RESEARCH PAPER

Effects of Intradialytic Aerobic versus Active Range-of-Motion Exercises on Functional Capacity and Cognition in Hemodialysis patients: Randomized clinical Trial

Faten Mahmoud El-Desouky Abd El-Salam[1], Azza Abd El-Aziz Abd ElHady[1], Zaghloul Elsafy Gouda[2,4], Lamiaa Mohamed Fahmy Ali [3], Shaimaa Ahmed Eid Ahmed [4], Gehad Ali Abd Elhaseeb[1]

[1] Department of Physical Therapy for Cardiovascular/Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, Cairo University, Egypt.

[2] Dialysis Unit, Itay El Baroud Central Hospital, El-Behera, Egypt.

[3] Department of Physical Therapy for Cardiovascular/Respiratory Disorder& Geriatrics in El Salhya El Gadida University.

[4] Department of Physical Therapy for Basic Science in El Salhya El Gadida University.

Corresponding Author Details:

Name: Faten Mahmoud El-Desouky Abd El-Salam

Email: [fateneldesouky546@gmail.com]

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Abstract:

Introduction: Chronic kidney disease is associated with high morbidity and mortality, and patients receiving maintenance hemodialysis often experience both physical decline and impaired cognitive performance. Because these limitations can affect independence and quality of life, rehabilitation strategies during dialysis are increasingly important.

Material and methods: A randomized controlled trial was conducted on 69 patients with end-stage renal disease aged 50–60 years. Participants were equally allocated into three groups (n=23 each): Group A performed aerobic exercise using a simple foot-pedal exerciser, selected because it is a practical and low-cost option in our setting, Group B followed an active free ROM program, and Group C received standard care only. Functional capacity was assessed using the 6-minute walk test, and cognitive function was evaluated using the Mini-Cog test. Outcomes were measured at baseline and after 8 weeks of intervention.

Results: Both intervention groups experienced statistically significant improvements in 6MWT distance and Mini-Cog scores compared with baseline ($p < 0.05$), while the control group showed no significant change. Between-group comparisons favored Group A over Group B, with larger mean gains in both 6MWT and Mini-Cog ($p < 0.05$).

Conclusion: Intradialytic aerobic exercise and active free range-of-motion exercises both improved functional capacity and cognitive performance in hemodialysis patients, with aerobic exercise producing the larger effect. These findings support implementing low-cost intradialytic aerobic programs to enhance physical and cognitive outcomes in this population.

Keywords: Renal failure; Fatigue; Executive function; Physical Rehabilitation.

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Introduction

Globally, chronic kidney disease (CKD) is recognized as a formidable public health crisis, with a prevalence reaching 10% to 15% of the general population. This condition is associated with substantial morbidity and mortality. While its negative effects stem from multifaceted origins, physical inactivity and sedentary behavior are critically linked to increased mortality risks, rapid disease progression, and a decline in the overall quality of life.[1]

Skeletal muscle wasting is a common complication among individuals with chronic kidney disease, manifested by a simultaneous decline in muscle mass, physical strength, and functional endurance. Such atrophic changes contribute to significant clinical challenges, including heightened cardiovascular risks, impaired glucose metabolism, and a marked reduction in muscular power and postural stability. Furthermore, the progressive loss of muscle volume is intricately linked to the severity and acceleration of CKD stages.[2]

Hemodialysis patients face a profound decline in health-related quality of life, which is intimately exacerbated by physical inactivity and prolonged sedentary behavior during non-dialysis days. Chronic sedentary bouts significantly restrict patients' daily functional capacity and overall physical well-being.[3]

Structured physical activity has emerged as a cornerstone of therapeutic management for hemodialysis patients. Beyond mitigating cardiovascular risks, exercise optimizes metabolic health, muscular strength, and cognitive performance. Regular participation enhances treatment efficacy and halts functional decline, ultimately fostering a superior quality of life.[4]

Intradialytic cycle ergometry is the most widely adopted exercise modality for hemodialysis patients. Beyond enhancing cognitive function, existing evidence suggests that these aerobic interventions provide a neuroprotective mechanism against cognitive deterioration in long-term dialysis populations.[5]

Intradialytic range-of-motion (ROM) exercises represent a pragmatic and cost-effective intervention that can be easily integrated into the clinical workflow of dialysis units. These movements offer a feasible alternative for physical conditioning, providing patients with significant therapeutic benefits without the need for specialized or expensive equipment. [6]

Evidence confirms that intradialytic active free range of motion (ROM) protocols are safe, feasible, and effective in achieving physiological and psychological gains. These interventions promote social engagement and play a crucial role in slowing cognitive decline within the hemodialysis population. [7]

Range of motion (ROM) exercises are easily integrated into hemodialysis routines with minimal clinical disruption. Typically administered in 15-minute intervals thrice weekly, this streamlined approach ensures consistent physical conditioning without compromising the primary treatment schedule. [8]

Therefore, it is hypothesized that intradialytic aerobic training and active-free exercises differ significantly in their impact on cognitive and functional outcomes. Thus, this study compared the therapeutic effects of these two modalities on the cognitive status and physical endurance of maintenance hemodialysis patients.

