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The Effects of Intradialytic Exercise on Hemodialysis Adequacy: A Systematic Review

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Practical Tips for Nephrologists

- Intradialytic exercise increases phosphate clearance and may be a potential adjunct therapy for patients with inadequate phosphate control.
- For practitioners looking to implement intradialytic exercise for improved phosphate control, the current evidence suggests light to moderate intensity intradialytic cycling exercise during most if not all weekly dialysis sessions.

Future Research

- The effects of intradialytic exercise on the clearance of toxic middle molecule and protein bound solutes warrants investigation.
- Future studies should investigate if intradialytic exercise is effective at improving solute removal in patients receiving inadequate dialysis (Kt/V_{urea} <1.2).
- Future studies aimed at improving patient centered outcomes should investigate whether intradialytic exercise could help alleviate the pill burden associated with phosphate control.

ABSTRACT

Dialysis adequacy is an independent predictor of high mortality rates in hemodialysis patients. Intradialytic exercise is a potential strategy to increase uremic solute removal by increasing blood flow to low perfusion tissue beds. The purpose of this review is to establish the efficacy of intradialytic exercise for hemodialysis adequacy. Additionally, this review aims to provide practical information to aid health care professionals implement intradialytic exercise for dialysis adequacy.

Database and hand searches identified 15 published interventional studies that implemented intradialytic exercise for dialysis adequacy as a primary outcome measure in adult maintenance hemodialysis patients. Data pertaining to dialytic solute clearance of urea, creatinine, $beta_2$ microglobulin, phosphate and potassium were extracted. Mean differences, normalized to percentages, and effect sizes were calculated and reported.

The current data pertaining to the use of intradialytic exercise for improving dialysis adequacy in terms of Kt/V_{urea} or small molecule uremic toxin clearance is equivocal. Limited data showed that intradialytic exercise has no effect middle molecule toxin ($beta_2$ - microglobulin) clearance. Intradialytic exercise favored increased phosphate removal showing medium to large effects for reduced serum concentrations, reduced rebound and increased clearance.

In summary, supervised light to moderate intradialytic aerobic cycling appears to be beneficial for increasing phosphate removal and may be an adjunct therapy for patients failing to meet clinical phosphate targets. Further work is required to establish the effect of intradialytic exercise on Kt/V_{urea} and other middle molecule and protein bound solutes. Research aimed at establishing the most effective exercise prescription for improved solute clearance is warranted.

INTRODUCTION

The prevalence of end stage renal disease (ESRD) has increased dramatically by 86% over the past two decades in the United States [1]. Hemodialysis is the most popular form of renal replacement therapy, with 87% of ESRD patients receiving this treatment modality [1]. Despite substantial medical and pharmacological advances in renal replacement therapies, dialysis patients continue to have strikingly higher mortality rates compared to the general population and Medicare populations with cancer, diabetes or cardiovascular disease [1]. The dose and adequacy of hemodialysis, typically determined by uremic solute clearance, is an independent predictor of this high mortality rate. Traditional strategies for improving dialysis adequacy involve increasing the dialysis time or frequency, both of which are limited by patient compliance and cost implications. Improving dialysis adequacy, therefore, remains a major challenge for nephrologists that warrants novel therapeutic approaches.

One such potential strategy that has gained attention over the past decade is intradialytic exercise. The underlying physiological rationale for intradialytic exercise to improve dialysis adequacy is the associated increase in blood flow to the skeletal muscle, which holds a large proportion of the total body water and would ordinarily be a low perfused tissue bed during hemodialysis. In support of this rationale, equation modelling that simulates the hyperemic effects of intradialytic exercise has predicted that increasing blood flow to low perfusion tissue beds will increase solute clearance and almost entirely eliminate post dialysis urea rebound [2]. Additionally, other prediction equations have suggested that 60 minutes of intradialytic exercise may be equivalent to the traditional prescription of increasing dialysis time by 20-30 minutes in terms of solute clearance [3].

Dialysis dose and adequacy is clinically quantified by Kt/V_{urea}, an index representing urea clearance throughout a dialysis session that is proportional to total body water. Current

KDOQI guidelines recommend a target single pool Kt/V_{urea} (spKt/V) of 1.4 per hemodialysis session, with a minimum delivered dose of 1.2 [4]. The clearance of urea is clinically utilized as a marker of uremic solute removal as its blood concentration is increased in uremia; it has a low molecular weight allowing for an easy transfer across the dialysis membrane and rapid compartmental diffusion; and it is a water-based solute that allows the implementation of a single pool model representation of total body water. However, the use of urea as the sole representation of dialysis adequacy remains controversial and may represent an oversimplified view of dialysis adequacy [5]. In this respect, urea does not represent the kinetic behavior of more toxic water-based solutes such as phosphate [6], or that of 'middle molecules' and protein bound solutes whose harmful effects are associated with inflammation, oxidative stress and cardiovascular disease [7].

