Review Article

The future of the artificial kidney

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ABSTRACT

End-stage renal disease (ESRD) is increasing worldwide. In India, diabetes mellitus and hypertension are the leading causes of chronic kidney disease and ESRD. Hemodialysis is the most prevalent renal replacement therapy (RRT) in India. The ideal RRT must mimic the complex structure of the human kidney while maintaining the patient's quality of life. The quest for finding the ideal RRT, the "artificial kidney"– that can be replicated in the clinical setting and scaled-up across barriers– continues to this date. This review aims to outline the developments, the current status of the artificial kidney and explore its future potential.

INTRODUCTION

Chronic kidney disease (CKD) affects about 10% of the world population, including about 1 in 4 men and 1 in 5 women aged 65–74.[1] End-stage renal disease (ESRD) is increasing worldwide, and its incidence and prevalence differ in various parts of the world.[2] In the USA, the age-gender-race adjusted incidence of ESRD is 384.6 per million/year in 2018.[3] The age-gender-race adjusted prevalence was 2242.1 per million/year in 2018.[3] Sixty-three percent of these are on hemodialysis (HD), 7% on peritoneal dialysis (PD), and about 30% on functioning transplanted kidneys.[3] In India, the prevalence of CKD is about 17%.[4] The leading causes of CKD worldwide are diabetes mellitus and hypertension. With the present rate of increase, by 2030, India is expected to have the highest number of diabetes cases worldwide.[4] In India, due to the lack of dedicated centers, lack of universal access to renal replacement therapy (RRT), and the absence of registry data, the actual burden of ESRD is unknown.[4] Ninety-per-cent of ESRD requiring RRT die because of a lack of affordability or access to care. Among those who start RRT, nearly 60% discontinue treatment for the same reasons.[4] Like the west, in India, HD is the most prevalent form of RRT, followed by transplantation (though more live-related), and PD is a distant third.[4]

The ideal RRT in ESRD strives to mimic a healthy kidney. None of the available RRTs match the complex and intricate structure of a million nephrons and their functions in their entirety.

This review aims to outline the developments, current status and future potential of the artificial kidney. This manuscript is based on the Dr. Sitharaman Best Essay award of the Urological Society of India for 2021.

METHODS

PubMed, Google Scholar, and Scopus databases were searched for English language literature for the search terms "Artificial kidney," "Enhanced dialysis," "Wearable Artificial Kidney (WAK)," "Portable Artificial Kidney (PAK)," "Bio-Artificial Kidney (BAK)," "Implantable Artificial Kidney (IAK)," "Kidney components," "Regenerative medicine in kidney disease" and "Kidney Organoids" till June 2020. The relevant articles were selected for this review. After screening the abstracts and reading selected

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full-text articles that addressed the keywords mentioned above, articles were selected for further elaboration in the following areas: history of the artificial kidney, limitations of existing RRT and future of artificial kidney (under the subheadings of enhanced dialysis, wearable and PAK, bio-hybrid artificial kidney, regenerative medicine in the artificial kidney, and artificial intelligence [AI] and machine learning [ML] in the artificial kidney).

History

The term "Artificial kidney" was first used by Abel, Rowntree, and Turner in 1912 during their animal experiments on dialysis. As the name suggests, it denoted a system that replicates the functions of a healthy kidney.[5] However, it was not until 1943 that a successful artificial kidney, the "Rotating drum" dialyzer, was produced by Willem Johan Kolff– the "Father of artificial organs."[6] Figure 1[5-12] shows some of the key developments in dialysis, transplantation, and the newer artificial kidney modalities. In India, the first HD was in 1962, the first successful renal transplantation in 1971, and PD in 1991.[4]

LIMITATIONS OF EXISTING RRT

Hemodialysis

The existing dialyzers are heavy (more than 60 kg), require large quantities of water (>120 liters), and power supply. These restrict patient's mobility, interfere with their routine life, decrease the quality of life (QoL), and act as barriers to home dialysis.[11] HD is a significant burden on healthcare systems worldwide. Further, HD removes only a fraction of the uremic toxins. There are large fluctuations in the internal environment (fluid depletion and overload) due to the intermittent nature of the dialysis – the thrice-weekly four-hourly HD (the most common schedule) being no match for the round-the-clock functioning healthy kidney. Even though HD is the most prevalent form of RRT worldwide, only about 50% on HD survive the first 3 years after the initiation of dialysis.[3]

