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Article

Acute Effect of Intradialytic Aerobic Exercise on Hemodynamic Response, Dialysis-Related Side Effects and Proteome in Patients with Kidney Failure: A Pilot Study

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ABSTRACT

Background/Objectives: Hemodialysis (HD) is the renal replacement therapy with the most adverse side effects, including variations in blood pressure (BP). Intradialytic exercise (IDE) seems to be the non-pharmacological approach of choice for managing treatment-induced symptoms. The objectives were (1) to evaluate the effect of acute IDE on hemodynamic response (BP) and short-term treatment-associated symptoms in patients with kidney failure and (2) to test the feasibility to quantify the proteome of these patients in response to IDE and establish its relationship with BP variations during HD.

Methods: Ten adults undergoing HD completed a randomized crossover study with two experimental conditions (HD; HD with IDE). BP was measured before and after HD, and at five time points following conditions. Symptom burden was assessed 24 h and 7 days after each condition. Blood samples were collected for proteomics analysis at the end of conditions.

Results: IDE downregulated BP during HD without adverse events and decreased the desire to sleep in the 2 hours following HD. Proteomics

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analysis revealed that five proteins were downregulated and seven upregulated in response to IDE, although it was not associated with BP variation.

Conclusion and Implications: A single session of moderate-intensity IDE seems sufficient to improve BP control and to reduce the desire to sleep after treatment without any adverse effects. This study also demonstrates that it is feasible to quantify the proteome in individuals with kidney failure, which could lead to the development of precision interventions in exercise to improve the quality of care for deconditioned, multimorbid individuals.

KEYWORDS: hemodialysis; intradialytic cycling; therapeutic targets; blood pressure; proteomics; treatment-related symptoms

INTRODUCTION

Over the past 20 years, the number of people with kidney failure in Canada has more than doubled from approximately 18,000 to 40,000 [1]. This prevalence is increasing with age, which poses significant challenges for health care considering the aging of the population we are witnessing [2,3]. Indeed, older adults with kidney failure are a complex population often presenting multiple chronic diseases and a higher risk of premature mortality [4]. Hemodialysis (HD), which is the most prevalent modality of renal replacement therapy, occurs thrice weekly and comes with adverse side effects both during and after treatment [5,6]. Intradialytic hypotension (IDHypo) and hypertension (IDHyper) are risk factors for cardiovascular and all-cause mortality in this population [7]. IDHypo, which is a more prevalent complication of ultrafiltration during HD treatment, represents a serious adverse effect for patients. Indeed, it is associated with high patient distress during HD, vascular access failure, as well as cardiovascular and neurological events [8]. End-organ damage and cognitive impairment are well-know short to long term effect of HD in adults with kidney failure [7,9]. Symptoms like cramps, dizziness and vomiting are also associated with blood pressure drop during HD [10,11]. While disrupted renal metabolism plays a role in the development of hypertension [12], it was reported that IDHypo is caused by acute hypovolemia during ultrafiltration with inadequate compensatory mechanisms [13], in addition to inappropriate dry weight setting, decline in plasma refilling rate, decreased cardiac function, and abnormalities of the autonomic nervous system [14]. More recently, it was also suggested that relative change in protidemia level surpasses ultrafiltration rate to predict the 30-day risk of IDHypo [15], raising the relevance of joining proteomics and clinical data to improve the management of side effects.

HD also has side effects that can last from a few hours to a few days after the treatment, which considerably impairs the health-related quality of life (HRQoL) of affected patients [5,16,17]. Fatigue, feeling drowsy and pain are the main physical symptoms experienced while feelings of sadness, irritability and nervousness are among the most reported at the psychological level [5,18]. A better symptom management is undoubtedly critical in this population. While most health interventions are developed with a disease-centered approach to optimize treatment, the patient-centered approach is known to increase adherence to treatment [19], such as physical exercise [20]. This explains the emergence of primary care models that incorporate patient-reported outcome measures (PROMs) in electronic medical records so that they can be systematically integrated with medical data and considered in medical decisions [21]. PROMs are recommended for use in performance evaluation because they have the potential to improve care quality and offer information on patient functional status and well-being. However, a recent scoping review showed that in exercise and kidney disease, studies assess PROMs with broad, generic HRQoL measures and that information on the effect of exercise on shorter-term symptoms is still scarce [22].

According to the latest report by the American College of Sports Medicine the popularity of aerobic training in the health sector among clinical populations (e.g., hemodialysis population) is growing in the last years [23]. Interestingly, aerobic intradialytic exercise (IDE) has been shown to be beneficial, among others, in improving physical and psychological dimensions of HRQoL, functional capacity, fatigue levels, blood pressure management and systemic inflammation [24–28]. IDE is also considered as a promising strategy for a better blood pressure control during and 24 hours after HD treatment and is recognized to reduce blood pressure instability as well as incidence and severity of IDHypo and IDHyper [6,29,30]. However, fundamental knowledge regarding the underlying mechanisms responsible for the benefits of IDE remains highly incomplete [31,32]. A better understanding of the biological networks influenced by IDE using non-targeted proteomics would most likely allow the identification of predictive biomarkers of a beneficial response (e.g., reduced incidence and severity of IDHypo/IDHyper), and thus the development of personalized exercise interventions. Finally, to our knowledge, no studies have evaluated the acute effect of aerobic IDE on short-term treatment-associated symptoms, apart from blood pressure control during HD. This would be relevant considering that the additive effect of these symptoms may increase patient's symptom-burden on the longer term [33]. Therefore, the main objective of this pilot study was to test the feasibility of evaluating the effect of acute IDE on hemodynamic

response and short-term treatment-associated symptoms in patients with kidney failure in HD. An exploratory objective was to quantify the proteome of these patients in response to IDE, and to establish its relationship with blood pressure variations during HD.

MATERIALS AND METHODS

Study Design and Protocol

A block-randomized crossover study with two experimental conditions (Exercise: EX; Control: CONT) was conducted in the HD service of the CIUSSS de l'Estrie—CHUS. Each experimental condition was performed under similar clinical conditions with a 7-day period between both conditions. After the explanation of the study and signature of the informed consent, the first experimental condition was scheduled. This research obtained ethical approval from the Research Ethics Board of the CIUSSS de l'Estrie—CHUS. During this condition (1st visit), blood samples were collected by qualified dialysis nurses at the beginning and the end of the treatment to assess dialysis efficacy (Kt/V). Afterwards, information about biological sex, gender identity, socio-demographic status (marital status, level of education), and lifestyle habits (smoking status, alcohol consumption, levels of physical activity) was collected to characterize the population. Age, comorbidities, list of medications, history of dialysis and kidney failure etiology were collected in electronic medical records. Each experimental condition (CONT or EX) started between 1:00 and 2:30 following the beginning of the treatment, as recommended [34], and lasted a total of 30 minutes. All participants had a minimum of 1:30 hours and a maximum of 3:30 left to their HD treatment at the end of experimental conditions. Both EX and CONT conditions were performed at the same moment during each participant's HD treatment. Blood pressure and heart rate (HR) were recorded following a standardized protocol at regular intervals: before and after HD (pre-dialysis by the medical team), before and after the experimental condition as well as at 5 min, 10 min and 15 min after the completion of each experimental condition (by the research team). Immediately after the experimental condition, a blood sample was collected (via the catheter or fistula already in place) for proteomic measures (Proteomics facility of the Université de Sherbrooke) as well as for the following routine clinical measures: total calcium, phosphorus, albumin, parathyroid hormone (PTH), and complete blood count (CIUSSS de l'Estrie—CHUS). For this pilot study, the choice to collect blood samples only at the end of each experimental condition (CONT and EX) was made because it was hypothesized that the large impact of HD treatment on serum proteome [35] would have hidden the effect of exercise. For this exploratory objective, it was expected that comparing the same time-point

with the removal of the intervention (IDE) would most likely provide preliminary insight on the acute effect of exercise. Figure 1 provides a visual representation of the course of the study.

