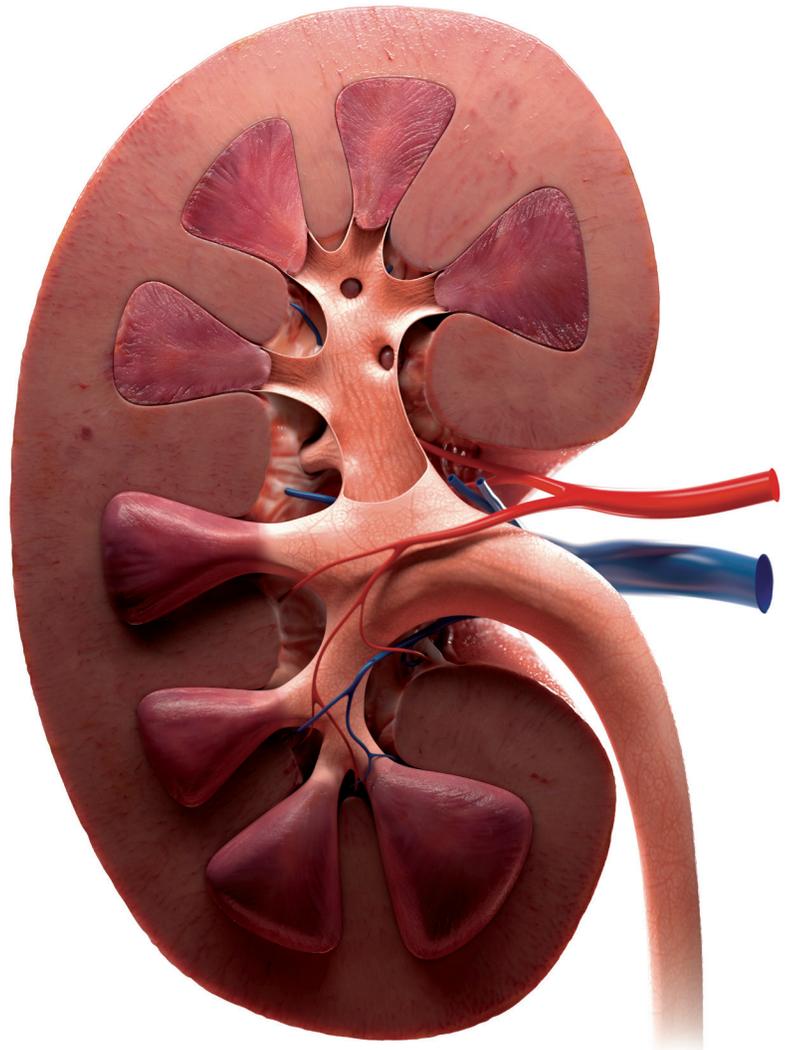

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Wearable
Artificial
Kidneys for
End-Stage
Kidney
Disease



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Summary

- Other than a kidney transplant, dialysis is the main treatment option for people with end-stage kidney disease; but dialysis facilities have limited capacity and are associated with significant costs – both to the health care system and to patients.
- Longer, more frequent dialysis sessions (ideally, daily or nightly) with home dialysis may provide better health outcomes at less cost, but most Canadian patients currently receive dialysis three times per week in dialysis facilities.
- Three small safety-and-feasibility human trials of one device, the Wearable Artificial Kidney (WAK), have been published.
- Several important technical issues with wearable artificial kidneys remain unresolved.
- Commercial availability of a wearable artificial kidney is still several years away.

