

β_2 -Microglobulin and Phosphate Clearances Using a Wearable Artificial Kidney: A Pilot Study

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Background: Additional small-solute clearances during standard thrice-weekly hemodialysis treatments have not improved patient survival. However, these treatments have limited middle-molecule clearances. Thus, newer therapies designed to increase middle-molecule clearances need to be developed and evaluated.

Study Design: Pilot clinical trial to measure β_2 -microglobulin and phosphate clearances with a wearable hemodialysis device.

Setting & Participants: 8 regular hemodialysis patients under the care of a university teaching hospital.

Intervention: Patients were fitted with a wearable hemodialysis device for 4 to 8 hours.

Outcomes: All patients tolerated the treatment.

Results: Average amount of β_2 -microglobulin removed was 99.8 ± 63.1 mg, with mean clearance of 11.3 ± 2.3 mL/min, and an average of 445.2 ± 326 mg of phosphate was removed, with mean plasma phosphate clearance of 21.7 ± 4.5 mL/min. These clearances compared favorably with mean urea and creatinine plasma clearances (21.8 ± 1.6 and 20.0 ± 0.8 mL/min, respectively).

Limitations: Proof-of-concept preliminary trial. Additional studies are warranted to confirm these positive preliminary data.

Conclusions: This wearable artificial kidney potentially provides effective β_2 -microglobulin and phosphate clearances and, by analogy, middle-molecule clearances.

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INDEX WORDS: Chronic kidney disease; hemodialysis; wearable artificial kidney; phosphate; β_2 -microglobulin; clearances.

Traditionally, the dose of hemodialysis delivered to a patient with chronic kidney disease (CKD) stage 5 has been based on urea clearance using the Kt/V model.¹ However, there are several paradoxes between survival of patients with CKD stage 5, particularly in the United States, and the general population. For example, morbid obesity (body mass index > 35 kg/m²) is an increased risk factor for

mortality in the general population, but a positive survival advantage in American hemodialysis patients with CKD stage 5.² Similarly, in the general population, women tend to outlive men, but the reverse was observed in the US-based Hemodialysis (HEMO) Study.³ One potential explanation for these paradoxical results would be that in a hemodialysis program more and more financially driven to achieve a critical Kt/V threshold, larger patients are dialyzed longer than smaller patients.⁴ This difference in duration of hemodialysis session may allow greater removal of solutes other than urea.

The European Dialysis and Transplant Association set up a working party to reexamine the concept of azotemia, rather than uremia. This working party has considered more than 50 potential azotemic toxins that are retained in patients with CKD.⁵ Typically, these molecules are larger than urea and in an ill-defined category of middle molecules.

There is mounting evidence from the treatment of dialysis patients with CKD stage 5 that removal of these so-called middle molecules is not only a function of dialysis efficiency,⁶ but

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Figure 1. Photograph of the wearable hemodialysis device. Reprinted from Davenport et al.²²

also is dependent on the actual duration of the dialysis session.⁷ Because many of these compounds require specialized analytical methods, β_2 -microglobulin often is used as a surrogate middle-molecule marker, and further analysis of the HEMO Study reported that increasing predialysis serum β_2 -microglobulin concentration was a primary risk factor for mortality.⁸ Recent studies have suggested that the addition of convection to conventional dialysis, by increasing

middle-molecule clearances, improves patient outcomes and survival.⁹⁻¹¹ Although hemodiafiltration and high-flux membranes enhance their removal compared with low-flux dialysis,^{5,6} their clearance is low and longer dialysis session time appears to be necessary to reduce plasma concentrations.⁷ Furthermore, the total amount of β_2 -microglobulin removed with standard thrice-weekly 4-hour hemodiafiltration sessions is much less than the estimated weekly generation of

