Review
Future Directions for Dialysis

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Abstract: Dialysis is life-saving for an exponentially growing number of kidney failure patients. Yet, the current concept also has several drawbacks, such as high societal cost, incomplete kidney function replacement, dismal outcomes, low quality of life and a considerable ecologic footprint. In spite of many changes over the last fifty years, the original concept remained largely unmodified and the drawbacks did not disappear. In this article, we present a number of alternative solutions that are currently considered or tested which might have a potential impact on uremic toxin concentration, quality of life or environmental footprint that goes beyond what is currently achieved with traditional dialysis. These comprise applications of regenerative medicine; bioartificial kidney; conceptual changes in extracorporeal removal; energy-neutral, water-limiting dialysis; material recycling; keto-analogues; xenobiotics; and preservation of residual kidney function. As metabolism generating uremic toxins also generates beneficial compounds, some of these options may also maintain or restore this balance in contrast to dialysis that likely removes without distinction. All proposed options are also exemplary of how out-of-the-box thinking is needed to disrupt the status quo in treatment of kidney diseases that has now persisted for too long.

Keywords: dialysis; hemodialysis; peritoneal dialysis; ecology; uremic toxins; wearable artificial kidney; regenerative medicine; xenobiotics; sorbents; quality of life

1. Introduction

After the development of the dialysis concept by Thomas Graham in the 19th century, a number of additional applications and modifications emanated in the first clinical hemodialysis to treat kidney failure in 1942 by Willem (Pim) Kolff [1], followed by a progressive increase in its use starting in the 1950s [2]. Peritoneal dialysis followed an almost parallel course [3].

Currently, dialysis prevalence is growing exponentially, due to improving patient outcomes and an increasing uptake in lower-income countries [2]. Nevertheless, dialysis is not available everywhere for all valid candidates [4].

2. Shortcomings of Current Dialysis

Despite being lifesaving for millions worldwide and of offering a bridge to transplantation, dialysis treatment has reached a crossroads, due to a number of drawbacks and bottlenecks (Table 1). First, dialysis cost covers at least 2% of overall healthcare expenditure for only 0.1–0.2% of the general population [5,6], resulting in CKD at large being one of the most costly non-communicable diseases [6]. Second, dialysis replaces only uremic solute clearance but not several other kidney functions (metabolic activities (e.g., solute conjugation), hormone production, blood pressure regulation, tubular reabsorption of essential substances (e.g., glucose and amino acids)), while clearance restoration is only partial and replaces glomerular, not tubular function. Third, outcomes are dismal, with lower survivals than for most cancers or kidney transplantation [6,7]. Fourth, the ecologic burden of dialysis is significant, and is ±20 times higher than that of kidney transplantation, due to water consumption and greenhouse gas and waste production [8,9]. Fifth,

dialysis heavily impacts quality of life [6,7] and cannot prevent distressing symptoms such as itching, cognitive dysfunction, pain or loss of appetite, concerns about physical appearance (fistula, peritoneal catheter), and restrictions in social deployment[6]. Most patients are treated by in-center hemodialysis [10], which necessitates transport and allows little flexibility in treatment time schedules and mobility. Peritoneal dialysis allows more flexibility, but the functional capacity of the peritoneal membrane may decline, hampering long-term application [11]. Finally, especially for hemodialysis, application is intermittent, with variable intervals separating removal sessions, emanating in unavoidable swings in electrolyte and volume status, which has a negative prognostic impact [12].

Table 1. Drawbacks of the current dialysis concept (hemodialysis and peritoneal dialysis).

Drawbacks	HD	PD
High cost per patient	+++	++
Replaces kidney function only in part	++	++
Replaces clearance function only in part	++	++
Replaces glomerular function not tubular function	++	++
Outcome worse than for cancer	++	++
Outcome worse than for kidney transplantation	+	+
Ecologic burden	+++ [1]	++
Decrease in quality of life	++ [1]	+
Decreased flexibility in time schedule and mobility	++ [1]	−
Decline of dialysis clearance capacity over time	−	+
Loss of residual kidney function	++	+
Irregular time schedule	+++ [1]	−/+ [2]

HD: hemodialysis; PD: peritoneal dialysis. The plus/minus signs indicate the perceived importance of the problem (− if no impact; +/++/+++ with increasing gradation of impact. [1]: Applies more to in-center hemodialysis, less to home hemodialysis; [2]: regular time schedule for Continuous Ambulatory Peritoneal Dialysis (CAPD), less regular for Automated Peritoneal Dialysis (APD).