Background

In end-stage kidney disease, the kidneys no longer adequately clear the blood of wastes and excess fluids. Most individuals with end-stage kidney disease receive dialysis treatment to compensate for some of the lost kidney function by removing excess fluids and metabolic wastes – such as urea – that accumulate in the blood. Although dialysis removes fluids and wastes, it does not replace the kidneys' role in regulating metabolism, endocrine function, and homeostasis (maintaining stable physiological processes such as blood pressure, electrolyte balance, acid-base balance, and temperature).¹⁻⁶

Providing patients who have end-stage kidney disease with more frequent and longer dialysis sessions can improve blood pressure control; weight and nutritional status; reduce stress on the heart; and clear the blood of toxins, wastes, and excess fluids at a more gradual rate that more closely resembles the continuous process performed by healthy kidneys.^{3,7-14} Unfortunately, because dialysis is an expensive treatment and dialysis centre capacity is limited, health care systems often lack the resources to provide more frequent or longer treatment sessions to patients.¹⁵⁻¹⁸ Moreover, the changes patients must make to their diets, and the need to travel to receive dialysis treatment, negatively affect the quality of patients' daily lives.¹⁹

Research is underway to develop a wearable artificial kidney that would allow individuals to receive dialysis as they go about their daily activities, improving the removal of wastes and fluids through more frequent, longer, or continuous dialysis sessions.³ This could improve patient health while reducing the impact of treatment on quality of life.^{12,19}

Current Practice

A kidney transplant is the best treatment for most patients with end-stage kidney disease, but the shortage of donor organs means this option is not available to many who might benefit.^{2,4} In 2014, 1,430 Canadians received kidney transplants, 3,473 were still on the waiting list, and 67 people died while waiting for a kidney transplant.²⁰

Dialysis is the only other treatment option for patients with end-stage kidney disease. It can be delivered in two ways: hemodialysis or peritoneal (through the abdomen) dialysis.

Hemodialysis

In hemodialysis, a patient is connected to a machine that circulates their blood through a membrane (dialyzer).⁹ The membrane removes waste products from the blood while at the same time returning other elements, such as red blood cells, back to the patient's body.⁹

Hemodialysis can be performed in dialysis centres or at home, with different frequencies and durations of treatment. Patients receiving in-centre hemodialysis usually have three four-hour sessions each week.^{18,21} Home hemodialysis may be performed on a more frequent schedule, or for longer periods of time, and can be done during the day or overnight.²²

Because it requires access to a patient's vascular system and anticoagulant drug therapy to prevent blood clots, hemodialysis is more complex than peritoneal dialysis (discussion to follow).^{6,9,23}

Peritoneal dialysis

Peritoneal dialysis uses the patient's peritoneum (the membrane lining the inner wall of the abdominal cavity) to remove wastes.^{9,23} Dialysate (a pre-packaged solution of purified water, glucose, and minerals) is placed in the abdominal cavity through a catheter. The dialysate remains inside the abdomen for a few hours, allowing wastes to diffuse from the blood vessels in the peritoneum into the dialysate solution. The dialysate is then drained from the abdominal cavity.

Peritoneal dialysis can be administered during the daytime as a continuous process during which patients are free to move about, and whereby the dialysate solution is kept in the abdomen and is drained and replaced usually three to five times per day, seven days per week.^{19,24,25} Or, it may be administered overnight through automated or nocturnal intermittent peritoneal dialysis, during which the patient is connected to a cyclor machine that automates the exchanges.^{19,24}

Peritoneal dialysis is usually performed at home, making it more convenient for patients. As it does not require access to the blood vessels or anticoagulant therapy, it offers some advantages over hemodialysis.⁶ However, it has an increased risk of peritonitis (infection of the peritoneum), less control over ultrafiltration (fluid removal), and lower waste clearance rates than hemodialysis.^{3,6} As well, after long-term exposure to glucose from the dialysate, the peritoneum may no longer function as well as previously for removing wastes.^{3,6,9}

Opportunities for technological advancement

Dialysis, in any form, has a negative impact on quality of life. Individuals undergoing dialysis must avoid certain foods and limit their consumption of fluids.¹⁹ Supplements and medications are needed to replace nutrients lost during treatment, and post-treatment fatigue is common.^{12,26}

Conventional hemodialysis machines are heavy, need to be connected to an electrical outlet, and use many litres of water each session.²⁷ Similarly, even though they are considered to be portable, the weight of home dialysis equipment and the need for an electrical connection, as well as the volume of dialysate needed, mean that the patient's mobility is restricted for many hours during treatment.^{3,6}