The purpose of this review is to provide an analysis of the literature that has reported indices of dialysis adequacy, including the removal of solutes other than urea, in association with intradialytic exercise in maintenance hemodialysis patients. The aim of the review is to establish a) the evidence base of the efficacy of intradialytic exercise for dialysis adequacy; b) the most effective exercise prescription parameters that may help guide health professional looking to implement intradialytic exercise for dialysis adequacy c) areas that warrant future research in this field.

METHODS

Literature Search

Pubmed database and hand searches were performed by one non-blinded author (DK) between August and November 2018. Searches utilized key terms relating to the disease condition (e.g. hemodialysis; renal failure, chronic), the intervention (e.g. intradialytic exercise; exercise therapy) and the outcome (e.g. dialysis adequacy; solute removal). From the results, one non-blinded author (DK) selected the relevant literature based on pre-determined criteria. Literature was excluded if it was a conference abstract or short communication; was a review paper; was not a peer reviewed published article; dialysis adequacy was not the primary outcome of interest; the exercise intervention was not intradialytic; included individuals <18 years; not published in English; did not report outcome measures relating to dialysis adequacy; included an additional intervention coupled with exercise (e.g. nutraceutical, transcutaneous electrical muscle stimulation); a duplicate; involved animal models or computer modeled simulations. During a hemodialysis session, there are many treatment parameters that can be changed that may greatly affect solute removal (e.g. blood flow rate, dialysate flow rate; treatment time). For this reason, we chose only to include studies that investigated the effects of intradialytic exercise on dialysis adequacy as the primary outcome as these studies would typically control these treatment variables. Studies that implemented dialysis adequacy for other outcomes (e.g. body composition, physical function, cardiovascular function) that reported a marker of dialysis adequacy as a secondary outcome were excluded as uncontrolled dialysis treatment parameters may potentially bias the interpretation.

Data Extraction

For each included study, the mean differences in outcome measures pertaining to dialysis adequacy or solute removal were extracted and normalized to percent changes. Effect

sizes were then calculated as (post intervention – pre intervention) / baseline or control group standard deviation [8]. For intervention studies with a comparable control arm, interaction effect sizes were subsequently calculated as (experimental effect size – control effect size) / 2 [8]. Effects sizes were interpreted as small (0.2), medium (0.5) or large (0.8).

Data pertaining to serum values and indices of dialysis adequacy and solute clearance (Table 1) for the following uremic solutes was extracted:

1) **Small molecules: urea and creatinine.** Urea and creatinine are both small molecule, water based solutes whose clearance represents a clinical marker of dialysis adequacy. Urea clearance is the currently the 'gold standard' clinical marker of dialysis adequacy and its clearance during dialysis is independently associated with survival [9].
2) **Middle molecule: beta-$_2$-microglobulin (B_2M).** B_2M is the representative marker of middle molecule uremic toxins. Middle molecule uremic toxins are associated with systemic toxicity with their accumulation predisposing patients to infection [6]. Increased serum concentrations of B_2M are associated with infectious related mortality [10].
3) **Inorganic substance: phosphate.** Phosphate is a water-based solute that is the representative marker of inorganic substances. Increased serum phosphate levels are related to cardiovascular complications and are independently associated with mortality [11].
4) **Electrolyte: potassium.** Potassium is the most frequently reported electrolyte in terms of dialysis clearance. Increased levels of serum potassium are causally related to cardiovascular related mortality [12].

Bias Reporting

Risk of bias for each study was determined by two non-blinded authors (DK, MS) based on 1) Selection Bias 2) Performance Bias 3) Detection Bias and 4) Attrition Bias. Each factor

was given a score of 1 (high risk/not known), 2 (medium risk) or 3 (low risk) and an overall composite score from A (low risk) to C (high risk) was administered.

RESULTS

Included Study Designs

A total of 15 studies were included in the review (Figure 1; Table 2). Eight studies investigated the effects of an acute bout of exercise on dialysis adequacy [3,13-19], whilst seven studies performed a chronic intradialytic intervention [20-26]. Seven of the acute studies utilized a within subject crossover design [3,14-19], with six of the seven randomizing the treatment order. One acute study implemented a randomized controlled design[13]. Four of the intervention studies performed a randomized controlled trial[20,22,23,25], one study utilized a within subject crossover design[24], and two studies observed pre and post changes in an intervention group without a control comparison arm (1 group intervention)[21,26].