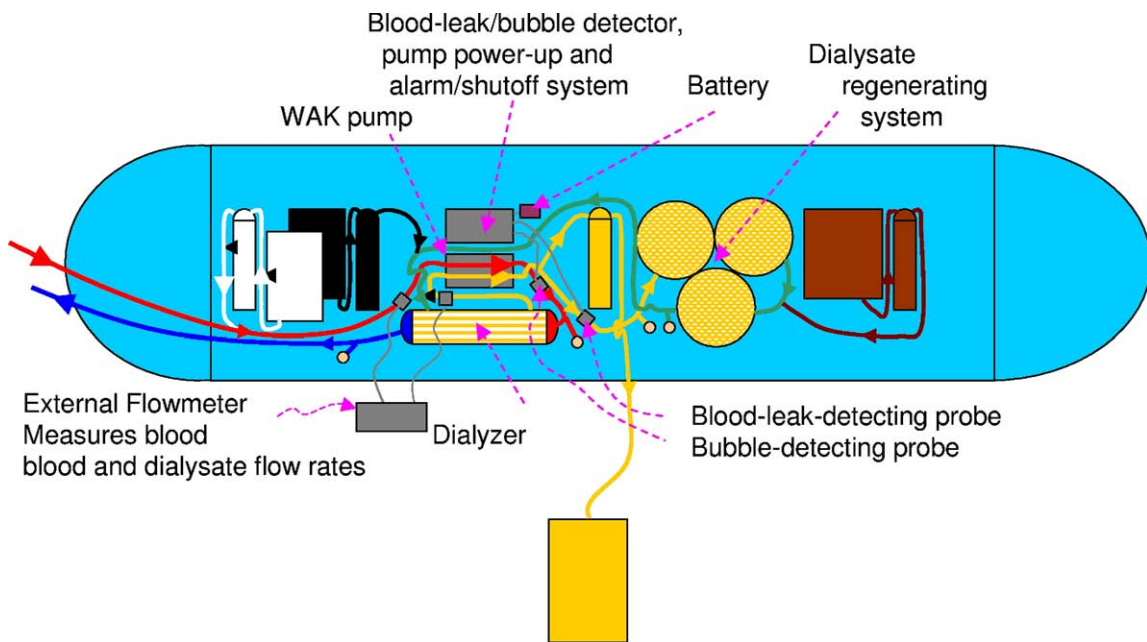


Figure 2. Circuit diagram of the wearable hemodialysis device. Abbreviation: WAK, Wearable Artificial Kidney. Reprinted from Davenport et al.²²

β_2 -microglobulin.¹² Because the volume of distribution of these molecules in the body primarily is intracellular and not intravascular, the prompt rebound in plasma concentrations after therapy supports the notion that only prolonged treatment can be effective in clearing middle molecules.^{7,13}

Similarly, phosphate retention is a common problem in hemodialysis patients because if patients achieve the nutritional targets set out for patients with CKD stage 5, their phosphate intake will be in the order of 1,000 to 1,500 mg/d (32 to 48 mmol/d), with 600 to 1,000 mg (19 to 32 mmol) absorbed from the gastrointestinal tract. Unfortunately, because the phosphate pool is mainly intracellular rather than intravascular, phosphate is not removed effectively by using conventional thrice-weekly dialysis.¹⁴ Increasing dialyzer surface area, dialysate flows, and even adding convective losses with hemodiafiltration have reported varying phosphate losses ranging from 750 mg (22 mmol)¹⁵ to 820 to 1,150 mg/treatment session (26 to 37 mmol).¹⁶

Data from patients with CKD stage 5 on daily dialysis therapy show that given enough time on dialysis, serum phosphate concentrations can become normalized or even necessitate phosphate supplementation.^{17,18} Therefore, a prolonged form of dialysis could help control phosphate and improve middle-molecule clearances. However, facilities to provide all patients with prolonged overnight dialysis are not readily available. One option would be to develop a wearable device, designed to be worn for prolonged periods. We developed a battery-operated Wearable Artificial Kidney (WAK) that delivers continuous ambulatory hemodiafiltration.^{19,20} A simplified version for hemofiltration has been tried successfully in humans,²¹ and we reported the clinical safety parameters of the first human trial of this WAK as an ambulatory push-pull hemodiafiltration device.²² We therefore elected to investigate whether this device has the capability to efficiently clear β_2 -microglobulin and phosphate from hemodialysis patients with CKD stage 5.