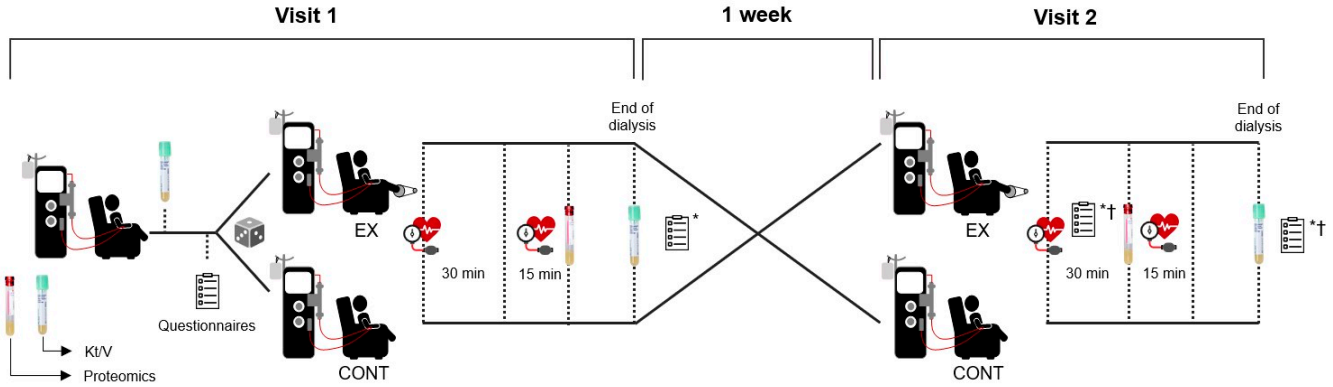

Figure 1. Graphic representation of the course of the study. CONT = control condition; EX = exercise condition; * = Visual analog scales, measured 24 hours after each condition; † = Dialysis Symptom Index, evaluated seven days after each condition; Kt/V: dialysis adequacy where K is the clearance of urea (L/min), t the duration of the dialysis treatment (min) and V the urea distribution volume in the body (L).

Participants

Among the 14 eligible patients routinely receiving HD treatment at the CIUSSS of Estrie—CHUS suggested by the medical team (medical authorization to perform exercise), a total of 12 were recruited and 10 completed the study. To be included, all participants had to meet the following criteria: (1) receiving HD treatments for kidney failure (defined as glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2 [36], at least 3 times per week for at least 3 months, and (2) have medical clearance to engage in exercise. The exclusion criteria were: (1) diagnosed neurocognitive decline preventing informed decision making, (2) hip fracture with recent hemiarthroplasty preventing hip flexion during pedaling, (3) COVID-19 positive, (4) a history of myocardial infarction, stroke, or pulmonary embolism within the last 6 months, (5) unstable angina pectoris, (6) neurological impairments with functional deficits limiting the ability to perform the exercise session; (7) any absolute contraindications to exercise according to the American College of Sports Medicine [37], (8) already included in another study.

Experimental Conditions

Both experimental conditions lasted 30 minutes, were performed the same day of the week, 7 days apart, and at the exact same moment during the HD treatment. During the 30-minute CONT experimental condition, each participant received usual care. During the EX experimental

condition, participants performed a standardized aerobic exercise session (IDE adjusted on an individual basis). The EX condition consisted of pedaling 30 minutes on a cycle ergometer prototype (designed for research purposes by our research group) either attached to the patient's bed or chair and with real-time data acquisition (exercise duration, power output, rpm). We selected a 30-minute duration as it aligns with current IDE guidelines, which recommend at least 30 minutes of moderate-intensity aerobic activity during each hemodialysis session, or 20 minutes of vigorous-intensity exercise [38,39].Because HR is not recommended to prescribe aerobic exercise in this population [40], the Borg CR10 rating of perceived exertion (RPE) scale was used to set exercise intensity and mean power output was collected. Indeed, a predicted HR percentage is not an appropriate tool to prescribe nor monitor exercise intensity in this population [37,41,42] considering that dysfunctions of the autonomic nervous system, key element of HR response, are frequent in individuals with chronic renal failure [43–45]. The IDE began with a 5-minute warm-up at an intensity not exceeding 2/10 on the CR10 Borg RPE scale. A 5-minute cool-down at the same intensity was performed at the end of exercise. The main portion consisted of 20 minutes of cycling at 3–4/10 on the CR10 Borg RPE scale with a target at 50 rpm. Participants performed the exercise in the same position they received HD treatment (seated or semi-reclined). This IDE protocol was previously safely used by our group [46]. Power output was continuously measured by the cycle ergometer, automatically imported with a secure Wi-Fi connection, and stored in the Research Centre on Aging servers (using OpenTera secure servers). All participants had visual feedback on exercise duration, power output and targeted rpm on the cycle ergometer.

Blood Pressure Monitoring, IDHypo and IDHyper

Systolic (SBP) and diastolic (DBP) blood pressures were automatically measured with the dialyzer (Artis Physio, Baxter, Deerfield, IL, USA) before and after each hemodialysis session, as well as at five time points: before, after, 5, 10 and 15 minutes following both experimental conditions. The device from the hemodialysis team was used for reproducibility concerns after the study and make possible measurement of BP in clinical settings, as most of the participants had their fistula on one arm and clinical BP cuff on the other side. Knowing the impact of plasmatic volume on BP, body weight and dry weight were also collected in medical record the day of both experimental conditions.

IDHypo was defined according to the 2005 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [34] guidelines as a decrease in SBP $\geq$ 20 mmHg with symptoms (abdominal discomfort,

yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety). However, as this definition was not consistently associated with adverse clinical outcomes [47], nadir intradialytic SBP of <90 mmHg for patients with pre-hemodialysis SBP < 160 mmHg and a nadir intradialytic SBP of <100 mmHg for patients with pre-hemodialysis SBP ≥ 160 mmHg were also considered as IDH [8]. IDHyper was defined as an increase in SBP from pre-hemodialysis to post-hemodialysis >10 mmHg after HD as it was recently suggested that any increase in SBP > 10 mmHg occurring at the end or immediately was associated with a high risk of mortality [48].

Patient-Reported Outcome Measures

After both experimental conditions, participants have left the hospital with a notebook containing four 100-mm visual analog scales, anchored with adjectives at both end (e.g., “no fatigue at all” at the left end and “complete exhaustion”). Participants had to fill in the 24 hours following the treatment: 2 hours post-HD and three times (10:00 am, 2:00 pm and 6:00 pm) the day after the experimental condition (CONT or EX), according to the Ecological Momentary Assessment method [49] to capture the variability of fatigue, sleepiness, mood, and delayed-onset muscle soreness (DOMS). Although there are no published minimal important differences for these dialysis-associated symptoms or DOMS when assessed with visual analog scale, a difference of 10 mm was considered as a minimal important difference as this was greater or equal than what was previously reported for fatigue.

Kidney disease and dialysis-related symptoms were also assessed one week after each experimental condition by using the Dialysis Symptom Index (DSI) scale that has been used in recent research on PROMs in dialysis patients [50–52]. The DSI contains 30 questions about the presence and severity of physical and emotional symptoms experienced by HD patients in the past 7 days. When a symptom was experienced, the perceived severity was assessed using a five-point Likert scale (1 = not at all, to 5 = a lot) and a score of zero was assigned to unreported symptoms. An overall symptom-severity score was formulated by summing the number of symptoms and their severity. A maximum score of 150 (if all the 30 symptoms were reported and rated as “bothers very”) would be considered as the highest severity and overall impact of symptoms [52].