Bias scoring showed an intermediate bias risk (B) for 67% of the studies, followed by a high risk (C) and low risk (A) reported in 20% and 13% of the studies, respectively (Table 3). Reassuringly, the majority of studies implemented a randomized crossover design ensuring an intermediate to low risk of selection and performance biases. Unfortunately, many studies failed to detail the randomization strategy. Overall, the majority of studies did not mention if outcome assessors were blinded to treatment allocation, thereby presenting a high risk of detection bias. No studies performed an intention to treat analyses.

Participant Characteristics

Data from 307 patients were included. Participants included both males and females with ages ranging from 18 years[15,22] to 76 years [22]. Hemodialysis vintage ranged from 16 months[21] to 58 months[14]. The majority of patients dialyzed 3 times per week for 3– 4 hours.

Mean dialysis dose reported as spKt/V_{urea} ranged from 0.9 [23] to 1.8 [25]. Many studies did not report co-morbidities but excluded patients with contraindications to exercise.

Exercise Interventions

Most studies implemented aerobic exercise, with intradialytic cycling being the most common modality of exercise. The use of a mini-stepper was also included in one study[26]. Aerobic exercises were prescribed at light to moderate intensities ranging from 20 minutes – 180 minutes. The duration of chronic interventions ranged from 8 – 12 weeks.

Lower body resistance exercises were implemented in one chronic intervention study lasting 8 weeks [21]. This type of exercise was performed utilizing venous anti statis slippers, 2-3 dialysis sessions per week for 60 minutes at an unknown intensity

An additional exercise modality included 15 minutes of range of motion exercises, which was implemented in two intervention studies lasting 8 weeks[22,23].

Most exercise interventions were prescribed during the first two hours of hemodialysis. Four studies allowed exercise into the third hour of dialysis [15,20,21,25]. One study specifically prescribed exercise in the last half of dialysis [16].

Harms

Only five studies actively reported harms[14,16,25,26]. No serious or unexpected adverse events relating to exercise were reported. Expected adverse events that were reported in a relatively small number of cases included episodic hypotension [16,25,26] and intradialytic cramping [14,16].

Dialysis Adequacy: Small molecule toxins urea and creatinine

Seven[14,16-19,24,25] of the 13 studies that reported spKt/V_{urea} showed no statistical significance and small effect sizes for intradialytic exercise. Six[3,15,20,21,23,26] of the 13 studies that reported spKt/V_{urea} favored intradialytic exercise with statistical significance or a large effect size. Only three studies reported eKt/V_{urea} [14,16,25], all of which showed intradialytic exercise to have no effect. Data pertaining to urea reduction ratios is equivocal with four studies showing statistical significance or a large effect size in favor of exercise[3,15,23,26] and five studies showing exercise to have little to no effect[14,16,17,19,25]. The majority of studies that report urea rebound[16,18,19], small molecule toxin dialysate clearance[13,16-18] and creatinine removal [13,16,18,25] show intradialytic exercise to have little to no effect. Studies that reported intradialytic exercise to be efficacious at improving Kt/V_{urea} and/or small molecule clearance [3,15,20,21,23,26] overall had a higher risk of bias compared to those who reported exercise to have no effect [14,16-19,24,25]. In summary, the slight majority of the research tends to lean towards intradialytic exercise having little to no effect on small molecule toxin clearance, however, overall the data is equivocal.

Dialysis Adequacy: Middle molecule toxin Beta-$_2$-Microglobulin

Only one acute intervention reported the effects of B_2M clearance and serum concentrations [16]. This study showed intradialytic exercise to have no effect on this marker of middle molecule toxins.

Dialysis Adequacy: Phosphate

Six [13,14,16,17,22,24] of seven[18] of studies showed a statistically significant result or a medium-large effect size for increased phosphate clearance and/or improved serum concentrations with intradialytic exercise. Two studies showed that intradialytic exercise was more efficacious than a longer dialysis treatment time for increasing phosphate removal [16,17].

Dialysis Adequacy: Potassium

Five[3,13,22,24,25] of seven[18,20] studies showed a statistically significant result or a large effect size for increased potassium clearance and/or reduced serum concentrations with intradialytic exercise.

DISCUSSION

Efficacy of Intradialytic Exercise for Dialysis Adequacy

Contrary to physiological hypotheses and simulated mathematical modelling[2], this review of the current literature trends towards a lack of efficacy for intradialytic exercise to improve Kt/V_{urea} and enhance small molecule uremic toxin clearance. These data, however, are contradictory and require follow up. There is currently insufficient data to determine the effect of intradialytic exercise on middle molecule and protein bound uremic toxin clearance. Interestingly, intradialytic exercise appears to be efficacious at improving phosphate kinetics and removal. In addition, intradialytic exercise holds promise for improving potassium balance and removal.

