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EDITORIAL

Lindner C, Riquelme R, San Martín R, Quezada F, Valenzuela J, Maureira JP, Einersen M. Improving the radiological diagnosis of hepatic artery thrombosis after liver transplantation: Current approaches and future challenges. *World J Transplant* 2024; 14(1): 88938 [DOI: [10.5500/wjt.v14.i1.88938](https://doi.org/10.5500/wjt.v14.i1.88938)]

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REVIEW

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MINIREVIEWS

Maqbool S, Baloch MF, Khan MAK, Khalid A, Naimat K. Autologous hematopoietic stem cell transplantation conditioning regimens and chimeric antigen receptor T cell therapy in various diseases. *World J Transplant* 2024; 14(1): 87532 [DOI: [10.5500/wjt.v14.i1.87532](https://doi.org/10.5500/wjt.v14.i1.87532)]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Isa HM, Alkharsi FA, Khamis JK, Hasan SA, Naser ZA, Mohamed ZN, Mohamed AM, Altamimi SA. Pediatric and adult liver transplantation in Bahrain: The experiences in a country with no available liver transplant facilities. *World J Transplant* 2024; 14(1): 87752 [DOI: [10.5500/wjt.v14.i1.87752](https://doi.org/10.5500/wjt.v14.i1.87752)]

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Observational Study

Pahari H, Raj A, Sawant A, Ahire DS, Rathod R, Rath C, Sankalecha T, Palnitkar S, Raut V. Liver transplantation for hepatocellular carcinoma in India: Are we ready for 2040? *World J Transplant* 2024; 14(1): 88833 [DOI: [10.5500/wjt.v14.i1.88833](https://doi.org/10.5500/wjt.v14.i1.88833)]

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SYSTEMATIC REVIEWS

Chongo G, Soldera J. Use of machine learning models for the prognostication of liver transplantation: A systematic review. *World J Transplant* 2024; 14(1): 88891 [DOI: [10.5500/wjt.v14.i1.88891](https://doi.org/10.5500/wjt.v14.i1.88891)]

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CASE REPORT

Sánchez Pérez B, Pérez Reyes M, Aranda Narvaez J, Santoyo Villalba J, Perez Daga JA, Sanchez-Gonzalez C, Santoyo-Santoyo J. New therapeutic strategy with extracorporeal membrane oxygenation for refractory hepatopulmonary syndrome after liver transplant: A case report. *World J Transplant* 2024; 14(1): 89223 [DOI: [10.5500/wjt.v14.i1.89223](https://doi.org/10.5500/wjt.v14.i1.89223)]

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Artificial kidney: Challenges and opportunities

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Abstract

This review aims to present the developments occurring in the field of artificial organs and particularly focuses on the presentation of developments in artificial kidneys. The challenges for biomedical engineering involved in overcoming the potential difficulties are showcased, as well as the importance of interdisciplinary collaboration in this marriage of medicine and technology. In this review, modern artificial kidneys and the research efforts trying to provide and promise artificial kidneys are presented. But what are the problems faced by each technology and to what extent is the effort enough to date?

Key Words: Artificial kidney; Implantable kidney; Hemodialysis; Peritoneal dialysis; End-stage kidney disease

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Core Tip: Different technologies of artificial kidneys have been proposed and still there is no one capable of fully replacing the renal function properly. Many problems such as bioavailability, potential contamination and other variables must be controlled to make such a device successful. Herein, the most important efforts for the creation of wearable and implantable kidneys are mentioned and in addition, the principles that these devices should be governed are discussed as well.

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INTRODUCTION

This report aims to present the developments occurring in the field of artificial organs and particularly focuses on the presentation of developments in artificial kidneys. Through the operation of the biological kidneys that takes place within the exhibition, the difficulties and requirements that must be overcome by the biomedical engineering community in order to achieve the creation of fully functional artificial kidneys can be seen. Next, the modern artificial kidneys and the research efforts trying to provide and promise artificial kidneys are presented. But what are the problems faced by each technology and to what extent is the effort enough to date?

