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The Revival of Sorbents in Chronic Dialysis Treatment

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ABSTRACT

Interest in the use of sorbents in chronic dialysis treatment has undergone a revival in the last decades, for which two major factors are responsible. The first is the potential of sorbents as adjunct therapy for the removal of substances that are difficult to remove by conventional dialysis therapies. The second is their use in regeneration of dialysate, which is of pivotal importance in the design of portable or even wearable treatments, next to the potential for reducing water use during conventional dialysis treatment. Sorbent-enhanced dialysis with synthetic polymers was associated with a reduction in inflammatory parameters as compared to hemodialysis and even associated with improved survival in smaller studies, although this needs to be confirmed in large randomized trials. Incorporation of sorbents within a dialysis membrane (mixed matrix membrane) appears a promising way forward to reduce the complexity and costs of a dual therapy but needs to be tested in vivo. For regeneration of dialysate, at present, a combination of urease, zirconium-based sorbents, and activated charcoal is used. Next to sodium release by the sorbent in exchange for ammonium and the CO_2 release by the hydrolysis of urea has been a bottleneck in the design of wearable devices, although short-term trials have been performed. Still, for widespread and flexible application of sorbent-assisted portable or wearable devices, a direct urea sorbent would be a major asset. In the near future, it will likely become apparent whether sorbent-assisted dialysis techniques are feasible for routine implementation in clinical practice.

1 | Introduction

The removal of uremic toxins during extracorporeal treatments in renal failure is based on separation of solutes from a liquid mixture. Conventionally, this is achieved by transport based on concentration (hemodialysis) of pressure gradients (hemofiltration, ultrafiltration) over a semipermeable membrane [1, 2]. Adsorption, that is, the binding of solutes on the surface of a solid agent, is used less far less frequently despite substantial interest from pioneers in the earlier days of dialysis. However, interest in sorbents has revived due to their potential as an adjunct to dialysis treatment for the additional removal of uremic toxins [3] and as a way to regenerate spent dialysis fluid in order to reduce water usage and to allow for portable or even wearable treatments.

Sorbents are also applied as an adjunct for removal of inflammatory mediators in intensive care medicine or for specific intoxications, which will however not the focus in the present paper. The aim of this review is to discuss some basic principles of sorbents used in chronic dialysis therapy to address recent (pre)-clinical developments in this area.

2 | Background of Sorbents Used in Dialysis Therapy

The physical principle behind sorbents used in extracorporeal treatments is adsorption. Adsorption is the binding of an ion, atom, or molecule dissolved in gas or liquid to the surface of a solid material. Adsorption is widely used in industrial processes. Adsorption is different from absorption, in which the bound substances enters the bulk of the sorbent material. Various physical or chemical principles can contribute to the binding of substances to an adsorbent. Important are van der Waals forces, based on fluctuating dipole moments that can also occur between nonpolar molecules. Hydrogen bonds are based on permanent dipoles between a partially charged hydrogen ion that can be linked to a partially negatively charged atom on a surrounding molecule with water

as a core example. Hydrophobic interactions, which refers to the exclusion of nonpolar substances from a watery solution, also is an important physical process in sorbent binding [4] (Figure 1). Examples of hydrophobic uremic toxins include protein bound toxins [5]. These processes, which do not alter the chemical structure of the bound substances, are referred to as physisorption.

Examples of organic sorbents that are based on physisorption and can bind nonpolar substances are activated carbon and non-ionic porous resins [6–8] (Table 1). Activated carbon is a very efficient sorbent material due to the very high surface to mass ratio (>500 m^2/gram) due to its microporous and fractal nature. Activated carbon can remove a wide spectrum of uremic toxins, including creatinine, uric acid, beta-2 microglobulin, and protein bound uremic toxins (PBUT) [9]. However, a disadvantage of activated carbon is its bioincompatibility [6]. This can be reduced by polymer coating, which on the other hand also diminishes its binding capacity [4]. Non-ionic porous resins used in extracorporeal treatments such as crosslinked divinylbenzene polymers, which can be coated with polyvinylpyrrolidone, are more biocompatible [6, 10]. These sorbents have been used for sorption of inflammatory mediators by hydrophobic interactions, for specific indications, such as paraquat poisoning [11] and for the additional removal of uremic toxins [12]. Manipulating the pore sizes of these sorbents allows for targeted use for different indications, such as sepsis, intoxications, or as adjunct for the removal of uremic sorbents [13, 14]. Pores are divided based on their inlet size, differentiating between micropores (<2 nm), mesopores (2–50 nm), and macropores (>50 nm). For removal of uremic toxins without albumin removal, mesopores appear the most relevant [14].