Proteomics Analysis

An 8.5 mL blood sample was collected via the catheter or fistula from HD patients immediately after completion of each experimental condition (EX and CONT condition). Samples were collected in a serum-separating

Vacutainer tube (SST serum separation tubes, #367988, BD Vacutainer®, Becton, NJ, USA) for proteomics and centrifuged at 3220 RPM, at 4 ℃ for 15 minutes. Supernatant was collected and stored at −80 ℃ until proteomics analysis. The BCA Assay was employed to determine the concentration of proteins. A total of 50 µg of proteins were reduced in a 50 µL solution comprising 10 mM HEPES-KOH pH 7.5, 1 M ammonium bicarbonate (NH_4HCO_3) from Sigma-Aldrich in Saint-Louis, and 8 M urea. This reduction process involved the addition of dithiothreitol (DTT) to reach a final concentration of 5 mM, followed by heating at 95 ℃ for 2 minutes, and subsequently incubating at room temperature for 30 minutes. Subsequently, the proteins were alkylated by adding chloroacetamide (ClAA) from Sigma-Aldrich in Saint-Louis to a final concentration of 7.5 mM. The alkylation step involved an incubation period of 20 minutes at room temperature, away from light. The urea concentration was then diluted to a final concentration of 2 M by adding 150 µL of 1 M NH_4HCO_3. Following this, the proteins were digested by adding 1 µg of Pierce MS-grade trypsin from Thermo Fisher Scientific in Waltham and incubated overnight at 30 ℃ with shaking. The resulting peptides were purified using micropipette tips containing a C18 column from EMD Millipore in Burlington, VT, and subsequently concentrated using a centrifugal evaporator. Finally, the peptides were resuspended in FA buffer and their assessment was carried out using a NanoDrop spectrophotometer from Thermo Fisher Scientific in Waltham, MA.

To conduct DIA LC-MS analysis, a total of 250 ng of peptides from every sample were introduced into an HPLC system (nanoElute, Bruker Daltonics). They were first loaded onto a trap column (Acclaim PepMap100 C18 column, 0.3 mm inner diameter × 5 mm, Dionex Corporation) at a constant flow rate of 4 µL/min. Subsequently, the peptides were transferred to an analytical C18 column (PepSep) with a particle size of 1.9 µm, measuring 75 µm in diameter and 25 cm in length. The analytical column was maintained at a temperature of 50 ℃ throughout the elution process. Peptides were eluted over a 2-hour gradient of ACN (5%–37%) in 0.1% FA at 400 nL/min while being injected into a TimsTOF Pro ion mobility mass spectrometer equipped with a Captive Spray nano electrospray source (Bruker Daltonics). Data was acquired using diaPASEF mode. Briefly, for each single TIMS (100 ms) in diaPASEF mode, we used 1 mobility window consisting of 27 mass steps (m/z between 114 to 1414 with a mass width of 50 Da) per cycle (1.27 seconds duty cycle). These steps cover the diagonal scan line for +2 and +3 charged peptides in the m/z-ion mobility plane. The raw files were analyzed using MaxQuant (version 2.0.1.0) and the Uniprot human proteome database (03/21/2020, 75,776 entries), with uploading in silico generated human library files (available

at: http://annotations.perseus-framework.org/) to run Maxquant in DIA discovery mode. The settings used for the analysis (with TIMS-MaxDIA type in group-specific parameters) were: 1 miscleavage was allowed; fixed modification was carbamidomethylation on cysteine; enzymes were Trypsin (K/R not before P); variable modifications included in the analysis were methionine oxidation and protein N-terminal. A mass tolerance of 20 ppm was used for both precursor and fragment ions. Identification values "PSM FDR", "Protein FDR" and "Site decoy fraction" were set to 0.05. Minimum peptide count was set to 1. Both the "Second peptides" and "Match between runs" options were also allowed. MaxQuant was run with a transfer q value of 0.3.

Health-Related Quality of Life

HRQoL was assessed once to characterize the population with the French version of the Kidney Disease Quality of Life 36 items version 1.3 (KDQOL-36). This questionnaire is an adapted version of the SF-36 questionnaire for the kidney disease population [53]. It assesses 8 domains of QOL (physical functioning, limitation due to physical problems, pain, general health perception, emotional well-being, limitation due to emotional problems, social functioning, and energy level), in addition to 11 domains specific to HD patients. Although the KDQOL-36 is validated for the study population and frequently used in intradialytic exercise studies [25,54], it does not capture small changes over a short period of time (<4 weeks). Therefore, we used the previously presented tools (VAS and DSI) to assess to evaluate small, shorter-term changes.

Physical Activity Levels

Physical activity (PA) levels were assessed with the Physical Activity Scale for the Elderly (PASE) to characterize the sample. Participants reported household, leisure and work-related activities undertaken during the previous week. These activities were then scored according to their intensity and duration, and a weekly total will be calculated to obtain an overall score representing the energy expenditure related to physical activity for the week (scores vary from 0 to 793, higher scores indicating greater PA) [55,56].

Biomarker Profile

Biomarkers used to characterize the population were selected based of the work of Liu et al. [57] that predicts physiological deterioration in patients with kidney failure and according to clinical routine. Although the frequency of measurement of these biomarkers varies, all the following markers were measured once a month and were extracted from the

medical records: Kt/V, albumin, creatinine, phosphate, total calcium, potassium, sodium, PTH, and fasting glucose. Complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count and platelet) was also retrieved from medical record. In addition, blood samples were collected at the beginning and the end of HD treatment to assess dialysis efficacy (Kt/V) and immediately after the end of each experimental condition (30 minutes of EX and CONT) to measure biomarkers known to be influenced by HD or which have been associated to blood pression variations: complete blood count, levels of albumin, calcium, phosphate and PTH. All these biomarker analyses were performed at the laboratory of the CIUSSS de l'Estrie—CHUS with the same standard clinical procedures used in HD.

Statistical Analyses

Considering that this article is a pilot study, no statistical power calculation was performed. Despite that there is no consensus in the literature, we used the general rule of thumbs stipulating a statistical power varying between 10–12 individuals is adequate for a pilot study [58]. Moreover, with an intra-individual cross-over study design with a power of 80% and α of 0.05, a large effect size can be detected with such a sample size (effect size f of 0.57 corresponding to an η_p^2 of 0.25). The normality of data was assessed with a combination of the Shapiro–Wilk test and visual evaluation of the quartile histograms and the Q-Q plots.

The comparison between the control and the exercise condition for visual analogue scale, biochemical analyses, and comparison of BP variations between the pre-HD value and 5 different time points during the conditions (deltas) were conducted with dependent t-tests or Wilcoxon tests when data were not normally distributed. The effect size for both tests were interpreted using Hedge's G value (0.2–0.5–0.8). For the Wilcoxon test, the following formula (r = z/sqrt *N*), where z represents the Wilcoxon test output and *N* the number of observations [59,60]. The evolution of variation of BP throughout and between the condition was analyzed with repeated measures ANOVA (2 groups 5 measures). Partial eta-square (η_p^2) are presented and the benchmarks suggested by Cohen, defined as small (0.0099), medium (0.0588), and large (0.1379), were used. Mauchly's test of sphericity was verified, and the alpha was set at $p < 0.05$. In case of violation of sphericity assumption, Greenhouse-Geisser correction was used if the epsilon was smaller than 0.75 and Huynh-Feldt correction if the epsilon was greater than 0.75. The same procedure was used for the comparison of HR during the CONT and EX condition [ANOVA (2 groups 12 measures)]. When a significant effect was detected, multiple pairwise comparisons were performed and then corrected with the False

discovery rate procedure (FDR) [61]. One way ANOVA was used to assess the change in RPE during the exercise session. Homogeneity of variance was assessed using Levene's test and Welch's test was used if the assumption of homogeneity of variance was violated. To determined where the difference is between the different mean, Tuckey post hoc test was used.