To begin with, the function of each organ in the human body is special and many times its function is irreplaceable since each one is charged with at least one distinct function. Nevertheless, there are functions in the organism that may be covered by two or more organs or systems since the control of a parameter may be influenced by more than one factor. An example is the pH balance of the blood which is controlled by the lungs, kidneys and by regulatory means within the tissues and blood. These include the need to control and measure the operation process of the instrument, which is a multifactorial function since each instrument is charged with many functions.

The kidney is the first organ to be replaced *ex vivo*[1] and today its support with artificial kidneys is a widespread rationale. Hemodialysis in general is an expensive procedure with alternatives to other methods of artificial kidneys and solutions, pharmaceutical methods and kidney transplantation. Transplantation is difficult to happen since it is difficult to find a donor but even if found it is very likely that the transplant will not be compatible. For all these reasons and for other shortcomings of conventional treatment, the existence and research of artificial kidneys is essential. But has it reached a satisfactory level so far? As stated in Groth *et al*[2], "By 2030, 14.5 million people will have end-stage kidney disease (ESKD, or CKD stage 5)".

TECHNICAL DIFFICULTIES OF CREATING AN ARTIFICIAL KIDNEY

A purely technical difficulty that needs to be overcome is the biocompatibility of an instrument. Biocompatibility according to IUPAC is "the ability of a material to be in contact with a living system without producing undesirable effects"[3]. Compatibility with blood is also required so that it does not coagulate or create clots and deposits in the devices. An additional technical difficulty is the risk of contamination in each of the existing artificial kidney devices that are being investigated especially in those handled by patients.

Another important factor for the creation of an artificial organ is the understanding of homeostasis, *i.e.* the innate function of the organism to keep its values constant is the main parameter that must be considered for the total replacement of an organ with an artificial one and an adequate device must cover all functions of the instrument. The artificial organ should be able to communicate with the organism's environment and not be a passive device that will include reagents to achieve the final result.

KIDNEYS

In the human body there are two kidneys that work in parallel in the blood flow. Their shape is cuboid and its size is about 11-13 cm long, 6 cm wide and 3 cm thick. They weigh approximately 120-170 g each and in the human body are located within the retroperitoneal space, lateral to the spine at the level of the T12-L3 vertebrae. The function of the kidneys in the human body is multidimensional. Its main function is to filter the blood from harmful and unnecessary substances for the functioning of the body and finally to clean it. It is typical that the kidneys produce about 2 L of excretes per day[4]. Blood pH, the concentration of various ions, blood pressure, blood toxicity and the volume of water excreted by the body are controlled.

In addition to these functions, the kidney is responsible for the secretion of hormones for the functioning of the body's homeostasis. For this reason, it is also called an endocrine organ. More specifically, the kidney can: Regulates blood pressure through renin, prostaglandins and kinins; Regulates red blood cell production with erythropoietin; It contributes to the regulation of vitamin D metabolism; They are a major source of the growth hormone BMP-7.

The kidneys receive 1.2-1.3 L/min of blood, about 25% of the minute blood volume. From this amount of blood the amount that is cleaned or filtered per unit of time from unwanted substances is the known glomerular filtration rate (GFR) and in a healthy kidney it is 50-60 mL/min[5]. 99% of the filtered liquid is reabsorbed. The GFR is a measure of whether a kidney is functioning adequately and whether a transplant or mechanical support is needed. When the two kidneys give a GFR of about 30 mL/min, then the symptoms of kidney failure begin to appear. Hemodialysis treatment is recommended when GFR is around 5-9 mL/min and when there are other indications without GFR being the only criterion[6].

Diseases in which the patient needs mechanical support or transplantation and which artificial kidneys aim to help are acute renal failure and chronic renal failure, but other diseases may also require a patient to use an artificial kidney. So each device should cover the above functions and requirements and if it is implantable it should cover the spatial requirements given by the human structure.

