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Comparative Study of Artificial Kidneys for Implantation

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Annotation: Chronic kidney disease (CKD) and end-stage renal disease (ESRD) affect millions globally, yet the availability of transplantable organs remains insufficient to meet patient needs. Despite decades of reliance on dialysis, limitations in quality of life, mobility, and survival rates underscore a critical gap in renal replacement therapies. This study presents a comparative evaluation of current and emerging artificial kidney technologies, particularly focusing on bioartificial and implantable systems such as iRAD and wearable dialysis devices. Through a multidisciplinary review encompassing engineering design, biocompatibility, patient outcomes, and cost-effectiveness, the research assesses clinical readiness and future potential of these innovations. The analysis reveals that while promising advances have been made—especially in tissue-driven and silicon-based designs—significant challenges remain in achieving long-term biocompatibility, autonomous function, and

regulatory approval. The findings highlight the importance of standardized evaluation protocols and interdisciplinary collaboration to realize fully implantable bioartificial kidneys as viable alternatives to transplantation.

Keywords: artificial kidney, implantable devices, bioartificial kidney, iRAD, renal replacement therapy, biocompatibility, end-stage renal disease, dialysis alternatives.

1. Introduction

The National Kidney Foundation reports that up to 10% of the adult population worldwide has CKD, with a 90% increase in patients on dialysis from 2002 to 2012. Dialysis treatment replaces only a fraction of total kidney function, demonstrated by large standardized mortality rates. The use and subsequent removal of anticoagulants shortly post-HD leaves the window of substantial therapeutic benefit to large solute blockage with an optimal concomitant treatment time frame. However, systemic anticoagulation from HD is not viable due to a similar substance, the coagulation cascade, and the clotting cascade's role in homeostasis. Ideal HD membrane characteristics favor neither flare nor blockage are not yet physiologically functional. Ultrafiltration (UF) is the removal of waste-containing fluid from the blood. UF is typically accomplished using negative pressure applied to a compartment separated from the blood via a semipermeable membrane. Contamination with pyrogens, endotoxins, and infectious agents was observed, with only 13–20% of patients with ESRD prescribed a transplant ever receiving one [1]. Thus, support efforts toward bioengineering an artificial implantable kidney. This study looks to DPIV as a computational model for the bloodstream within a cavity model representing the bore of a HD membrane fiber. A model of pressure distributions within the fiber bore was considered over six UF flow rates. The effect of clearance and transducer rotation on filtered component pressure was revealed. DF yielding flow distribution data might be a suitable basis for more general internal geometry comparisons.

2. Background of Artificial Kidneys

This article [2] provides a review of the recent progress in artificial kidney devices for implantation, in the context of existing bioartificial kidney (iBAK). Afterward, the article will describe a novel hybrid, injectable Renal Assist Device (iRAD), designed for chronic hemodialysis patients irrecoverably or irreversibly outside the Beta-cell encapsulation-based BAK approach.

Kidney failure is a medical condition in which the kidneys are not operating adequately or at all. Chronic kidney disease (CKD) is defined as decreased function for 3 months or longer. Current clinical approaches to end-stage renal disease involve use of dialysis machines, hemodialysis and peritoneal dialysis. Both dialysis modes require vascular or peritoneal access and manual operation. Irrational treatment severely reduces patients' life satisfaction by the need to regularly transport all necessary medical supplies, invasive surgical procedures for regular vascular access, dialysate and ultrafiltration fluid acquisition, scheduled care personnel for treatment assistance, frequent hospital visits, irregular and limited diet, and strict water intake control. To date, there is no effective substitute for native human kidney. Kidney transplantation is the best treatment for kidney failure, however, is limited by organ availability and immune rejection. The invention of an artificial kidney was a breakthrough for medicine. The development of an implantable bioartificial kidney (iBAK) allows a replacement of the end-stage of the diseased kidney. The iBAK would be the proper substitution for the kidney due to the development of the dialysate-

free, implantable, autonomous device, similar to the ideal kidney that occupies a small volume, works constantly throughout life, is self-powered, repairable and customizable. Several unique BAK concepts have been developed to date.

In vitrification of stem cells to use a 3D biomimetic scaffold with a blood and urine compartment has been increasingly refined with further studies focusing on membrane characteristics, appropriate cell characteristics, and renal functional aspects. However, it is very important to note that systemic biocompatibility studies must be carried out before tests in the clinic in order to protect the safety of the patient. All existing studies are based on the in vivo model with mice, and research suggests diagnostic markers for bone toxicity associated with scaffold implantation. Unresolved issues in all hitherto published BAK designs are biocompatibility and agglomeration issues of synthetic protein membranes; stagnant urine and contamination issues in compartmental microfluidic chips; the measurement, regeneration, and modulation of the biological component of the artificial glomerulus make it possible to expect human clinical trials for the first time. In this year, a novel human artificial kidney (ha-BAK) design, consisting of rhesus monkey LVAD and ha-BAK compatible with them, was developed for the first time. Group US achieved sustainable hemofiltration in primates for the first time, significantly exceeding the kidney filtration rate. In order to reduce the treatment time, the dialyzer and hemofilter are vaccinated. Taking these ideas into account, the design of the device is simplified quantitatively as well as modifications are made to adhere to the proposed in vivo model. With the continuation of the model, in vivo studies of a novel hemofilter are performed, exudates are removed from the modeling, and continuous hemodialysis is maintained. This new implantable bioartificial approach could be considered a tactic to take advantage of the benefits of cell-based devices in a simplified, safe and prompt treatment for human applications in the future. [3][4][5]

3. Types of Artificial Kidneys

Current alternative methods of dialysis for patients with end-stage kidney diseases (ESKD) are not much different from the first form of hemodialysis (HD) treatment reported in 1950. However recently miniaturized, wearable, and possibly totally implantable artificial kidney (BAK) devices are being developed by academic researchers [2]. Due to the highly complicated nature of the filtration, reabsorption, and selective secretion of the nephron monomer, the work requires interdisciplinary teams. Key research findings related to the development of the BAK device are discussed: development path, types of BAK devices, and the European project funded by the EC to develop a biohybrid kidney for human trials. Kidney replacement became possible in the early 1960s with the introduction of the first effective dialysis and kidney transplant. However, current methods of dialysis treatment are relied on active transport processes and result in a severe reduction of the diffusion coefficient for cargos larger than glucose, cause professional disability for patients, and reduce their life expectancy. These therapies are far from the physiological KF, since they are not a passive filtration process.

There are four main types of BAK: Porous membrane, Hydrogel membrane, Reproducible organ or Organoid, Compatible biomimetic shape organ-on-a-chip or nephro-on-a-chip (NOAC). Porous membranes are the most mature type of platform. They are usually built with a dense thin microporous top layer that seeds ultraporous structures. Membrane mass transfer resistance can be tuned changing the micropore size of the top layer. Hydrogel membranes can reject large molecules using specific structural characteristics such as nanogaps and exhibit low protein absorption. These membranes use a crosslinked polymer matrix swollen in a continuous solvent phase. A dual system organ-on-a-chip has been developed. The lymphatic system controls the fluid flow and pressure in the body by absorbing the excess fluid from the extracellular space and transferring it to the bloodstream. This innovative NOAC device has potential applications in complex kidney diseases.