Peritoneal dialysis

PD offers a more continuous form of dialysis, but the clearance of uremic toxins is lower than HD. The bagged fluid (8–12 L/day) again restricts mobility. The median life span on PD is 3.7 years only, which is due to the damage of the peritoneal membrane due to high glucose concentrations of the dialysate required for osmotic clearance of toxins and peritonitis.[12]

Transplantation

The best form of RRT is limited by a significant demand-supply mismatch, with a daily death of 12 patients awaiting transplantation.[3] Moreover, transplanted kidneys also have an average lifespan of 10–20 years, after which the patient needs to restart dialysis when awaiting transplantation.

FUTURE OF ARTIFICIAL KIDNEY

There are exciting new developments in the field of the artificial kidney, often parallel and inter-related. Barring some of the enhanced dialysis applications, most of these are still in the trial stages and presently unavailable for clinical use. The paradigm in the management of ESRD has changed from "disease-centered" to "patient-centered" with patient choices, and QoL playing an essential role in decision making.[13] Figure 2 shows the traditional and potential future management pathways in ESRD. The developments and the likely order in which these will translate to clinical use are in these four areas – enhanced dialysis, portable and WAK, bio-hybrid and IAK, and regenerative medicine and kidney components.

ENHANCED DIALYSIS

Conventional HD clears low molecular weight uremic toxins-(LMW) (<500 kDa) such as urea and creatinine. It does not clear middle molecular weight-(MMW) (500-15000 kDa) and high molecular weight-(HMW) (>15000 kDa) toxins such as beta-2 microglobulin, phosphate, and protein-bound uremic toxins (PBUTs) such as indoxyl sulfate and p-cresol-sulfate.[14] These cause malnutrition, inflammation, atherosclerosis, amyloidosis, and cardiovascular morbidity.[14]

In contrast to conventional dialysis, enhanced dialysis aims to improve the clearance of toxins and reduce volume

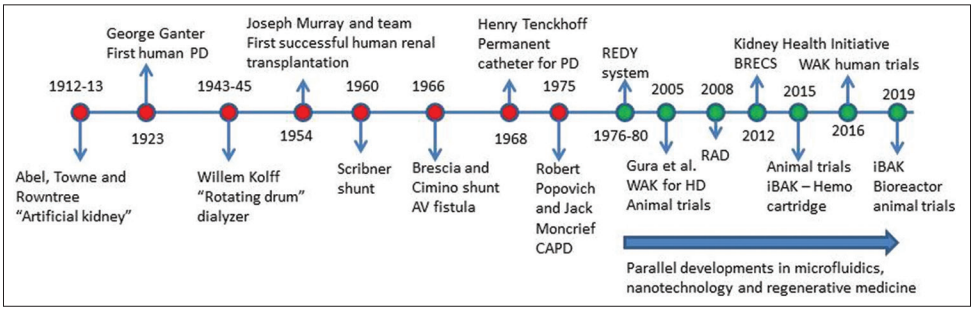

Figure 1: Timeline showing key developments in hemodialysis, peritoneal dialysis and transplantation (red dots) and in newer artificial kidney modalities (green dots). PD = Peritoneal dialysis, AV = Arteriovenous, CAPD = Continuous ambulatory peritoneal dialysis, REDY - REcirculating DialYsis sorbent system, HD = Hemodilaysis, WAK = Wearable artificial kidney, iBAK = Implantable bio-artificial kidney