DIALYSIS

Dialysis is an old method that was used and is still used today by patients with kidney failure. Dialysis and specifically hemodialysis devices are the first artificial kidneys, even though they were not implantable in the body.

It is based on the use of diffusion as well as ultrafiltration. In essence, the blood flows on one side of a semi-permeable membrane and on the other side of the membrane there is a solution and due to the difference in concentrations of the substances, waste leaves the body. An obvious shortcoming of the method is that it cannot replace the endocrinological function of the kidney. That is, it does not produce or provide the body with the hormones produced by a kidney.

Dissolution includes two main types by which it is applied: Hemodialysis (HD); Peritoneal dialysis (PD).

The operating principle of hemodialysis is simple blood and a solvent liquid with approximately similar concentrations of substances to human plasma. The two fluids flow countercurrently for greater efficiency separated by a semipermeable membrane where substance exchange takes place and thus unwanted components are removed from the blood. During hemodialysis, however, only the blood is cleaned, not all the substances produced by a normal kidney are produced by the artificial kidney device.

Hemodialysis is performed continuously for patients in hospitals and in hemodialysis care units or clinics, but it is also performed intermittently for 3-5 h each time and 3-4 times per week, constituting a time-consuming process. To avoid this dead time (*i.e.*, 9-20 h per week), which can affect a patient's psychology, the procedure in some countries is done while the patient is sleeping at night. Another negative of hemodialysis is that since the blood is cleaned periodically, there are times when the patient has very high concentrations of harmful and unnecessary substances in the blood, so they may feel discomfort. Although hemodialysis technology has improved considerably, patient mortality and morbidity rates seem to be quite high for decades[7]. It is also worth noting that researchers have shown that better results for the patient exist with continuous hemodialysis or more frequently than is done now[7].

Peritoneal dialysis is a method that does not involve blood. It is done inside the peritoneal cavity and the patient has a tube with which he can put a solvent into the cavity, exchange substances with the vessels in the cavity and the liquid expels it through the tube outside the cavity. Relatively fewer patients choose this route, approximately 11% of the population, than hemodialysis[8]. The method can be applied to the patient with mechanical support, with automated peritoneal dialysis or done manually by the patient with continuous ambulatory peritoneal dialysis (CAPD).

Due to the above, many researchers thought that portable devices should be created that, in the best of cases, could be worn by the patient in a vest or a special case in order to achieve continuity in hemodialysis or peritoneal dialysis and to provide the possibility for the patient to be more autonomous from the hemodialysis clinics.

THE WEARABLE DEVICES

The idea of creating a portable kidney that can be applied on a belt or vest would give benefits from more frequent hemodialysis and the psychological benefit that patients would have from the ability to go wherever they want and not have the routine of hemodialysis in hospital is worth researching such a device. These devices show several advantages over conventional methods.

The first attempts were made by Willem Kolff and coworkers, as stated in a recent paper of Kooman *et al*[9], where they created a wearable artificial kidney device that weighed 3.5 kg a downside to the hypothesis was that it required the device to be periodically connected to 20 L of diluting fluid[9]. A few years later in 1986 a technique using adsorbents and enzymes was developed on which the wearable artificial kidney (WAK) device was based[9]. The device was tested on humans using it as a dialysis device for 4-8 h[9,10]. The device went through many improvements, and it was studied whether the blood and diluent supply should be continuous or pulsatile, where pulsatile flow was found to be better[11]. It is a device that was among the three winning devices in the Food and Drug Administration's (FDA) Innovation Pathway 2.0 competition in April 2012[12]. In general, it is the crown jewel of wearable artificial kidneys and is expected to greatly help patients with kidney failure. In a recent FDA-approved human trial of the wearable artificial kidney the results showed that the treatment with the wearable artificial kidney was well tolerated and in addition the treatment resulted in fluid homeostasis and effective uremic solute clearance and maintenance of electrolyte[13].