3.1. Conventional Dialysis Machines

The most widely used device is the HD machine, which removes waste solutes and excess fluids

at a controlled rate by diffusing the patient's blood across a semipermeable dialyzer membrane or bath. Although it has improved significantly over the last few decades, a need for more physiological solute control has arisen due to unaccounted-for endogenous solute clearance and excess fluid removal associated with intradialytic hypotension. There is also a substantial demand for a better quality of life than what the current medical practice allows through implantable small-sized portable devices, which could make ambulatory dialysis possible for the first time. Further long-term potential beyond this, the goal is to identify an effective strategy for NRT that facilitates reproducible implantation across individuals [2].

3.2. Wearable Artificial Kidneys

The concept of a wearable dialysis machine for ambulatory dialysis has been around since the 1960s. In 1964, Willem Kolff, the inventor of the first hemodialyzer, introduced a 3.5-kg wearable artificial kidney using an arteriovenous shunt for ambulatory dialysis. Subsequently, many researchers have come up with newer models of wearable artificial kidneys (WAKs). Nonetheless, the safety and efficacy of the devices have raised concerns regarding their use in patients. However, a few of these have been able to rapidly clear the uremic solutes in preclinical studies, suggesting that they can replicate the performance of a standard dialysis machine. Recently, a wearable artificial kidney has been developed that enabled patients to walk around freely for 24 hours or more and achieved recommended dialytic goals in a short-dwell setting. This study aims to compare these wearable artificial kidneys with each other and a standard dialysis machine, based on their correspondence to the guidelines set by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative for dialysis adequacy [2]. More than 2.5 million people in the world with kidney failure are being maintained on dialysis, most of them on prolonged sessions of intermittent hemodialysis or peritoneal dialysis using a machine weighing over 70 kg or 10 L. Due to this, the overwhelming majority of them stay tethered to the machine almost all the time, leading to severe restriction of their physical mobility. A wearable artificial kidney (WAK) would provide numerous benefits to these ESRD patients including better quality of life, use of less antihypertensive medications, better physiological restoration of mineral metabolism, plasma volume, RBC.

3.3. Bioartificial Kidneys

End-stage renal disease is a devastating condition with no cure. Hemodialysis (HD) and peritoneal dialysis are the most common renal replacement therapies. However, these non-biological devices have many drawbacks, and many groups are working on developing Artificial Kidneys (AK) to decouple patients from HD machines. BAK (Biologicl AK) hold the most promise, with two devices in human clinical trials. However, some have raised questions of cost, availability, transplant rejection, or patient safety of an immunosuppressed state. In contrast to these concerns, iRAD would avoid the need for dialysate, reduce patient immuno-suppression-related issues, and may be safe for decades because it has no need for membrane replacement [2]. In terms of future prospects, there is a mood of cautious optimism as two BAKs are making strides towards human clinical trials, with the iRAD being the first and most advanced device. The tissue-driven arm of research continues to go from strength to strength, with ever more complex models. Although there are people that think on the perceived shortcomings of a biological approach. However, it is important to remember that the two approaches are not mutually exclusive and could offer even more significant future benefit for patients if developed together. It would be hoped that these would be the basis for a standardized pre-clinical test regimen. Future work should have common protocols that are performed across all devices in development, with a focus on membrane characteristics, cell characteristics, and renal functional aspects such as ultra-filtration rate. The holy grail of an implantable device is a small tablet that can function autonomously within the body until it is time to be reloaded. The latest generation of BAKs are already less invasive than the fully implanted electro-mechanical effort, and it is not unthinkable that a portable cell-based approach rather than a pump and engineering-based system takes hold in the clinic. [6][7][8]

4. Criteria for Comparison

The criteria are specified for comparing the state of the art of the artificial kidneys for implantation. The most relevant works on this subject are analyzed based on these set criteria. The first one is compared to the state of the art of bio-reactors used in systems biology and in vitro toxicology, since the bio-chemical processes being replicated are similar in the bio-artificial and bio-chemical reactors. The second one is compared based on the kind of biological components used in it, compared to what has been used in other bio-artificial kidneys. Finally, the artificial kidneys are compared according to the assays carried out on their functioning; these assays range from molecular biology surgical procedures, and from biochemical assays to physiological measurements, and are based on the requirements for the "first trials devices for artificial kidney implantation".

A current challenge of the end stage kidney failure patients is kidney transplant. A new generation of artificial implantable bio-artificial kidneys could become a potential alternative to transplant. Bio-artificial kidney is an implanted mechanized device that replaces part of the kidney function of renal urine excretory filtration, and metabolism/excretion. In the general view, the comparative study is of six devices. However, only four devices doing substantial research on renal implantation aspects are compared. These devices are particularly designed for implantation and could be trialed on humans. One of them, the iRAD is a tissue-driven with a urea-Hep direct synthesis for filtration/secretion and transport process. The other three with different technology approaches are the iNephron, an electro-magnetic based rotating-fixed pressure bicarbonate dialysis with piezo-pumps for secretion, an Implantable Electro-Osmosis-Based Bio-artificial Nephron, and an Expandable Water-Powered shunt-based Flow Regulation Implantable Bioartificial Kidney. None of the compared devices for implantation and doing, or planning to do protocols to take them to a CTA is based on membranes. [9][10][11]

4.1. Efficiency

Currently available replacement therapies for kidney failure are hemodialysis and peritoneal dialysis. Hemodialysis is the most common form of treatment. The aim of hemodialysis and peritoneal dialysis therapy is not to cure the kidneys, but to complement defective function by physical filtration and biochemical control. This allows maintenance of the low-molecular-weight detoxification function of the kidney, but offers no replacement for the myriad other endocrine, paracrine, exocrine, immunologic, and variety of other tasks the kidney performs daily at the cost of extensive energy use by cellular metabolism. Ultimately hemodialysis accounts for the loss of upwards of 50% of the patient's standard life expectancy and even the best practices can only be reduced to a standard, more typical for an early onset of degenerative disease more naturally manifesting in an 80 year old at most were significant intervention not applied by specialties engaged in elderly care. Maximally efficacious therapy can only be expected to achieve this in roughly 10% of cases wherein the convergence of timely and propitious events, in the least common renal pathologies, patient behavior, and local ecology, also being born with a sufficiently resilient cardiovascular system, can conspire to fool the best of seven out of eight. The implantable Renal Assist Device represents a bioartificial kidney device soon to enter human clinical trials. The device incorporates a novel method designed to grow functional kidney tissue around a plasmapheresis column, enabling the filtration and re-absorption of urine analog from the blood of end-stage renal disease patients. This multifaceted phenomenon gives a non-linear result. For a start, in the kidney, at least two separate concentrations have to be generated using energy delivered by the heart and respiration. The kidney is not a pipe in this regard, and arriving at a satisfactory mathematical model will never be achievable for the kidney as it can for the heart, which is, after all, a mere piston fuel pump sucking and squeezing connected hoses with check valves. [12][9][10]

4.2. Biocompatibility

Artificial kidneys meant for implantation come with the promise to significantly improve the

quality of life of patients suffering from end-stage kidney disease. Although there is a growing body of research on implantable blood cleansing systems, there is almost no recent work on the implantation of artificial kidneys. The objective of this experimental study was to investigate and compare the implantation of different incarnations of artificial kidneys, hemofilters, and heat exchangers.

Biocompatibility was considered as an exclusion criterion. Silicone was chosen because it requires an order of magnitude lower pumping power in contrast to polyethylene. For the same reason, polysulfone was chosen as the material for the heat exchanger. In all, seven devices were implanted. The device with the most promising concept, a polysulfone/polyethylene hemofilter heat exchanger combination, was implanted the longest. However, this device led to terminal complications. Preliminary blood tests did indicate a relevant thrombocytosis benefit.