The out-of-pocket costs of home peritoneal or home hemodialysis may be a barrier for some patients.²⁸ These costs include increased utility bills for water and electricity, consumables (such as dialysate), and home plumbing and electrical renovations needed to accommodate the equipment.^{18,28} Home dialysis may also place demands on caregivers who take responsibility for monitoring the safety of the person undergoing the procedure.²³

Out-of-pocket costs to patients for in-centre dialysis — in particular, the potential loss of employment because of the time needed for dialysis and the transportation costs of travelling to and from dialysis treatments several times each week — can also cause difficulty, particularly for elderly patients and those in remote communities.^{19,23,29}

The Technology

Building a wearable artificial kidney

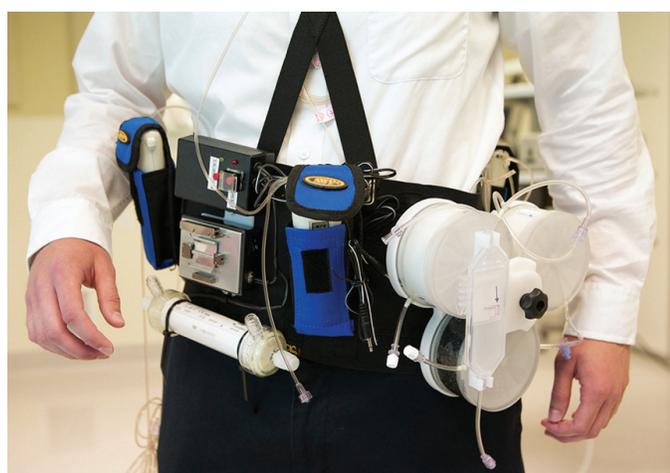
Researchers have attempted to develop a wearable artificial kidney since the early days of dialysis but were limited by the technologies available at the time.^{19,27} Since then, developments in various fields of research have made lightweight, wearable dialysis systems feasible. These advances include the miniaturization of sensors and pumps;⁷ small, long-lasting batteries;^{27,30,31} ultra-permeable membranes that reduce dialyzer size;^{7,32,33} and new filtration materials to cleanse and reuse dialysate solutions without the need for large quantities of purified water.^{7,19,34,35}

The main components of a wearable artificial kidney are, as follows:

- dialysis membrane
- dialysate regeneration
- vascular access
- patient monitoring
- power source
- pumping system.⁷

Table 1: Wearable Artificial Kidneys in Development

Device Name	Company/Developer (Country)	Type of Dialysis	Website
Wearable Artificial Kidney (WAK) ^{12,16}	Blood Purification Technologies Inc. (formerly Xcorporeal Inc.) (US)	Hemodialysis	https://www.facebook.com/Wearable-Artificial-Kidney-by-Blood-Purification-Technologies-Inc-361780453898407/
Automated Wearable Artificial Kidney Peritoneal Dialysis System (AWAK PD) ^{23,38,39}	AWAK Technologies Pte. Ltd.(US/Singapore)	Peritoneal dialysis	http://www.awak.com/
Vicenza Wearable Artificial Kidney (ViWAK PD) ^{6,23,27,34}	International Renal Research Institute of Vicenza/IRRIV, San Bortolo Hospital (Italy)	Peritoneal dialysis	http://www.irriv.com/
Nanodialysis (the NaNo) ^{23,40}	Nanodialysis BV (The Netherlands)	Hemodialysis and peritoneal dialysis combined	http://www.nanodialysis.nl/
Carry Life Renal	Triomed AB (Sweden)	Peritoneal dialysis	http://triomed.se/renal



The WAK. Image courtesy of JCI Insight.¹²

In a 2011 paper, three of the leading researchers in the field described the following requirements for a wearable artificial kidney for performing hemodialysis:²⁷

- vascular access that allows blood flow of around 100 mL per minute – a flow less than is used for conventional hemodialysis but adequate because the system would operate for longer periods (or continuously)

