control over pore size [85], allowing for more precise regulation of the substances that can pass through the membrane. This attribute contributes to improved biocompatibility, as it minimizes the risk of adverse reactions during the dialysis process [85].

Furthermore, synthetic membranes reduce the risk of complications associated with cellulose-based materials. Cellulose membranes were once widely used in HD but were associated with biocompatibility issues. These primarily included complement activation, leading to inflammatory responses in patients. This activation was observed due to the direct contact of blood with the cellulose membrane, triggering the body's immune response and resulting in complications such as dialysis-related amyloidosis [86]. These synthetic materials also offered enhanced higher flux rates, better clearance profiles and uremic symptoms. The introduction of these advanced membranes allowed for more efficient and safer dialysis procedures, addressing many of the limitations inherent in cellulose membranes [83].

The evolution towards synthetic alternatives reflects a commitment to enhancing the overall effectiveness and safety of the dialysis procedure [87].

In HD, the dialyzer membrane plays a central role as a selective barrier. This semipermeable membrane is therefore fundamental to the success of the entire treatment.

However, current synthetic membranes—despite their clinical performance—are designed for single use and are made of non-biodegradable plastic polymers. This generates significant environmental waste, especially considering the high frequency and global volume of HD treatments [71].

This limitation has sparked growing interest in exploring sustainable alternatives, particularly those based on biodegradable and renewable biopolymers. This limitation has sparked growing interest in exploring sustainable alternatives, particularly those based on biodegradable and renewable biopolymers. While such innovations are still emerging,

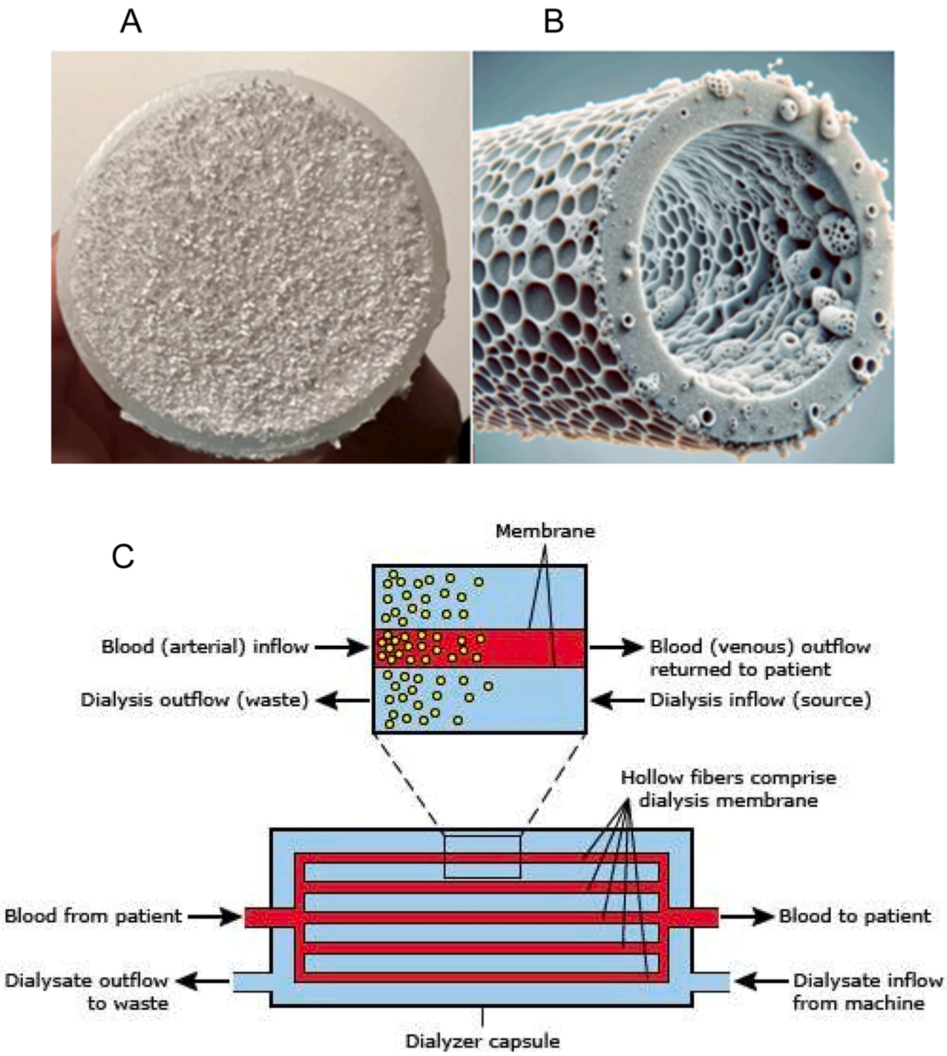

Fig. 5. (A) - Top view of FX® CorDiax HD dialyzer by Fresenius Medical Care displaying the arrangement of the hollow fibre membranes; (B) - Magnified illustration of the interior of a hollow fibre membrane used in a dialyzer for HD, the intricate structure and texture of the membrane wall. This image was created with the assistance of DALL·E 2.; (C) Schematic illustration of solute movement in dialyzers.

current dialyzer designs continue to rely predominantly on synthetic materials—especially in hollow fibre membranes, which remain the standard in contemporary HD due to their efficiency and compact structure [12,72,86].