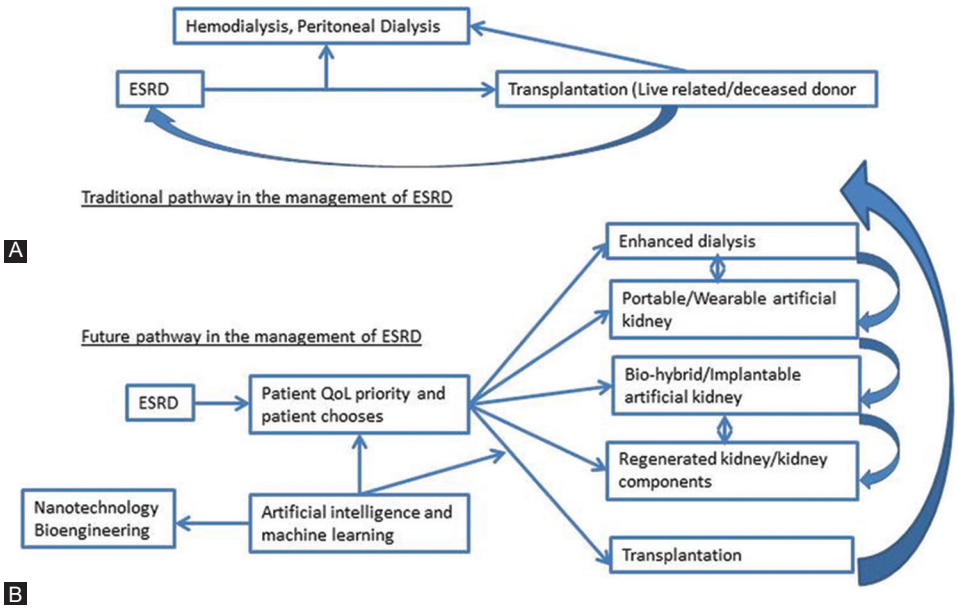

Figure 2: ESRD: End-stage renal disease; QoL: Quality of life; Panel A – Traditional pathway in the management of ESRD where the patient is on hemodialysis or peritoneal dialysis awaiting transplantation. Panel B – Future pathway in the management of ESRD. Patient QoL and choices drive management. Options include parallel and inter-related future "artificial kidneys". The likely sequence of availability and use would be enhanced dialysis, portable/wearable kidney, and bio-hybrid/implantable kidney and regenerated kidney. However, developments overlap; for example, wearable/portable kidneys enhance dialysis by increasing the opportunity for home dialysis and increasing frequency and autonomy. Similarly, regenerative medicine may provide specialized cells for bio-hybrid/implantable kidneys and membranes for enhanced dialysis. Artificial intelligence/machine learning helps patients make an individualized decision; gives inputs to bioengineering technology, and can even provide specific data points regarding the performance of each of the "artificial kidneys"

and blood pressure shifts. Some of the forms of enhanced dialysis are – hemodialysis by convection, alternate dialysis schedules, and improvements in peritoneal dialysis – as follows.

Convection clears MMW and HMW toxins by using a solvent drag instead of passive diffusion of conventional dialysis. As discussed below, the various aspects of convection are hemofiltration and hemodiafiltration, substitution fluids, and membrane modifications (expanded dialysis).

Hemofiltration and hemodiafiltration

Hemofiltration uses only high trans-membrane pressure and convection and clears MMW and HMW toxins at the cost of LMW toxins. On the other hand, hemodiafiltration uses both diffusion and convection, clearing LMW toxins also.

Substitution fluids

The large amounts of water removed by ultrafiltration to achieve solute transport have to be replaced by appropriate fluids. Bicarbonate-based fluids have replaced Ringer-lactate-based fluids with better hemodynamic stability. In addition, the use of "ultra-pure" dialysates overcomes the risk of exposure to pyrogenic toxins.[15]

Membrane modifications (expanded dialysis)

Membranes with larger pore diameter and narrow distribution to mimic the glomerulus have been developed. These have a "High retention onset" whereby MMW and HMW toxins are removed, but albumin is retained.[16] The other modification is the use of mixed-matrix membranes for the clearance of PBUTs, consisting of polyethersulfone, polyvinylpyrrolidone, and activated carbon, enabling both diffusion and adsorption to occur across a single membrane.[17] Other strategies to remove PBUTs include the use of binders and displacers.[18]

The benefit of convective therapy and challenges

Convective dialysis has shown superiority over conventional dialysis in terms of hemodynamic stability, cardiovascular morbidity, and QoL. However, the survival advantage is equivocal, warranting further studies before this can become the standard of care.[19] Membrane challenges such as compatibility, blood clotting, and safety of exposure to pyrogenic toxins need further studies.

Alternate dialysis schedules

Two large randomized trials-HEMO[20] and the ADEMEX[21] showed no added benefit in survival by increasing the dose of HD and PD, respectively. However, alternate schedules such as long intermittent, short daily, and nocturnal dialysis have shown lesser inter-dialytic fluid shifts with better efficiency and hemodynamic stability.[22,23] The key to their success is to increase patient and family involvement to facilitate home-dialysis sessions and address safety concerning vascular access and adequate central monitoring.