- vascular access that poses a low risk for infection and clotting, and is easy for patients to connect and disconnect
- a minimal quantity of dialysate solution that can be regenerated and reused by the system
- a non-clotting membrane for the dialyzer
- a solute clearance rate of approximately 20 mL per minute, with ultrafiltration of not more than 5 mL per minute
- patient monitoring to alert for air bubbles, blood leakage, or other safety problems, and to shut down the system when necessary
- wearability that allows the patient to be mobile (i.e., not too heavy, designed to fit the body, and not requiring a connection to an electrical outlet).²⁷

Urea removal is another challenge in the design of wearable artificial kidneys – because of the quantity of urea produced each day.^{3,36} Resolving this is critical for developing a system that can regenerate the dialysate.^{3,36}

The WAK Wearable Artificial Kidney

Five wearable artificial kidneys appear to be in development (see Table 1). Only one of these devices – the Wearable Artificial Kidney or WAK (Blood Purification Technologies Inc., Los Angeles, California) – has published results from studies in humans.^{12,16}

The WAK is worn on a belt around the waist and weighs approximately 5 kg.¹² The device includes a miniature, battery-powered pump to power the flow of both the blood and dialysate, and additional micro pumps to control ultrafiltration (fluid removal), the infusion of anticoagulants, and the delivery of other substances to the dialysate. Safety mechanisms include a bubble detector and wetness sensors at the arterial and venous access sites to detect blood leaks. Unlike hemodialysis systems intended for home use, which can require large volumes of purified water, the WAK requires only 400 mL of sterile water.^{12,37}

Availability

No wearable artificial kidney has received regulatory approval for marketing in Canada or elsewhere. In the US, the FDA accepted the WAK system for the Expedited Access Pathway (EAP) program.¹⁷ This program is intended to improve clinical data collection and reduce the time to regulatory approval for innovative technologies that serve important clinical needs.⁴¹

“Currently, 77% of Canadians receiving dialysis are treated with in-centre hemodialysis.”

Who Might Benefit?

The number of new cases of end-stage kidney disease in Canada, and worldwide, is increasing — mainly due to aging populations and increasing rates of diabetes and hypertension.^{15,42,43} The prevalence of end-stage kidney disease in Canada increased by approximately 3% each year from 2004 to 2009.⁴⁴ The 2014 Canadian Organ Replacement Register reported that 35,281 Canadians (not including Quebecers) were living with end-stage kidney disease, and 20,690 Canadians were receiving dialysis.²¹ Each year, approximately 3,000 more Canadians begin long-term dialysis therapy.⁴⁵

Currently, 77% of Canadians receiving dialysis are treated with in-centre hemodialysis.²¹ The remainder receive some form of dialysis treatment at home. Peritoneal dialysis use varies across Canada, ranging from about 20% to 36% of dialysis patients (not including those in Quebec).⁴⁵ About half of these patients use automated nocturnal peritoneal dialysis.¹⁵

In the US, the ECRI Institute estimated that 40% to 60% of eligible American patients, particularly those already using home peritoneal dialysis and hemodialysis, may choose to use a wearable artificial kidney — if they are found to be as safe and effective as conventional forms of dialysis.⁴⁶

The Evidence

To date, the WAK is the only wearable artificial kidney that has been tested in human studies, with published results.^{12,13,16,47,48} Our literature search found one recent trial of the WAK, published in 2016.¹² This was a small, non-randomized pilot study of seven patients who wore the device in a US hospital.¹² Five of the seven patients in the study used the WAK for the full 24-hour study period. All patients had conventional hemodialysis for four hours shortly before using the WAK and received anticoagulant therapy to prevent clotting. Participants were not required to follow any dietary restrictions during the study.¹²

Clinical efficacy

The outcomes measured in the trial included solute clearance, and electrolyte and volume homeostasis while the patients were using the WAK.¹² Participants' electrolyte levels remained stable throughout the 24 hours. Solute clearances and fluid removal were gradual and adequate, but clearance of beta2-microglobulin (a middle molecule used as a surrogate for the clearance of other similar-sized wastes) was lower than with conventional hemodialysis, possibly because of the lower blood flow used (see Table 2: Outcome Measures in the US WAK Trial). Phosphorous binding medications were not used, although in some patients blood serum levels of phosphorous increased over the 24 hours.¹² Average systolic blood pressure declined from 140 ± 23 mm Hg at baseline to 127 ± 6 mm Hg after the WAK treatment.¹²