Small Molecule Toxins. In order to explain the equivocal findings in relation to small and middle molecule clearance with intradialytic exercise, it is important to consider the current models of uremic toxin kinetics. With regards to small molecules urea and creatinine, the physiological hypotheses and mathematical models that predict intradialytic exercise to be efficacious at improving dialysis adequacy are based on a parallel regional blood flow kinetic model that separates organ systems to high or low flow systems based on their perfusion during dialysis [27,28]. An alternative model is the classic serial diffusion model that incorporates a total body distribution of urea and stipulates that there is a rapid transfer of small molecules

from the intracellular to the extracellular compartments resulting in a precipitous equilibration of whole-body concentrations [29]. According to this model, intracorporal changes in blood flow would not affect small molecule kinetics and may therefore explain why intradialytic exercise is not efficacious at improving dialysis adequacy in terms of small molecule clearance in the slight majority of studies.

Middle Molecules Toxins. With regards to middle molecules such a B_2M and protein bound molecules, their high transfer coefficient resulting in slower intercompartmental transfer would appear to be the rate limiting factor of their removal [30]. Therefore, in terms of increasing removal of these solutes, increased cardiac output and blow flow to low perfusion regions would be less important than toxin distribution volume and intercompartmental clearance coefficients [31]. Although the effects of exercise on middle molecule clearance were only investigated in one study[16], this may explain the negligible effects observed regarding B_2M kinetics.

Inorganic substances. In comparison, intradialytic exercise appears to beneficial for phosphate removal. A four-pool model explains the biphasic regulation of phosphate kinetics during dialysis whereby extra phosphate is generated by erythrocytes and bone when phosphate levels become low[32]. It has previously been speculated that during intradialytic exercise phosphate is produced from skeletal muscle metabolism[33] and therefore prohibits the need for increased phosphate generation from the erythrocytes and bone[16]. After exercise, phosphate released from the skeletal muscle is then utilized for energy replenishment leading to reduced serum phosphate levels[16].

Electrolytes. During exercise, there is a release of potassium ions from the skeletal muscle thereby decreasing intracellular concentrations and increasing plasma concentrations[34]. To maintain whole body homeostasis, sodium potassium pumps are typically activated to increase potassium uptake and prevent serum concentrations from rising to toxic

levels[34]. During intradialytic exercise however, it is possible that the increased serum potassium is removed via the dialyzer, thus reducing the intracellular re-uptake. This could potentially explain the observed decrease in potassium serum concentrations and increased removal that are observed with intradialytic exercise.

Exercise Interventions. While the majority of studies have implemented aerobic cycling exercise at a light to moderate intensity, there is a large amount of variation in the exercise parameters between studies to establish what the most effective exercise prescription for dialysis adequacy is. Along with the intradialytic kinetics, it is also important to consider aspects of the exercise prescription that may lead to more effective solute removal. For example, exercise intensities prescribed below the lactate threshold may be more appropriate as decreases in blood pH may alter intercompartmental shifts of solutes and therefore affect their removal during dialysis[35]. In addition, during the first half of dialysis, the dialyzer clearance capacity is the rate limiting factor of removal[2] and therefore exercise during the second half of dialysis, once a large portion of solutes have already been removed, may be more effective. If exercise prescription is based on previous mathematical simulations, then exercise needs to performed for at least 60 minutes to substantially affect urea rebound[2].

The exercise prescription parameters deemed most efficacious at altering solute kinetics and potentially increasing solute removal therefore warrant further investigation. One study by Parsons *et al.*[25] included a small pilot study that established intradialytic cycling or use of a mini-stepper more effective at increasing urea removal compared to resistance exercise with ankle weights. No other studies have compared exercise prescription parameters.

Finally, the exercise response in this population needs to be fully understood to provide effective exercise prescription. For example, hemodialysis patients have impaired cardiac

function[36], vascular endothelial dysfunction[37] and altered autonomic function[38], all of which may blunt the blood flow response to exercise. This may potentially explain why a fair proportion of the findings observed in the reported studies do not replicate simulated mathematical models based on exercise hyperemia.

Practical Implications for Practitioners

Despite concerted clinical efforts to reduce phosphate levels, many patients fail to obtain target values with a large number of limitations to currently implemented interventions including poor adherence to the large pill burden of phosphate binders[39]. The findings of this review suggest that intradialytic exercise may be a potential adjunct therapy for patients with inadequate phosphate control.

For practitioners looking to implement intradialytic exercise for improved phosphate removal, the current evidence would suggest intradialytic aerobic cycling at a light to moderate intensity exercise (Rating of Perceived Exertion 9 to13 on the Borg 6 to 20 scale) during most if not all weekly dialysis sessions. While most studies have implemented exercise during the first two hours of dialysis, a few have safely implemented exercise during the third hour[16,21,26].