Peritoneal dialysis improvements

Biocompatible fluids with multi-compartments to decrease the glucose degradation products showed a decrease in the

deleterious effect of high glucose concentration on the peritoneal membrane.[24]

PORTABLE AND WEARABLE ARTIFICIAL KIDNEY

Miniaturization of dialysis achieves portability, which leads to patient freedom, autonomy, greater normalcy in life, and a better QoL. In addition, there is a potential for more frequent and continuous dialysis, with lesser fluid fluctuations, better toxin clearance, and improved overall clinical outcomes.[12] The concept of smaller dialysis devices existed from the 1970s; advances in microfluidics and nanotechnology have now allowed the realization of this concept.

The key to smaller units is the dialysate regeneration system. Regeneration is made possible because of the modified REcirculating DialYsis sorbent system (REDY system), which has cation and anion exchanges (for potassium and phosphate clearance), activated carbon (for removal of organic wastes) and, a urea-removal system using urease and adsorbents. Thus, the used dialysate is purified and returned for dialysis, obviating the need for a water source.[25]

The various portable and wearable devices in development are discussed below. Only WAK™ for HD has had proof of concept and feasibility-human-trials. None of these are presently available for commercial use.

Portable artificial kidney

First and second-generation PAKs weigh 10-25 Kg and 1.5-10 kg, respectively. Those in development include NeoKidney (a multi-center collaboration), EasyDial (Dharma™), Medtronic PAK, and Fresenius PAK.[12] All are portable, and some are in the form of a suitcase and can be used for home-based dialysis. They all work on the modified REDY sorbent technology.

Wearable artificial kidney™ for hemodialysis

The WAK™ is a <5 kg device designed to be worn as a belt/vest. It is driven by batteries and only 400 ml of sterile water. The components [Figure 3] include– pumping systems, dialysis membrane, dialysate regeneration system, battery, and patient monitoring system (for air bubbles and blood leak).[12] One of the crucial aspects of the success of WAK is the availability of safe vascular access. Arteriovenous fistula and grafts are not ideal for WAK, considering the frequent use by the patient himself/herself, as there is a risk of dislodgement of the needle resulting in complications. Chronic venous catheters and subcutaneous port devices (with a relatively lower flow rate – around 100 ml/min) are likely to be the solution.[26]

Gura *et al.* started animal experiments in 2005. Following this, the first human trial was conducted in 2016.[27] The study aimed to recruit ten patients for 24-h dialysis using WAK. However, only seven enrolled due to technical problems (carbon-di-oxide bubbles in the dialysate circuit) and variable blood and dialysate flow rates. However, there were no adverse hemodynamic changes, target ultrafiltration rates were achieved, and the patient satisfaction rates were reasonable, establishing proof of concept.[27] Further modifications and studies are needed.

Wearable artificial kidney for peritoneal dialysis

It has the potential for better clearance of toxins compared to conventional PD (given a more continuous dialysate flow) and lesser peritoneal membrane damage (given lesser exposure to glucose and possibly lesser peritonitis due to decreased bag exchanges). The following devices are under development for wearable PD.

A carry life system for PD (CLS PD) is a wearable continuous flow PD (CFPD) system with replaceable sorbent cartridges. Recruitment for human trials is ongoing.[28]

Automated WAK for PD (AWAK PD) is a wearable tidal flow PD system working on the modified REDY sorbent technology. The regenerated dialysate is supplemented with glucose and electrolytes before being returned to the peritoneum. An animal study showed adequate