Identification and quantification of serum proteome resulting from MaxQuant analysis were processed with the LFQ-Analyst platform [62]. Briefly, LFQ intensities were uploaded to compare the two experimental conditions (EX and CONT), by using a paired-test with an adjusted *p*-value cutoff of 0.05 and a log2 fold change cutoff of 1. Imputation of missing values was performed by using a maximum likelihood estimation (MLE). A t-statistics-based FDR correction was also selected during analysis. This quantitative approach allowed an investigation of the modulation of protein expression profiles (protein signature) according to the erosive or non-erosive stage, depending on the activity. The proteomic profile of participants was compared using hierarchical Spearman correlation clustering to observe the relationships between clinical observations and the proteome. Except for proteomic analyses, all statistical analyses were performed with SPSS (version 27.0.0, IBM SPSS Statistics, IL, USA) and the significance level set at $p \leq 0.05$). However, *p*-value was not only interpreted in a dichotomous manner, but rather as a continuous value [63]. Data are presented mean ± SD or median [IQR] when data are not normally distributed and mean ± SEM in figures.

RESULTS

Recruitment and Participants Characteristics

A total of 14 participants undergoing dialysis in the CIUSSS de l'Estrie—CHUS were screened by the medical team for approval (nurse practitioner and nephrologist). Two patients refused to participate (acceptation rate = 86%), one dropped out due to the unpleasant pedaling sensation during the exercise session and one was excluded due to the COVID-19 diagnostic after the control condition (dropout rate = 17%). Therefore, 10 individuals had complete data for both proteomics (CONT and EX condition) and clinical outcomes (Figure 2).

Participants of the present study were aging adults, mostly male (70%) with a multimorbid profile undergoing dialyses for the past 3 years (Tables 1 and 2). All individuals had HD treatment 3 times a week for an average of 4 hours per treatment.

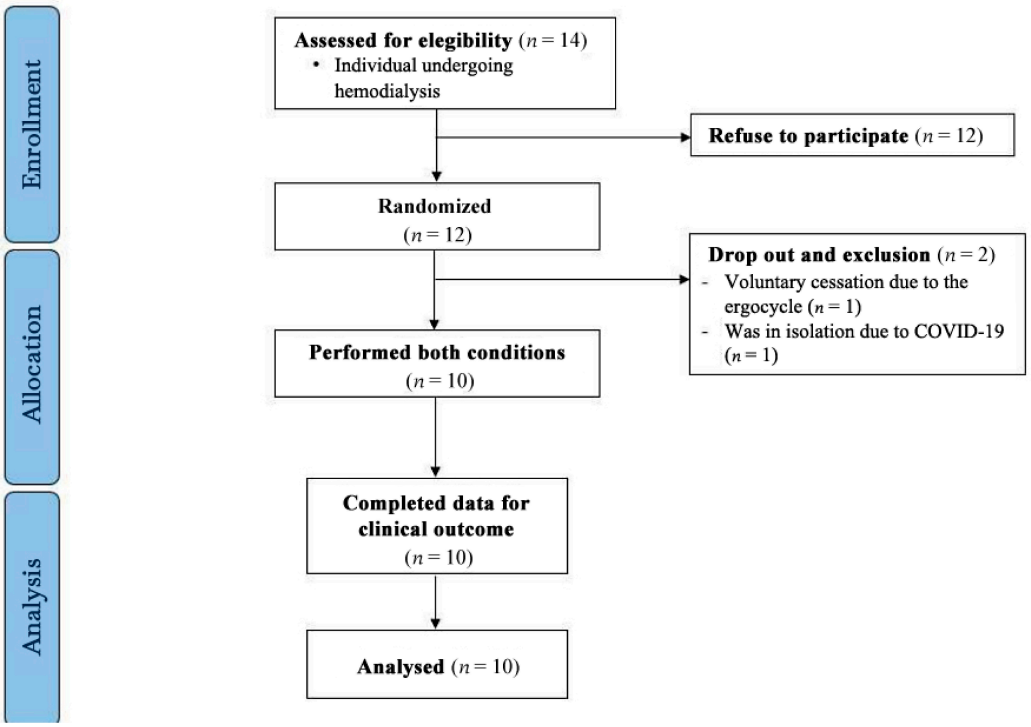

Figure 2. Flow chart of the study.

Table 1. Participants baseline characteristics.

Characteristics	Total sample (*n* = 10)
Biological sex (female/male (*n*))	3/7
Age (years)	70.0 ± 12.1
Weight (kg)	95.8 ± 23.7
BMI (kg/m^2)	33.7 ± 9.4
Duration of dialysis (years)	3.0 ± 2.6
Access of dialysis (*n*)	
Arteriovenous fistulas	2 (20%)
Arteriovenous grafts	8 (80%)
Etiology of kidney failure (*n*)	
Hypertension/vascular disease	4 (40%)
Glomerular disease	2 (20%)
Genetic/Congenital	2 (20%)
Other/Unknown	2 (20%)
Smoking status (*n* (%))	
Current	2 (20%)
Former	6 (60%)
Never	2 (20%)
Alcohol consumption (*n* (%))	
Never	7 (70%)
Occasionally	2 (20%)
1–2 drink a day	1 (10%)

Table 1. *Cont*.

Characteristics	Total sample (*n* = 10)
Comorbidity (*n* (%))	
Hypertension	10 (100%)
Coronary artery disease	7 (70%)
Pulmonary disease	4 (40%)
Type 2 diabetes	4 (40%)
Cancer	3 (30%)
Hepatic disease	2 (20%)
Anemia	2 (20%)
Number of medication	8.0 ± 1.4
Antihypertensive medication (*n* (%))	
• Calcium channel blocker	2 (20%)
• Diuretic	6 (60%)
• Beta blocker	2 (20%)
Hypoglycemic medication (*n* (%))	
• DPP-4 inhibitor	1 (10%)
• Sulfonylurea	2 (20%)
Insulin (*n* (%))	3 (30%)
Hypolipidemic medication (*n* (%))	4 (40%)
Anti-coagulant medication (*n* (%))	2 (20%)
Anti-platelet medication (*n* (%))	5 (50%)
Antiarrhythmic medication (*n* (%))	2 (20%)
Antianemia medication (*n* (%))	6 (60%)
Antidepressant/anti anxiolytic (*n* (%))	5 (50%)
Level of education (*n* (%))	
• Elementary	2 (20%)
• Secondary	5 (50%)
• Post-secondary	3 (30%)
Marital status (*n* (%))	
• Single	5 (50%)
• Married or lived with a partner	3 (30%)
• Widowed	2 (20%)
KDQOL-36 PCS	36.2 ± 10.5
KDQOL-36 MCS	52.2 ± 7.2
KDQOL-36 KDCS	68.4 ± 15.0
Physical activity levels (PASE score)	62.4 ± 31.0

Data are presented as mean ± SD and *N* (%) when specified; BMI = body mass index; KDCS: Kidney disease component summary; KDQOL-36: Kidney Disease Quality of Life 36-item short form; MCS: Mental component; PASE = physical activity scale for the elderly; PCS: Physical component score. See Supplementary Table S1 for the complete KDQOL-36 results.