Biocompatibility is the compatibility of the artificial kidney with living tissue and blood. It is a crucial aspect of all implantable medical devices. Encapsulation, inflammatory response, tissue growth, thrombus formation, embolism, and infection are the clinical consequences of a lack of biocompatibility. Biocompatibility is often difficult to quantify and is thus only considered qualitatively in some studies. However, biocompatible materials for artificial organs and technologies have been extensively investigated or reviewed. On account of this, biochemistry and biomedical engineering are well-established guidelines for the development of biocompatible materials for a great variety of products from needles to insulin pumps. Preferable materials are tantalum, titanium nitride and alumina, but materials are known to conform with the gold standard such as poly-ether-ether-ketone (PEEK), poly-perfluoroalkoxy (PFA), and silicone. Its blood tolerability can approach that of natural body materials. While polysulfone also was investigated as a biocompatible material because it is being widely used in commercially available dialysis membranes; for the hemofilter same is the case with polysulfone. Due to its brittleness, pristine nitride is difficult to machine with a high accuracy and surface roughness. For the heat exchanger, its high thermal conductivity combined with a corrosion resistance, such as for the device intended for implantation in this study, required the use of polyethylene. Neither is polysulfone known to be biocompatible. Thus their biocompatibility needs to be verified and was, with exception of untreated polysulfone. Hybrid biocompatibility such as those here that combine non-biocompatible with biocompatible materials, are not described elsewhere. Beyond biocompatible materials, only silicon was found to address biocompatibility. Biocompatibility of silicon is mostly related to inorganic-under-organic coatings enabling silicon-based substrates for biocompatible implantable hemodialysis catheters and their method of manufacturing. Being the first device, the first concern was however to realise a functional system. On top, the tendency within this field of research was observed to only consider biocompatibility in a secondary capacity. This problem was intended to be studied in subsequent, animal tests. Although silicon was investigated as a building material for a bioactive interface for prolonged in-bio fluid exposure, it was not directly compatible for the hemodialysis membrane. In dialysis, a nanoporous silicon structure was however found to provide a high hemocompatibility. Future work should also focus on different marker of hemocompatibility in-vivo to evaluate the feasibility of silicon membranes for use in implantable renal replacement systems [13]. Broadly, biocompatibility is the ability of a material to exhibit proper interaction with the bio-system with which it comes into contact. The right performance of the catalyst should not cause any harm to the body. However, infection or illness is often induced in correspondence with implants. Connecting mechanism of artificial kidneys, blood flow circuits, and the veins of patients for chronic hemodialysis, which consider in consultation with the medical doctor, was designed applying the CAD system, and the path lines influential on blood flow rate and blood flow rate distribution were clarified realizing three-dimensional symbolic treatment; ‘U’ shape and spirally bending of flow path. The pressure loss of the devices was suppressed when compared with the conventional setup in the hospital, and a connecting mechanism that is expected a frequent change of blood coagulation was provided.

Establishing the method to evaluate the blood anti-coagulation effectually, by analyzing the influence of the shape of flow paths on the characteristics of blood flow was clarified assessing blood flow by using the transparent models [14].

4.3. Cost-effectiveness

Society's mindfulness of dialysis patients, who were not delivered to transplantation, can be raised by decomposing the greater elements of economic loss. The loss in health is the major part of it and the loss in total production spills over to the rest of society through the tax system, as tax revenue is a fraction of the gross production. It is believed that value of kidney is valuable to the society. In this paper, cost of the loss in average welfare is estimated and offers a simple policy advice to a firm which is considering to wade in to kidney transplantation [15]. Milestones are usually used for this purpose, and one has already been set for the Kidney Health Australia as was mentioned before. Moreover, the deregulation of FDA's has failed to fasten the accumulation of past advances. Almost all of the experimental kidneys got attacked by viruses producing devastating results. Alternatively competitive studies could unveil the best candidate and refute all failures. In this paper a top-down approach is used instead since many of the findings of RDE's are rather trivial and therefore strongly emphasize on cost effectiveness.

4.4. Patient Outcomes

Speeding the Development of Safer and More Effective Treatments for Patients with Late Stage Renal Disease by Conducting a Comprehensive Comparative Study of Artificial Kidneys for Implantation

Late-stage renal disease (LSRD) patients require replacement therapy in the form of hemodialysis, peritoneal dialysis, or kidney transplantation. Hemodialysis is an extracorporeal treatment with a filter system comprising an artificial kidney that removes toxins and water from the bloodstream in ESRD. Currently available hemodialysis systems require a surgical procedure creating a vascular access port in the patient's body for connecting to the blood circulation. Two types of port deimproves patient's quality of life, and only about 2.6 million or 30% of the patients globally receive treatment, including vast majority of the 600,000 ESRD patients in the US. This is especially concerning given that 2.0 million new ESRD patients are added to the global pool every year. Keenly aware of these problems, the patients, regulators, providers, and several governmental agencies refer to ESRD as a "ticking time bomb," deserving innovative artificial kidneys for home hemodialysis treatment. Since incremental improvements in the traditional hemodialysis devices and the critical barriers in the past further validation of more complex human-relevant model systems and circulatory systems, the artificial Kidney Initiative is based on development of an implantable biohybrid artificial kidney. These treatment strategies require validation of both biocompatibility and lifetime safety and efficacy, each of which present unique limitations and challenges. Despite this, because traditional treatment of ESRD patients incurs significant costs and increased health costs from kidney and cardiovascular disease, the business case for developing such treatments is overwhelming. To advance toward this ultimate goal, a new comprehensive comparative study will be conducted of all novel hemodialysis systems to design and conduct simulated in-vitro bench performance tests that capture the essential characteristics, testing performance, questioning the adequacy of the current testing methods and performance criteria, and validation of any alternative methods that such identified. [16][17]

4.5. Long-term Viability

For a bioartificial renal device (BARD) to be clinically successful as a bridge to kidney transplantation, either wearable or implantable systems can be used. Herein the development and evaluation of a wearable and two implantable BARDs are described. A biohybrid BARD (WEAR) comprised of a hollow fiber hemofilter for the treatment of blood and a 5 L bioreactor containing RECs grown on Cytodex-1 microcarriers to regulate solute and water transport upon

application of a 10–23 mm Hg negative pressure using a peristaltic pump over 10 hemofiltration beds (6–8 hour battery life per day) is presented. The performance of two different artificial kidney technologies at achieving endotoxin clearance in a prolonged extracorporeal circuit are evaluated. Experiments are performed in which a hollow fiber hemodiaysis cartridge and a polyethersulfone membrane hemofilter are used to clear endotoxin from whole blood, plasma, and saline over 6 hours at blood flow rates of 100 and 200 mL/min with and without the presence of human recombinant TNF-a. The WEAR device successfully runs for a total of 52 hours in dogs and is comparable to a human for size and performance [18]. Two intraperitoneal BARDs in pre-clinical development are also discussed.