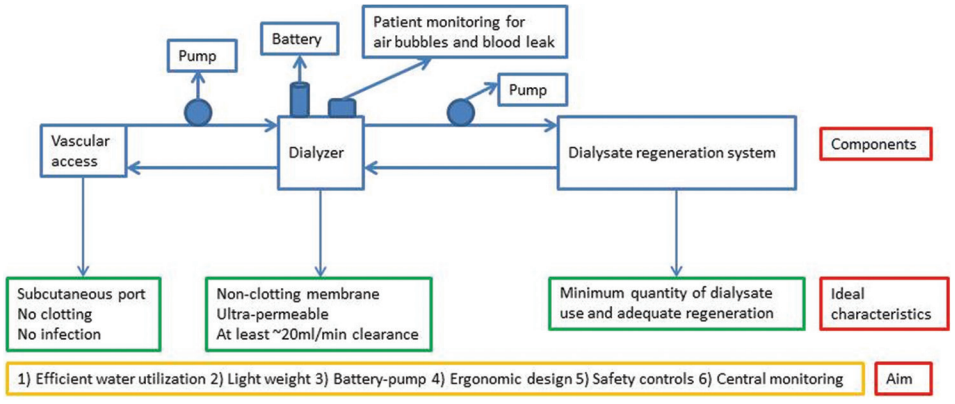

Figure 3: The components, ideal characteristics and aim of wearable artificial kidney for hemodialysis[26]

ultrafiltration and toxin clearance (except phosphate clearance). The cartridge component needs replacement every 7 h.[29]

Wearable artificial kidney (WEAKID project) is a multi-center collaboration under the European Union's Horizon 2020 project. Initially designed for an 8-h night-time tidal flow dialysis with an optional cartridge for day-time dialysis.[30]

Vicenza WAK for PD is a CFPD system. An *in vitro* study conducted in 2007 demonstrated a lack of a urea clearance system, no provision for glucose and bicarbonate administration, and fibrin deposition in the sorbent cartridge.[31] There have been no further studies so far.

Wearable artificial kidney using electro-deionization

US Kidney Research Corporation reported a novel waterless, dialysate-free, and cell-free system using electro-deionization.[32] Ultrafiltration, nano-filtration, and reverse osmosis are combined with electro-deionization to replicate glomerular and tubular functions.[33] Animal studies were successful, but human trials are awaited.

BIO-HYBRID AND IMPLANTABLE ARTIFICIAL KIDNEY

WAK and PAK devices do not perform renal tubular functions. The following systems aim to improve on this limitation.

Renal assist device

It is an additional extracorporeal device in series with the hemofiltration unit, lined by human proximal tubular epithelial cells (PTECs). This attempts to re-create metabolic, secretory, absorptive, and endocrine functions of the renal tubules. The blood from the patient first passes through the hemofiltration unit (like a glomerulus), and the ultra-filtrate then passes through the renal assist device (RAD) (like renal tubules). A phase II human trial by David Humes' team on 58 acute kidney injury patients showed RAD to have better survival and renal recovery compared to conventional HD.[34] The RAD remains the only BAK-like device successfully tested in humans. The production, storage, and transport of PTECs limited further progress.

Bio-artificial renal epithelial cell system (BRECS)

PTECs derived from adult progenitor cells are cultured on a scaffold of niobium-coated carbon discs. These can be cryopreserved, stored for a long time, and used at the required site like an "off-the-shelf" product.[35] In an attempt to eliminate limitations of the blood-circuit in HD, a WEarable Bio-Artificial-Kidney for PD using bio-artificial renal epithelial cell system underwent animal testing with favorable metabolic, endocrine and immunological parameters and retained cell viability.[36] Human trials are awaited.

Implantable bio-artificial kidney

The ultimate achievement in the field of artificial kidneys would be to have an unlimited supply of a device that can be implanted inside the body and performs the normal renal function. The Kidney Project, a collaboration with the University of California San Francisco (Dr. Shuvo Roy's team) and Vanderbilt University (Dr. William Fissell's team), aims to achieve the same.[37] Their implantable BAK (iBAK) is a confluence of silicon nanotechnology and tissue engineering and makes use micro-electromechanical system to decrease the size of the RAD. It consists of two parts– the hemo-cartridge (made up of silicon nanopore membranes and replicating glomerular function) and bio-cartridge/Bio-reactor (using PTECs and replicating tubular function) [illustration in Figure 4]. It is electrical-pump-free. It runs on the patient's blood pressure; dialysate-free as the bioreactor performs the tubular function and maintains electrolyte balance; clot-free (by a combination of bio-compatible polymers and flow patterns), and immunosuppression-free due to biocompatible materials used.[38] After successful *in vitro* and animal studies of the hemo-cartridge, recently, the bio-reactor was successfully tested in animals.[39] The long-term effects like "culture-stress" (the viability of the bio-reactor) and maintenance of biocompatibility need to be studied further.

