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INTRODUCTION

Kidney is one of the most important organ in human body playing many crucial roles in homeostasis, reabsorption, hormone production, filtration and removal of wastes from blood. Kidneys produce important hormones like erythropoietin, calcitriol and enzyme like renin. The most important function of the kidney is the filtration of blood from the body, which remove harmful waste materials along with excess amount of nutrients by means of urine through the urinary bladder. The excretory material termed as urine generally contains ammonia and urea. Kidneys also help in the reabsorption by which it again reabsorbs important amino acids, glucose and water. Reabsorption is performed by means of the nephron tubules which are originally present inside the kidney. During this process essential ion, molecules and nutrients which are required by the human body are again reabsorbed as the blood filtrate passing through the nephron tubule. The proper function of kidney is a basic requirement of human body but the partial or complete dysfunction of kidney result in several.

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I. INTRODUCTION

Kidney is one of the most important organ in human body playing many crucial roles in homeostasis, reabsorption, hormone production, filtration and removal of wastes from blood. Kidneys produce important hormones like erythropoietin, calcitriol and enzyme like renin. The most important function of the kidney is the filtration of blood from the body, which remove harmful waste materials along with excess amount of nutrients by means of urine through the urinary bladder. The excretory material termed as urine generally contains ammonia and urea. Kidneys also help in the reabsorption by which it again reabsorbs important amino acids, glucose and water. Reabsorption is performed by means of the nephron tubules which are originally present inside the kidney. During this process essential ion, molecules and nutrients which are required by the human body are again reabsorbed as the blood filtrate passing through the nephron tubule. The proper function of kidney is a basic requirement of human body but the partial or complete dysfunction of kidney result in several kinds of medical illness. The deposition of waste material due to non-filtration of blood is a major issue and dysbalance of homeostasis result into failure of the kidney. When the function kidney is in a declined state, dialysis treatment becomes necessary for the removal of waste materials from the body. Thus dialysis proves as a great life saver but it is expensive. In a time period of one year nearly about $50,000 is spent by the affected patient for the dialysis. There are two kinds of dialysis process one is hemodialysis and another one is peritoneal dialysis process(1).

Hemodialysis is a renal replacement therapy based on the use of an artificial kidney (dialyzer) that removes waste products, chemical substances, and fluids from blood(2). Risks of hemodialysis includes poor blood flow, infection and clotting, cramping of muscle, a sudden drop in blood pressure & fatigue(1).

Stationary hemodialysis machines hinder mobility and limit activities of daily life during dialysis treatments. New hemodialysis technologies are needed to improve patient autonomy and enhance quality of life(2).

Peritoneal dialysis uses the patient's peritoneum (the membrane lining the inner wall of the abdominal cavity) to remove wastes. Dialysate (a pre-packaged solution of purified water, glucose, and minerals) is placed in the abdominal cavity through a catheter. The dialysate remains inside the abdomen for a few hours, allowing wastes to diffuse from the blood vessels in the peritoneum into the dialysate solution. The dialysate is then drained from the abdominal cavity. Peritoneal dialysis is usually performed at home, making it more convenient for patients. As it does not require access to the blood vessels or anticoagulant therapy, it offers some advantages

London Journal of Medical and Health Research

over hemodialysis. However, it has an increased risk of peritonitis (infection of the peritoneum), less control over ultrafiltration (fluid removal), and lower waste clearance rates than hemodialysis (3).

Dialysis, in any form, has a negative impact on quality of life. Individuals undergoing dialysis must avoid certain foods and limit their consumption of fluids. Supplements and medications are needed to replace nutrients lost during treatment, and post-treatment fatigue is common(4).

II. WEARABLE ARTIFICIAL KIDNEY (WAK)

Renal transplantation is the treatment of choice for chronic kidney disease (CKD) patients, but the shortage of kidneys and the disabling medical conditions these patients suffer from make dialysis essential for most of them. Since dialysis drastically affects the patients' lifestyle, there are great expectations for the development of wearable artificial kidneys, although their use is currently impeded by major concerns about safety. On the other hand, dialysis patients with hemodynamic instability do not usually tolerate intermittent dialysis therapy because of their inability to adapt to a changing scenario of unforeseen events. Thus, the development of novel wearable dialysis devices and the improvement of clinical tolerance will need contributions from new branches of engineering such as artificial intelligence (AI) and machine learning (ML) for the real-time analysis of equipment alarms, dialysis parameters, and patientrelated data with a real-time feedback response(3).