Within this, hollow fiber membranes (Fig. 5), the predominant type used in contemporary HD, are designed to maximize the surface area for dialysis in a compact form. These dialyzers consist of thousands of tiny, hollow fibers, each acting as a semipermeable membrane.

The diameter and wall thickness of these fibers are precisely engineered to optimize treatment efficacy and patient safety.

Such design innovations in hollow fibre dialyzers have significantly improved the quality of HD treatment, making it more efficient and safer for patients with renal failure [71].

Dialyzers are categorised as either high flux (HF) or low flux (LF) based on the membranes' capacity to permeabilize water. Larger solutes cannot be effectively removed by LF dialyzers (ultrafiltration coefficient less than 15 mL/h/mmHg), however minor uremic toxins can be removed with sufficient effectiveness. On the other hand, both tiny and big uremic toxins may be removed with comparatively satisfactory results using HF dialyzers (ultrafiltration coefficient more than 15 ml/h/mmHg). The ultrafiltration profile is volumetrically controlled by an ultrafiltration pump which creates a negative pressure gradient in the dialyzer [79].

4.3. Current membranes used in hemodialysis

Dialyzer performance may be maximised by carefully selecting the kind of membrane, considering aspects like cost-effectiveness, permeability, and biocompatibility.

These days, a few businesses dominate the worldwide HD market, and they are all competing for the same customers by producing high-quality membranes for dialysis machines.

To date, Fresenius's PSu-based dialyzer is known as one of the best options in the market since offers optimal biocompatibility and solute removal [88]. This dialyzer has always been used as the main reference to the development of new dialyzers over the recent years. Recently, Fresenius presented a new class of PSu-based dialyzers, which combine a new housing design and an advanced membrane (FX-class) [88].

Dialyzers can be made from various polymeric materials, including PES and polymethylmethacrylate (PMMA), in addition to PSu.

For instance, Baxter's Polyflux® and Revaclear® dialyzers employ membranes composed of polyamide (PA), polyvinylpyrrolidone (PVP), and PES, while Toray Medical Co. Ltd.'s Filtryzer® series uses PMMA membranes. The aim of this product, manufactured in Tokyo, Japan, is to offer high biocompatibility and effective removal of intermediate and small-molecular toxins [89].

The natural and porous nature of these materials made it easier to efficiently remove waste from the blood while preserving vital blood components, thanks in large part to the intrinsic porosity of cellulose-based membranes. However, with the development of technology, there has been a noticeable shift towards synthetic substitutes [90]. Despite their clinical effectiveness, current HD membranes—particularly those made from PSu, PES, and other synthetic polymers—are non-biodegradable and designed for single use, generating considerable medical waste. This environmental burden underscores the urgent need for alternative, sustainable solutions in dialyzer membrane development [71].

Consequently, many of the dialyzers currently on the market remain based on these synthetic polymers, reflecting the industry's continued dependence on established materials. Recently, companies in the biomedical industry like WEGO in Shenzen, China, and Nipro in Osaka, Japan, have been making strides in dialyzer production. Table 4 shows all the dialyzers the major companies are making.

A development in the quest for improving sustainable dialyzer membranes involves the incorporation of chitosan, a naturally derived biopolymer. It is derived from chitin found in the exoskeletons of crustaceans, insects, and other sources and is a biocompatible and biodegradable material [91].

Table 4
Commercial dialyzers in the current market. Adapted from Noresah et al [71].

Origin	Series Name	Commercial	Polymers[a]
Germany	FX-class	Fresenius	PSu
	F-Series		PSu
	Hemoflow™		PSu
The United States of America	Polyflux	Baxter	PVP and PA
	Theranova		PAES and PVP blend BPA-free
	Xevonta	B-Braun	PSu
	Diacap Pro		PSu
Japan	ELISIO S	Nipro	PES
	Sureflux		CTA
	SolaceaTM		CTA
	APS-U	Asahi	PSu
	ViE Series		Vitamin E-coated PSu
	Rexeed Series		PSu
	Toraysulfone TS	Toray	PSu
	Renak	Kawasumi	PSu

[a] BPA (bisphenol A); CTA (cellulose triacetate); EVAL (ethylene vinyl alcohol copolymer); PA (polyamide); PAES (polyarylethersulfone); PES (polyethersulfone); PMMA (polymethylmethacrylate); PSu (Polysulfone); PVP (polyvinylpyrrolidone).