As opposed to phosphate, dialytic potassium clearance is typically efficient and therefore its removal poses less of a clinical challenge. Based on the findings reported herein that intradialytic exercise reduces serum potassium levels and increases potassium removal, it is important to also consider that hypokalemia is also associated with mortality in dialysis patients[12]. Whilst intradialytic exercise may be beneficial for hyperkalemic patients, patients on lower potassium baths should be monitored for subsequent hypokalemia.

To reduce the risk of episodic hypotension following exercise, a prolonged cool down should be implemented and the ultrafiltration rate can be reduced to minimum during the last 10 minutes of exercise and throughout the cool down. An emergency clinical algorithm for

episodic hypotension should be established and known by all health care professionals working in the dialysis unit. Patients who experience intradialytic cramping should try to exercise earlier in the dialysis session before they are close to achieving their dry weight.

Exercise should be supervised by a nurse, physical therapist or clinical exercise physiologist who monitors hemodynamic responses to exercise and checks blood glucose levels before and after exercise in diabetic patients. The addition of an exercise program to an outpatient dialysis unit would therefore likely require an expansion of the clinical staff to provide accurate training and supervision of exercise.

Limitations

A limitation of this review is that it did not calculate weighted scores for outcomes based on the sample size of each study. Due to the indefinite findings in relation the effects of exercise on small molecule toxin clearance, this review should be followed up with a meta-analysis to provide more detailed and objective analyses of the data.

Future Areas for Research

As with many other areas in the field, future research is needed to refine the parameters of the exercise prescription and establish the minimum dose required to elicit the most beneficial effect on solute removal. In addition, the effects of intradialytic exercise on the kinetics and clearance of the more toxic middle molecules and protein bound solutes remains to be established.

The majority of patients included in these studies already reported an adequate dialysis with a Kt/V_{urea} of ≥1.2. Whether intradialytic exercise could be more effective for improving dialysis adequacy in patients with a lower Kt/V_{urea} who are have a higher risk of hospitalization and mortality is unknown.

Finally, phosphate control contributes substantially to the pill burden of this patient population with patients taking between six to twelve phosphate binders per day[39]. Non-adherence to phosphate binders increases with the number of pills prescribed per day, contributing to poor phosphate control[39]. Based on the beneficial effects of intradialytic exercise on phosphate removal, future studies aimed at improving patient centered outcomes should investigate whether intradialytic exercise could help alleviate the pill burden in these patients.

Conclusions

In summary, it remains unclear whether intradialytic exercise is effective for improving dialysis adequacy in terms of Kt/V_{urea} or small molecule uremic toxin clearance. Supervised, light to moderate aerobic cycling during dialysis appears to be beneficial for increasing phosphate removal and may be an effective adjunct therapy for patients failing to meet clinical phosphate targets. Further work is required to establish the effect of intradialytic exercise on other uremic toxins such as middle molecules and protein bound solutes. In addition, research aimed at establishing the most effective exercise prescription parameters for improved solute clearance is warranted.

It should also be noted that KDOQI have recently emphasized the need to expand the concept of dialysis adequacy to include and prioritize the improvement of quality of life[40]. Intradialytic exercise has consistently proven to be efficacious at improving patient's physical and mental quality of life and, in this respect, it should be considered as an adjunctive therapeutic intervention for dialysis adequacy.

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Figure 1. Flow of literature search.