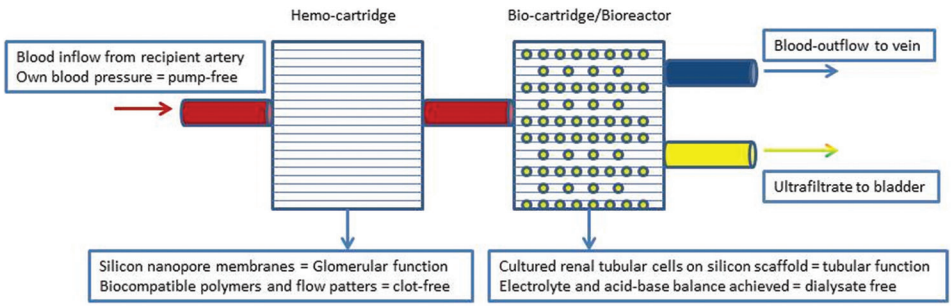

Figure 4: Illustration of components and functions of implantable bio-artificial kidney

The comparison between the key features of WAKs and iBAK has been summarized in Table 1 (adapted with permission from Salani *et al*.[39])

REGENERATIVE MEDICINE FOR ARTIFICIAL KIDNEY

The potential of Regenerative medicine's role in artificial kidneys ranges from repair and restoration of damaged tissue to the development of organoids and the entire kidney itself. The human kidney consists of many specialized cells, and the nephron has an inherently limited regenerative capacity.[40]

Repair and promoting endogenous regeneration

Bone-marrow-derived mesenchymal stromal cells (MSCs) have been shown to act on renal progenitor stem cells by paracrine action to aid in the repair of renal tubular cells damaged due to injury.[40] The paracrine effect of MSCs occurs by interaction with tubular epithelial cells and secretion of growth factors such as hepatocyte growth factor (HGF), Insulin-like growth factor 1 (IGF 1), and vascular endothelial growth factor (VEGF).[40] The MSCs decrease inflammatory cytokines such as Interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF) while increasing anti-inflammatory cytokines such as IL-10. Extracellular vesicles (EVs) are nano and microparticles classified by size, generation mechanism, and secretion mode. EVs include exosomes and microvesicles.[40] The primary role of EVs is to promote intercellular communication by protein, RNA, and micro-RNA transport, thereby promoting the paracrine effect of MSCs. Preclinical and clinical trials have shown promising results in the use of MSCs in various kidney diseases such as acute kidney injury (AKI) due to ischemia/reperfusion (I/R), Cisplatin chemotherapy related AKI, polycystic kidney disease, diabetic nephropathy, and post-transplant kidney injury.[41] The mechanism of action of the MSCs in these disease conditions is multifactorial and includes decrease in inflammation, apoptosis, tubular proliferation, interstitial fibrosis and glomerulosclerosis while increasing vascular density.[41] By these mechanisms, MSCs effect immunomodulation, promote differentiation and renoprotective effects at the site of renal injury.

In addition to bone-marrow-derived MSCs, human adiposed-derived stromal cells (hASCs) have shown encouraging results in AKI due to I/R.[42] hASCs are multipotent mesenchymal progenitor cells that functionally and phenotypically resemble pericytes. Compared to bone-marrow-derived MSCs they are easier to isolate and highly expandable; hence they are potentially more feasible for clinical translation.[42] hASCs, by their pro-angiogenic and anti-inflammatory properties, aid in vascular preservation, decreasing capillary rarefaction and reducing the effects of renal hypoxia and subsequent interstitial fibrosis. In an animal model, hASCs successfully preserved post-I/R AKI structural integrity and also mitigated chronic changes by preventing interstitial fibrosis.[42]

More studies are needed regarding the stem cell type, administration route, dose, tracking of cells, and their efficiency for MSCs to be used in clinical practice.[41]

Regeneration of kidney

3-D bio-printing or de-cellularized kidney matrix (from fresh cadavers/genetically engineered animal sources) forms the scaffold on which desired specialized cells may be re-populated. The source of cells may be genetically edited host somatic cells-induced pluripotent stem cells or embryonic stem cells. CRISPR/Cas-9 (clustered regularly interspaced palindromic repeats) achieves the editing.[43] Xenotransplantation using tissue-engineered animal kidneys is another area of research. Owing to their availability, size, and decreased infection spread, the bovine kidneys are presently undergoing studies. They may mainly play a role in pre-sensitized multiple failed transplants, those with