Ion exchange sorbents, which are a different class of sorbents, operate by ionic bonds or electrostatic interactions. These sorbents combine supporting material with a fixed (positive or negative) ionic charges combined with permeability to a solution that contain ions with an opposite charge. In case of cation exchangers, positive ions are attached to a negatively charged supporting material. The positive ions that are bound to the supporting material can be exchanged for other, similarly charged ions present in the solution. For supporting material, resins can be used. In past and present dialysis systems based on dialysate recirculation, non-organic crystalline materials, such as zirconium phosphate or iron oxide hydroxide (FeOOH) [15] (Figure 2), are used as ion exchangers, as will be discussed later.

Although different molecules have different affinity to sorbents, most sorbents used in dialysis therapy can be regarded as relatively non-specific binding agents, which has the disadvantage that also useful substances such as drugs are bound. Covalent bonds (chemisorption) allow for more specific binding of uremic solutes. Covalent bonds are strong and difficult to reverse. As will be discussed later, sorbents based on covalent bonds, such as carbonyl compounds, are tested for binding of urea, although also these are not fully specific for this purpose [16].

In general, sorbents are characterized by a high surface to volume ratio due to their porous design and sometimes fractal nature. The binding of substances to sorbents is a complex process in which next to surface binding also transport into the pores is a major factor. In this regard, 3 principles are distinguished. The first (external or interphase) is the transfer of the solute by convection, the second (internal or intraphase) is the mass transfer of the solute from the outer surface into the internal pores of the sorbent, and the last is the diffusion along the surfaces of the internal pores and the adsorption on the sorbent's surface [4] (Figure 3). In contrast to diffusion and convection, adsorption is limited by saturation of the sorbents. For modeling of toxins to sorbents, various techniques are available, of which the Langmuir isotherm model is the best known [1].

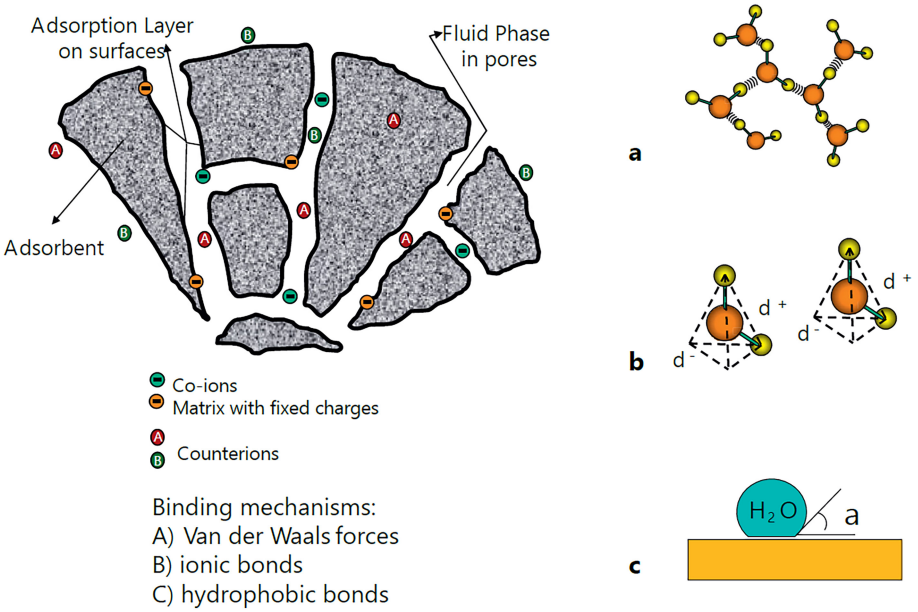

FIGURE 1 | Left: Physicochemical mechanisms regulating molecular surface adsorption. Right: Examples of mechanism involved in binding of solutes to sorbents. From [4], with permission from Karger Publishers.