METHODS

This was a prospective nonrandomized pilot study designed as proof of concept that was approved by the UK Medicines Health Regulation Authority (MHRA) and the local hospital ethics committee.²² Eight patients (5 men)

with a mean age of 51.7 years (range, 26 to 67 years) with established CKD treated by using regular thrice-weekly hemodialysis were studied.

The WAK (Xcorporeal Inc, Los Angeles, CA) used a standard commercially available dialyzer (Polyflux 6H; Gambro Dialysatoren, Hechingen, Germany). Dialyzer specifications were polysulphone membrane (Gambro Dialysatoren), effective membrane area of 0.6 m², wall thickness of 50 μ m, inner diameter of 215 μ m, ultrafiltration coefficient of 33 ± 20 mL/h · mm Hg, in vitro clearances with a dialysate flow of 500 mL/min reported as 50 ± 5 mL/min for both urea and creatinine and 49 ± 5 mL/min for phosphate, and a sieving coefficient of 0.63 ± 0.13 for β_2 -microglobulin, with a specially designed pulsatile blood pump that used a standard



Figure 3. Photograph of patient wearing the wearable hemodialysis device.

9-V battery as the energy source, which pumped the blood and dialysate in a countercurrent direction (Figs 1 and 2). To allow wearability, 375 mL of dialysate was recirculated and regenerated by using a series of sorbent canisters. Briefly, the sorbent system consisted of an initial layer of urease that splits urea into ammonium and carbon dioxide. The carbon dioxide remains in solution and is removed by using a degassing mechanism with a semipermeable membrane. The ammonium then is adsorbed by a layer of zirconium phosphate, which also removes cations (calcium, magnesium, potassium, and other metals that may be present). The next layer removes phosphate and fluoride. Next there is a layer of activated charcoal that removes creatinine, as well as other organic compounds, and middle molecules. Mean blood flow was 58.6 ± 11.7 (SD) mL/min, with a dialysate flow of 47.1 ± 7.8 mL/min.²² There were additional micropumps (Sorenson, West Jordan, UT) to regulate heparin infusion into the blood circuit, sodium bicarbonate, calcium, and magnesium acetate and control ultrafiltration. The total weight of the device was 5 kg (Fig 1).

Dialysate and blood samples for β_2 -microglobulin and phosphate were obtained during our original study.²² β_2 -Microglobulin was measured by using rate nephelometry on a Beckman Coulter Image 800 (Beckman Coulter, Fullerton, CA) using reagents (β_2 -microglobulin PET kit catalogue no. K0052) from DakoCytomation, Denmark A/S, Glostrup, Denmark. Phosphate was measured by using an autoanalyzer colorimetric assay with end-point determination and sample blanking. In the presence of sulfuric acid and ammonium molybdate, inorganic phosphate forms an ammonium phosphomolybdate complex with the formula $(\text{NH}_4)_3[\text{PO}_4(\text{MoO}_3)_{12}]$. The complex was determined photometrically in the UV region (340 nm) by using a Roche Modular P analyzer (Roche Diagnostic Systems, Maidenhead, UK), which also was used to analyze urea and creatinine.

Calculated clearances were obtained from the formulae:

$$\text{Amount removed} = \text{Qb} \cdot t(1 - \text{hct})(C_{\text{in}} - C_{\text{out}})$$

$$\text{Clearance (K)} = \text{Qb} \cdot (1 - \text{hct})(C_{\text{in}} - C_{\text{out}})/C_{\text{in}}$$

$$\text{Standard urea clearance} = \text{K} \cdot t/V$$

where Qb is blood flow rate in milliliters per minute, t is time, hct is hematocrit, C_{in} is the concentration of solute

entering the dialyzer, C_{out} is the concentration of solute exiting the dialyzer, and V is volume of body water.