Past Improvements of the Dialysis Concept

With time, several adaptations of the original concept were introduced to make dialysis safer, more reproducible, and more efficient. These included dialysis water purification, high-flux hemodialysis, hemodiafiltration, various alternative time schedules, and many other changes (Table 2). However, convincing evidence that such changes drastically improved outcomes remained limited [2,13,14] and many of the drawbacks mentioned above (Table 1) persisted.

In spite of these refinements, the general principles of dialysis have remained virtually unmodified since the development of the early prototypes [1,3], and have, apart from volume homeostasis, remained basically uremic toxin removal and restoration of electrolyte balance through a semipermeable membrane, based on the concentration gradients between blood and dialysis water. It is unlikely that there is still much room for spectacular improvements of dialysis adequacy if the current concept is maintained.

In this review, we will discuss a number of alternative solutions to modify the current concept of dialysis or uremic toxin removal (Table 3). These may also help to reduce/solve a number of shortcomings of current dialysis.

Table 2. Examples of adjustments in dialysis concept since the development of the basic technologies.

Improvement of access	Arteriovenous shunt Arteriovenous fistula Central vein dialysis catheters Prosthetic access devices Tenckhoff catheters
Dialysate buffering	Bicarbonate dialysate
Pump technology	Rotor pump
Dialyzer geometry	Flat sheet filters Capillary filters
Membrane technology	Biocompatible membranes High-flux membranes Super-flux membranes Medium-flux membranes Filter sterilization
Hemodiafiltration	On-line Pre-dilution Post-dilution Mixed dilution
Dialysis machines	Automated peritoneal dialysis Hemodialysis machines
Dialysis water preparation	Reverse osmosis Water purification Dialysate temperature regulation Regulation of dialysis water electrolyte content Biocompatible peritoneal dialysis fluid
Anticoagulation	Low molecular weight heparins Non-heparin anticoagulants (e.g., argatroban) Regional citrate anticoagulation
Monitoring	Volume monitoring Blood pressure monitoring Ultrafiltration control Sensor technology Feedback systems Access function and patency Peritoneal membrane tests
Assessment of dialysis adequacy	Kt/V_{urea} and variants
Alternative time schedules	Daily dialysis Extended hemodialysis Incremental dialysis Automated peritoneal dialysis
Miscellaneous	Dialyzer sterilization Alternative peritoneal dialysis osmotic agents

Table 3. Innovative concepts to decrease uremic toxin concentration.

- Regenerative medicine
  - ○ Stem cell-based bioengineered organs and organoids
  - ○ Stem cell administration for repair of damaged kidneys
  - ○ Bioartificial kidney
- Conceptual changes in removal process
  - ○ Intestinal sorbents
  - ○ Extracorporeal sorbent application
    - ■ Direct blood purification (hemoperfusion cartridges)
    - ■ Sorbents seeded on dialysis membranes
    - ■ Dialysate purification for recycling
    - ■ Plasma purification for reinfusion
  - ○ Modification of physical dialysis conditions
    - ■ Application of electromagnetic/electrostatic fields to plas-ma
    - ■ Increase ionic strength in plasma (hypertonic substitution in hemodiafiltration setting)
    - ■ Modification plasma pH
    - ■ Administration of displacers
    - ■ Metabolic sorbents to be removed by magnets before regen-eration
  - ○ Wearable artificial kidney
  - ○ Portable artificial kidney
  - ○ Green dialysis
    - ■ Limitation of water consumption
    - ■ Energy-neutral production and delivery
    - ■ Waste recycling (circular concept)
  - ○ Ketoanalogues + protein restriction
  - ○ Xenobiotics
    - ■ Probiotics
    - ■ Prebiotics
    - ■ Synbiotics
    - ■ Metabiotics
  - ○ Preservation of residual kidney function
    - ■ Primary prevention (lifestyle)
    - ■ Secondary prevention of comorbidities (hypertension, dia-betes, acidosis, dyslipidemia)
    - ■ Nephroprotective drugs
      - ● RAAS inhibitors
      - ● SGLT2 inhibitors
    - ■ Prevention of kidney fibrosis
    - ■ Specific approaches for rare kidney diseases

RAAS: renin–angiotensin–aldosterone system; SGLT2: sodium–glucose cotransporter.

3. Innovative Concepts for Uremic Toxin Removal

3.1. Regenerative Medicine

The optimal solution to replace kidneys by a de novo bioartificial structure is by growing a kidney out of stem cells of the recipient. This organ would contain the genetic code of the recipient and obviate rejection, one of the major drawbacks of current transplantation. Progress in this domain has generated bioengineered organs with characteristics of normal kidneys, but especially filtration function remains suboptimal and applications up to now remained limited to small animals [15]. It will probably take time before sufficiently functioning organs can be generated for human application. Using stem cells for repair of damaged kidneys may be a closer therapeutic possibility [16–19].