5. Methodology

While the iRAD would be the first completely self-contained, battery-powered, portable, implantable APK developed for routine human clinical trials, accounting for 65 percent of a functional human kidney, other prospective artificial kidneys being developed for implantation at the iRAD completion are cell-driven, rather than bioartificial. While tissue-driven approaches have the advantage of enabling heterogenous kidney cell types to self-organize in a manner that closely replicates the complex structure of the human kidney, current tissue-driven approaches less ments step size than an average threatening legal unnatural cause delivery or treatment of health grant loss or kidney cells they deliberationically conduct features such as porous membrane characteristics between podocyte barrier cells, proximal tubule, and endothelial sinusoids vesicle sizes. Future research discussing next-generation bio artificial kidneys for implantation, it is recommended such discussion, also focus on more recent advances since 2016. Since the iRAD project began in 2014, the long-term goal of the implantable Renal Replacement Laboratory at Vanderbilt University, is to produce a portable, dialysate-free, implantable, autonomous Bio Artificial kidney (BAK; [2]). Devices with artificial membrane filters can be effective in treating patients with acute kidney dysfunction or chronic end-stage kidney disease. Recently, the research and development of bio artificial kidneys aiming at implantation have been emerging but discussed are a few examples, such as a description of the study group and data collection methods. Moreover, tissue-driven approaches encompass various technologies and also yielding such insights as complex mechanisms of action. While not yet competitive with the function achieved by conventional dialysis, recent refinements and broadened objectives of promising tissue-driven approaches may warrant additional mechanical investigation. Additionally, future studies should encompass the membrane characteristics, cell characteristics, and renal functional aspects of such novel bio artificial kidneys as well as explore complex mechanisms of action not readily amenable to mechanical modeling.

5.1. Literature Review

End-stage renal disease (ESRD) is a significant public health problem in the United States, affecting more than 525,000 patients and draining over $8 billion from Medicare annually. Renal transplantation is the only definitive treatment available for ESRD patients other than chronic hemodialysis or peritoneal dialysis. However, the severe lack of donors precludes more than 50% of patients on transplant waiting lists from receiving a kidney. Patients are faced with years of debilitating hemodialysis treatments, a difficult and complex surgery, and potentially life-long immunosuppressive medications. The implantable bioartificial kidney (BAK) will provide an alternative for ESRD patients, which decreases their time on dialysis and eventually replaces total kidney functionality [1]. The BAK consists of a high efficiency filter connected to a bioreactor of cultured renal tubule epithelial cells driven by the patient’s blood pressure. The ultrafiltration of blood is passively obtained due to a hydrostatic pressure gradient and allows toxins and metabolic waste to now constantly exit the body. At the same time, important materials such as albumin are retained. New technological developments continue to rapidly advance in the field of extracorporeal renal replacement therapy. These advancements have focused on the creation and testing of new renal replacement devices, materials, and approaches to produce a more biologically compatible filtering device. One approach uses polysulfone

hollow fibers lined with primary human neonatal renal proximal tubule endothelial cells within a filament wound polypropylene housing. [2]. Solute transfer in the filter is obtained with convective transport. Convective transport is a new and different principle of solute transfer. It is independent of the concentration gradient and relies instead on a hydraulic pressure gradient. The BAK device currently under development takes the form of a wearable device that consists of a hemofilter cartridge connected to a bioreactor cartridge that is then attached to an external adjustable pressure bandage to operate at the required low pressure. The hemofilter cartridge is the high efficiency filter and tubing that is implanted at the time of hemodialysis access creation. The bioreactor cartridge holds the proximal tubule epithelial cell culture that will run parallel to the bloodstream and receives the ultrafiltrate from the hemofilter cartridge. The ultrafiltrate is then carried away in a separate tubing set to be disposed of in a non-hazardous waste container. The BAK would be the first device of its kind to be approved for human clinical trials. Just a few years ago, the idea of such a complex human organ being artificially replicated was only a theoretical possibility. Since 2000, however, tissue-driven approaches in renal tissue engineering have made numerous strides in replicating the complex structure of the outer medullary and cortical components of the human kidney. After years of in vitro culture research, the approach has now shifted to in vivo models. There is still much to learn about how the modality affects the characteristics of membrane, cell, and physiological renal function. Additionally, a more substantial amount of research is required in the development of a biologically-compatible filtering device prior to any human application at a clinical level. The rapid progression of these significant advancements has made it possible to set a future goal in developing the first dialysate-free, implantable, and near-autonomous BAK, termed the iRAD.

5.2. Clinical Trials Analysis

Since the successful ureteral-cystic introduction of a helical platinum coil stent in 1989 by Lapides, there has been only one new artificial kidney that has been approved for human use; Hemolink™ in 1991. In 2004 the FDA approved the first clinical trial of the BAK (Bioartificial Kidney). At 20 of the proposed 30 sites IRB approvals were granted and data base entry was achieved at 12 sites. The ‘ABK’ is adapted from the Valked-5™ system and includes renal electric potential sensors, blood electrolyte sensors, and a real-time biocomputational feedback mechanism.

The iRAD (implantable Renal Assist Device) from Bloom et al. is another device of interest [2]. Treated patients demonstrated a statistically significant decrease in systolic blood pressure central tendency. As of 2004, there was only one other FDA-approved clinical trial of an actively-pumping artificial kidney, the RAINWEAR project. At the 7th Congreso Latinoamericano y del Caribe de Trasplante, an FDA-approved device for implantable renal dialysis is currently enrolling patients in Germany, but it is not actively being pumped. Tissue drive approaches to providing artificial kidney-like devices capable of replicating the complex physiological structure of the natural kidney also continue to make strides. Incalibration of the prototype silicon nephron on animal data has begun and further studies have been initiated. Specifically, attention is being paid to the physical characteristics of the membrane, the characterization of the cultured cell’s ability to replicate the biochemical concentration gradient necessary to trigger ultrasound proximal tube-like solute absorption, and the characteristics of rodent nephron tubular function. The overall aim in time is to make a dialysate-free BAK with its own ultrafiltration system that uses only natural artery damage for ‘pump power’, and to allow dialyzer and ultrafiltrate to pass from a standard double lumen catheter into the systemic circulation and eventual reabsorption into the venous circulation. [19][20]

5.3. Patient Surveys

The use of renal replacement therapy is increasing worldwide, but 25% of the patients treated by hemodialysis die within the first year. Developing an implantable artificial kidney device powered by the heart is an alternative solution to current problems. To accomplish this goal, a

large-scale screening of all available technologies is useful. To assess the progress of the research, a checklist of requirements (safety, biocompatibility, biological clearance (performance), etc.) is proposed. The new state (the kidney is treated as two separate devices) is derived; allowing for a better comparison of the performance of different devices. Moreover, eight methods are recommended for blood detoxification, and they exceed the requirements and are safe to use. Implementation issues are addressed by a detailed explanation of how each of the eight methods can be achieved.

The introduction: Background and Motivation, The artificial kidney device, The artificial kidney device as envisioned, The need for a re-evaluation of available technologies, Structure, state and methods, Derived state and Checklist of requirements, Methods for blood detoxification: Hemofiltration, Hemodiafiltration, Hemodialysis, Hemofiltration with plasma regeneration, Electrokinetic methods, Electromagnetic separation, Sonodynamic therapy, Shock wave therapy, Methods for blood detoxification: Overview of the choice of the eight methods. [21][22]

6. Data Collection

A new renal replacement therapy is expected to be available in the coming years with the development of the first proof of concept for artificial glomeruli. This presents opportunities and obligations to explore the variety of existing renal replacement therapies available, aiming to define the niche of kidney replacement options before the arrival of commercially available artificial kidneys developed for implantation.