Statistical Analysis

Student *t* test and analysis of variance were used for analysis, and for paired data, Student *t* test was used. Statistical significance was considered at $\alpha = 0.05$ by using Prism, version 3.02, graphics and statistical package (GraphPad, San Diego, CA). Data are expressed as mean \pm SD unless otherwise specified.

RESULTS

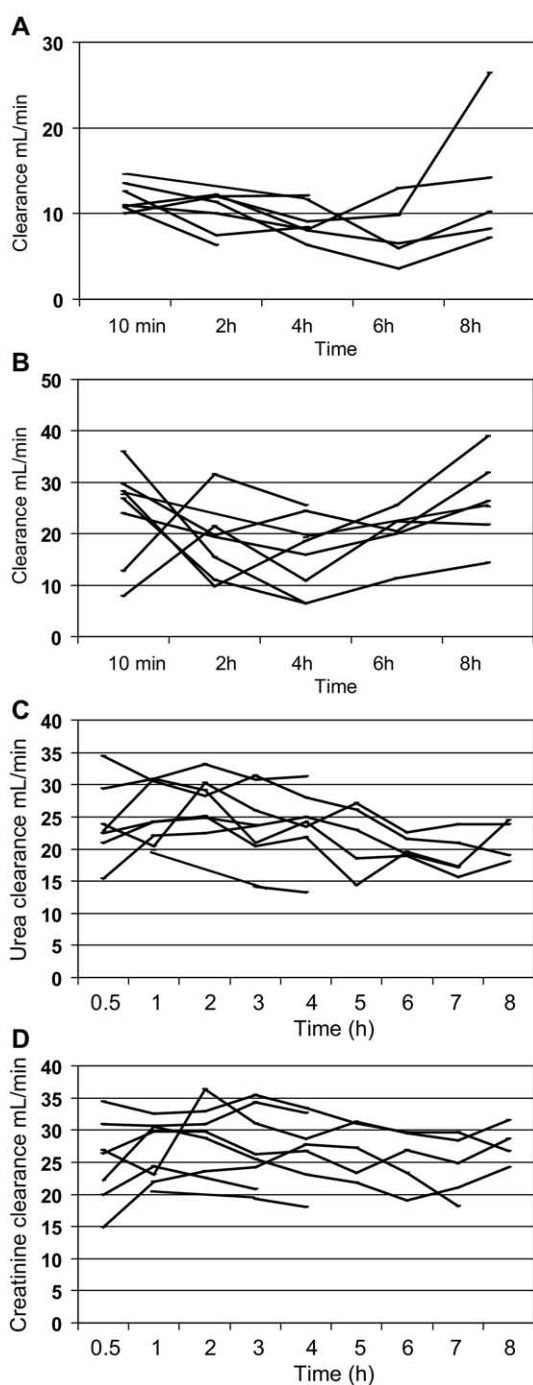
We previously published safety data for this trial, and all patients were hemodynamically stable during treatment.²² No patient reported symptoms or ill effects and all were satisfied with treatment using the WAK (Fig 3). Patients underwent systemic anticoagulation using unfractionated heparin according to their standard regimen for intermittent hemodialysis. As per practice, the heparin infusion was discontinued 20 to 30 minutes before the end of the treatment session.²³ In 2 patients, this led to clotting of the WAK dialyzer either at the time of discontinuation or shortly before. The MHRA required that all patients use their standard vascular access, and in 1 patient, there was dislodgement of the venous needle from an arteriovenous fistula. Unlike a conventional dialysis machine, this was detected promptly by the safety sensor and the blood pump stopped. The needle was reinserted and treatment continued.