As shown in Table 2, most of the participants (70%) achieved the recommended Kt/V of 1.2. Nevertheless, both hemoglobin levels and red blood cell count were low while fasting glucose level was high due to type 2 diabetes (n = 4) or prediabetes (n = 2).

Table 2. Participants biological profile.

Biological markers	Total sample (n = 10)	Reference values*
Laboratory profile		
Kt/V	1.4 ± 0.3	>1.2
Albumin (g/L)	38.2 ± 3.1	31–49
Creatinine (µmol/L)	695 ± 212	-
• Male (n = 7)	603 ± 164	-
• Female (n = 3)	908 ± 151	-
Phosphate (mmol/L)	1.52 ± 0.43	0.87–1.45
Calcium (mmol/L)	2.17 ± 0.13	2.07–2.55
Potassium (mmol/L)	4.7 ± 0.6	3.5–5.1
Sodium (mmol/L)	139.5 ± 3.8	135–145
Parathyroid hormone (pmol/L)	59.7 ± 32.0	1.6–6.9
Fasting glucose (mmol/L)	6.9 ± 2.2	3.3–5.5
Hematological parameters		
Hemoglobin (g/L)	101 ± 13	-
• Male (n = 7)	95 ± 7	130–175
• Female (n = 3)	116 ± 14	120–160
Hematocrit (%)	30.4 ± 4.4	-
• Male (n = 7)	28.6 ± 1.7	40–50
• Female (n = 3)	35.0 ± 5.5	35–47
Red blood cell count (10^{12}/L)	3.2 ± 0.5	-
• Male (n = 7)	2.9 ± 0.3	4.4–5.9
• Female (n = 3)	3.7 ± 0.6	3.8–5.2
White blood cell count (10^9/L)	7.5 ± 2.5	3.8–10.6
Platelets (10^9/L)	248.5 ± 133.7	130–400

Note: Values are presented as mean ± SD. Kt/V: dialysis adequacy where K is the clearance of urea (L/min), t the duration of the dialysis treatment (min) and V the urea distribution volume in the body (L). *References values are from the laboratory of the CIUSSS de l'Estrie—CHUS where all these analyses were performed.

Blood Pressure Variation

Resting SBP measured at the beginning of the HD and just before the beginning of the experimental condition were higher the day of the EX condition compared to the CONT condition (pre-dialysis: EX 140 ± 27 vs. CONT 132 ± 22 mmHg; pre-experimental condition: EX 140 ± 23 vs. CONT 130 ± 20 mmHg; all $p \leq 0.030$). However, post-dialysis SBP (EX 142 ± 20 vs. CONT 144 ± 27 mmHg; p = 0.754) and DBP measurements (pre-dialysis: EX

71 ± 10 vs. CONT 73 ± 11 mmHg, pre-experimental condition: EX 74 ± 10 vs. CONT 72 ± 12 mmHg; all $p \geq 0.187$) were not different. Participants were categorized according to the American Heart Association hypertension guidelines [64]. For the control condition, two individuals were in the "normal" category, two in the "high" category, two in stage 1 hypertension and four in stage 2 hypertension at arrival in HD. For the exercise condition, one individual was in the "normal" category, two in the "high" category, four in stage 1 hypertension and three in stage 2 hypertension at arrival in HD.

Regarding the impact of exercise on intradialytic hypotension and hypertension (Table 3), comparison of ΔSBP (= changes pre-dialysis value − post-condition value) between both conditions showed a greater SBP reduction at 10 min and 15 min after the end of IDE compared to the 10- and 15-min mark after the end the CONT condition ($p < 0.044$). When analyzing SBP reduction (ΔSBP) after the end of both experimental conditions, 1/10 participants experienced a SBP reduction > 20 mmHg in the CONT condition compared to 3/10 in the EX condition. However, these participants did not exhibit IDHypo nor IDHyper symptoms, did not require medical intervention, and SBP remained above the threshold used to qualify IDHypo (i.e., <90 mmHg for resting SBP < 160 mmHg and <100 mmHg for a resting SBP ≥ 160 mmHg; Supplementary Figure S1). Moreover, although not statistically significant (McNemar χ^2 $p = 0.375$), while 6/10 participants experienced an intradialytic hypertension (pre- to post-hemodialysis SBP increase > 10 mmHg) in the CONT condition, it happened in only 3/10 in the EX condition.

Table 3. Variation of systolic blood pressure in response to IDE compared to usual care.

Time of measurement	Control	Exercise	Comparison of conditions *p*-value	Effect size (Hedges' g)
ΔSBP pre-dialysis to post-condition	−0.4 ± 9.8	0.6 ± 19.3	0.869	−0.049
ΔSBP pre-dialysis to post-5 min	2.2 ± 9.6	−3.3 ± 13.4	0.261	0.364
ΔSBP pre-dialysis to post-10 min	4.1 ± 12.5	−7.5 ± 12.8	**0.044**	**0.676**
ΔSBP pre-dialysis to post-15 min	2.2 ± 13.0	−8.4 ± 12.5	**0.007**	**1.000**
ΔSBP pre-dialysis to post-dialysis	10.0 ± 9.0	4.0 ± 18.5	0.352	0.284

Data are presented as mean ± SD. Δ: changes pre-dialysis value − post-condition value; SBP: systolic blood pressure. Values in bold denote significant differences between conditions in SBP changes at different time points after IDE compared to pre-exercise values.

Pre-dialysis body weight ($p = 0.760$), dry weight ($p = 0.678$) and body weight reduction (CONT: −1.7 ± 1.2 kg vs. EX: −1.5 ± 1.1 kg; $p = 0.082$) as well

as pre-dialysis urea levels (CONT: 21.3 ± 4.5 mmol/L vs. EX: 20.8 ± 5.8 mmol/L; p = 0.879) were similar between both conditions.

Proteomics Response to IDE

Overall, 1024 proteins were identified and quantified in the serum of patients. After pre-filtering, all LFQ intensities were converted to a log2 scale and grouped by conditions (CONT and EX). Protein-wise linear models combined with empirical Bayes statistics were used for the different expression analyses for all possible paired measurements, to allow comparison of the two experimental conditions for everyone (EX and CONT; Supplementary Figure S2).

We identified 7 proteins that were found to be significantly increased, and 5 proteins that were found decreased (p < 0.05, minimum 3-fold difference), and which were sufficient to separate the patients with and without exercise. The heatmap representation provides an overview of the differentially selected proteins (Figure 3).