TABLE 1 | Examples of sorbents and bound substances.

	Example	Sorption principle	Substances bound
Activated charcoal		Van der Waals	Creatinine
		Hydrophobic	Beta2 microglobulin
		Interactions	PBUT
Non-ionic organic polymer	Resins	Van der Waals	PBUT
		Hydrophobic	Cytokines
Organic ion exchanger	Resins	Ionic bonds	Ions
Crystalline ion exchanger	Zirconium	Ionic bonds	Ions
	FeOOH		
Specific binders	Ninhydrin	Covalent bonds	Urea

Abbreviation: PBUT = protein bound uremic toxins.

FIGURE 2 | Examples of two sorbents. Left: Ion exchange resin impregnated with FeOOH. Right: Spheric activated carbon. Courtesy from Dr. Frank Simonis. Nanodialysis®.

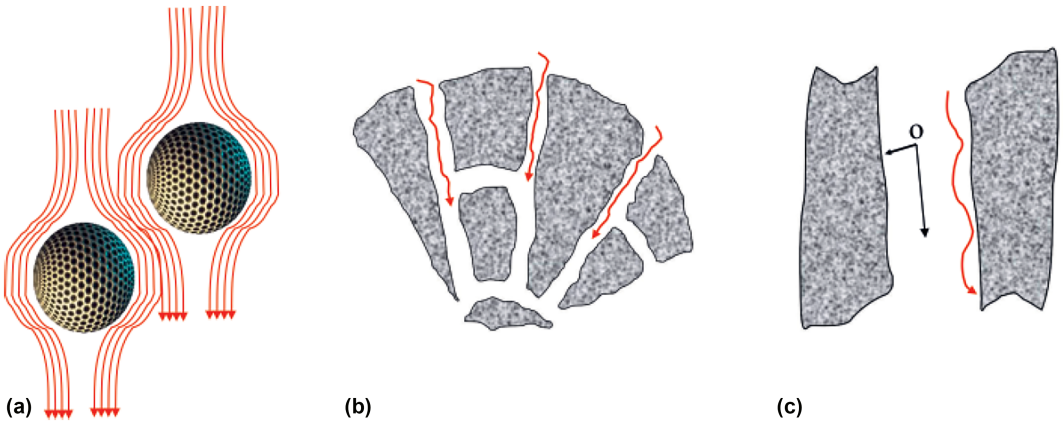

FIGURE 3 | Mechanisms of mass transport from the solution to the sorbent surface. (a) External (interphase) mass transfer of the solute by convection from the bulk solution to the sorbent and diffusion through the boundary layer to the surface of the sorbent. (b) Internal (intraphase) transfer of the solute to the inner surface of the porous structure. (c) Surface diffusion along the porous surface and adsorption of the solute onto the surface of the sorbent. From [4], with permission from Karger Publishers.

For a sorbent to be used in dialysis therapy, it has to fulfill various characteristics, such as relatively low resistance to flow, mechanical strength, and thermal and chemical stability, and (when placed within the bloodstream) biocompatibility and antifouling properties are of major importance. Sorbents are produced in different forms such as powder, flakes, or beads. For an efficient application of sorbents, adequate cartridge design is of major importance for an adequate flow through to the sorbent in order to maximize its binding capacity [1, 17]. For a deeper technical and theoretical background of sorbents used in dialysis treatment, the reader is referred to excellent recent reviews [1, 4, 16].

3 | Sorbents Combined With Hemodialysis

When sorbents are placed directly in the bloodstream, this is referred to as hemoperfusion [18]. Because hemoperfusion is not able to correct disturbances in acid–base, electrolyte, and volume status, it is not suitable as a sole treatment for end-stage renal failure. Another disadvantage of sorbents is that the clearance of toxins becomes limited after the passage of time due to the saturation of the column.

HP as standalone treatment is at present only used for a small number of intoxications, such as paraquat although other possible indications such as venlafaxine and amlodipine are emerging [19].