Beyond this logic there is also another way to create an artificial kidney capable of being worn using peritoneal dialysis as a starting point. For the creation of such a device it has been proposed under the name Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)[14]. The device has not yet been tested in clinical trials and does CAPD[14], the device uses minimal solvent fluid which is regenerated using sorbent media. Even with the device, the patient can see the course of his treatment through a control panel or a computer.

The efforts of scientists from California[15,16] are also in the same way, *i.e.* the creation of a peritoneal dialysis device, called AWAK (Automated Wearable Artificial Kidney), that can be worn by the patient. Their device is already manufactured and cannot be bought yet[16].

Additionally, another notable effort is that of Wearable Bioartificial Kidney which uses sorbents to filter the peritoneal fluid and bioartificial renal epithelial cell systems (BRECS), units in which human renal epithelial cells are preserved, technology to give metabolic abilities thanks to the renal epithelial cells[17]. With the use of BRECS, a corresponding portable device could be made where hemodialysis would be performed instead of peritoneal dialysis[17].

Although the above devices solve the problem of the periodicity of blood purification by giving continuous hemodialysis and give patients the possibility to move autonomously, they are not implantable and are visible when the patient wears them.

A recent idea for a miniaturized wearable dialysis device capable for CE marking is the Wearable Artificial Kidney (WEAKID). WEAKID is based on continuous flow peritoneal dialysis using single lumen fluidic access (*i.e.*, abdomen). The peritoneal dialysate is continuously circulated and refreshed by a wearable sorption unit. Thus the device is removing toxins from the dialysate. The technology of the WEAKID has been demonstrated in preclinical research. It is suited both for portable dialysis (8 h/night) and wearable dialysis (16 h/d)[18].

Another device is the Carry Life System that was designed by the Swedish company Triomed AB (Lund, Sweden)[2]. This device uses two single-lumen catheters that provide continuous flow peritoneal dialysis with continuous dialysate recirculation. More on this device can be found on the recent review of Groth *et al*[2].

BIOARTIFICIAL KIDNEY

In this category belong devices that use, in addition to filtering the blood, the technology of biotechnology. These are devices that are connected in series with a membrane or some other material to filter the blood, but also a bioreactor with kidney cells inside to achieve metabolic and endocrinological functions corresponding to those of a natural kidney.

This operating concept was first initiated by Aebischer[7] and his colleagues and thus began the bioartificial kidney (BAK). Since the late 1990s, two main groups have been working on the idea of creating such a device, although there are several other researchers[10]. One team is based in Japan with Akira Saito and his colleagues and the other team is based in the United States with David Humes and his colleagues.

Humes' team created the first BAK device to receive approval for clinical trials from the FDA. The device had a polymeric semipermeable polysulfone or polysulfone membrane. To get there he started using porcine kidney cells or LLC-PK1 getting positive results and later for safety reasons in case toxins were created in the body, human kidney epithelial cells were used and finally human cells were clinically tested in humans. However, the program was terminated for safety reasons[1,10]. More specifically, the device construction and maintenance as well as the problem of cell maintenance and supply were reasons why the program did not proceed to the next phase [1]. It is worth noting that the device that the device worked as an extracorporeal device and needed a pump for blood flow. Saito's group also did many tests with LLC-PK1 and concluded that it would be better to use other cells[7]. In 2013 a group of Oo *et al.* made a BAK device with better than usual hemocompatibility and better results than other studies, the study was done in large animals[19].

General difficulties in creating BAK are that there is a good filter to filter the blood, that there is safe and sufficient functioning of renal epithelial cells, and that all parts of the system are fully biocompatible and do not react with blood so that the filter does not clog. There was still the difficulty of preserving the cells so that there would be enough of them, which was done with BRECS where they can store epithelial kidney cells from humans and they were able to preserve them through cryopreservation of cells for six months (Buffington *et al*[1], 2014). So, the cell preservation problem seems to have a solution. BRECS have only been tested in preclinical settings.