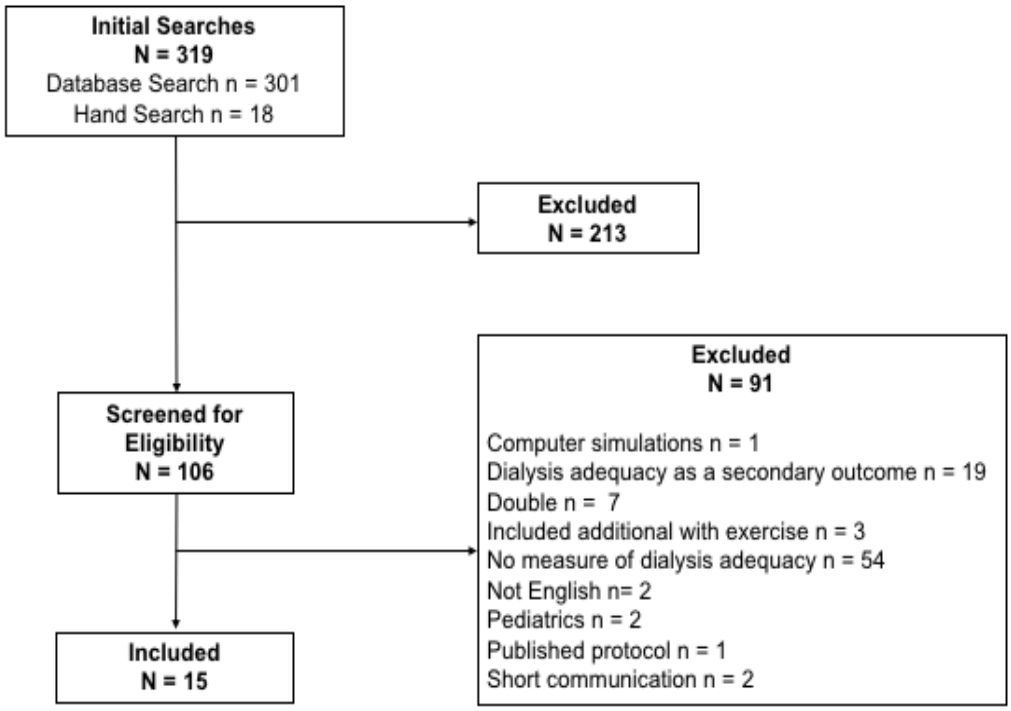

Table 1. Markers of solute removal and kinetics included in data extraction

Markers of Solute Removal and Kinetics	
Single pool Kt/V_{urea}	$-\ln(C_t/C_0 - 0.0083 \times T) + (4 - 3.5 \times C_t/C_0) \times dBW/BW$
Equilibrated Kt/V_{urea}	$-\ln(C_{t30}/C_0 - 0.0083 \times T) + (4 - 3.5 \times C_{t30}/C_0) \times dBW/BW$
Reduction Ratio (%)	$100 \times ((C_0 - C_t)/C_0)$
Rebound Ratio (%)	$100 \times ((C_{t30}/C_0) / (C0/Ct))$
Spent Dialysate Content	Total Dialysate Sampling (TDS)
	Partial Dialysate Sampling (PDS)
	Continuous Sampling of Spent Dialysate (CSSD)
Clearance Time	$T \times \ln(C_{t30}/C_0) / \ln(C_0/ C_{t30})$

BW, post dialysis weight (kg); C_0, pre-dialysis blood urea nitrogen; C_t, post dialysis blood urea nitrogen; C_{t30}, 30-minute post dialysis blood urea nitrogen; T, dialysis time; dBW, body weight loss during dialysis (kg).

Table 2. Studies investigating intradialytic exercise for dialysis adequacy as a primary outcome measure in adult maintenance hemodialysis patients

Author	Design	Groups	Intervention	Outcome Measures	Difference (% change)	Effect Size
			Acute Interventions			
Bohm (2017)[13]	Randomized Controlled Trial	Exercise Control (N = 30)	[A]Aerobic (cycling) [B] 1 trial [C] 60-70% HR_{max}; 13-14 RPE [D] 30 minutes [E] n/a [F] 60-90 minutes	**Urea** Serum (mg/dL)	Exercise + 3.60 Control -2.40	0.50(Medium)
				Dialysate Content (ml/min;TDC)	Exercise +0.55	0.08 (Trivial)
				Creatinine Serum (md/dL)	Exercise +3.19 Control -1.13	0.2 (Small)
				Dialysate Content (ml/min;TDC)	Exercise +2.44	0.2 (Small)
				Phosphate Serum (mg/dL)	Exercise +6.87 Control -4.62	0.5 (Medium)
				Dialysate Content (ml/min;TDC)	Exercise -10.10	-1.0 (Large)
				Potassium Serum (m/EqL)	Exercise +6.27 Control -3.16	1.2 (Large)
				Dialysate Content (ml/min)	Exercise -9.37	?
Farese (2008)[14]	Randomized Crossover	Exercise Control TEMS (N = 9)	[A] Aerobic (cycling) [B] 3 trials [C] Passive [D] 20 minutes [E] n/a [F] ?	**Urea** spKt/V	Exercise +2.92	0.2 (Small)
				eKt/V	Exercise +2.76	0.2 (Small)
				Reduction Ratio (%)	Exercise +1.32	0.2 (Small)
				Dialysate Content (mg/dL;CSSD)	Exercise +33.33 *	1.3 (Large)