Researchers have attempted to develop a wearable artificial kidney since the early days of dialysis but were limited by the technologies available at the time. Since then, developments in various fields of research have made lightweight, wearable dialysis systems feasible. These advances include the miniaturization of sensors and pumps; small, long-lasting batteries; ultrapermeable membranes that reduce dialyzer size; and new filtration materials to cleanse and reuse dialysate solutions without the need for large quantities of purified water.

The main components of a wearable artificial kidney are:

- dialysis membrane
- dialysate regeneration
- vascular access
- patient monitoring
- power source
- pumping system.

The WAK is worn on a belt around the waist and weighs approximately 5 kg.12 The device includes a miniature, battery powered pump to power the flow of both the blood and dialysate, and additional micro pumps to control ultrafiltration (fluid removal), the infusion of anticoagulants, and the delivery of other substances to the dialysate. Safety mechanisms include a bubble detector and wetness sensors at the arterial and venous access sites to detect blood leaks. Unlike hemodialysis systems intended for home use, which can require large volumes of purified water, the WAK requires only 400 mL of sterile water.

A small, non-randomized pilot study was conducted inorder to determine the clinical efficacy of WAK in seven patients who wore the device in a US hospital. Participants' electrolyte levels remained stable throughout the 24 hours. Solute clearances and fluid removal were gradual and adequate, but clearance of beta2-microglobulin (a middle molecule used as a surrogate for the clearance of other similar-sized wastes) was lower than with conventional hemodialysis, possibly because of the lower blood flow used. Phosphorous binding medications were not used, although in some patients blood serum levels of phosphorous increased over the 24 hours.12 Average systolic blood pressure declined from 140 ± 23 mm Hg at baseline to 127 ± 6 mm Hg after the WAK treatment. Patients reported more satisfaction with the WAK treatment than with conventional hemodialysis, particularly in terms of convenience, freedom, fit with their lifestyle, reduced treatment related side effects, and less discomfort during treatment.

The second WAK study, a small UK pilot study, included eight patients who used the prototype device for four to eight hours. Their usual hemodialysis vascular access and anticoagulant doses were used, and they were allowed to eat and drink without restriction. Participants' heart rate, blood pressure, and electrolyte and acid balances all remained stable. No clinically significant damage to red blood cells (hemolysis) was noted. Clearance of urea, phosphates and middle molecules was lower than that with conventional three-times-a-week hemodialysis, but was adequate given the longer and more frequent dialysis treatment anticipated with the WAK. No serious adverse events were reported. Some patients reported mild hand or leg cramping, which resolved either when the ultrafiltration rate was decreased or without treatment. In five patients, temporary episodes of irregular heartbeat were noted. Vascular access for a wearable dialysis unit is also complicated by movement, which may dislodge the needle or the tubing, thus causing blood leakage, or kinking of the tubing thus causing blockage(4). No signs of clinically significant hemolysis were apparent(3). This proved that wearable artificial kidney can be developed as a viable novel alternative dialysis technology(2).

To meet the requirements imposed on new genera tion equipment for RRT, a wearable artificial kidney device should be:

- safe in use and biocompatible (the device should be equipped with sensors of temperature, volume, pH, and ion composition, as well as a system for prevention of bacterial contamination);
- Easy to use (the device should be light and ergonomic);
- Reliable (long service life);
- Affordable (less expensive than conventional RRT procedures);
- Powered by battery providing continuous operation for at least 8 h;
- Portable or implantable (the device should not considerably reduce patient's mobility);
- Providing elimination of the substances removed from human body by healthy kidneys (i.e., the device should provide the normal level and rate of removal of uremic toxins)(5).

Widespread implementation of the WAK as the standard for renal replacement therapy would result in vast savings in labor and costs of operating a dialysis unit. This savings would be incremental on the savings in drug use and hospitalizations brought about already with daily dialysis. The estimated cost of the WAK and disposables is expected to be less than that of current machines(6).