Chitosan has antimicrobial properties, potentially reducing the risk of infections during dialysis. Moreover, it may contribute to the overall biocompatibility of the membrane, making it a promising avenue for further research and innovation in dialyzer technology [92].

The composition of dialyzer membranes has evolved, transitioning from cellulose-based materials to synthetic alternatives with improved biocompatibility and control over pore size. However, addressing the environmental impact of these synthetic options is now a key priority The exploration of materials like chitosan highlights the continuous efforts to enhance the performance and safety of dialyzer membranes, ultimately aiming to improve the quality of care for individuals undergoing RRT [93].

5. Chitosan properties and its contributions for the biomedical field

Chitosan is a naturally occurring biopolymer composed of glucosamine and N-acetylglucosamine units [94] and is typically produced by the deacetylation of chitin, which involves the removal of the acetyl groups from the N-acetylglucosamine units in chitin [95].

Chitosan has been also widely used in medical fields (Table 5), such

Table 5
Biomedical applications of the chitosan.

Biomedical Application	Description
Wound Healing	Chitosan promotes hemostasis and accelerates tissue regeneration in wound sites [98]
Drug Delivery Systems	Utilized for targeted and controlled drug delivery, especially in cancer treatment [99]
Tissue Engineering	Serves as a scaffold in regenerative medicine, supporting cell growth and differentiation [100]
Antimicrobial Agents	Exhibits antibacterial and antifungal properties, useful in preventing infections [92]
Dental Applications	Used in dentistry for periodontal regeneration and as a component in dental implants [101]
Vaccine Adjuvants	Enhances the efficacy of vaccines by improving immune response [102]
Hemostatic Agents	Effective in blood clotting [103]
Ophthalmic Applications	Employed in ocular drug delivery systems for treating eye diseases [104]
Weight Loss Supplements	Used in weight management products due to its fat-binding properties [105]

as anticoagulant, antihypertensive agent, to reduce the risk of vascular disease and to have anticancer effects that inhibit the growth of cancer cells, to promote the growth of beneficial bacteria in the intestine and activate cells by adsorbing and excreting too much harmful cholesterol from the body [96] and it revealed to have an immune-boosting action [97].

Chitosan is also widely used in drug delivery systems due to its ability to enhance the absorption and bioavailability of drugs. Due to its mucoadhesive properties, chitosan can bind to mucosal tissues and improve the transport of drugs across biological barriers, such as the gastrointestinal tract or nasal mucosa. This property is beneficial for drugs with low oral bioavailability or poorly absorbed in the body. Chitosan systems, like micro/nanoparticles, membranes, and/or hydrogels can encapsulate drugs, protecting them from degradation and ensuring a controlled release over time. This not only enhances therapeutic efficacy but also reduces the frequency of dosing, improving patient compliance [106].

For example, chitosan-based nanoparticles have been studied for the delivery of anticancer drugs. These nanoparticles can be targeted to specific tissues, such as tumors, by modifying their surface properties with ligands that bind to cancer cell receptors. This targeting reduces the side effects associated with traditional chemotherapy by ensuring that the drug is delivered primarily to cancerous tissues while minimizing its exposure to healthy cells [106]. Moreover, chitosan's natural ability to bind to negatively charged molecules, such as DNA or RNA, makes it an excellent vector for gene therapy, where it can facilitate the delivery of genetic material to cells to treat diseases at the molecular level [107].

One of the most promising applications of chitosan in biomedicine is in tissue engineering and regenerative medicine. Chitosan's ability to support cell attachment and proliferation makes it an ideal scaffold material for tissue regeneration. Its structure can be tailored into various forms, such as hydrogels, films, and sponges, providing the necessary support for cells to grow and form new tissues. Chitosan scaffolds are often used in the regeneration of skin, cartilage, bone, and nerve tissues [100].

In skin regeneration, for instance, chitosan hydrogels are used as dressings for burns or chronic wounds. These hydrogels maintain a moist environment, which is crucial for wound healing, and their biocompatibility ensures they do not provoke an immune response when applied to the body [108]. Chitosan also has antimicrobial properties, which help reduce the risk of infection in wounds. In bone regeneration, chitosan-based scaffolds can be combined with bioactive molecules like growth factors or calcium phosphates to promote osteogenesis, or the formation of new bone [109]. These scaffolds provide structural support and create a microenvironment conducive to the growth of bone cells [110].