Patient satisfaction

Patients reported more satisfaction with the WAK treatment than with conventional hemodialysis, particularly in terms of convenience, freedom, fit with their lifestyle, reduced treatment-related side effects, and less discomfort during treatment.¹²

Table 2: Outcome Measures in the US WAK Trial

Study	Number of Patients/Average Age	Average Blood Flow \pm SD (mL/min Over 24 Hours)	Average Dialysate Flow \pm SD (mL/min Over 24 Hours)	Average Solute Clearances \pm SD (mL/min Over 24 Hours)	Average Ultrafiltration Volume \pm SD (mL Over 24 hours)
Gura et al.(2016) ¹²	7 (5 completed the study) /49 years (range 27 to 73 years)	42 \pm 24 mL/min	43 \pm 20 mL/min	BUN (17 \pm 10) creatinine (16 \pm 8) phosphorus (15 \pm 9) beta2-microglobulin (5 \pm 4)	1,002 \pm 380 mL (the difference between prescribed and actual ultrafiltration was 3 \pm 15 mL)

BUN = blood urea nitrogen; mL/min = millilitres per minute; SD = standard deviation; WAK = the Wearable Artificial Kidney (Blood Purification Technologies Inc.).

Technical problems

The WAK study intended to enrol up to 10 patients, but the trial was stopped after the seventh patient because of technical problems with the device; two patients did not wear the WAK for the full 24-hour study period.¹² Although the sorbents used to regenerate the dialysate generally worked as anticipated, ammonia levels were elevated in the dialysate circuit for one patient, possibly due to saturation of the sorbent, which was subsequently replaced. Problems with the tubing occurred multiple times (affecting blood or dialysate flow and requiring repositioning or unkinking). Other problems included a pump dysfunction; bubbles forming in the sorbent cartridges, dialysate, or blood circuit; a cracked bubble trap; and low battery power on the main pump.¹²

One patient experienced clotting at the venous access port. One patient stopped using the WAK after four hours because of clotting in the blood circuit, and the other stopped after 10 hours because of pinkish discoloration of the dialysate.¹² Two devices required battery replacement during the 24 hours. Variability in blood and dialysate flow was noted in most patients, possibly caused by excess carbon dioxide bubbles causing resistance in the circuit. Gas bubbles were removed from the circuit in three devices. However, the bubble detector alarm worked and shut down the main pump, as intended.¹²

Earlier research

Two earlier pilot studies of the WAK have also been reported.^{13,16,47,48} One study, conducted in Italy and published in 2008, assessed the WAK's potential as an ambulatory ultrafiltration device for patients with congestive heart failure.⁴⁸ Six hemodialysis patients with fluid overload used the device anywhere from four to six hours. The amount of fluid removed ranged from 120 mL to 288 mL per hour. Patients' heart and respiratory rates remained stable, and most experienced a slight decrease in blood pressure.⁴⁸

The second WAK study, a small UK pilot study, included eight patients who used the prototype device for four to eight hours.^{13,16,47} Their usual hemodialysis vascular access and anticoagulant doses were used, and they were allowed to eat and drink without restriction.

Participants' heart rate, blood pressure, and electrolyte and acid balances all remained stable. No clinically significant damage to red blood cells (hemolysis) was noted. Clearance of urea, phosphates and middle molecules was lower than that with conventional three-times-a-week hemodialysis, but was adequate given the longer and more frequent dialysis treatment anticipated with the WAK.^{13,16}

All participants in the UK pilot study stated they would recommend the treatment to other patients.¹⁶

Safety

In the seven-patient US study, no serious adverse events were reported.¹² Some patients reported mild hand or leg cramping, which resolved either when the ultrafiltration rate was decreased or without treatment.¹² In five patients, temporary episodes of irregular heartbeat were noted.¹² No signs of clinically significant hemolysis were apparent.¹²

“...the use of wearable artificial kidneys will cost substantially less (30% to 40%) than conventional dialysis if remote monitoring systems are incorporated to allow for reduced staff-to-patient ratios...”