				Phosphate		
				Dialysate Content (mg/dL; CSSD)	Exercise +30.99 *	1.4 (Large)
Giannaki (2011)[15]	Crossover	Exercise Control (N = 10)	[A] Aerobic (cycling) [B] 1 session [C] 40% Max Exercise Capacity [D] 180 minutes [E] n/a [F] 30-210 minutes	**Urea**		
				spKt/V	Exercise +20.18 *	7.3 (Large)
				Reduction Ratio (%)	Exercise +11 *	?
				Creatinine		
				Reduction Ratio (%)	Exercise +26 *	?
Kirkman (2013)[16]	Randomized Crossover	Exercise Control Extra Time (N = 11)	[A] Aerobic (cycling) [B] 2 sessions [C] 90% Aerobic Threshold [D] 60 minutes [E] n/a [F] 120-180 minutes	**Urea**		
				eKt/Vurea	Exercise +2.26	0.2 (Small)
				spKt/Vurea	Exercise +1.99	0.2 (Small)
				Reduction Ratio (%)	Exercise +1.37	0.0 (Nil)
				Urea Rebound Ratio (%)	Exercise -16.67	0.0 (Nil
				Dialysate Content (mmol;CSSD)	Exercise +1.41	0.04 (Trivial)
				Creatinine		
				Reduction Ratio (%)	Exercise +1.52	0.4 (Small)
				Rebound Ratio (%)	Exercise 0.00	0.0 (Nil)
				Dialysate Content (µmol; CSSD)	Exercise +0.62	0.007 (Trivial)
				Beta-$_2$-Microglobulin		
				Reduction Ratio (%)	Exercise +6.00	0.3 (Small)
				Rebound Ratio (%)	Exercise -31.25	0.5 (Medium)
				Dialysate Content (mg; CSSD)	Exercise +9.29	0.2 (Small)
				Phosphate		
				Reduction Ratio (%)	Exercise +18.00 *	0.5 (Medium)

				Rebound Ratio (%)	Exercise -23.08	0.4 (Small)
				Dialysate Content (mmol;CSSD)	Exercise +27.27	0.9 (Large)
Kong (1999)[3]	Randomized Crossover	Exercise Control (N = 11)	[A] Aerobic (cycling) [B] 1 session [C] 25-75 Watts [D] 60 minutes [E] n/a [F] ?	**Urea** eKt/V	Exercise +15.00 *	2.21 (Large)
				Reduction Ratio (%)	Exercise +7.94 *	?
				Rebound Ratio (%)	Exercise -12.10 *	?
				Clearance Time (min)	Exercise -21.57 *	?
				Creatinine Reduction Ratio (%)	Exercise +11.76 *	?
				Rebound Ratio (%)	Exercise -18.87 *	?
				Clearance Time (min)	Exercise -29.47 *	?
				Potassium Rebound Ratio (%)	Exercise -29.03 *	?
Leung (2004)[19]	Randomized Crossover	Exercise Control (n=15)	[A] Aerobic (cycling) [B] 1 session [C] RPE 3 [D] 60 minutes [E] n/a [F] ?	**Urea** Rebound Ratio (%)	Exercise -11.16	0.2 (Small)
				Dialysate Content (mmol; PDS)	Exercise +5.99	0.3 (Small)
Orcy (2014)[18]	Randomized Crossover	Exercise Control (N = 22)	[A] Aerobic (cycling) [B] 3 sessions [C] RPE 13; < 80% HR_{max} [D] 60 minutes [E] n/a [F] 0-120 minutes	**Urea** spKt/V	Exercise -0.77	-0.05 (Trivial)
				Rebound Ratio (%)	Exercise -18.18	? (?)
				Dialysate Content (CSSD)	Exercise -8.32	? (?)
				Creatinine Rebound Ratio (%)	Exercise 0.00	0.0 (Nil)
				Dialysate Content (CSSD)	Exercise 0.00	0.0 (Nil)

				Phosphate		
				Rebound Ratio (%)	Exercise -7.41	?
				Dialysate Content (CSSD)	Exercise +9.80	?
				Potassium		
				Rebound Ratio (%)	Exercise +2.63	?
				Dialysate Content (CSSD)	Exercise +3.76	?
Vaithilingam (2004)[17]	Randomized Crossover	Exercise Control Extra Time (N = 12)	[A]Aerobic (cycling) [B] 3 sessions [C] ? [D] 30-60 minutes [E] n/a [F] ?	**Urea**		
				spKt/V	Exercise 0.00	0.0 (Nil)
				Reduction Ratio	Exercise +2.78	0.2 (Small)
				Dialysate Content (mg; PDS)	Exercise +6.06	0.2 (Small)
				Phosphate		
				Serum (mg/dL)	Exercise -3.51	-0.2 (Small)
				Dialysate Content (mg; PDS)	Exercise +9.16 *****	0.4 (Small)
				Chronic Interventions		
Adam (2017)[20]	Randomized Controlled Trial	Exercise Control (N = 34)	[A] Aerobic [B] ? [C] HR 100bpm [D] 60 minutes [E] 24 weeks [F] 1st 15 min/hour	**Urea**		
				spKt/V	Exercise +16.67 Control 0	1.5 (Large)
				Serum (mg/dL)	Exercise -41.86 Control 12.66	1.09 (Large)
				Creatinine		
				Serum (mg/dL)	Exercise -34.74 Control -2.93	0.1 (Trivial)
				Potassium		
				Serum (mEq/L)	Exercise -5.12 Control -5.41	0.0 (Nil)
Kern (2009)[21]	1 Group Intervention	Exercise (N = 12)	[A] Resistance [B] 2-3days/week [C] ? [D] 60 minutes	**Urea**		
				spKt/V	Exercise +7.97 *****	0.2 (Small)