Moreover, chitosan is being explored for nerve tissue regeneration, a challenging area in regenerative medicine [111]. Studies have shown that chitosan conduits can support the growth of neurons and guide nerve regeneration in cases of peripheral nerve injuries. By providing a scaffold that mimics the natural extracellular matrix, chitosan encourages the regrowth of damaged nerves, potentially restoring function to injured areas [112].

Also, other *in vitro* studies with chitosan demonstrated its ability to linked with various crosslinkers to assess the impact of various crosslinking parameters on the material's hemocompatibility, biodegradability, serum stability, cytotoxicity, and cell survival, which shows its suitability as a matrix polymer for the development of versatile biomaterials [113].

Given the environmental limitations of current HD membranes—such as their synthetic, non-biodegradable nature and single-use design—there is a clear need to develop greener alternatives. Chitosan, due to its natural origin, biodegradability, and tunable functional properties, has emerged as a strong candidate in this search for sustainable membrane materials [114–117].

6. Chitosan membranes profile for hemodialysis

Chitosan membranes have been explored and tested in various studies, though most research is still in the experimental stage. These studies generally focus on the *in vitro* and *in vivo* performance of chitosan-based membranes for HD, particularly in their ability to filter waste products, their biocompatibility, and their ability to prevent biofouling.

Studies have shown that chitosan membranes can achieve selective permeability, meaning they can effectively filter out small molecules like urea while retaining larger, essential molecules like proteins.

Researchers demonstrated that chitosan's positive charge under physiological conditions allows it to interact with negatively charged toxins, enhancing its filtration efficiency. Thakur *et al.*, quoted that the hydrophilicity of chitosan provides a significant advantage by ensuring larger water fluxes (many times higher than with technical polymers) and the optimum efficiency for the separation process [92,118].

One of the standout features of chitosan membranes, as highlighted in various studies, is their antimicrobial activity. This property is especially relevant for HD, as membrane fouling by bacteria or other microorganisms is a common issue in conventional dialysis membranes. Biofouling can reduce membrane efficiency, increase the risk of infections, and need frequent membrane replacement [119]. Chitosan's antimicrobial properties, which are linked to its ability to disrupt microbial cell walls, have been validated in studies. In *in vitro* tests, chitosan membranes were shown to inhibit the growth of common bacteria, including *Escherichia coli* and *Staphylococcus aureus* [120], both of which are common sources of infection in dialysis patients. This antimicrobial effect helps reduce biofilm formation, extending membrane life and improving safety in HD applications.

Pogorielov *et al.* developed composite membranes using chitosan and polycaprolactone nanofibers incorporated with silver nanoparticles. These membranes displayed strong antimicrobial properties against both Gram-positive and Gram-negative bacteria, demonstrating their potential for HD applications. The incorporation of silver nanoparticles enhanced the antibacterial activity, while maintaining high biocompatibility, making these membranes promising for use in infection-resistant medical devices such as HD filters [114].

Ke *et al.* reviewed the antimicrobial activity of chitosan and its derivatives, focusing on their use in various biomedical applications. This study also highlighted the potential of chitosan-based membranes in HD, due to their ability to inhibit the growth of common pathogens like *E. coli* and *S. aureus*, making them ideal for reducing the risk of infection during dialysis procedure [121].

According to fouling experiments made by Akbari *et al*, results indicated that modified membranes by chitosan polymer have relatively better anti-fouling properties than unmodified membrane which in turn lead to increased hydrophilicity degree and decrease of roughness [122].

Also, Zhao et al proved that the addiction of chitosan layers improved the antifouling properties of their tested membranes [123]. Nazari and Abdelrasoul reviewed various surface modification techniques designed to enhance the antifouling properties of HD membranes. They found that by modifying the surface to increase hydrophilicity, these membranes can significantly reduce protein adsorption and the accumulation of blood components, which are the primary causes of membrane fouling [124].

Gul *et al.* discussed the critical role of membrane hydrophilicity in minimizing fouling. Their review highlighted that hydrophilic chitosan membranes are more resistant to protein and microbial attachment, which helps maintain efficient filtration over time. They also examined cleaning methods that complement the antifouling characteristics of these membranes [125].

Yan *et al.* modified PSu membranes with sulfonated chitosan, significantly enhancing hydrophilicity and reducing protein and platelet adsorption, thereby preventing fouling and improving dialysis efficiency

[126]. Radu and Voicu explored the functionalization of PSu hemodialysis membranes with chitosan-based materials. The study showed that this approach increased membrane performance by reducing protein fouling and improving biocompatibility [127].