Hemoperfusion can also be combined with hemodialysis or hemodiafiltration for the additional removal of toxins that are difficult to remove by convection or diffusion. Previously, these sorbents focused on removal of middle molecules like beta 2 microglobulin (such as the Lixelle® column) [20] although with the advent of hemodiafiltration and medium cut off membranes, the need for a secondary extracorporeal removal technique for this purpose has diminished. However, one class of toxins that remain difficult to remove by either diffusion or convection are PBUT. Activated carbon effectively removes PBUT [21], but its use is complicated by its bioincompatibility and binding of thrombocytes and divalent ions [4]. Coating of the sorbent improves biocompatibility but also reduces the adsorptive capacity of the sorbent due to size exclusion [4]. Placing the sorbent column in a secondary circuit following a plasma filter (plasma filtration adsorption) [18] or otherwise in a separate circuit [21] should prevent these complication but requires a more complicated and expensive setup and is unlikely to be wisely used for chronic dialysis treatment.

Newer sorbents based on organic cross-linked non-ionic polymers, such as Jafron® and Cytosorb®, are more biocompatible and have been used as an adjunct treatment for the removal of inflammatory mediators in sepsis and major surgery, although the effects of sorbents on mortality in sepsis have not been demonstrated [22]. However, various studies also assessed organic synthetic polymer sorbents as an adjunct to chronic HD [10, 23]. These sorbents are also able to remove PBUT [24] without significant albumin binding, due to the fact that PBUT are mainly removed by hydrophobic interactions whereas albumin interacts through hydrophilic bonds [14].

As an example of clinical studies, Li et al. randomized 150 patients to HD with polysulfone membranes and HP combined with a Jafron® HA130 sorbent cartridge and observed a reduction in inflammatory parameters after a 6-month follow up period [23]. In another randomized study using the same cartridge that included 438 patients, Zhao al. observed a reduction in uremic pruritis when the same sorbent cartridge was added to both low-flux and high-high flux hemodialysis [25]. In a systematic review, a reduction in mortality was observed when HD and HP were compared with HD, although most included studies were not published in the English language [26]. On the other hand, Tiranathanagul et al. could not show superior removal of PBUT with superflux HD combined with hemoperfusion using organic polymers as compared to high volume hemodiafiltration [27].

Summarizing the current evidence, there appears to be a rationale for combining sorbents with conventional dialysis techniques, especially in cases where on-line hemodiafiltration or medium cut off membranes are not available. However, larger randomized trials are needed to establish the value of this combination.

4 | Mixed Matrix Membranes

Within a mixed matric membrane (MMM), microporous adsorptive participles are integrated within a macroporous membrane matrix [28] (Figure 4). The blood-contacting inner side of the membrane is particle free to enhance biocompatibility and to prevent release of particles into the blood stream. For the matrix, cellulose acetate and polytehersulphone/polyvinylpyrrolidone blends are used with activated carbon of the adsorbent. Various in vitro studies showed that MMMs loaded with activated carbon were able to combine diffusion and adsorption, with significant sorption of creatinine and PBUT [30, 31]. However, the removal of the latter may be limited because only the free fraction can pass the filter [32]. Until now, despite improvements in engineering, MMM have yet to be tested in (pre)clinical settings.