Before starting treatment, mean serum β_2 -microglobulin level was 23.48 ± 4.44 mg/L (0.020 ± 0.004 mmol/L) and phosphate level was 3.53 ± 2.48 mg/dL (1.14 ± 0.80 mmol/L). Average hourly amount of β_2 -microglobulin removed was 15.59 ± 9.86 mg/h (1.32 ± 0.84

Table 1. Total Amounts and Clearances of Phosphate and β_2 -Microglobulin Removed During Treatment With the Wearable Artificial Kidney

Patient No.	Time (h)	Inorganic Phosphate Removed (mg)	β_2 -Microglobulin Removed (mg)	Inorganic Phosphate Clearance (mL/min)	β_2 -Microglobulin Clearance (mL/min)
1	4	252.1	28.7	19.2	10.0
2	4	331.4	79.7	23.1	12.1
3	4	317.1	62.7	23.9	12.1
4	7	1,105.8	183.5	25.0	12.1
5	8	590	123.5	24.2	10.9
6	8	151.3	12.9	27.1	7.1
7	8	662.0	146.8	16.9	15.2
8	8	151.6	160.7	14.0	11.0
Mean \pm SD	6.4 \pm 2.0	445.2 \pm 325.9	99.8 \pm 63.1	21.7 \pm 4.5	11.3 \pm 2.3

$\mu\text{mol/h}$), with β_2 -microglobulin clearance of 11.3 ± 2.3 mL/min (Table 1). During the study period, β_2 -microglobulin clearance appeared to remain relatively stable and did not decrease significantly after 6 or 8 hours (Fig 4A).



Similarly, the average amount of phosphate removed was 445.2 ± 325.9 mg at a mean hourly rate of 69.56 ± 50.92 mg/h (2.24 ± 1.64 mmol/h), with plasma phosphorus clearance of 21.7 ± 4.5 mL/min (Table 1). During the study period, plasma phosphate clearance was stable and did not appear to decrease with time (Fig 4B). Mean plasma urea and creatinine clearances were 21.8 ± 1.6 and 20.0 ± 0.8 mL/min and did not decrease over time, respectively (Fig 4C and D).

DISCUSSION

Typically, β_2 -microglobulin and phosphate clearances are much less than those of urea and creatinine during standard thrice-weekly hemodialysis. However, in this study, average β_2 -microglobulin clearance was almost 50% that of urea and 55% that of creatinine, with phosphate clearances greater than 85% of and greater than 95% those of urea and creatinine, respectively. These data are consistent with our previous in vitro laboratory studies, which showed that the pulsatile blood/dialysate pump produced a “push-pull” type of hemodiafiltration, effectively removing β_2 -microglobulin from normal blood because nearly all the β_2 -microglobulin cleared into the dialysate was adsorbed by the sorbents.²⁴ Operating blood and dialysate flows of the WAK are very low compared with conventional thrice-weekly hemodialysis, but more in keeping with those during continuous hemodialysis and/or filtration,²⁵ as practiced in the intensive care unit, rather than conventional thrice-weekly hemodialysis. Previous clinical studies of solute clearances with similar dialysate flow rates and dialyzer surface area, but greater blood

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Figure 4. Clearance measurements for individual patients during treatment with the wearable hemodialysis device. (A) Plasma β_2 -microglobulin clearance (10-minute clearance versus 2 hours, $P = 0.1$; versus 4 hours, $P = 0.008$; versus 6 hours, $P = 0.1$; versus 8 hours, $P = 0.3$). (B) Plasma phosphate clearance (10-minute clearance versus 2 hours, $P = 0.4$; versus 4 hours, $P = 0.1$; versus 6 hours, $P = 0.5$; versus 8 hours, $P = 0.5$). (C) Plasma urea clearances during the study (0.5 hours compared with 1 hour, $P = 0.3$; 2 hours, $P = 0.09$; 3 hours, $P = 0.5$; 4 hours, $P = 0.7$; 5 hours, $P = 0.6$; 6 hours, $P = 0.2$; 7 hours, $P = 0.1$; 8 hours, $P = 0.3$, respectively). (D) Plasma creatinine clearances (0.5 hours compared with 1 hour, $P = 0.2$; 2 hours, $P = 0.2$; 3 hours, $P = 0.1$; 4 hours, $P = 0.2$; 5 hours, $P = 0.8$; 6 hours, $P = 0.5$; 7 hours, $P = 0.3$; 8 hours, $P = 0.9$, respectively).