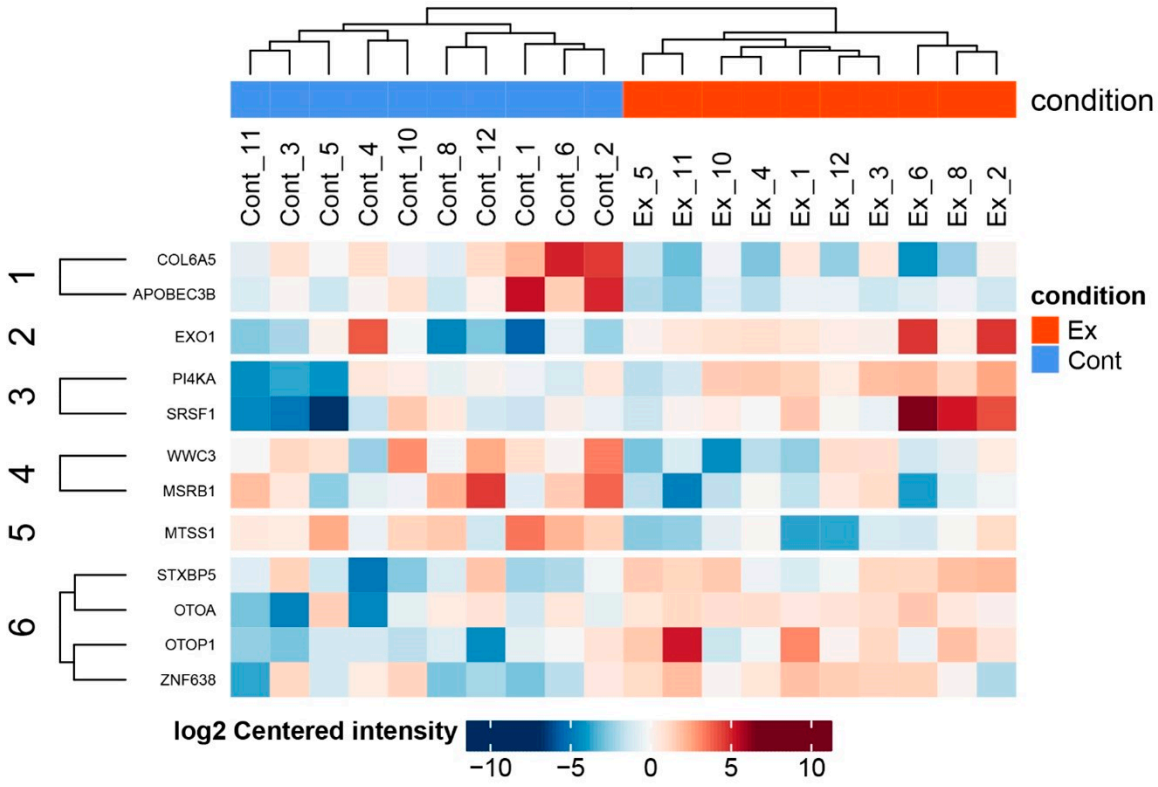

Figure 3. A plot representing an overview of expression of all significant (differentially expressed) proteins (rows) in all samples (columns). The results of hierarchical clustering on both proteins (row) and sample (column) are indicated.

Interestingly, the significant SBP decrease post-IDE (ΔSBP post 10 and 15 min) were significantly correlated with the otoancorin (OTOA) protein levels measured at the end of IDE (−0.721 ≤ rho ≤ −0.675, 0.021 ≤ p ≤ 0.032).

However, OTOA protein levels were also associated to SBP variation between the pre-dialysis and pre-IDE condition (rho = −0.841, p = 0.002). Finally, the upregulation of OTOA levels observed in response to IDE compared to HD alone was not associated to BP variation (all p > 0.328).

Visual Analog Scales and Dialysis Symptom Index

Exercise reduced the desire to sleep in the 2 hours following dialysis (p = 0.042; effect size r = 0.71; Supplementary Table S2), effect that faded away the next day (Figure 4). No difference was observed for any of the other variables such as fatigue, mood, or muscle soreness (p ≥ 0.88) for both conditions.

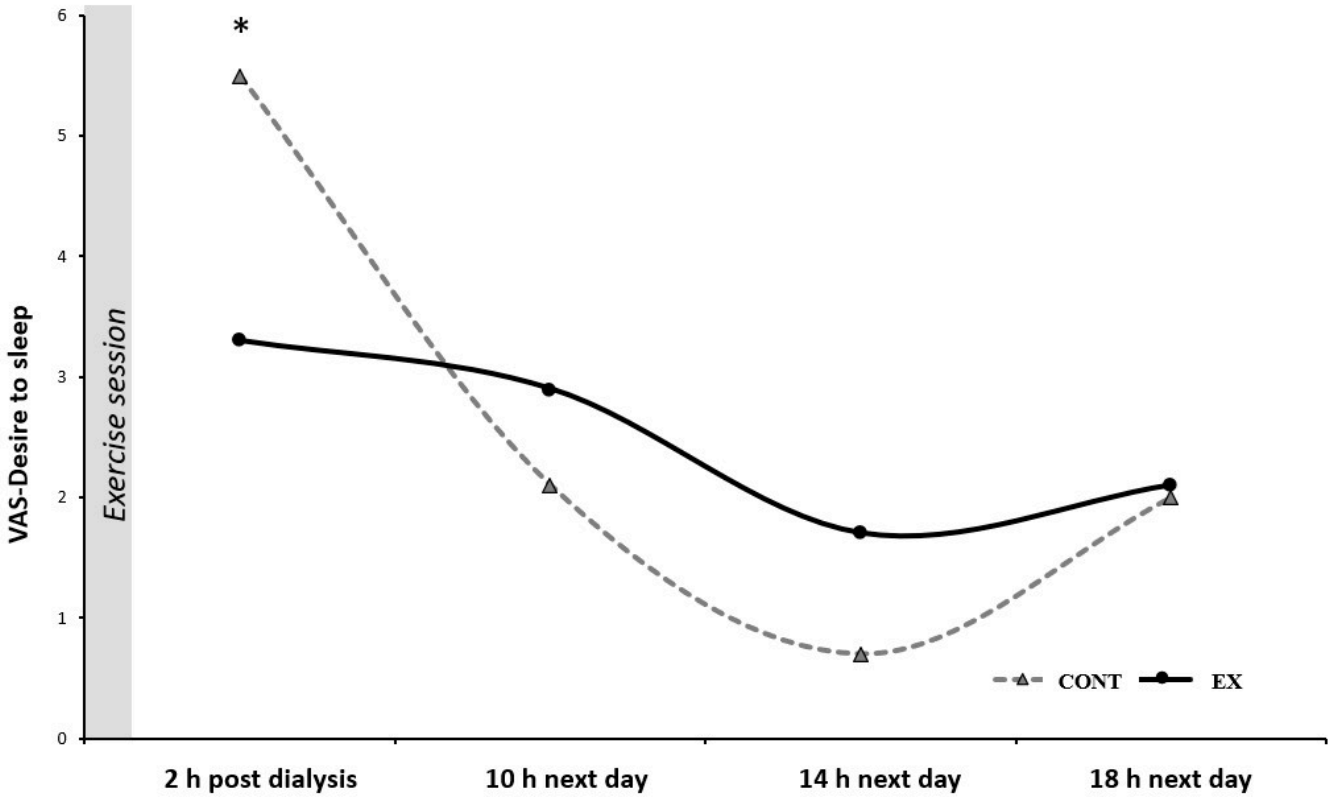

Figure 4. Visual analog scales for desire to sleep after both experimental conditions. Data are presented as median. VAS = Visual analog scale. Measurements at 10-14-18 h were completed the day after treatment. * Denotes significant differences between conditions.

Regarding the symptoms experimented during the past 7 days, the DSI scores was not different one week after each experimental condition (CONT: 9.5 [7.0–24.3]; EX: 14.0 [8.0–26.0]; p = 0.213).

Power Output, Heart Rate and Rate of Perceived Exertion

During the EX condition, a mean power output of 37 ± 14 watts (min-max: 16–64 W) was achieved at 50 ± 8 rpm and a perceived exertion of 3.5 ± 0.5 (modified Borg scale). Warm up and cool-down were performed at 23

± 14 watts (50 ± 7 rpm) and 23 ± 10 watts (47 ± 12 rpm), respectively. Repeated measures ANOVA revealed a time effect ($p < 0.0001$; $\eta_p^2 = 0.340$) and an interaction between the two conditions ($p = 0.022$; $\eta_p^2 = 0.161$) for HR. Post hoc analyses with FDR correction showed that each time point, except before exercise, is statistically different between both conditions ($p \leq 0.016$). As expected, repeated measures ANOVA showed a significant increase in RPE during the exercise session ($p = 0.001$). When compared to the warm-up, all RPE measures were statistically higher (all $p \leq 0.041$). HR and RPE data are presented in Supplementary Figure S3.