Vascular access is one of the most problematic areas for hemodialysis because of risks of blood loss, air embolism, infection, and clotting.^{3,49} In the UK pilot study, clotting occurred in two patients who were not receiving adequate doses of anticoagulant at the time.¹⁶ Vascular access for a wearable dialysis unit is also complicated by movement, which may dislodge the needle or the tubing, thus causing blood leakage, or kinking of the tubing thus causing blockage.^{3,49}

One patient in the UK study experienced needle dislodgement, but, as intended, the safety system of the device stopped the blood pump.¹⁶ Carbon dioxide bubbles were also reported in the dialysate but not in the blood compartment of the device. The investigators noted that this problem will need to be resolved in future iterations of the device.¹⁶

In the Italian study, a clot formed in the catheter in one of the six patients and treatment was stopped after four hours. No other serious adverse events or technical problems were reported.⁴⁸

Administration and Cost

Peritoneal dialysis and at-home hemodialysis are less costly than in-centre hemodialysis.^{15,50} In 2013, the estimated annual per-patient costs of the three treatment modalities used in Canada were \$56,000 for peritoneal dialysis; \$71,000 to \$90,000

for home hemodialysis; and \$95,000 to \$107,000 for in-centre or satellite unit hemodialysis.¹⁵

None of the wearable artificial kidneys in development are currently marketed, and cost information is not available. The developer of the WAK believes the costs of the WAK and monthly disposable supplies will be less than those of current hemodialysis systems.⁵¹ A 2014 ECRI Institute report forecasts that the use of wearable artificial kidneys will cost substantially less (30% to 40%) than conventional dialysis if remote monitoring systems are incorporated to allow for reduced staff-to-patient ratios for dialysis care.⁴⁶

Dialysis patients who use a wearable artificial kidney will still need to be monitored by health professionals and attend regular clinic visits for the replacement of supplies and device maintenance. However, the frequency of these visits is not yet known.^{52,53}

As with other forms of home dialysis, patients, caregivers, and health care professionals will need training on the use of a wearable artificial kidney.⁴⁶ No information specific to training requirements for wearable artificial kidneys was found, but it may be similar to the training provided for home dialysis.

Concurrent Developments

Home dialysis

Home dialysis has advantages over in-centre hemodialysis, and offers potential cost-savings to the health care system (although costs to patients may be higher).^{3,15,19,50} Several portable home hemodialysis systems are available in Canada; for example: NxStage System One (NxStage Medical Inc.), 2008K@home (Fresenius Medical Care), and SC+ hemodialysis system (Quanta).^{4,54,55} A clinical trial of the Tablo hemodialysis machine (Outset Medical, Inc.) for use by patients both in-centre and at home is underway.^{56,57}

Bioartificial kidneys

Still only in animal studies, researchers are trying to grow a kidney using embryonic kidney cells, adult stem cells, and by cloning kidney tissue.² Several research groups are working on implantable, bioartificial kidney prototypes.^{1,5,17,58} The bioartificial kidney under development through The Kidney Project at the University of California in San Francisco is intended to be fully implantable, similar to a kidney transplant but without the need for immunosuppressant drugs; a wearable version may be developed in the interim.^{59,60}

Innovative BioTherapies, Inc. (Ann Arbor, Michigan) is developing a Bioartificial Renal Epithelial Cell System (BRECS) – a wearable bioartificial kidney grown from adult, progenitor kidney cells sourced from non-viable donor organs.^{61,62} According to the company website, preclinical trials followed by human trials are expected within three to five years.⁶³

Other innovations

Qidni Labs Inc. (Kitchener, Ontario) is investigating potential nanotechnologies for miniaturized dialysis components in implantable systems.^{26,64}

A peritoneal dialysis system that can recycle dialysate will require fewer connections and reconnections, possibly reducing the risk of peritonitis.¹⁹ Because the additional complications of vascular access are not involved, wearable peritoneal dialysis devices could reach the market before wearable hemodialysis devices.³

Rate of Technology Diffusion

No wearable artificial kidney is commercially available and timelines for availability are unknown.