"A wearable artificial kidney is intended to improve patient quality of life but evidence of this is still lacking." (4)

"A quantum leap in technology making the WAK a reality rather than a dream"(7)

III. AUTOMATED WEARABLE ARTIFICIAL KIDNEY (AWAK)

Sorbent technology has enabled dialysate regeneration leading to the development of wearable PD devices.AWAK PD therapies were performed in human without severe adverse events and solute clearance was found to be comparable to conventional PD(8).

IV. SURGICALLY IMPLANTABLE ARTIFICIAL KIDNEY :

A promising alternative to kidney transplantation or dialysis for people with end stage kidney disease is the Development of a surgically implantable, artificial kidney. More than 430,000 of those with kidney failure now undergo dialysis, which is more costly and less effective than transplantation and typically requires hours-long stays at a clinic, three times weekly. Only about one in three patients who begins dialysis survives longer than five years, in comparison to more than four in five transplant recipients. Inorder to create a permanent solution to the scarcity problem in organ transplantation, Along with Roy at UCSF and Fissell at Vanderbilt, a national team of scientists and engineers at universities and small businesses are working toward making the implantable artificial kidney.

One component of the new artificial kidney is a silicon nanofilter to remove toxins, salts, some small molecules, and water from the blood. Roy's research team designed it based on manufacturing methods used in the production of semiconductor electronics and microelectro- mechanical systems (MEMS). The new silicon nanofilters offer several advantages—including more uniform pore size—over filters now used in dialysis machines, according to Roy. The silicon nanofilter is designed to function on blood pressure alone and without a pump or electrical power.

The second major component is a "bioreactor" that contains human kidney tubule cells embedded within microscopic scaffolding. These cells perform metabolic functions and reabsorb water from the filtrate to control blood volume.

A bioreactor, used in combination with ultrafiltration in an external device, greatly increased survival in comparison to dialysis alone in the treatment of patients with acute kidney failure in a hospital intensive care unit.

The artificial kidney being developed, is designed to be connected internally to the patient's blood supply and bladder and implanted near the patient's own kidneys, which are not removed. Unlike human kidney transplant recipients, patients with the implantable artificial kidney will not require immunosuppressive therapy. The nonreactive coatings developed for device components are unlikely to lead to filter clogging or immune reactions, he said, and that bioreactor cells can survive for at least 60 days under simulated physiological conditions(9).

V BIOARTIFICIAL KIDNEY (BAK)

Tissue engineering of an implantable bioartificial kidney composed of both biologic and synthetic components Bresult in substantial benefits for patients by increasing life expectancy, mobility, and quality of life; with less risk of infection and reduced costs. This approach could also be considered a cure rather than a treatment for patients. Essential features of kidney tissue must be utilized to direct the design of bioartificial kidney for renal function replacement through tissue-engineering project.

The critical elements of renal function must be replaced, including the excretory, regulatory transport, and endocrinologic functions. Therefore, a bioartificial kidney requires two main units, the glomerulus and the tubule, to replace excretory and metabolic functions of the kidney(10).

Bioartificial kidneys (BAKs) combine a conventional hemofilter in series with a bioreactor unit containing renal epithelial cells. The epithelial cells derived from the renal tubule should provide transport, metabolic, endocrinologic and immunomodulatory functions. Currently, primary human renal proximal tubule cells are most relevant for clinical applications. BAK-based therapies are usefu; for ESRD patients(11).

Current technology has developed methods to replace the glomerular and excretory functions of the kidney via dialytic techniques, either HD or PD. These methodologies all address water and electrolyte balance functional replacement of the kidney; however, they fail to provide for the lost metabolic function. Thus the metabolic, endocrine, and immune roles of the functioning kidney are candidate mechanisms for improving the poor outcomes in acute and chronic renal failure treated with current RRT. To develop more complete RRT, the last decade has been focused on tissue engineering the development of a renal tubule cell device to add the missing second metabolic component of RRT for more complete renal function.

As to the development of a tissue-engineered kidney, a step function approach towards a fully implantable bioartificial kidney (BAK) has been adopted. An initial focus was to develop an

London Journal of Medical and Health Research

extracorporeal BAK comprised of a conventional synthetic hemofilter with a renal tubule cell assist device (RAD) in an acute extracorporeal blood circuit. With success of this formulation, proof of concept for a wearable bioartificial kidney (WEBAK) combining PD with a bioartificial renal epithelial cell system (BRECS) has been recently achieved.