DISCUSSION

The purpose of this pilot study was to (1) to evaluate the effect of acute intradialytic aerobic exercise on blood pressure response and short-term side effects of treatment in patients with kidney failure in HD, and (2) quantify the proteome of these patients in response to IDE, and to establish its relationship with blood pressure variations during HD. Our main finding was that among patients with kidney failure receiving HD treatment, one IDE session seemed to improve blood pressure regulation without any adverse clinical effects and decreased the desire to sleep in the 2 hours following HD. We were also able to identify twelve proteins that were differentially regulated in response to IDE. However, none of them seemed a potential biomarker for exercise-associated SBP reduction.

Among the 10 individuals who completed both experimental conditions, the reduction in blood pressure from pre-dialysis values was significantly greater during the exercise condition than during the control condition. This decrease occurred without clinically significant hypotension as the lowest SBP values achieved was 121 mmHg among the three participants who experienced a SBP drop superior to 20 mmHg. This is of particular interest as the day of EX condition, participants exhibited a higher SBP before HD compared to CONT condition, while they did not exhibit a higher pre-dialysis weight or uremia. These results suggests that aerobic IDE has the capacity to favorably regulate blood pressure during HD in individuals with kidney failure presenting a higher blood pressure before the start of dialysis. Although participants were not informed of the condition prior to the day of experimentation, we can speculate that a higher level of apprehension might have been experienced in relation to participation in the exercise session would have induced an increase in pre-dialysis blood pressure [65]. Nevertheless, the block randomization strategy used in the present study should have limited the impact of this potential bias. Furthermore, the higher pre-dialysis blood pressure during the EX condition was not exclusive to those who performed the EX condition in second.

The blood pressure response suggests that a single session of moderate-intensity aerobic exercise (mean 3.5/10 Borg CR10) is sufficient to improve BP management and control and reduce intradialytic hypertension. Our results agree with the study of Kim et al. [29] who did not report a significant increase in blood pressure after a first 20 minutes of IDE, as well as no postexercise hypotensive effect and no IDHypo. However, the authors also reported a postexercise hypotensive effect of IDE after participants completed a second set of 20-min moderate-intensity aerobic exercise, 1 hour after the first one. This suggests that IDE volume, load and timing should be further investigated with regards to the blood pressure regulation during HD. Interestingly, a recent study compared the effect of IDE at the start of HD with IDE in the second half of HD (six sessions for each condition) on the incidence of IDHypo/IDHyper episodes [66]. The authors reported no difference between performing IDE in the first or second half of HD on the overall rate or on the incidence of symptomatic IDHypo/IDHyper, suggesting that IDE can be safely performed throughout HD treatment, if hypotension or hypertension during HD is specifically addressed. Until now, the optimal IDE protocol to favor an optimal blood pressure control during HD treatment remains unknown and deserves future studies.

While this is the first study to identify serum proteins that are regulated by IDE in patients with kidney failure, some changes in the proteome are intriguing and pertinent for potential future therapeutic approaches for renal diseases. A previous study showed that Syntaxin-binding protein-5 (STXBP5) transcriptome is upregulated with exercise in joint tissue of rats with arthritis [67]. Among others, in human and murine models, STXBP5 blocks endothelial cell exocytosis by inhibiting membrane fusion between transport vesicles and the plasma membrane [68,69]. One of the crucial steps leading to vascular inflammation and thrombosis is endothelial exocytosis of Weibel-Palade bodies (WPBs), storage granules that contain multiple pro-inflammatory and pro-thrombotic mediators as Von Willebrand factor (vWF) and P-selectin [70,71]. On the other hand, STXBP5 appears to promote platelet exocytosis and secretion of membrane-enclosed dense granules, α granules and lysosomes, which is a necessary physiological process to promote thrombus formation I response to vascular damage [68,72]. Also, an animal study looking at the anti-inflammatory effects of exercise and the associated metabolic improvement also reported Otopetrin (OTOP1) upregulation after exercise [73]. In fact, exercise increased the expression of genes that are beige adipocyte markers and regulators of mitochondrial biogenesis, including OTOP1, which is in line with the body of literature that supports that adipose tissue also adapts to exercise training and has positive metabolic

benefits in a systematic way [73–75]. Specifically in the context of blood pressure control, exercise has been reported to activate perivascular brown adipose tissue and to promote the browning of white adipose tissue, which may reduce hypertension [76,77]. Furthermore, OTOA protein, which was associated to blood pressure in this study, has been identified as a marker of tissue injury and inflammation in Alport syndrome [78] which is characterized by impairments in production and deposition of collagen network in the membranes of the glomerulus, cochlea (inner ear), and eye [79] . Glomeruli are the tiny kidney filters located in the nephrons, the kidney's structural and functional unit for urine formation. Glomerulonephritis is an inflammation of this structure, characterized mainly by the activation of pro-inflammatory cytokines and adhesion cells (including OTOA), the presence of fibrosis markers (e.g., collagen 1), and the expression of vasoconstrictor substances (e.g., endothlin-1) [80] although significant reduction in SBP at 10 and 15 min post-EX significantly correlated with upregulation of OTOA protein levels measured at end of exercise, they were also associated with the variation in blood pressure between pre-HD and pre-IDE measurement. It therefore appears that OTOA is a marker of hypertension rather than a biomarker of favorable hemodynamic response to IDE. The fact that only twelve proteins were regulated by IDE could also be related to the exercise intensity and duration. In fact, it could be hypothesized that a higher intensity (>4/10 CR10 Borg) or longer duration (>30 minutes) would have induced more pronounce proteome changes, considering that these are very short durations in comparison with usual protein turnovers. Indeed, Guseh et al. found that acute circulating protein changes during high-intensity exercise are larger in both number and magnitude than those seen during moderate-intensity exercise, suggesting that the human circulating proteome varies in an intensity- or "dose"-dependent manner [81]. However, aging adults with kidney failure often exhibit a low cardiorespiratory fitness, limiting their capacity to perform high-intensity exercise, especially if there is no chronic training. Moreover, anemia, as observed in the current study and often reported in patients with kidney failure, limit exercise tolerance [82] and thus, acute IDE benefits. This suggests that future study aiming at investigating acute effect of IDE should be performed after few weeks of chronic training and when anemia is improved. Nevertheless, the identification and quantification of over a thousand proteins from these samples demonstrate the feasibility of performing proteomics for the discovery of biomarkers and the characterization of differences amongst patients.

Concerning side effects management, IDE was able to reduce the desire to sleep for the first two hours following the end of the HD. This is not to

be overlooked as many patients report a high level of fatigue in the hours following the end of dialysis [83–85]. Interestingly, while desire to sleep (or feeling drowsy) and fatigue are usually found in the same symptom cluster in the HD-treated population [85,86], we did not observe an effect of exercise compared to control on fatigue in the present study. However, desire to sleep and fatigue are strongly correlated for both conditions. This is not surprising considering that fatigue is a construct that can be measured with multiple variables (e.g., sense of weakness, lack of energy, tiredness) and located on a continuum, with weakness, lack of energy, and tiredness on one end, and energy and vitality at the opposite [84,87]. Finally, a recent meta-analysis [88] reported that intradialytic training significantly decreased fatigue symptoms in adults undergoing HD, which makes us believe that our result could be transposed to the long term. Since we know that post-dialysis fatigue is associated with sedentary behaviors [89] and that these are known to be risk factors for chronic diseases and all-cause mortality, feeling less tired after treatment could benefit this population at high risk of comorbidities.