Some of the barriers to self-care noted with other home dialysis modalities may also affect the eventual adoption of wearable artificial kidneys; for example, the need for patient training and support to use the technology, and health system reimbursement for the devices and the supplies required.²⁹

“A wearable artificial kidney is intended to improve patient quality of life but evidence of this is still lacking.”

Implementation Issues

A wearable artificial kidney will need capabilities for remote monitoring of both equipment and patient-related data to ensure patient safety and allow changes in dialysis parameters.^{30,31}

Patient monitoring systems are needed to alert the user and remote medical staff to problems and to low battery charge on the pump.^{27,49} These safety systems should also detect potential adverse events, such as low blood pressure, fluid imbalance,

and changes in blood composition.⁵³ A 2011 paper noted the following patient and device-related parameters that should be monitored with a wearable artificial kidney for hemodialysis:³¹

- **patient parameters** including blood pressure, pulse, blood levels of oxygen, heart rate, blood volume, access flow, needle dislodgement (“wetness sensor”), the patient’s dialysis prescription, and time and duration of dialysis³¹
- **device parameters** including air or bubble detection; blood leakage; dialysate, blood, and ultrafiltration rates; clearance; anticoagulant administration; hemolysis; and battery life.³¹

Processes for the safe use of the wearable artificial kidney during sleep and to ensure sterile storage of the device when it is not in use also need to be determined.⁵²

Concerns about the environmental impact of dialysis – in particular, the energy requirements, water use, and disposables involved – have led researchers in some countries to explore “green dialysis.”^{65,66} This includes the use of alternative energy sources, such as solar energy, to power dialysis facilities; post-treatment uses for the purified waste water; and plastics recycling.⁶⁵ Wearable artificial kidneys may offer a more environmentally friendly dialysis option – at least in terms of reducing water use,¹⁹ and possibly reducing the carbon footprint for travel to in-centre treatments.

Final Remarks

A wearable artificial kidney is intended to improve patient quality of life but evidence of this is still lacking. Ideally, it will improve fluid balance and, therefore, blood pressure control. It may also allow patients to eat and drink without dietary restrictions on fluid intake and on foods that contain salt, potassium, or phosphorus. Consequently, the need for vitamin supplements and medications (such as phosphate binders) may be reduced.^{13,27} A wearable artificial kidney may also reduce the time and costs associated with travel to in-centre treatments.¹⁹

Whether patients will want to wear a dialysis unit continuously or for extended periods of time is not yet clear.³ As with home peritoneal dialysis and hemodialysis, the wearable artificial kidney will place more responsibility for self-care on the patient, and not all patients (or their caregivers) will be comfortable with or be capable of managing the processes involved.⁵³

As home dialysis systems become smaller, cheaper, and easier to use, some of the impetus for developing a wearable dialysis device may diminish (personal communication: Dr. Robert Pauly, University of Alberta, Faculty of Medicine and Dentistry, Edmonton, AB, 7 Nov 2016). CADTH, furthermore, is currently assessing how existing dialysis modalities, including home-based peritoneal dialysis and hemodialysis, could be most effectively used and in a way that more appropriately supports patient needs and preferences.⁶⁷

There are still many technical hurdles to be overcome, and longer-term studies with patients in home settings are needed.^{12,51} For this reason, several more years of development are likely before a wearable artificial kidney is commercially available.^{68,69}

Methods – Literature Search Strategy

A literature search was conducted using the following bibliographic databases: PubMed, MEDLINE, Embase, the Cochrane Library (2016, Issue 6), and the Centre for Reviews and Dissemination databases (DARE, NHS EED, and HTA). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published within the last five years (January 1, 2011 to June 22, 2016). Regular PubMed, MEDLINE, and Embase alerts were established to update the search until November 29, 2016.

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