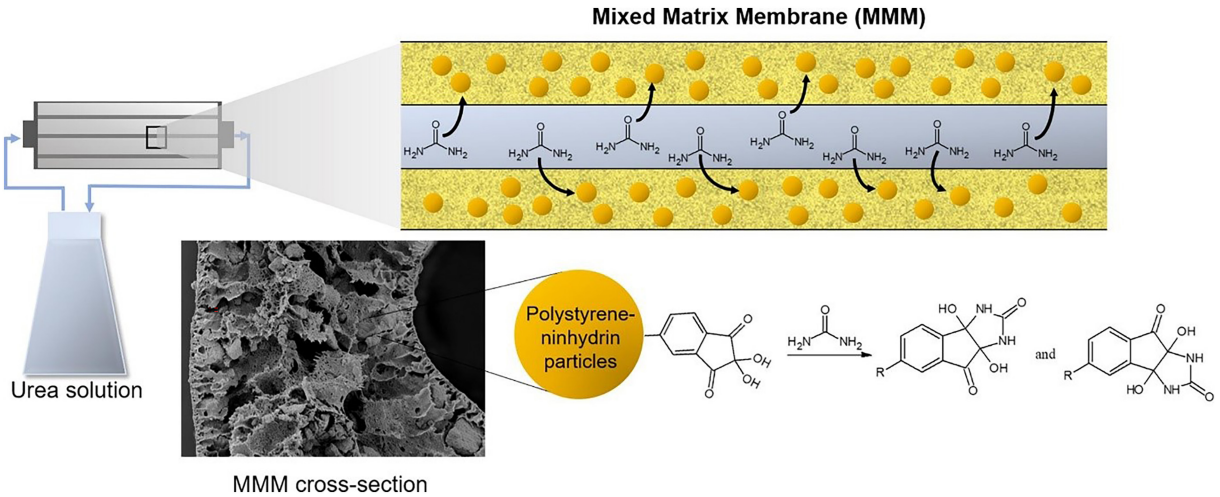

FIGURE 4 | Mixed matrix membranes with urea sorbent. From [29]. Under creative commons license.

Given the increased thickness of the fibers which may necessitate the incorporation of a lesser amount of fibers within a cartridge, further developments should show whether it is possible to construct MMM dialyzers that add to the overall clearance profile of modern conventional dialyzers in high efficiency modalities such as high volume hemodiafiltration.

5 | Recirculation of Dialysis Fluid

In conventional hemodialysis, dialysis fluid is produced by a single-pass system, which means that after passage of the dialysis filter, the fluid is discarded. This necessitates large amounts of dialysis fluids per treatment (up to 120 L). Both from environmental perspectives as well as from the growing interest for portable or even wearable dialysis devices, there is a need for technologies that enable the reduction in the amount water used for dialysis treatment, which can be achieved by purification of the dialysate after the exchange with blood in the artificial membrane [8, 33]. Advantages of single pass dialysis treatment are the ability to individualize the dialysate and the fact that the experience is far larger as compared to sorbent dialysis. For home-based treatments however, the need for an additional separate water treatment system is a disadvantage for which sorbent-based therapies can provide a solution. Moreover, sorbent-based dialysis systems are more easy to transport and would need only a relatively small amount of water and a power source [34], which would also be a major advantage for dialysis in remote places and in disaster medicine [35]. Although also from an environmental perspective, sorbent-based dialysis would appear attractive especially with respect to water consumption, and the environmental impact of producing and recycling of sorbent materials when produced in high volumes is still unknown [36].

There is already substantial clinical experience with the recirculation of spent dialysate with the regenerative dialysis (REDY) sorbent device, based on developments in the 1960s, which was in clinical use from the 1970s until 1991 [34]. This device needed only 6 L of dialysis fluid and provided a blood and dialysate flow rates of 250 mL/min. In principle, the purification of spent dialysate is achieved by different sorbents packed in a cartridge [37] (Figure 2). The first layer is a "scavenger" layer that removes heavy metals and solids. The second is the urease layer, which converts urea to ammonium and carbonate. The ammonium is adsorbed in the third layer containing zirconium phosphate, in exchange for sodium and hydrogen. In this layer, also potassium, calcium, and magnesium are adsorbed, requiring infusion through a separate line. In the last layer, phosphate is adsorbed by zirconium carbonate and/or zirconium oxide and in exchange for respectively bicarbonate or acetate. The first or last layer contained activated carbon, by which toxins like creatinine and uric acid are adsorbed [34, 38]. Treatment with the REDY system was discontinued before several reasons such as lesser efficacy as compared to conventional HD due to factors such as lower blood and dialysate flows and the possibility of ammonium breakthrough [38]. Next to this, economical reasons due to the costs of the sorbents and likely the overall upscaling dialysis process resulting in larger dialysis centers and more uniform treatment processes played a role. Later attempts to revive the method including improvements by the Allient® system that included more potent sorbent columns and possibility for higher blood and dialysate flow rates were not marketed [39]. Still, as will be discussed in the following paragraph, all wearable or portable systems that have until now made it to (pre)clinical trials are still based on this approach.