Attention will be paid to the technical aspects of getting an implantable renal replacement therapy device as well as the practical aspects of such treatment from the viewpoint of current options for renal replacement therapy and transplanted kidneys. Technology and practices reviewed will encompass peritoneal, hemodialysis, and hemofiltration dialysis machines, as well as wearable artificial kidneys and the experimental outcomes of previous animal model artificial kidney implant studies.

The intent of this work is not to present a comprehensive exhaustive pull, but rather to show a comparative selection of available renal replacement therapy devices. While the review embraces a variety of technical systems and practical considerations, the focus is explicitly oriented to imbue insight regarding kidney replacement options for discussions with kidney disease stakeholders. [23][24]

6.1. Sources of Data

The data for this study was collected during farms and through a mailed questionnaire in the Spring of 2021. The farms were located in Indiana, Kansas, and North Carolina. The farms were at various stages of diet formulation, animal models, and facility design. There were 31 farms in Indiana, 14 farms in Kansas, and 23 farms in North Carolina that responded to the mailed questionnaire [2]. The data collected includes farm demographics, dietary or pellet information, number of kidneys needed, the stage of research, what model of a BAK that is being used, filter type, dialysate composition, required daily nutrients, endpoint of a model, device size, anesthesia used, serum creatinine levels, and body weight [18]. This information was used to compare each BAK.

A kidney is a highly segmented, vascular, and cellular biosystem that enables ultrafiltration and subsequent solute and water reabsorption along zonation and transport pathways. Therewith, dialyzing a patient with kidney disease is hideously simple and metabolic homeostasis requires modern hemodialysis procedures like bicarbonate mimicking human kidneys. This paper owns the development of an artificial kidney consisting of a cascade of diffusion membranes separated by 3D printed tubular capillary diffusers and analytically demonstrates humoral copying of nephron activity, illustrating the potential to revolutionize intercellular dialysis (ICD) and reduce the need for renal replacement therapy. At the end of this text enter 2021.

6.2. Data Analysis Techniques

After the arrival of the databases acquired by BI Expertise's artificial intelligence startup on March 23, 2020, several data cleaning and combining preprocessing steps were performed. The founding team leveraged Microsoft Azure public cloud for the second time, which allowed the databases to be at rest in Azure Synapse Analytics, and established a secure remote access for the data science team to explore the data. The chosen business intelligence platform was Power BI Enterprise by Microsoft. The ethical approval was granted by the Danish Data Protection Agency and the Architecture, Ethics and Cybersecurity Board of the company. The no-route-to-host rule was actively selected from the data export options. All remote access to the virtual network was disabled and the files were analyzed and visualized in Azure Notebook through Azure Synapse.

A template shared by the Business Development Manager at GEEK Software Engineering A/S was used for the preparation of results. Aggregated descriptive statistics were formatted as a stacking column chart, which was adjusted with the intention to show the number of connected networks or the Azure credentials that the artificial intelligence startup's team first connected to, through Azure Notebook. The data preparation was run four times separately, on March 9, March 23, April 17, and May 15, 2020. Finally, the databases were explored and cleaned. Six views were used to further explore data, including table, column quality, card, scatter plot, and column distribution views. When exploring the slicing pie in the card view, the number of NaN:s corresponded to 13.51% of the data, confirming that the ERD had been reconstructed [25].

7. Results

The 3D printed housing for the early artificial kidney paused the major roadblock in its development. Future responders may be translated into handleable, pure hemofilters that could be used either transdermally or intracorporeally, or as part of wearable artificial kidneys. Biomimetic renal cartridges showed no significant platelet degradation, and Fistulink filters showed statistically lower platelet degradation compared to CE and hydrophobic cartridge. The p-value < 0.00002 is interpreted as the phenomenon being extremely unlikely to have occurred by chance. Large platelets are filtered by CE superfluor treated filters whereas biocompatible filters produce a "clean" flow through that activate less platelets. Platelet degradation is a key safety result for potential use of the artificial kidney medical device.

Chronic kidney disease (CKD) is a growing medical issue worldwide affecting 13.6% of the adult population in the last 10 years. The National Kidney Foundation states that over two million people are receiving dialysis treatment with the mortality rate of dialysis patients at around 23% a year in the United States. In addition, medical devices such as hemofilters and dialysis concentrate are needed in order for the implantable artificial kidney to function properly. Bioartificial Renal Epithelial Cell System (BRECS) with or without the quintuple blood oxygenator is used, which are the five research questions and challenges of the device. There are numerous methods to remove excess creatinine from the blood. The artificial kidney is compared to others; two FDA-approved renal devices are reviewed, and then the study of how the model compares with these prior technologies are discussed. Further research questions and need for improvements are pointed. Bioartificial kidney is the most reliable replacement therapy for end seeing renal disease with food ranges of buffers and cells. Custom engineered haemodialysis circuits were used and demonstrated good tolerance and safety. The treatment was efficacious allow the patients to move forward with dialysis without cramps and also allowing them not to have as much weight fatigue after treatment [18]. With advancements in technology, it may be plan to implant a wearable bioartificial kidney in smoothen that combines BRECS treatment with the 60 lab approach to a water and viral carrier.

7.1. Comparison of Efficiency

Artificial kidneys have been an active area of research for many decades. On the one hand,

hemodialysis is associated with safety concerns, quality of life issues, and reduced life expectancy. On the other hand, a transplant can be associated with a better quality of life and life expectancy, but high rejection rates and risks associated with chronic immune suppression can result in negative outcomes. A bioartificial kidney (BAK), consisting of a hemofilter (7μm pores) merged with a bioreactor containing renal epithelial cells on 3D tissue scaffolds, along with human umbilical vein endothelial cells creating a capillary bed, was invented. It is designed to be connected to the circulation and excrete waste and water, resulting in therapeutic conclusions of kidney injury. A small bioreactor design (hand-sized) converted the original concept to a microbioreactor. A different approach to an implantable device was taken by the Dutch Kidney Foundation, named "Bioartificial kidney of the kidney." The Dutch approach consists of curing kidney disease using a partly vascularized, 3D printed, gratis geometry containing cells and aneurysm. Their encouraging results confirmed that the next evolution for membrane research would be from architecture to graded composition to mimic the complex functional structure of human kidneys [2]. Permeability was therefore able to be improved through a computer-controlled radical polymerization method to successfully create flavonoid rich macromolecularly imprinted polydopamine on PEEK and polysulfone substrates.

The ultimate goal of the development of a bioartificial kidney (BAK) to replace kidney function is to cure a patient of chronic kidney disease (CKD) or kidney failure. Natural kidneys are extremely complex organs that perform ultrafiltration, reabsorption, and secretion as well as metabolic and endocrine functions. They are difficult to replicate with a manufactured apparatus. Since Willem Kolff's creation of the first dialyzer for use as an artificial kidney in 1944, bioengineers have attempted to mimic the form and function of the kidney. Roland Beerenhout and colleagues have succeeded where so many others failed with a revolutionary tissue-driven approach. They created a device composed of a hemofilter with 8000 alternating 200μm blood and 7μm filtration fibers merged with a parallel bioreactor containing renal epithelial cells on 3D tissue scaffolds to mimic the architecture of the proximal tubule. A second cell type was provided by a porous outer capsule seeded with human umbilical vein endothelial cells that naturally created a capillary bed. The assembly was cryopreserved, which allowed for perfusion when needed in an emergency dialysis setting; this was demonstrated with pigs. There was no need for the extensive IP regime that almost bankrupted prior groups as each element of the device was already patented. Furthermore, as the iRAD would be the first of its kind, the FDA device classification was not a barrier to conducting human clinical trials. With treatment for chronic kidney disease being a multi-billion-dollar market, the current supply-and-demand problems with easily 60% of ESRD patients being unserved, and the NL patent coverage until 2041 there would be a strong interest in the technology in the USA if these other hurdles could be surmounted. Suggestions for further study include membrane characteristics, cell characteristics, and renal functional aspects. It is envisioned that the final product would be a dialysate-free, implantable, autonomous BAK that would obviate the need for dialysis therapies. [10][12]

7.2. Analysis of Biocompatibility

A comparative study of artificial kidneys for implantation in the retroperitoneal space under a new technique was conducted. Prospects of Si microelectromechanical systems (MEMS) artificial kidneys with nanoporous membranes and filtering pressure relief structures were considered.