flow rates and lower hematocrit, reported β_2 -microglobulin clearance to be 20% that of urea and 22.9% of creatinine, and similarly, for phosphate to be 84% that of urea and 96% that of creatinine.²⁶ In particular, β_2 -microglobulin clearance was 40% greater than that previously reported when using continuous slow dialysis.²⁶

This was the first time that patients were treated using this WAK, and as such, duration of treatment was strictly limited by the UK MHRA. Additional trials are required to determine the capacity of the current sorbent system. During treatment (4 to 8 hours), there was no apparent decrease in β_2 -microglobulin clearance after 6 and 8 hours, although the number of patients studied was small. If these clearances were to be repeated in additional trials, extrapolation of these preliminary results to a daily basis suggests that the WAK theoretically would be able to remove 5.3 mg/kg/d (an average of 16 mg/h for a 70-kg adult), thus potentially exceeding the reported daily production rate of 3.65 mg/kg/d.¹² However, prolonged treatment would be expected to reduce baseline serum concentrations and thus reduce overall clearance. We have to determine whether removal of β_2 -microglobulin by using this WAK is representative of the clearance of other potential middle-sized uremic toxins.

Effective removal of phosphate by using the conventional thrice-weekly dialysis schedule appears impossible to achieve because the total amount removed is far less than typical dietary phosphate intake.²⁷ Despite dietetic advice,²⁸ restriction of phosphate in the diet alone similarly cannot achieve effective control of hyperphosphatemia, and about half the patients with CKD stage 5 have significant hyperphosphatemia.²⁹ Failure to adequately clear phosphate during conventional thrice-weekly hemodialysis occurs because the rate-limiting step to phosphate removal is time for adequate refilling of plasma from intracellular stores.

However, longer dialysis time achieved by means of daily or nocturnal dialysis has achieved adequate control of hyperphosphatemia, either greatly diminishing the number of phosphate binders required³⁰ or making these agents completely unnecessary.³¹ Similarly, it is well recog-

nized that hypophosphatemia is a complication of continuous renal replacement therapy in the intensive care unit setting.³²

The amount of phosphate removed by using this WAK was 0.026 mmol/min (0.806 mg/min) and did not decrease during the study period. However, these encouraging results require further substantiation with longer trials. Because this WAK is intended to be used continuously, it allows sufficient time for effective phosphate clearance,¹⁶ and extrapolating the clearance, daily phosphate removal would approximate 37 mmol/d (1,161 mg/d). The total amount of phosphate absorbed by a healthy adult has been estimated to range from 10 to 30 mmol/d (0.32 to 0.97 mg/d).^{33,34} Thus, the daily rate of removal by this WAK could potentially reduce or eliminate the need for phosphate binders, similar to that observed with frequent nocturnal dialysis.¹⁷

The WAK is designed to work continuously, and as such, maintaining the integrity of the circuit and preventing extracorporeal thrombosis is important because circuit clotting is the Achilles' heel of continuous renal replacement therapy.³⁵ In this pilot study, circuit clotting occurred in 2 patients shortly after heparin dose was reduced and/or withdrawn. Increased exposure to heparin potentially could lead to the development of platelet factor 4-heparin complexes.³⁶ Thus, future trials will need to explore the use of alternative anticoagulants, such as the oral direct thrombin inhibitors.

Control of hyperphosphatemia and clearance of middle molecules seems to be solved best by more frequent and longer dialysis duration. Development of a WAK as a continuous treatment potentially would afford enough treatment time to accomplish this objective and may potentially improve both morbidity and mortality for hemodialysis patients.

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