6 | Urea Removal

Urea removal represents the most challenging problem in the regeneration of dialysate. Urea is in quantitative terms the most important uremic toxins. Despite the fact that its toxicity has been debated, accumulation in high levels is undesirable given its association with, among others, protein carbamylation, insulin resistance, oxidative stress, and endothelial dysfunction at higher levels [16].

Urea is produced in relatively high quantities (240–470 mmol daily [14–28 g]) and is an uncharged and relative unreactive compound for which conventional sorbents have relatively low binding capacity (e.g., 0.4 mmol/g for activated carbon), which would necessitate very high quantities of sorbents to bind the daily load [16]. Moreover, as urea in a polar compound, it has to compete with other substances, such as water, for hydrogen bonds. Thus, in contrast to diffusion, which is highly effective process for urea removal, adsorption is limited by the low capacity of conventional sorbents. The present solution is, as mentioned previously, to convert urea to ammonium and carbon dioxide by urease, which is an efficient process for which only a relatively small amount of urease is necessary [38]. However, ammonium is far more toxic than urea and has to be adsorbed by another sorbent, such as zirconium phosphate, in exchange for other cations such as H+ and Na+. Whereas H+ is subsequently bound by zirconium oxide, the releases Na+ can result in an increased sodium load, which is, next to the potential for ammonium breakthrough, the largest disadvantage of the urease technology next to the CO_2 release, although modification of the sorbents can to some extent alleviate this problem [39]. Therefore, direct sorption of urea would be a major advantage for any portable or wearable system. At present, various different compounds are tested for urea sorption, including zeolites, MXenes (Titanium-based compounds), and molybdenum disulfide nanosheets, and carbonyl compounds, such as ninhydrin, are currently under development [16, 25, 40]. Interestingly, recently, a MMM containing polystyrene-based ninhydrin particles was produced, by which a urea sorption of 3.4 mmol/g was obtained, 2-fold higher as compared to ninhydrin particles in suspension, albeit both under optimized circumstances not achievable during dialysis treatment [29] (Figure 4).

Electro-oxidation, in which urea is catalyzed, has been attempted as an alternative and was shown to be a potentially effective method for urea removal. However, the side effects include oxidation of other products such as glucose [41]. At present, the associated bioincompatibility of this technique is yet a barrier for implementation. Whether a further development in electrodes used and the use of membranes which allow a more specific passage of urea would provide a solution [42] is the focus of further research. For more information on urea removal strategies, the reader is referred to an excellent recent review [16].

7 | Wearable and Portable Applications of Sorbent-Based Dialysate Regeneration Systems

Two examples of wearable and portable hemodialysis systems that have been tested in vivo are the Wearable Artificial