The concepts of regenerative medicine and hemodialysis are merged more directly in bioartificial dialyzers, in which living tubular cells are seeded on dialysis membranes [20–22]. This development should be helpful to remove uremic solutes more efficiently by causing

an extra solute shift from blood to dialysate via the transport systems in tubular cells (especially for protein-bound toxins, which are less efficiently removed by hemodialysis). However, it might be difficult to apply this concept on a large scale and to keep cells sufficiently functional over time.

All these options have the potential to replace kidney removal functions in a more natural way than current dialysis and they may also restore a broader array of kidney functions than standard dialysis.

3.2. Conceptual Changes in Removal Process

3.2.1. Personalized Dialysis Schedules

Currently, especially hemodialysis schedules adhere too much to the classical 3×4–5 h/w pattern. If this concept is abandoned for schedules where patient characteristics and preferences are taken into account, this is likely to result in a higher patient satisfaction and quality of life. For this to come to pass, home hemodialysis allows more flexibility to implement such alternative schedules.

3.2.2. Adsorption

Oral sorbents that are aimed to remove specific solutes such as potassium and phosphate are in use since many decades [23]. Additionally, less specific sorbents that remove a broad range of solutes are administered to CKD patients, particularly in Asia [24]. There is no debate that most of these formulations offer add-on toxin removal to dialysis, but evidence of their hard outcome impact is largely missing [23,25–27].

Sorbents are also used to directly remove solutes from blood or dialysate. They may be in direct contact with blood, via beads in cartridges [28], seeded on dialysis membranes [29,30], or applied for dialysate regeneration and reduction of dialysate volume. Early batch dialysis (Redy^R) [31] was based on dialysate regeneration, but was abandoned because of sodium retention and aluminum toxicity. Current sorbent characteristics have been modified to minimize problems and are used in prototypes of compact mobile dialysis devices with low water consumption (see below) [2,32]. Removal capacity is especially appropriate for protein-bound solutes and larger peptides (so-called middle molecules) but is of no use for urea removal, for which alternative options are sought [33]. Sorbent adsorption has also been combined with fractionated plasma separation [34]. Added value could further be created by the regeneration of sorbents after their contact with solutes, allowing repeated use [35].

3.2.3. Modification of the Physical Dialysis Conditions

Several interventions to modify the physical conditions in uremic plasma have been considered, essentially with the intent to release solutes from their protein-binding sites, thus facilitating their diffusion. Various options in different developmental phases illustrate how innovative approaches may help modify the current dialysis concept. Examples are the application of electromagnetic and electrostatic fields [36]; the generation of increased ionic strength by infusing hypertonic fluid at the dialyzer inlet in a hemodiafiltration setting, to remove the excessive osmoles into the dialysate by diffusion [37]; modification of plasma pH [38]; the administration of displacers [39]; or the instillation of metal sorbent beads followed by the application of magnetic fields for their removal [40].

3.2.4. Wearable/Portable Artificial Kidney

Research institutions around the globe are developing wearable or portable artificial kidneys [2,41] and could use the technical innovations depicted above to optimize removal. Ideally, the wearable artificial kidney would allow the patient to walk around independently while blood purification is a continuous process [42]. A potential drawback is the need to maintain continuous blood flow through the dialyzer. Alternative access systems to the current options, e.g., bioartificial vascular access systems developed form the patient's own stem cells, and the use of materials that do not trigger coagulation are possible solutions.

Portable artificial kidneys use compact dialysis systems allowing more flexibility in time schedules while also reducing the dialysis water need. They can be easily packed in a suitcase allowing to travel and to dialyze at work, in remote places and at home [43]. They could also function as a transition step to wearable dialysis.

From peritoneal dialysis, we know that protracted dialysis results in similar outcomes as intermittent dialysis despite lower overall clearances per time unit [44–46]. It is, thus, likely that also for wearable/portable artificial kidneys, a more continuous solute removal profile will be beneficial, even if less adequate per time unit than intermittent therapies. As Kt/V_{urea}, the current tool to assess dialysis adequacy, is suboptimal to compare continuous and intermittent strategies, this might encourage to reconceive the current definition of adequacy, as urea is a small water-soluble compound which is not representative for the kinetic behavior of most other uremic retention solutes [47,48].

4. Green Dialysis

The ecologic burden of the current dialysis concept is huge. Even without considering manufacturing, hemodialysis, including reverse osmosis reject, consumes several hundred liters of water per treatment session that usually ends down the drain [49–51]. Energy consumption and greenhouse gas production are considerable [52,53], while most materials used, including ancillary aids such as sterile gloves, are not recycled; thus, plastic waste is another major problem [54].