			[E] 8 weeks [F] 0-180 minutes			
Makhlough (2012)[22]	Randomized Controlled Trial	Exercise Control (N = 47)	[A] Range of Motion [B] 3days/week [C] ? [D] 15 minutes [E] 8 weeks [F] 0-30 minutes	**Phosphate** Serum (mg/dL) **Potassium** Serum (mg/L)	Exercise +192.96 ** Control +0.57 Exercise -11.88 ** Control -3.01	1.0 (Large) -0.3 (Small)
Mohseni (2013)[23]	Randomized Controlled Trial	Exercise Control (N = 50)	[A] Range of Motion [B] 3days/week [C] ? [D] 15 minutes [E] 8 weeks [F] 0-120 minutes	**Urea** spKt/V Reduction Ratio (%)	Exercise +33.33 ** Control +5.56 Exercise +50.00 ** Control 0.00	0.7 (Medium) 1.00 (Large)
Musavian (2015)[24]	Crossover	Exercise (Active) Exercise (Passive) Control (N = 18)	[A]Aerobic(cycling) [B] 3days/week [C] ? [D] 30 minutes [E] 8 weeks [F] 0-120 minutes [A]Aerobic(cycling) [B] 3 days/week [C] Passive [D] 30 minutes [E] 8 weeks [F] 0-120 minutes	**Urea** spKt/V Reduction Ratio (%) **Phosphate** Serum (mg/dL) **Potassium** Serum (mEq/L)	Passive +9.16 Active -4.32 Passive +1.99 Active -3.33 Passive -0.40 Active -13.2 Passive 0.00 Active -9.74 **	0.4 (Small) -0.2 (Small) 0.2 (Trivial) -0.3 (Trivial) -0.03 (Trivial) -0.7 (Medium) 0.0 (Nil) -0.5 (Medium)
Parsons (2004)[25]	Randomized Controlled Trial	Exercise Control (N = 13)	[A]Aerobic(cycling) [B] 3 days/week [C] 40-50% WL_{max} [D] 45 minutes [E] 8 weeks [F] 0-180 minutes	**Urea** spKt/V eKt/V Serum (umol/L) Dialysate Content (mmol; PDS)	Exercise 0.00 Control -4.47 Exercise +0.79 Control -3.17 Exercise -2.29 Control +8.33 Exercise +15.00 ** Control -1.00	0.2 (Small) 0.1 (Trivial) -0.2 (Small) 1.1 (Large)

				Creatinine		
				Serum (umol/L)	Exercise +0.59 Control +1.19	-0.03 (Trivial)
				Potassium		
				Serum (mEq/L)	Exercise -6.38 ***** Control +2.13	-0.7 (Medium)
Parsons (2006)[26]	1 Group Intervention	Exercise (N = 13)	[A] Aerobic (cycling or mini stepper) [B] 3 days/week [C] self-paced [D] 60 minutes [E] 20 weeks [F] 0-120 minutes	**Urea**		
				spKt/V	Exercise +15.49 *****	0.9 (Large)
				Serum (umol/L)	Exercise +3.30	0.2 (Small)
				Reduction ratio (%)	Exercise +7.11 *****	0.8 (Large)

CSSD, continuous sampling of spent dialysate; eKt/V, equilibrated Kt/V; PDS, partial dialysate sampling; spKt/V, single pooled Kt/V; TEMS, transcutaneous electrical muscle stimulation; ?, information not available from paper.

A, exercise modality; B exercise frequency; C, exercise intensity; D, exercise duration; E, exercise time during dialysis; F, length of exercise intervention; *, statistical significance ($p < 0.05$).

Table 3. Study Bias Risk

First Author	Bias				
	Selection	Detection	Attrition	Performance	Overall Score
Adam (2017)[20]	3	1	1	2	B
Bohm (2017)[13]	3	1	1	3	B
Farese (2008)[14]	2	1	3	3	B
Giannaki (2011)[15]	1	1	1	3	C
Kern (2009)[21]	1	1	3	1	C
Kirkman (2013)[16]	3	3	3	3	A
Kong (1999)[3]	2	1	1	3	B
Leung (2004)[19]	2	1	3	3	B
Makhlough (2012)[22]	3	3	1	2	B
Mohseni (2013)[23]	3	3	3	2	B
Musavian (2015)[24]	1	1	3	2	B
Orcy (2014)[18]	3	3	3	3	A
Parsons (2004)[25]	2	1	3	2	B
Parsons (2006)[26]	1	1	3	1	C
Vaithilingam (2004)[17]	2	1	1	3	B