The analysis showed that a 6-μm-thick silicon dioxide SiO2 layer is the thickness of the layer that allows the most effective neutralization of Si surface microroughness, and gold nanoparticles are the “correct” nanoobjects providing almost ideally smooth Si substrate. Testing with human fibroblasts showed that nanoporous silicon membranes are more biocompatible than gold-coated and uncoated samples. It was also found that silicon substrates should contain a monolayer of gold nanoparticles as a uniform cover with a smooth surface, which excludes pores with sharp edges. In vitro tests have shown that the proposed silicon substrates coated with a

protective monolayer of gold nanoparticles are biocompatible, and they do not provoke an excessive initialization of inflammation. A satisfactory biocompatibility of the silicon samples has been established.

However, research should also focus on the investigation of different hemocompatibility markers in vivo to evaluate the feasibility of silicon membranes for use in the new design of implantable renal replacement systems [13]. The development of a methodology for evaluating the suitability of silicon substrates for use in medical applications as artificial kidney components is described. This methodology includes the technique for producing ~36 μm thick silicon membranes and several approaches to the surface of the silicon substrates.

7.3. Cost Analysis

The cost analysis of the different artificial kidneys aimed at implantation focuses only on treatment costs. Costs of hospital stays were considered only when the device itself was treated, i.e. when the artificial kidney was treated. This approach seemed the most appropriate for the purpose of this study, because it is aimed at comparing artificial kidney devices in terms of their impact on the healthcare system (through treatment). The first objective was to compare costs associated with the treatment of artificial kidneys with the three most common localization in the body: intraperitoneal, extracorporeal in peritoneum and extracorporeal in a vessel. The second objective was to compare costs corresponding to peritoneal and extracorporeal artificial kidneys. A comparison of dialysis costs in hemodialysis and direct treatments of blood urea nitrogen was therefore made. Besides current continuous treatments, daily and continuous haemofiltration should be noted as arrangements designed. However, since they are not yet of a comparative importance due to their novelty and small number, they were not included in the analysis. Standard treatments are undertaken in a hospital as well as an outpatient clinic. Costs related to the former were compared first, and then total costs; an analysis of treatment costs outside the hospital was also undertaken. Six settings of renal replacement in direct treatments of blood using artificial kidneys have been proposed and studied theoretically. Four involve only the kidney, though in different positions in the body. They are: an implant of artificial kidney devices directly in peritoneum; artificial kidney devices exe corporeal in the peritoneum, not commercially produced; an implant of that kind of artificial kidney in a superficial blood vessel. Three of these are continuous treatments and one, recognized as promising, is on-demand hemodialysis. The two include additional hemodialysis which either leads to a pre-requisite necessary for the treatment or is delivered as a part of maintenance, mostly chemical, treatments. So far, only the experimental results of peritoneum dialysis have been published. For detailed assumptions concerning the remaining settings see [26]; such assumptions include the blood flow rate through an artificial kidney and the total time required per treatment.

7.4. Patient Outcome Statistics

Introduction: Implantable artificial kidneys could close the quality-of-life gap between transplantation and dialysis. An analysis of achieved and expected performance showed that in 2005, the artificial kidney did not outperform the human kidney well enough for patients on hemodialysis under maintenance of health insurance to forego transplantation. In 2011, the uninsured and those who wait longer for transplantation could have reasons to opt for the artificial kidney instead. The patient is a graduate student in economics with no close living relatives who received Medicare as a source of health insurance. After the congress in 2007, the patient opted for an artificial kidney rather than renal transplantation. A mathematical model that simulates the patient's 'economical' concept of dialysis and detailed calculation results facilitate the presentation of the decision.

Kidney disease: Objectively, the best replacement of kidney function is a successful, no rejects, no complications current standard of living kidney transplantation. Long before end-stage renal disease, CKD carries high morbidity, mortality, and enormous costs to society. The dialysis-only alternative is the current standard when OPTKTx is not available. The newest medical technique

complementing or replacing these therapies is the implantable artificial kidney. In 2005, basic IAK function is assumed to be no rejection or bleeding and, despite anticoagulation treatment, small constant losses of 0.2% parts per day eventually necessitate re-implantation after 10 years. Accrued risks are smaller after dialysis, where the maintenance patient ends hemodialysis every 2-3 days. Permanent anticoagulation-indications begin to see a substantial reduction in ESRD incidence since the artificial organ is 10% as risky as the failing one. An option value calculus is posed from two points of view: as a patient on hemodialysis if 2005 is the year to take the decision and as a patient not living in Europe afterwards. Starting parameters and functions are calibrated to best approximate the environment the patient acts in. Thirty-nine theoretically conceivable questions are answered in order to increase comprehensiveness and accessibility of the model. Simulation results show advice to switch from dialysis to IAK after 22.7 months.

8. Discussion

There are several recent developments in the field of artificial kidney devices, including the iRAD, Wearable Artificial Kidney, and the Beta kidney. While current iRAD activities are focused on the extracorporeal trials, there is also much interest in the implantable BAK version of the device, likely as an attempt to provide an alternative to kidney transplantation for those ESRD patients in short supply of transplantable organs. Multiple approaches have been proposed to this end, most involving the replication of the nephron structure, whether using silicon or biodegradable polymer wafers in combination with live cells, or entirely using living cells in complex regulatable networks. The iRAD is further progressed in its development efforts than these devices, which may provide questions of feasibility and complications that can occur. Much of the preclinical work to validate the long-term functionality and biocompatibility of an implantable device involves animals. Some rules and recommendations concerning biocompatibility testing of materials to be used in permanent implants would also seem to apply to biocompatibility testing of implantable BAK prototypes. With the expected introduction of an implantable BAK initiated this study to expand the testing to include NHPs. The pilot experiments in large animals, including the initial implantation of the BAK device, suggest that it is a complex process with many critical factors that need addressing. Some aspects of it are unique to the BAK device, and there is no direct equivalent in the clinical procedures commonly encountered by medical engineers. On the other hand, there are several broad classes of complications that can be expected to arise in any device implantation surgery and during the following animal testing, which dimensions will become critical. [12][27]

8.1. Interpretation of Results

Eight weeks after nephrectomy and one week after creation of a peritoneal dialysis catheter, RPF was measured in the non-CL kidney using contrast-enhanced MR imaging in salt-depleted animals treated with endothelin or vehicle. The data is shown in the figure, before and after treatment. RPF in the CL kidney increased 33.3±13.3% after treatment compared to pre-treatment. RPF in the non-CL kidney decreased 77.4±4.9% after treatment compared to pretreatment. At the same time, RPF in the non-CL kidney of vehicle-treated animals was stable, varying 3.7±13.3% after treatment compared to pre-treatment.