Table 1: Comparison between wearable artificial kidneys and implantable bio-artificial kidney (adapted with permission from Salani *et al*. Am J Kidney Dis. 2018[39])

Key feature	WAK	AWAK	iBAK
Type of artificial kidney	Hemodialysis	Peritoneal dialysis	For implantation
Central principle	Modified sorbent system	Modified sorbent system	Bio-hybrid: Hemocartridge (=glomerulus) and bioreactor (=tubular function)
Weight	<5 kg	<2 kg	~500 g
Power	Battery operated	Battery operated	No battery. Uses blood pressure of the cardiovascular system
Fluid requirements	~6 L dialysate/treatment	~2 L dialysate/ treatment	No dialysate, patient drinks electrolyte-rich fluids to keep up with losses
Creatinine clearance presently achieved (ml/min)	20–30	20–30	~30
Immunosuppression	Needed	Needed	Not needed
Stage of development	FDA clinical trials	Trials in humans	Animal trials
Strengths	Portable, low ultrafiltration and electrolyte balance seen in clinical use	Portable, bloodless, high toxin clearances	Low burden to the patient, minimal waste generation
Limitations	Bleeding and clotting issues	Frequent change of cartridges ~7 h	Long term biocompatibility and viability not known. May require repeated invasive procedures

WAK=Wearable artificial kidney, AWAK=Automated wearable, iBAK=Implantable bio-artificial kidney, FDA=US food and drug administration

rapid recurrence of ESRD after transplant, and as a bridge for those awaiting transplantation.[40]

Kidney Organoids which differentiate and self-assemble in response to environmental stimuli represent the structure and function of a biological kidney. Organoids are likely to be available earlier than the whole organ itself. These may be used to study disease models, drug screening, and various forms of RRT.[44]

Challenges facing regeneration of kidneys include cell-source and generation, distribution, fear of tumorigenesis and immunogenicity, ethical issues for stem cells and animal use, up-scalability, and timely manufacture of specific regenerated tissue compatible with those awaiting them.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN ARTIFICIAL KIDNEY

AI and ML are approved for use in medical areas like an emergency brain computed tomography scan for stroke and trauma and cardiac imaging.[45] Its use in the artificial kidney is emerging. AI and ML make use of large amounts of input data, internet of things (IoTs), and use artificial neural networks (ANN) and "Deep" learning. Reinforce-able learning, and computational thinking, are used for problem-solving, planning, and decision-making. The data is obtained by point-of-care global network databases such as the EuCliD^{R}.[45] AI can be used for multi-end point models and algorithms to predict outcomes and future patterns. In HD and PD, this can be used for real-time monitoring and feedback of blood pressure, fluid shifts, dialysis dose, anemia status, and prescribe "Personalized/precision" medicine.[45.46] The integration of AI and ML with WAKs and PAKs makes "Smart" dialysis possible for self-care dialysis systems. In renal transplantation, AI helps in providing data for organ-sharing and organ retrieval, predict graft survival, and monitor immunosuppression and diet.[45]

The challenges that face AI and ML include the privacy of data, safety of "Deep learning," the size of machines required to process enormous data, network connectivity, robust validation of algorithms and ANN, and cost-effectiveness. Further studies and regulations will solve some of these challenges.

KIDNEY HEALTH INITIATIVE

The kidney health initiative (KHI) is a public-private partnership between the American Society for Nephrology (ASN) and US-FDA started in September 2012. It aims at delivering safe and effective treatment for kidney diseases. In 2016, a roadmap was made by KHI for RRT innovations with short-, mid-, and long-term goals. It is an internationally-oriented, multidisciplinary approach to involve clinicians, patients, researchers, regulators, technology engineers, and investors, to channelize research and industry toward finding solutions to technical and market challenges in a focused priority-driven manner.[13,47] US-FDA has granted devices such as WAK™ for HD and iBAK expedited access pathways under KHI.

India should envision an active part in this collaboration with the Government, regulatory bodies, research organizations, and public-private partnerships to make new artificial kidneys a reality.

CONCLUSIONS

The future landscape of the artificial kidney is exciting and fast-changing. Hopefully, in the coming decade, novel inter-related therapies such as enhanced dialysis, PAKs and WAKs, bio-hybrid and iBAK, and regenerated kidney will be available for clinical use to improve "patient-centered" management and outcomes in CKD and ESRD.

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