In contrast to the proteome, blood markers analyzed during HD were not influenced by IDE (see Supplementary Table S3). Interestingly, Sovatzidis et al. investigated changes in redox status and inflammatory indicators in patients with kidney failure following a 6-month IDE training intervention and found that IDE reduced redox status indices as hs-CRP (high-sensitivity C-reactive protein), a marker of inflammation that is often used to assess the risk of cardiovascular diseases, and improved total antioxidant capacity [90]. This leads us to believe that a longer intervention could positively alter the biochemical profile following IDE. Similarly, treatment efficacy (Kt/V) was not increased in response to a single IDE session, contrary to what was observed by Brown et al. [91]. The authors found a significantly greater Kt/V after IDE compared to a control session with only dialysis. Interestingly, there was no difference between a session performed at 55% of maximal HR (HRmax) versus one at 70% HRmax [91]. Although it is not recommended to prescribe IDE with HR [37], it was monitored during IDE in this study to compare with the study of Brown et al. [91]. In our study, it was observed that our participants trained at 53 ± 6% HRmax, with 6/10 participants who performed IDE under 55% HRmax (data not shown). The possible difference with the study of Brown et al. suggest that a higher exercise intensity is needed to influence treatment's efficacy [91]. However, knowing that HR is a limited tool to prescribed exercise during HD with this population, future studies should use power output and Borg scale to appropriately investigate this question. Unfortunately, as there is currently no valid submaximal test to assess peak power output in patients with kidney failure during HD, it

remains difficult to compare IDE protocols in the literature. Even if others have used maximal test between HD treatments, it remains problematic to use these data for exercise prescription as conditions of testing and training differ.

This pilot study presents some limitations that need to be considered when interpreting the results. This one-center pilot study was performed with a small sample size to assess the feasibility of evaluating the proteome response to IDE and collect preliminary efficacy data on blood pressure and dialysis-associated symptoms. Nonetheless, we used a crossover study design that limits interindividual variability and able to detect a large effect size and thus a homogenous response. Also, blood pressure was monitored during a short recovery period and at the end of HD only. However, this choice was made based on our previous study [46] where we observed that post-exercise blood pressure came back to resting values within 5–10 minutes after the end of exercise. Also, using RPE, as well as HR, to control exercise intensity has its limitations in term of exercise prescription [92]. Using power output should guide exercise prescription to better understand the mechanisms underlying acute and chronic benefits of IDE. Therefore, submaximal exercise testing during HD treatment should be developed to appropriately prescribe IDE and compare the literature, since an appropriate exercise intensity prescription is a key feature of training to promote the desired physiological response [93]. Among other limitations, the fact that serum pH was not measured limit our capacity to rule out any exercise-induced metabolic acidosis that could occurred due to low GFR in this population. However, blood lactate accumulation is less significant at low to moderate exercise intensities, such as those achieved by the participants in this study, which helps reduce concerns about exacerbating metabolic acidosis [94]. Regarding the biochemical profile, a clinical instability was observed among participants for some biomarkers (e.g., Hb, PTH and glucose), which could potentially have influenced study findings because they can alter exercise capacity and response. Finally, we are aware that proteome is highly dynamic and can be influenced by different factors, including HD [95–97] and that a blood sample could have been collected before each experimental condition also. Nevertheless, given the fact that the proteome is strongly influenced by the treatment itself, the exploratory nature of this objective led the authors to hypothesize that it could mask the effect of exercise on the circulating proteome [35]. Based on these results, future studies could explore the acute and chronic effect of IDE on proteome when exercise intensity is controlled with optimal tools. This study also has valuable strengths, including the combination of clinical and experimental data, which offers a comprehensive understanding of

the subject matter. By directly evaluating the impact of acute exercise on treatment-related side effects within the healthcare environment, it explores the feasibility of a practical approach. Furthermore, its novelty lies in exploring the proteome's response to IDE, unveiling potential associations with relevant clinical outcomes such as BP. Nonetheless, this study is the first to demonstrate that proteomics analyses are feasible during IDE and provide the IDE-associated proteome. Along with broader studies such as the Kidney Precision Medicine Project (KPMP), these first results will pave the way to future studies with targeted proteomic to better understand the benefits of IDE on clinical outcomes such as blood pressure, treatment adequacy or HD-related symptoms, and hopefully offer predictive biomarkers of IDE-associated benefits [96].

CONCLUSIONS

This study showed that exercise performed during dialysis could be considered as an appropriate strategy to better control blood pressure during HD and decrease the desire to sleep after treatment. On the long run, this could translate into greater time spent at performing light physical activity and less sedentary behaviors. This is the first study to demonstrate the possibility to investigate serum proteome in response to IDE in a complex and deconditioned population. While a total of 12 proteins were regulated in response to IDE, it remains to be determined if a greater exercise intensity and volume would have induced greater proteins regulation and better blood pressure control during HD.

Future randomized control trials investigating the impact of chronic IDE could discover predictive biomarkers of beneficial exercise response and reduce the number and magnitude of intradialytic hypotension and hypertension episodes. Knowing the severe risk of mortality associated with an altered blood pressure control during HD and the high symptom-burden in kidney failure patients, more studies using superiority design should also compare different exercise doses to provide more information about the optimal exercise intervention that must be used with this population.

SUPPLEMENTARY MATERIALS

The following supplementary materials are available online at https://doi.org/10.20900/agmr20240006. Supplementary Table S1: KDQOL-36 subscales; Supplementary Table S2: Treatment-related symptoms after dialysis; Supplementary Table S3: Biochemical profile after both experimental conditions; Supplementary Figure S1: Blood pressure before and after both the control and exercise condition. Data are presented mean ± SEM. A = systolic blood pressure (SBP); B = diastolic blood pressure

(DBP); CONT = control condition; EX = exercise condition; Supplementary Figure S2: Volcano plot of the log2 fold changes versus the −log10 *p*-values. Potentially interesting candidates are located on the top right (increased after exercise) and top left (decrease after exercise) quadrants; Supplementary Figure S3: Heart rate and rate perceived exertion. Data are presented mean ± SEM; HR = heart rate; BPM = beat per minute; RPE = rate perceived exertion; CONT = control condition; EX = exercise condition. * Statistical difference between CONT and EX condition; † statistical difference for RPE compared to the 5 minutes time mark.

ETHICAL STATEMENT

Ethics Approval

This study was approved by the Ethics Committee of the CIUSSS de l'Estrie—CHUS (protocol code 2023-4591, approved on 2022-05-25). Trial was registered in clinicaltrials.gov, identifier: NCT05404698. URL: https://classic.clinicaltrials.gov/ct2/show /NCT05404698.

Regarding the Informed Consent Statement, informed consent was obtained from all participants involved in the study.

Declaration of Helsinki STROBE Reporting Guideline

This study adhered to the Helsinki Declaration and the Tri-Council Policy Statement. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guideline was followed.

DATA AVAILABILITY

The dataset of the study is available from the authors upon request.

AUTHOR CONTRIBUTIONS

Conceptualization, MG and ER; Methodology, ER; Software, DL and FMB; Validation, LP, AMC, RT, LD, MG, DL, FMB and ER; Formal Analysis, LP, AMC, RT, DL, FMB. and ER; Investigation, LP, AMC, RT and LD; Resources, MG; Data Curation, ER; Writing—Original Draft Preparation, LP; Writing—Review and Editing, LP, AMC, RT, LD, DL, FMB and ER; Supervision, ER; Project Administration, ER; Funding Acquisition, ER. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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