Material and methods

Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Physical Therapy, Cairo University, Egypt (Approval No. P.T.REC/012/004902). Before enrollment, the trial was prospectively registered at ClinicalTrials.gov (NCT05915572). Each participant received a full explanation of the study and subsequently provided written informed consent.

Sample Size

The G*power version 3.1.9.7 was utilized to calculate the sample size. A prior type of power analysis was used with α error probability of 0.05 and power (1-β error probability) equal to 0.95. A total of 69 patients was the minimum sample size for the study. Patients were randomized equally into three groups (n=23/group) via sealed envelopes by a blinded researcher. **(Fig. 1)**

Study participants

This clinical trial, conducted at Itay El Baroud Central Hospital (Egypt), involved 69 ESRD patients (aged 50–60 years) on maintenance hemodialysis for ≥3 months. Participants were randomized into three equal groups (n=23): Group A (aerobic pedaling), Group B (active free ROM), and Group C (standard care), with exercise protocols lasting 8 weeks (thrice weekly). Eligible subjects possessed a functional AV fistula (Stage 5 CKD), a BMI of 18.5–24.9 kg/m², and sufficient cognitive ability for informed consent. Conversely, exclusion criteria included uncontrolled hypertension (>200/120 mmHg), obesity (BMI >35 kg/m²), pre-existing neurological or psychiatric disorders, severe musculoskeletal limitations, and a history of malignancy or epilepsy. All procedures were performed in accordance with the ethical standards of the Helsinki Declaration, and a written informed consent was obtained from all participants.

Procedures

Prior to the intervention, all participants underwent a comprehensive physical screening conducted by a certified physical therapist to verify adherence to the eligibility criteria. Anthropometric data, including body weight (kg) and height (cm), were accurately recorded for each subject. Subsequently, the Body Mass Index (BMI) was calculated using the standard formula to ensure all participants fell within the predefined study range.

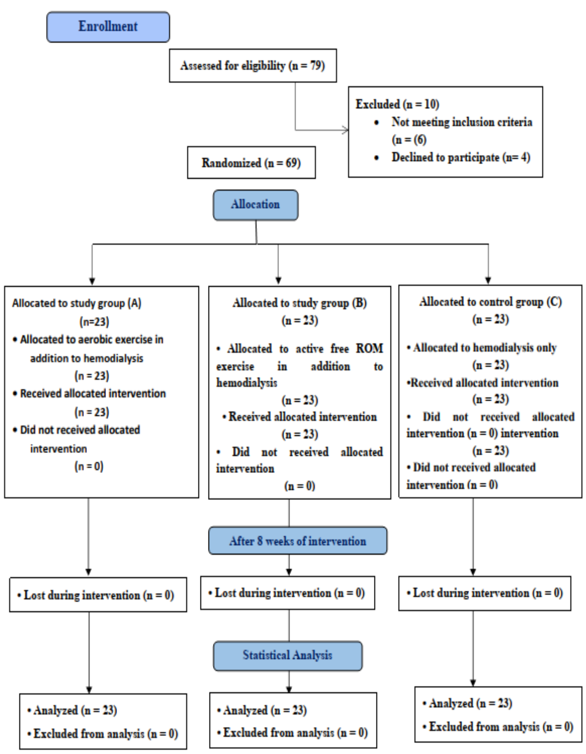

Figure 1. Consort flow diagram of the study

Group C (Control Group):
Participants in Group C followed standard medical care and routine hemodialysis without participating in structured physical interventions. This cohort provided a comparative baseline to isolate the therapeutic effects of the aerobic and ROM protocols employed in the experimental arms.

Outcomes measures

The primary outcome measures of this study were the 6-Minute Walk Test (6MWT) to assess functional capacity and the Mini-Cog Test for cognitive evaluation. Secondary outcomes encompassed the Fatigue Severity Scale (FSS) alongside biochemical markers, specifically urea and creatinine levels. All primary and secondary parameters were rigorously evaluated at baseline and following the 8-week intervention period to determine the clinical impact of the exercise protocols.