Despite favorable steps over the last years, especially for manufacturing, more drastic changes are needed to make the current dialysis concept energy neutral and recyclable, principally at the provider level. Steps might include reduction of water consumption by dialysate regeneration and using reverse osmosis reject for a second purpose (e.g., toilet flush), making material production and the dialysis process itself energy neutral, and recycling plastic waste [8,49]. It is desirable that manufacturers, providers, and consumers alike enforce these changes.

5. Ketoanalogues

A low-protein diet reduces uremic toxin production, but this may happen at the expense of increasing malnutrition risk. Ketoanalogues, combined with a low-protein diet, provide the building stones for protein synthesis and, thus, obviate malnutrition, while reducing the intestinal delivery of amino acids which are at the origin of urea, ammonia, and several other uremic toxins. Currently, ketoanalogues have mainly been used to delay the start of dialysis and decrease mortality in non-dialyzed CKD [55–57]. They have also the potential to become an adjuvant to decrease uremic toxin concentration in dialysis, although this hypothesis has, to the best of my knowledge, not yet been tested. A potential problem for maintenance treatment may be patient adherence [58], due to the number of doses to be taken, but this should not be an obstacle to their use.

6. Xenobiotics

The intestinal microbiome is a major source of mainly protein-bound solutes [59], but also of water-soluble compounds such as trimethyl-amine-N-oxide (TMAO) [60]. Their generation from precursors entering the intestine via food ingestion is due to specific microbial strains [61]. Production may be influenced by ingestion of xenobiotics (probiotics, prebiotics, symbiotics, or metabiotics), to change either the composition or the function of the intestinal microbiome [62,63]. Even if the early concept of intestinal overproduction of uremic toxins in CKD has been debated [64], it is still worthwhile to decrease microbiome toxin generation, as corroborated by several studies [62,63,65]. There is another, as of yet insufficiently explored benefit to this approach. The intestinal microbiome not only originates many toxins, but also beneficial solutes. For instance, intestinal metabolism of tryptophan generates not only the toxins indoxyl sulfate and the kynurenines but also beneficial compounds, such as indole propionic acid [66] and indole carboxaldehyde [67]. It can be hypothesized that it is more likely that xenobiotics at least maintain or even restore

the balance between toxins and beneficial compounds, whereas dialysis probably removes without distinction. However, again, this hypothesis needs to be confirmed, as well as the impact of probiotic administration on hard outcomes or quality of life.

Preservation of Residual Kidney Function

Even in patients with kidney failure, toxin removal by the own kidneys may still be substantial. In dialyzed patients a significant inverse correlation between GFR and uremic toxin concentration has been noted [68]. Thus, refraining kidney deterioration will offer added value to dialysis strategies for removing uremic toxins, even if prevention of progression of CKD has up to now mainly been used to postpone the start of dialysis, not to increase removal after the start of dialysis.

Primary lifestyle prevention (fighting sedentarism, unhealthy diet, obesity, and smoking) is inexpensive but necessitates careful organization and education of the entire population [5]. Health illiteracy should be tackled, as it is an essential cause of inadequate self-care and mortality [69,70]. Unfortunately, education is often only reaching the educated and studies that specifically address health illiteracy in kidney disease are scarce.

Apart from secondary prevention by drugs for hypertension, hyperglycemia, acidosis, and dyslipidemia, secondary prevention of progression of kidney dysfunction by the administration of specific nephroprotective drugs remained up to recently limited to blockers of the renin–angiotensin–aldosterone system [23]; however, with an ambiguous impact on kidney function in more advanced kidney disease [71]. The development of novel blood sugar-lowering drugs recently offered an alternative for large-scale secondary prevention [72,73]. Whether such drugs would also protect kidney function in dialysis patients has to the best of my knowledge not yet been assessed.

The number of optional drugs tackling the progression of kidney disease has remained strikingly low, which is in sharp contrast with the many novel therapies developed lately for other chronic diseases. There is an urgent need for more approaches to refrain kidney fibrosis and its driving factors, as well as for therapies to handle the patho-physiologic mechanisms of specific, especially rare, kidney diseases.

7. Conclusions

The basic principles of dialysis have remained unmodified for at least five decades. The nephrology community, especially the patients with kidney failure, are in urgent need for innovation of the dialysis concept, improving survival, hard outcomes, and quality of life and decreasing cost and environmental burden. Likewise, this need includes adjuvant therapies that additionally decrease uremic toxin concentrations. Some of these options might additionally be associated with improved production of compounds with positive impact (xenobiotics, preservation of kidney function). All stakeholders, including patients, professionals, researchers, providers, insurers, dialysis manufacturers, pharmaceutical companies, and policy makers, have the responsibility to promote the investment in innovation to improve the outcome of patients, in analogy with many other chronic diseases such as cancer and diabetes.

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