The principle of operation of Humes' devices was taken as a basis for work by a group of scientists led by Shuvo Roy and William H. Fissell and with several collaborators among them and Humes' idea was to create an implantable BAK device which created the kidney project and in turn the implantable BAK, which was one of the three winning ideas in the Innovation Pathway 2.0 competition[12]. The device contains a series of silicon membranes and will be coated to achieve biocompatibility with blood, which has been tested in short-term trials in pigs and rats[20]. Another innovation of the device is that it does not require a pump for blood flow to the device but only needs the human heart to work[20]. The device has not yet entered human clinical trials and is expected to begin during this decade. Currently the device is on a Phase 2 trial and program leaders aspire that the device will begin manufacturing[21]. In Table 1, there is a summary of the wearable and implantable devices referred in the current article. A great question to be answered is what will be the fouling in the silicon-based filters and how this could be overcome. In addition, what kind of renal cells will be used and how their perpetual growth will be sure for a prolonged period. What is the cutoff cell mass and total surface area necessary to mimic the working performance of two fully functional kidneys? Finally, will this device be economically viable for a company and the patients.

FUTURISTIC APPROACHES

From a technology that is already almost in use (*i.e.*, wearable kidneys) and a technology that could be used in this or the next decade in patients (*i.e.*, implantable kidney) we are moving to technologies that are quite far from clinical application considering the problems that these technologies must solve for successful clinical application and large-scale production. This technology concerns tissue engineering and regenerative medicine, both are branches of biomedical engineering, as well as the previous devices (*i.e.*, wearable kidneys and implantable kidney) are also included, where from scratch or with the use of a scaffold it is attempted to create a part of the organ or a fully functional organ.

Table 1 A summary of the wearable and implantable devices referred in the current article

Device name	Brief characteristics	Mode of work
WAK	Hemodialysis device	Wearable
ViWAK PD	Not yet tested in clinical trials, peritoneal dialysis device	Wearable
AWAK	Peritoneal dialysis device	Wearable
WEBAK	Peritoneal dialysis device	Wearable
WEAKID	Peritoneal dialysis device	Wearable
CLS	Peritoneal dialysis device	Wearable
iBAK	Contains silicon membranes, not yet tested in clinical trials, does not require external power source	Implantable

WAK: Wearable Artificial Kidney; ViWAK PD: Vicenza Wearable Artificial Kidney for Peritoneal Dialysis; AWAK: Automated Wearable Artificial Kidney; WEBAK: Wearable Bioartificial Kidney; WEAKID: Wearable Artificial Kidney; CLS: Carry Life System; iBAK: Implantable Bioartificial Kidney.

To better understand the achievements of tissue engineering and regenerative medicine, their efforts should be divided into efforts to create a whole kidney and efforts to create a part of the kidney.

The first category includes techniques such as the decellularization and recellularization of a scaffold and 3D printing. The second category includes techniques such as 3D printing as well as the use of microfluidics in order to create glomerulus-on-a-chip and tubule-on-a-chip. It is useful to comment that even if not used in the near future in kidney transplantation, it is possible that these technologies will be used in drug testing and in the study of disease pathophysiology. More on these technologies can be found in two recent reviews of Peired *et al*[22] and Ibi *et al*[23].

CONCLUSION

Comparing all the functions and different technologies of artificial kidneys from the first devices until today it is evident that the researchers wanted to provide the first and main solution to the non-functioning of the kidneys, *i.e.* the purification of the blood from unnecessary substances. The other functions of the kidneys were replaced by medicinal solutions. The problem of non-portability and the inability to move due to the large devices gave efforts to the research of wearable artificial kidneys, this solution looks very promising, but these devices are not implantable. Also, the logic of fully approaching the functions of the kidneys by a device is given by the Renal Assist Device and they are still being studied today and have reached very good and promising results to achieve the final goal of an implantable kidney. The research effort so far has positive results and indications for even better, but even more work and research are needed now that the population of the earth is increasing, and the costs of conventional hemodialysis remain high.

FOOTNOTES

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