Within this, it is known that one of the primary challenges for chitosan membranes in HD is ensuring their mechanical strength and long-term durability under the demanding conditions of dialysis. HD membranes are subjected to high pressures and constant blood flow for several hours during each treatment session. Chitosan, while inherently strong, may not possess the same mechanical properties as PSu or PES, which have been specifically engineered for such purposes [128]. To address this, ongoing research is exploring ways to reinforce chitosan membranes. Techniques such as cross-linking, which chemically bonds chitosan molecules together to enhance membrane rigidity, and the development of chitosan-polymer composites are being investigated [128]. These composites combine chitosan with other materials to improve the overall strength and structural integrity while maintaining chitosan's desirable biological properties. However, more testing is required to ensure these reinforced membranes can withstand the mechanical stresses of dialysis over time without degradation. A study by Reay *et al.* explored the degradation of chitosan–genipin hydrogels, examining their structural stability under physiological conditions. The study focused on how the cross-linking of chitosan enhances stability while allowing controlled biodegradation [129].

Chitosan is biodegradable, which is one of its key advantages. However, its rate of biodegradation poses a challenge in the context of dialysis. HD requires membranes that can function effectively over multiple sessions before needing replacement. If chitosan degrades too quickly, it might limit the membrane's lifespan, necessitating frequent replacements, which would increase costs and operational challenges [130]. To mitigate this issue, researchers are investigating ways to control the biodegradation rate of chitosan membranes. This might involve chemical modification or the incorporation of stabilizing agents that slow down the natural breakdown of chitosan, thereby extending the membrane's usable life. At the same time, it is important to maintain the biodegradable nature of chitosan to avoid long-term environmental impact after disposal [131]. For example, Gheorghita *et al.*, while focusing on hemostatic applications, reviewed the biodegradability of chitosan-based materials and their potential to maintain structural integrity under physiological conditions [132]. Furthermore, Reay *et al.*, examined the biodegradability and structural integrity of chitosan-genipin hydrogels, which maintained stability over time when exposed to lysozyme in physiological conditions [133]. A study conducted by Mawazi *et al.*, focused on PSu membranes functionalized with chitosan, showing improved stability and biodegradability. The controlled degradation of these membranes ensures long-term durability [133].

6.1. Chitosan membrane outlook

There is a growing body of *in vitro* research demonstrating the potential of chitosan-based modifications to improve membrane performance by reducing fouling and enhancing hemocompatibility. However, *in vivo* studies, particularly clinical trials, are limited. Future research is expected to focus on translating these promising *in vitro* findings into *in vivo* settings, assessing long-term safety, biocompatibility, and the antifouling efficacy of chitosan-modified HD membranes [51,126]. Clinical trials will help determine how these membranes perform under actual dialysis conditions, including how well they filter toxins, how long they can function effectively, and what impact they have on patient outcomes.

So far early-stage animal studies have been encouraging, showing that chitosan membranes can provide effective filtration while being well-tolerated in terms of biocompatibility and hemocompatibility. Chitosan membranes have demonstrated a wide range of advantageous properties, but several challenges need to be addressed for their successful integration into mainstream HD treatments.

Researchers have evaluated chitosan membranes *in vitro* for blood compatibility, including platelet adhesion, hemolysis, protein adsorption, and complement activation.

Unmodified chitosan surfaces tend to bind some platelets, but significantly less than bio-incompatible cellulose (*Cuprophan*) membranes. In one study, chitosan did not provoke the high platelet activation seen with *Cuprophan* [134]. Further, modifying chitosan with anticoagulant coatings (e.g. heparin or dextran sulfate) greatly reduced adherent platelets and their activation on the surface. For example, heparin/dextran-treated chitosan had only a few platelets per unit area (versus dozens on unmodified surfaces) [134]. Grafting hydrophilic polymers onto chitosan can virtually eliminate platelet adhesion – poly (HEMA)-grafted chitosan films showed negligible platelet attachment in blood-contact tests [135].

Chitosan is generally considered non-hemolytic or only mildly hemolytic. Pristine chitosan membranes typically cause low red blood cell lysis (e.g. ~6.5 % hemolysis in a 1-hour contact test) [135], which is near acceptable thresholds. With surface modifications, this improves further, for instance, HEMA-grafted chitosan caused no detectable hemolysis upon direct blood contact [136]. Similarly, crosslinking chitosan with anionic polymers has been shown to reduce hemolysis from ~6 % to ~4.6 %, falling into the "non-hemolytic" range. These findings suggest that chitosan membranes can be engineered to exhibit minimal hemolytic activity and high biocompatibility with erythrocytes [136].