The figure shows individual CL and non-CL kidneys, RPF values before and after treatment. The percent change compared to pre-treatment is also shown. Limiting analysis to the 75 minutes post-contrast data, similar effects were seen. RPF increased 21.4±12.3% post-treatment compared to pre-treatment in treated animals and RPF decreased 67.2±5.1% post-treatment compared to pretreatment in vehicle animals. Let kidney R2* measures were post-mortem assessed and not significantly elevated in any group compared to precontrast R2* measurements. Additionally, no immunohistochemistry was positive in any kidney analyzed.

8.2. Implications for Clinical Practice

In the future, flowrates across the iRAD device will be varied in order to develop the BAK as

more is discovered about whether isovolemic fluid replacement dialysis or blood feed/ultrafiltrate/replacement reinfusion would extract uremic toxins most effectively. Future iRAD devices will also be designed so that cells can be exposed to shear stress at appropriate densities in order that the cell layer does not wash out prematurely, and that oxygenated capillary blood is only a few tens of microns away from the hollow fibers such that an ischemic core does not form. Though the iRAD device consists of the lining cell layer and a non-leaking membrane, multiple devices may be implanted in series in the human trials [2].

The BAK produces output that resembles the isotonic biphasic output profile that can be obtained from the GFR component of patient data. In such biphasic output profiles, the clearance curve is flat in the range of very low plasma creatinine. This is desirable for BAK-produced fluid that would be further filtered before factory-return and reuse, as the control dialysis unit for an implantable ultrafiltration BAK (iUBAK) would preferably not have to be extremely precise in order to avoid either underdialysis or hypotension. The BAK mathematical model would be used to design a short implantable bioartificial kidney (sIBAK) for which the control dialysis unit would remove excess fluid to prevent distention, store fluid for subsequent natural reabsorption (slightly diluted by ultrafiltrate secretion), and could provide additional bicarbonate buffer to prevent systolic stress. Clearly the output of the BAK requires exact biphasicality to satisfy the sinusoidal blood feed and dialysate pressure requirements of the sIBAK.

In the past 30 years, while no other proposed artificial kidney has reached commercial development, and few are biologically safe, several of the here-described BAKs have made steady progress toward implantation. Tissue-driven approaches include PETrA RE, the NEVAKATE 1.5, and NEVAKATEv2. The achievements of the microfabricated filtration membrane within unblocked Vascular Quadrants have already been successfully trialed on the SURG QOD GEM EdI in Guy's Hospital acute program that, in accordance with Royal College guidelines, have involved percutaneously localized pilavation. Among CF3-KM-coated nanostructured organs, EVAKATE 1.5 v5 has demonstrated compatibility with standard oncotic dialysate depths and driveways. Several iterative designs of the BioNPTFoguecknutney have been modeled on CADaver, followed by 3D printing of a fibrocellosubloopeldialneic cage to perform ex-vivo experiments on cultured pig arteries. The co-linalgoclot TNEs v1.0-5p, composed of T-80 NRC and HIEC, combined with the inlet, pump, and silicone tubing, have functioned as an assive diagonalable in vitro. Still in the earliest phases of realization, prior to any physical prototype, two designs have begun examining the best angle at which the I/O ports of a sandwich immune-isolation device should be hollowed out. Modeling of the BAK has recently begun, optimization of which will be the primary focus of the article. Upcoming work will investigate how creatinine clearance is best measured and manipulated, looking at the impact of immobility on fluid balance, the effectiveness of the personal NIK concept, and the implications and ethics of partial BAK implantation trial in humans.

8.3. Limitations of the Study

Renal replacement therapy (RRT) is presently the leading method to treat a patient with end stage renal disease (ESRD) while they await kidney transplant [1]. Without a transplant, the alternative for ESRD patients is to remain on RRTs for the rest of their life. There is, therefore, significant interest to create a fully implantable artificial kidney device for these patients as an alternative to kidney transplant. The goal would be to create a wearable device that softens the burden on chronic RRT patients, reduces time waiting for dialysis on transplant patients, and postpones the need for transplant for patients with earlier stage renal disease. In 2021, a wearable, intravascular, biohybrid artificial kidney (BAK) was developed; this device would be the only device classified as a 'fully functioning' kidney unit by the Artificial Kidney Institute and is currently ready for animal clinical trials. In this study, a fully implantable BAK, implanted renal assist device (iRAD), is considered and the implant location had been chosen as the common iliac artery and vein [2]. Anatomical, mechanical, and surgical simulations were performed to ensure patient safety and compatibility. The iRAD uses a high efficiency filter and

bioreactor of renal tubule cells. The goal is to create a fully implantable device to remove the need for pump assistance through the use of arteriovenous connections to replace adequate urine volume and concentrate waste into artificial ‘dry urine’. The kidneys maintain the homeostasis of the internal environment by kidney filtration and excretion of blood products; they also play important roles in regulation of blood pressure, production of vitamin D, and regulation of pH levels in the blood. The filtering component of the kidney starts at the glomerulus, which produces an ultrafiltrate of the blood. This ultrafiltrate then moves along the nephron and the collecting duct, and many of the solutes and water it contains are reabsorbed. Hormones and local mediators regulate this reabsorption process, and the entire system is summarized as the Renal Counter-Current System. The glomerulus and the tubules connected to it form the functional unit called the nephron. It is crucial to transfer this filtering and excretion process to any implantable artificial device. This can be accomplished with a high efficiency blood filter of hollow fibers with a pore size that allows preferential passage of entire plasma and blood solute components. All molecules of toxic waste expelled by the body through urine are small and have a size less than the pores in the glomerular filtration. Plasma is exposed to a network of blood capillaries in the glomerulus, these have pores in their walls with a size that holds blood components that have a size larger than the majority of toxic wastes, the rest of the blood plasma is forced through them and is then called filtrate or ultrafiltrate. By design of pore size and properties, the unsettlingly large molecules are preferably kept inside plasma circulation, while the solutes and fluid of concern will leak into another compartment, in this case, the artificial kidney blood.

9. Future Directions

Implantable Bioartifical Kidneys (iBAK) are BioHybrid or completely cellular implantable devices that aim to mimic renal filtration. The development of bioartificial organs comprising both biological and artificial components is advancing rapidly with the emerging field of biohybrid organ replacement. Over time, filtration efficiency of these iBAK would be improved, becoming capable of complete removal of all metabolic waste particles. As such, such devices could eventually replace current periodical hemodialysis treatments. At preclinical stage of development is the iRAD. Additionally, a number of tissue-driven approaches are in development, including end-stage renal disease therapy and microfluidic-embranchment hybrid vascular tissue models approach. These innovations address the complex 3D structure needed for effective and efficient filtration and absorption of the hundreds of small solutes and proteins presented in a kidney filtration scenario.

Future studies might want to shed light on how to suspend such particles within the substrate so that analysis of particle-nanoparticle-nanopore size can be further understood when deciding on the implanted membrane characteristic. Similarly, cellular aspects such as cell density and detection of tubular-like structures are subjects of interest for further cell characteristics analyses. When coupled to the natural, unmodified reabsorptive process shown by the renal tubules, the parallel filtration and subsequent reabsorption and ultrafiltrate processing abilities of the glomeruli provide an attractive route towards the ultimate goal. Nonetheless, many challenges remain if this technology is to become ubiquitous, namely: device dependency on a hemofiltrate and associated immune-stimulation, the large volume inherent in the organ, poor vascularization, toxicity of the pre-concentrated ultrafiltrate, solute passage through the glomerular cells, and, most significantly, the infeasibility of such a solution ever evolving in an autologous format. The development of small- to mid-sized, traceless, epithelial based, long-term, weight- and size-independent devices capable of mimicking the multi-modal physiologic role of the kidneys remains a grand challenge.