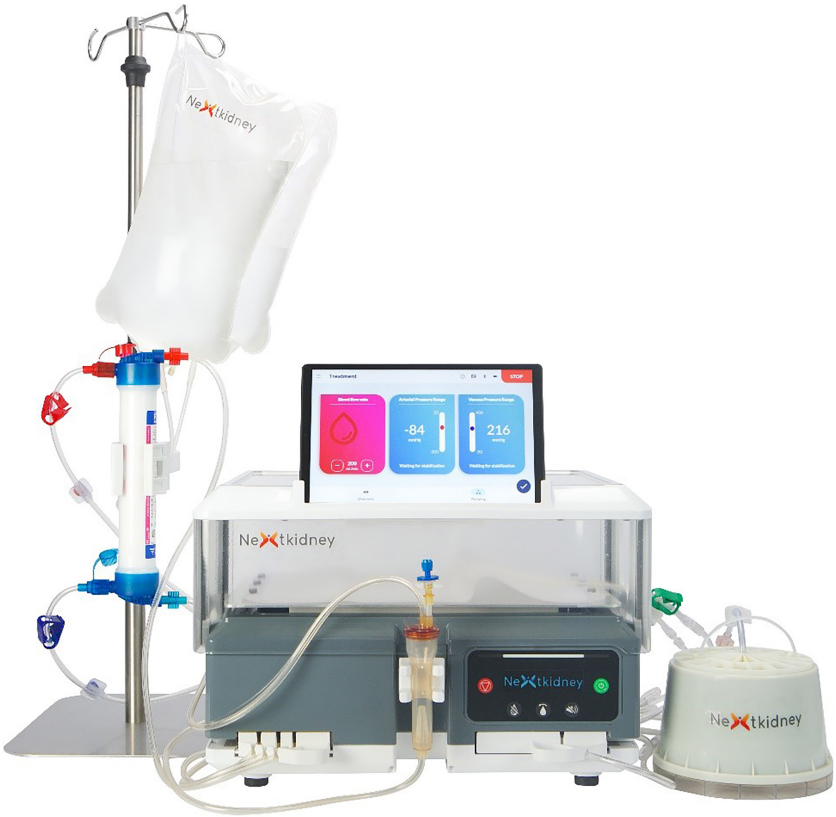

FIGURE 5 | Nextkidney portable sorbent-based hemodialysis device. With permission from Nextkidney®.

Kidney (WAK) developed by Gura et al. and more recently the Nextkidney® device. The WAK is based on the sorbents used in the REDY system and was developed as a wearable system weighing 5 pounds with liters of dialysate. The WAK was tested in 2 in human trials, one during 8 h and the follow up trial during 72 h. Although the treatment was well tolerated and provided sufficient clearance rates for the intended goal, a problem with CO_2 bubble formation remained [43, 44]. The Nextkidney® device is developed as a portable system using modified REDY sorbents and is designed presently for 6 times weekly 2-h treatments (Figure 5). The device has a weight of 11 kg and requires 4.5 L of dialysate. This system was recently tested in an animal trial and is awaiting a first in human trial.

Also peritoneal dialysis can benefit from the use of sorbents by allowing higher dialysate flow rates, which may enhance diffusion by maintaining a higher concentration gradient and increasing the peritoneal surface area for diffusion. In addition, it may provide more gentle ultrafiltration with lesser peritoneal glucose exposure by continuous glucose infusion [45]. The only sorbent-based peritoneal dialysis system presently tested in humans is the automated wearable artificial kidney (AWAK) system, also based on the REDY sorbent system with separate infusion of glucose, was tested in, and provided dialysate flow rates of up to 2 L/h. However, a drawback was abdominal pain during recirculation in a significant subset of patients as well as abdominal bloating, likely due to CO_2 release or incomplete mixing of concentrated hypertonic dialysate. Next to this, ultrafiltration was limited, which may necessitate changes in the glucose dosing protocol [46].

In the WEAKID device, activated carbon as well as FeOOH sorbents are used for sorption of phosphate and substances like creatinine and protein bound toxins during a 2.3-kg daytime system in which ultrafiltration is controlled by glucose infusion [47]. However, in the absence of sorbents that remove potassium and urea, this system is dependent on additional exchanges with 10-L conventional dialysis solutions during the nighttime. This system was tested in a uremic pig [48] and is likely to enter a first in human trial soon.

8 | Conclusion

Recently, interest in sorbents in dialysis therapy has re-emerged. Sorbents can be applied in combination with hemodialysis as an adjunct to enhance clearance of toxins that are difficult to remove, most notably protein bound uremic toxins. Preliminary data suggest that the combination of hemoperfusion and hemodialysis may improve surrogate outcomes and even survival, although this needs to be confirmed in larger randomized trials. For the future, combining diffusion and adsorption in a mixed matrix membrane appears an attractive option both for pragmatic as for economic reasons, which efficacy and safety needs however to be tested in vivo. With the increased interest in the development of portable and even wearable dialysis modules, sorbent-based recirculation of dialysate has undergone a revival. Still, the two-step urea removal process by urease with subsequent sorption of ammonium in exchange for sodium remains a drawback that can only be resolved by direct sorption of urea. Whereas this remains a major challenge, promising developments in this field are underway. New developments in sorbent materials and membrane technology may enable wider implementation of sorbent-assisted dialysis in the near future.

Conflicts of Interest

The author declares no conflicts of interest.

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