The positively charged chitosan surface can adsorb blood proteins, but its high hydrophilicity helps limit irreversible fouling compared to hydrophobic plastics. Studies report lower protein adsorption on chitosan-based membranes after appropriate modifications. For instance, a glutaraldehyde-crosslinked chitosan/carboxymethylcellulose membrane showed significantly less bovine serum albumin adsorption than a pure chitosan control. Reducing protein adhesion is important to preserve membrane flux and avoid triggering coagulation; chitosan's nature (and blending with PEG or other hydrophilic polymers) gives it an advantage here. Indeed, blending chitosan with poly (ethylene oxide) (PEO) was found to decrease protein fouling and reduce platelet adhesion and activation on the membrane surface [136].

Contact of blood with artificial surfaces can trigger the complement system (inflammatory cascade). Notably, chitosan does not strongly activate complement pathways. Early experiments showed that chitosan membranes induced negligible complement activation (measured by iC3b levels), especially compared to Cuprophan which raises complement fragments significantly [134]. Even without heparin, chitosan's surface caused minimal complement conversion – a stark contrast to first-generation cellulose dialyzers known for inducing complement-mediated leukopenia [134]. This suggests chitosan is inherently friendly to immune components of blood. Overall, *in vitro* assays consistently show that chitosan membranes can achieve high hemocompatibility (low hemolysis, low complement and platelet activation), particularly when surface chemistry is optimized for blood contact.

Preclinical animal models have been used to test chitosan-based membranes for HD to assess inflammation, thrombogenicity (clotting tendency), and overall compatibility in a living system. While full-scale animal dialysis studies are not yet widespread, promising results have been reported. A recent study demonstrated an anticoagulant dialyzer using a chitosan-like strategy in pigs, achieving HD without systemic heparin. In a chronic swine dialysis model, a membrane functionalized with abundant carboxylate groups (comparable to carboxymethyl-chitosan coating) was able to run a dialysis session with no clotting throughout the treatment. Clot formation was significantly inhibited, indicating excellent thrombo-resistance. This is a critical *in vivo* validation that modified chitosan-based membranes can contact circulating blood for extended periods without triggering thrombosis [137].

In the same pig model, the chitosan-modified membrane did not provoke acute inflammation or obvious immune rejection.

Comprehensive blood analyses showed no abnormal elevation of complement or cell activation markers during dialysis [137]. The absence of neutropenia or cytokine spikes suggests the membrane was well-tolerated by the immune system. Histology or organ function tests were not detailed in that report, but the lack of any adverse reaction in a large-animal dialysis is an encouraging sign of biocompatibility *in vivo*. Similarly, other biopolymer membranes (bacterial cellulose with chitosan particles) have been implanted or tested *ex vivo* in animals without toxic or inflammatory effects, aligning with chitosan's reputation as a biocompatible material.

The pig model study also assessed dialysis efficacy. The experimental dialyzer achieved clearances on par with conventional membranes – for example, an *in vivo* urea clearance of ~185 mL/min and similarly high removal rates for creatinine, phosphate, and β2-microglobulin. These clearances are comparable to high-flux synthetic dialyzers used clinically, indicating that chitosan-based membranes can perform the core toxin filtration function effectively *in vivo*. Meanwhile, albumin and other essential proteins were retained, showing selectivity like standard dialysis filters. Animal studies (though still limited in number) suggest that chitosan membranes can function safely and effectively in a live bloodstream, with low thrombogenicity and manageable immune response when properly engineered. As of now, chitosan-based dialysis membranes have not yet reached human clinical trials in the published literature. The development of these membranes is still in the preclinical stage (laboratory and animal research). This absence of human data means safety and efficacy in patients remain unproven so far. Any *in vivo* biocompatibility benefits observed in animals would need to be confirmed in humans. Patient tolerance (e.g. no allergic reactions to chitosan), effective anticoagulation management, and long-term performance are key considerations before clinical use. It's worth noting that chitosan is already used in other medical applications (like wound dressings and hemostatic bandages) with good safety. The current dialysis market continues to rely on synthetic membranes like polysulfone, in part because they have decades of clinical data behind them [138]. Chitosan membrane technology will require clinical evaluation in the future, but at present it should be regarded as an experimental approach awaiting translation to human use.