Replacement of the multivariate tubular functions of the kidney cannot be achieved with inanimate membrane devices, as has been accomplished with the renal ultrafiltration process, but requires the use of the naturally evolved biologic membranes of the renal tubular epithelium. In this regard, the tissue engineering of a bioartificial renal tubule as a cell therapy device to replace these missing functions can be conceived as a combination of living cells supported on synthetic scaffolds.

A bioartificial tubule can be constructed utilizing renal tubule progenitor cells cultured on semipermeable hollow-fiber membranes on which extracellular matrix has been layered to enhance the attachment and growth of epithelial cells. These hollowfiber synthetic membranes not only provide the architectural scaffold for these cells but also provide immunoprotection. These hollow fibers were packaged in bioreactor cartridges with membrane surface areas as large as 0.7 m2, resulting in a device containing up to 108 cells. In animals studies, fluid and electrolyte balances as reflected by plasma parameters, were adequately controlled with the bioartificial kidney. Plasma potassium and blood urea nitrogen levels were more easily controlled during RAD treatment. RAD, allowed the fractional reabsorption of sodium and water to achieve 40–50 % of the ultrafiltrate volume. Active transport of potassium, bicarbonate, and glucose by the RAD was demonstrated. Successful metabolic activity, such as ammoniagenesis was also observed(9). Transport of H2O, Na+, and glucose were significantly increased when 2.5 g/dL of albumin was added (12).

Phase I and II trials of RAD treatment conducted in humans resulted in significant declines compared to baselines in granulocyte-colony stimulating factor (G-CSF), IL-6, IL-10, and especially IL6/IL-10 ratios, suggesting a greater decline in IL-6 relative to IL-10 levels and a lessened proinflammatory state. These results were encouraging and led to an FDA-approved.

With the early clinical success of the RAD in RRT for AKI requiring dialytic therapy, two key missing components for the successful commercialization of cell-based therapeutic devices were identified. The first was the need for a reliable and consistent source of cells to manufacture thousands of these cell devices. The second was the requirement to develop a cost-effective manufacturing, storage, and distribution process for these devices.

VIII. WEARABLE BIOARTIFICIAL KIDNEY (WEBAK)

The WEBAK is comprised of the use of sorbent-based technologies to replace the excretory function of the kidney.

Sorbent-based hemodialysis was developed in the late 1960s and introduced into the clinic in the 1970s. Sorbents provide the ability to reduce the large volumes of dialysis solutions utilizing highly purified water from 100 to 200 l per dialysis sessions to as little as 6 l of potable water. With sorbent dialysis, spent dialysate from the dialyzer cartridge is not discarded but is regenerated by processing the dialysate through the sorbent cartridge. The sorbent cartridge has several layers of sorbent compounds which regenerate used dialysate into fresh, bicarbonate dialysate. The cartridge is based upon carbon binding, enzyme conversion, and ion exchange. This compact and disposable regeneration process promotes this sorbent system to remove key uremic toxins and regenerate dialysate.

VI. IMPLANTABLE ARTIFICIAL KIDNEY

An implantable “biohybrid” or bioartificial device has the potential to avoid both supply limitations to renal transplant and the burden of therapy of intensive maintenance dialysis.

The design of the implanted device will have to be guided by the planned therapeutic strategy. Specific means for patients to self-monitor and reprogram device function will be critical for truly independent self-care using an implanted device. Lifecycle management of the device, including recognition of impending device failure and a minimally invasive approach to renewing or replacing failed components, modules, or cartridges, seems essential. Selection of implant site will be guided by the paramount need to preserve vascular sites for future allografts(10).

VII. CONCLUSION

Despite all the advances in renal replacement therapies, a portable, continuous, dialysate-free bioartificial kidney has not yet been achieved and still remains the ultimate goal of renal tissue engineering. The enabling platform technologies discussed in this review advance this goal from a dream to the laboratory bench and even to the bedside. Future research in renal tissue engineering will need to focus on reproducing mechanisms of whole-body homeostasis. A high priority must be given to sensing and regulating extracellular fluid volume, even if only at the crude level of having the patient weigh daily and adjust ultrafiltration and reabsorption by the bioartificial kidney. In addition, progress has been made in the field of cryopreservation and thus the ability to manufacture, store, and distribute bioartificial organs is advancing. The next decade, like the previous, will likely see substantive advances in renal tissue engineering(10).

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