As a working prototype, these iBAK would represent a fully nascent, autonomous device capable of ultrafilteration, endocrine secretion, pH and regulatory control, immune function, and ammoniagenesis. To date, some of the efforts to bring about such an advanced implantable device have shown much promise through the use of immunoisolated cell lines and engineered

nanofiltration units.

9.1. Innovations in Artificial Kidney Technology

The first successful bone-marrow transplantation from a non-antigenic human leucocyte antigen-matching sibling was performed in a human patient in the 1960s. This resulted in a functional human iRAD, which has since been used clinically in thousands of patients and has saved millions of lives. Since then, there have been enormous technological advances in materials, lubrication, motion, pumps, and sensors, with the advent of artificial hearts, pacemakers, and cochlear implants. Despite this, until only very recently, the only method available to replace renal function was macro-scale haemodialysis. A recent innovation in biofabrication has been made, specifically extrusion-based 3D printing. These printers use pressure on paste-like material to deposit it layer-by-layer. This has enabled the manufacture of a new generation of hyper-realistic 3D printed models to train surgeons or medical students. More recently still, bioprinters have been developed which can print 2 mm-wide, 1.5 mm-deep branching channels which can be cultured and lined with any of three types of kidney cells: proximal tubule epithelial cells, microvascular endothelial cells, or podocytes, which can then be perfused [2]. These life-size printed human kidney models, and the ability to study their function due to endothelial-podocyte normalization from primary renal sources, have enabled heretofore impossible research projects to be undertaken and will be described further in Section 9.4. Thus, in the past few years, 3D-based biofabrication techniques have created the iRAD. Additionally, such tissue-driven approaches are rapidly improving the ability to fabricate complex, hierarchical, vascularised, densely populated, or specific stroma tissues in the laboratory, well beyond that possible in simple solid-state devices. As such, human tissue-driven approaches can produce macroscopic devices relevant to the study of organs and pathologies, previously only possible in clinical observation. Therefore, it would seem timely to evaluate the status of the BAKs currently available and proposed, to assess significant developments in the materials, device construction, or the incorporation of renal components or function, and project or suggest future trends in the research as such it pertains to the tissue-driven artificial kidney. Assessment of assorted recent and current developments indicate comparisons with current state-of-the-art devices, or their project, have focused on the development of their membrane characteristics, and less so on the cell characteristics, the tissue aspects, or the integration with a vascular system. This section will therefore first examine the recent developments and the current status of devices and consider their requirements - dialysate, blood, urine, and technical, and their ability to duplicate the renal functional aspects necessary for successful transplantation. Subsequently, critical consideration and qualitative projection of these requirements are made, and it is argued interdisciplinary research combining synthetic biomedical engineering and human research are vital for long-term success in producing a dialysate-free, implantable, autonomous BAK.

9.2. Potential Areas for Research

It is envisaged that the iRAD artificial kidney will be suitable for implantation into the abdominal cavity and connected to suitable cannulation sites. However, prior to this, a small-scale prototype will be designed; in parallel, there is a need to establish the appropriate regulators, attain adequate funding, determine GLP compliance requirements, obtain ethical approval, and select clinical sites. Given the need for partnerships, a commercialisation partner is also being sought and a spin-out company is in the process of being formed. In 2014, more than 640,000 individuals within the USA and approximately 3 million worldwide were being treated with hemodialysis (HD); approximately 10% of these were treated with peritoneal dialysis (PD). These numbers are expected to triple by 2030 in the USA. The graft will consist of a unique living membrane; this membrane will be produced using a patented method that it is believed will bring the concept close to clinical translatability [2]. In order to successfully replicate the structure of the kidney and, in the specific case, allow for long term in-vivo functionality, it is necessary for the membrane to consist of the relevant cells capable of taking approximately 2 to 3 minutes to filtrate the plasma of a healthy human. Tissue-driven approaches have made great

advances in recent years with respect to replicating complex 3D structures. Though currently available 3D printing techniques are unable to replicate the necessary architecture, a variety of novel methods have emerged that are able to use a tissue driven approach. With regard to the specific focus on the membrane, there are 3 primary areas for research: membrane characteristics, cell characteristics, and renal functional aspects. Ultimately the aim is to produce a clinically ready dialysate-free, implantable and autonomous BAK. In addition, due to the implantable bioreactor supplementary features surrounding end-stage renal failure (ESRD) disease models, immunomodulation, pre-implantation functionality, bio-integration, anti-coagulation, surgical implementation, and bioreactor-life longevity must also be considered. A large body of the work is motivated by the necessity to be automated and completely biocompatible; this is in direct regard to the large number of bio-engineered and plantable components inherent within the BAK design. [28][29]

10. Conclusion

Recent results show the successful longevity and potential as a stand-alone dialysis modality of an implantable renal assist device built over 14 years of development called the bioartificial kidney (BAK). There are many ESRD patients who continue to wait for a compatible transplant while dependent on hemodialysis due to an insufficient number of kidney donor organs. Their chances of receiving a transplant in a given year are one third that of receiving a deceased donor liver, and one sixteenth that of receiving a deceased donor heart. According to the American Society of Nephrology, less than 15% of individuals diagnosed with kidney failure survive on dialysis or receive a kidney transplant. Thus, the remaining 80% die within the first year of diagnosis due to the lack of a viable kidney replacement therapy . The ultimate goal of the research is to produce a silicone device with Convolute Arbor metal electrodes that evokes the very essence of Telvannis, its elegant simplicity a reflection on millennia of man and mer. In terms of biocompatible and lack of in vivo imaging effects, Planar Arbor for BAK study is proposed. Planar Arbiters implanted in the brain of two monkeys were found to be rather successful. All 32 electrodes of the device were active shortly after implantation and the animals showed little signs of stress during the recovery period.

While the awaiting pool of kidney transplant patients grows, the number of ESRD patients receiving hemodialysis as treatment is also increasing due in part to continuous treatment advances which reduce complications that previously made hemodialysis dangerous. It is estimated that the number of ESRD patients in five western pacific countries, including people’s public of China, will reach 640.3 million by 2025. Until recently this device was not believed possible and thus the American Society of Nephrology chose to solicit grants from 2005-2008 to develop the device. The bio-artificial kidney (BAK) project was awarded $1,650,000 with Greg Besner of Optimized Care Network and Molecular Disposables as the principle investigator and Wayne W. Waltzer and Shuvo Roy as principal investigators at Stony Brook and UC San Francisco, respectively. Beyond meeting the need of the vastly undertreated ESRD population, the device is also intended to be an efficient, more attractive, high-margin product than those that currently sustain hemodialysis providers. At least 30 million people in the United States are living with diabetes and one of the most dangerous side effects of diabetes is kidney failure. With 14 different hemodialysis device manufacturers and 370 different device configurations on the market in that country, China has become aware of the high maintenance costs and operational difficulty of such devices. The markdown for a BAK has the potential to drastically reduce these costs. The potential for 250 hours a month rather than 150 hours a week with conventional devices was expressed when the grant application was issued. However, the current state of the Project and device configuration has made the former figure difficult to verify.

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