6.2. Chitosan-based membranes: benefits and challenges

Chitosan-based membranes offer several advantages over conventional synthetic membranes in HD, they also present certain challenges and limitations that must be addressed before they can be widely implemented as a replacement for synthetic materials like PSu and PES. One of the main concerns with chitosan-based membranes is their mechanical stability and durability comparing with synthetic polymer membranes which are highly robust, resistant to deformation. This can lead to reduced membrane lifespan and potential structural failures during dialysis, requiring reinforcement with crosslinking agents or blending with other materials to enhance stability. However, one of the key advantages of chitosan is its biocompatibility and hemocompatibility, which reduces the risk of immune reactions and clot formation, a common issue with synthetic materials [51,83,87,71,139,140]. Another critical issue is limited solubility and processability. Unlike synthetic polymers, which can be precisely engineered for membrane fabrication using well-established industrial processes, chitosan requires specific pH conditions and solvent systems for proper membrane formation. The need for acidic dissolution (typically in acetic acid) and controlled gelation complicates large-scale production and standardization, making its processing more challenging than that of synthetic materials [141]. Nonetheless, chitosan exhibits antimicrobial properties, which are absent in conventional membranes. This unique feature reduces the risk of infections and biofilm formation, a significant concern in long-term dialysis treatments. Chitosan's intrinsic antimicrobial properties help reduce the risk of infections in HD patients by inhibiting bacterial adhesion and biofilm formation on the membrane surface. Unlike synthetic membranes, which often require antimicrobial coatings or chemical modifications, chitosan naturally disrupts microbial cell membranes, preventing bacterial proliferation. This property is particularly beneficial in reducing catheter-related bloodstream infections, a major complication in long-term dialysis treatments. By lowering bacterial colonization, chitosan-based membranes may also decrease the need for antibiotic interventions, contributing to better infection control in dialysis patients [142,143].

Moreover, while chitosan's hydrophilic nature may promote some degree of protein adsorption, potentially leading to biofouling, it also provides selective permeability, allowing improved clearance of uremic toxins while preserving essential proteins such as albumin. This is a major advantage over synthetic membranes, which often require additional surface modifications to achieve similar selectivity [81]. From an environmental standpoint, chitosan membranes provide a sustainable and biodegradable alternative to synthetic membranes, which are derived from petroleum-based, non-biodegradable polymers. The push for eco-friendly biomaterials in medical applications makes chitosan a strong candidate for the development of sustainable dialysis membranes. Lastly, regulatory and safety considerations must be addressed. Chitosan-based membranes would require extensive biocompatibility and safety evaluations before clinical approval. While synthetic membranes like PSu and PES have already been extensively studied and approved for HD, chitosan-based alternatives would need to undergo rigorous testing to ensure long-term safety, lack of unintended immune reactions, and compatibility with existing dialysis protocols. However, the potential for functionalization with bioactive molecules, such as anti-inflammatory or anticoagulant agents, offers an additional advantage, as it opens the possibility of developing "smart" HD membranes with therapeutic functionalities, something that synthetic membranes do not inherently provide [144,145].

Cellulose-based membranes in HD have prompted researchers to explore alternative materials like chitosan, which offers several advantages over cellulose in this application [146].

Cellulose-based membranes tend to have relatively poor biocompatibility, meaning they can trigger immune reactions when in contact with the blood. This is primarily due to the hydroxyl groups present on the cellulose surface, which can interact with proteins and other blood components, leading to the activation of immune cells and promoting inflammation. Over time, this can cause complications in patients undergoing regular dialysis [147]. In contrast, chitosan is a naturally derived polymer that has demonstrated much better biocompatibility [148]. Indeed, chitosan has a molecular structure that reduces the likelihood of provoking immune responses [149]. Its positive charge also enhances its interaction with negatively charged cell membranes, creating a more favourable environment for blood contact without causing inflammation or clot formation [150].

Chitosan-based HD membranes may reduce immune system activation. Unlike synthetic membranes, which trigger complement activation and inflammation, chitosan's positively charged surface interacts favorably with blood components, minimizing immune responses. Its hydrophilic nature prevents excessive protein adsorption, reducing biofouling and secondary immune activation. Additionally, chitosan decreases platelet adhesion and fibrinogen deposition, lowering clot formation and reducing reliance on anticoagulants like heparin. By mitigating inflammation, chitosan membranes may enhance patient tolerance to dialysis and reduce complications such as systemic inflammatory response syndrome (SIRS) and dialysis-related amyloidosis [151].

Cellulose membranes are known to activate blood platelets and the complement system, which increases the risk of blood clotting during dialysis. To prevent this, patients often need to take anticoagulants like heparin, which can introduce other risks, such as excessive bleeding. Chitosan, on the other hand, has natural anticoagulant properties. It has been shown to reduce platelet activation and prevent clot formation, thus reducing (not eliminating) the need for anticoagulant drugs. This feature makes chitosan a much safer and more effective option for use in HD, particularly for patients at higher risk of clotting disorders [152].

In terms of antimicrobial properties, cellulose membranes offer little to no protection against bacterial or viral contamination. This is a significant issue because dialysis treatments require the blood to be in contact with the membrane for prolonged periods, increasing the risk of infections, particularly from biofouling, where bacteria and other microorganisms accumulate on the membrane surface [152]. Chitosan, however, has natural antimicrobial activity. It inhibits the growth of a wide range of bacteria, fungi, and viruses, making it much more effective at preventing infections during dialysis. This antimicrobial activity not only improves patient safety but also prolongs the life of the dialysis membrane, as it reduces the risk of biofouling, which can degrade the performance of cellulose-based membranes over time [153].

When it comes to selective permeability, cellulose membranes have a relatively simple pore structure, which can limit their effectiveness in filtering out waste products while retaining essential blood components [154]. The molecular structure of chitosan, on the other hand, allows for greater control over membrane porosity. Chitosan membranes can be fine-tuned to selectively filter out small waste molecules, like urea and creatinine, while retaining larger molecules such as proteins and other essential blood components. This selective permeability makes chitosan a more effective material for dialysis, as it can be customised to meet the specific needs of patients, improving overall treatment outcomes [155].

Mechanical strength is another area where cellulose-based membranes fall short. Although cellulose is relatively strong, it can become brittle over time, especially after repeated use in high-pressure dialysis conditions. This can lead to membrane failure, requiring frequent replacements and increasing the cost and complexity of dialysis treatment [156]. Chitosan, while not as mechanically strong on its own, can be blended with other polymers or chemically modified to improve its durability. By creating composite membranes, researchers have been able to produce chitosan-based membranes that not only withstand the mechanical stresses of dialysis but also maintain their filtration properties over time [157].

Moreover, chitosan offers the potential for functionalisation in ways that cellulose cannot. Chitosan's molecular structure allows for chemical modifications, such as grafting or cross-linking, to introduce additional functionalities that can enhance the membrane's performance. For example, chitosan membranes can be engineered to adsorb specific toxins or release therapeutic agents, offering a dual-function approach that not only filters waste but also delivers targeted treatment during dialysis [158]. This adaptability makes chitosan a more versatile material compared to cellulose, which is more limited in its capacity for chemical modifications.

Finally, the biodegradability of chitosan offers a significant advantage over cellulose. While both materials are biodegradable, chitosan's breakdown products are more biocompatible and less likely to cause adverse reactions in the body. As a result, chitosan represents a promising alternative to cellulose in the ongoing development of more sustainable, effective and patient-friendly HD membranes.

6.3. *Chitosan-based membranes for clinical use: the scale-up*

Integrating chitosan into mainstream HD treatments will require a detailed cost-benefit analysis. While chitosan is derived from sustainable sources and has the potential to lower some of the operational costs (e.g., reduced need for antibiotics or anticoagulants due to its antimicrobial and anticoagulant properties), the overall production costs of high-quality chitosan membranes must be competitive with existing synthetic membranes. Additionally, environmental impact considerations, particularly in terms of waste management and the biodegradability of the membranes, will play an important role in determining the long-term viability of chitosan in the healthcare sector [159,160]. Another scalability challenge of chitosan membrane production is the process of converting raw chitin into chitosan and then fabricating membranes in a consistent and reproducible manner at a commercial scale [151,161,162]. Additionally, ensuring uniformity in membrane properties (such as pore size, thickness, and permeability) during large-scale production is essential for maintaining the high standards required in medical applications. Inconsistencies in the membrane fabrication process could affect filtration efficiency, biocompatibility, and durability.

Also, for chitosan membranes to be approved for clinical use, they must pass rigorous regulatory requirements that synthetic membranes have already met. Regulatory agencies such as the FDA (United States), EMA (Europe), and ANVISA (Brazil) require extensive biocompatibility testing, long-term stability studies, and clinical trials before new materials can be introduced into medical devices. Synthetic membranes have decades of data supporting their safety and efficacy, while chitosan-based membranes would require comprehensive preclinical and clinical validation to ensure they meet dialysis performance standards [162–165].

7. Conclusions

In this sense, while chitosan membranes hold immense potential for revolutionising HD by offering improved biocompatibility, hemocompatibility, and selective permeability, several technical and clinical challenges must be addressed before they can be fully integrated into standard dialysis treatments. Further research and clinical validation will be crucial in advancing the technology, ensuring its long-term stability, scalability, and effectiveness, and confirming its benefits for both patients and healthcare systems.

CRediT authorship contribution statement

Maria Martingo: Writing – original draft, Visualization, Investigation, Formal analysis. **Sara Baptista-Silva:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Manuela Pintado:** Writing – review & editing, Validation, Project administration. **Sandra Borges:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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