Primary outcomes

6-Minute Walk Test

The 6-Minute Walk Test (6MWT) was employed to evaluate functional exercise capacity in accordance with the American Thoracic Society (ATS) guidelines. Participants were instructed to traverse the maximum possible distance along a flat, unobstructed 30-meter corridor within a six-minute timeframe. The total distance covered (in meters) was documented both at baseline and following the 8-week intervention. The 6MWT is recognized as a highly reliable indicator of aerobic endurance in this population, with a reported reliability coefficient of $r = 0.88$.[9]

Cognitive function (Mini-Cog test)

Cognitive performance was evaluated using the Mini-Cog test, a concise screening instrument specifically designed to detect cognitive impairment. The assessment incorporates two primary components: a three-word recall task to evaluate short-term memory and a clock-drawing test to assess executive function and visuospatial proficiency. Total scores range from 0 to 5, with higher values reflecting superior cognitive status. This tool was administered at baseline and post-intervention, leveraging its established clinical sensitivity of approximately 76% for identifying cognitive deficits in clinical populations[10]

Secondary outcomes

Biochemical markers (Urea, Creatinine)

To monitor renal clearance efficiency and metabolic status, serum urea and creatinine levels were quantified. Venous blood samples were collected following a 12-hour fasting period and prior to the initiation of the hemodialysis session (pre-dialysis). The laboratory analysis was conducted at baseline and after the 8-week intervention, with concentrations recorded in milligrams per deciliter (mg/dL). This biochemical monitoring served as an objective indicator of the

Intervention:

To facilitate patient engagement and ensure optimal adherence to the treatment protocol, all participants received a comprehensive orientation. This session provided detailed information regarding the exercise procedures and the anticipated physiological benefits, aimed at enhancing motivation and cooperation throughout the 8-week study period.

Group A (Aerobic Exercise).

Participants in Group A engaged in an intradialytic aerobic exercise program utilizing a simple foot-pedal exerciser. The intervention was conducted three times weekly over an 8-week period, totaling 24 sessions. To ensure physiological stability, exercise was performed during the initial two hours of the hemodialysis session. Each 30-minute session was structured into three phases: a 5-minute warm-up (stretching and low-intensity pedaling), a 20-minute conditioning phase, and a 5-minute cool-down (light pedaling, stretching, and diaphragmatic breathing). During the conditioning phase, intensity was maintained at a moderate level, targeted at a Borg Rating of Perceived Exertion (RPE) of 12–14 and a heart rate (HR) between 50% and 70% of the age-predicted maximum. Safety was strictly monitored; sessions were terminated if oxygen saturation (SpO_2) fell below 88%, HR exceeded 85% of the maximum, or if any adverse clinical symptoms emerged. The pedaling resistance was dynamically adjusted to maintain the target RPE (and reduced to 8–11 during the cool-down phase).[13]

Group B (Active Free ROM Exercise):

Participants in Group B followed an 8-week active-free range of motion (ROM) regimen, conducted thrice weekly. Each 30-minute session was performed in a semi-Fowler's position, with exercise postures adapted to patient comfort, including supine, long-sitting with back support, or sitting in a chair. The session comprised three distinct phases: a 5-minute warm-up involving 8 repetitions of active ROM for the non-shunt upper extremity and lower limbs; a 20-minute conditioning phase starting with flexibility exercises (20 repetitions) followed by full-range active flexion and extension of the hip and knee joints at a comfortable pace; and a 5-minute cool-down targeting an RPE of 8–11. This final phase integrated deep diaphragmatic breathing for a safe metabolic recovery, with no external resistance applied throughout the protocol.[14]

physiological impact of the exercise protocols on metabolic waste products.[11]

Fatigue Severity Scale:

Patient-reported fatigue was quantified using the Arabic version of the Fatigue Severity Scale (FSS-Ar), a 9-item self-report questionnaire. Each item is rated on a 7-point Likert scale (ranging from 1 to 7), with higher total or mean scores indicating a greater impact of fatigue on daily functioning. The FSS-Ar was administered at baseline and following the 8-week intervention to assess subjective changes in fatigue levels. This Arabic version is highly regarded for its internal consistency and psychometric stability in clinical populations, with a reported Cronbach's alpha = 0.84.[12]

Statistical analysis:

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as mean ± SD. Data normality and homogeneity of variance were confirmed using the Shapiro-Wilk and Levene's tests, respectively, to meet parametric assumptions. A one-way ANOVA was utilized to compare baseline demographics across the three groups, while a doubly multivariate repeated measures MANOVA assessed the group × time interaction for all primary and secondary outcomes (6MWT, Mini-Cog, FSS, urea, and creatinine). Significant main or interaction effects were further analyzed via post-hoc pairwise comparisons. Effect sizes were quantified using partial eta squared (η_p^2). Statistical significance was set a priori at $p < 0.05$.

Results

Baseline demographic and anthropometric characteristics showed no significant differences among the three groups ($p > 0.05$), confirming baseline homogeneity (Table 1).

Table 1. Baseline Demographic and Anthropometric Characteristics of the Study Participants with 23 patients per group

Variables	Aerobic Group A	Active range of motion Group B (Mean ± SD)	Control Group C	*F*-value	*p*-value
Age (yrs)	54.6 ± 2.9	54.5 ± 2.9	54.7 ± 2.7	1.59	0.207
Height (cm)	160.2 ± 4.3	158.5 ± 4.4	159.5 ± 4.4	2.98	0.406
Weight (kg)	60.4 ± 6.2	60.4 ± 6.2	60.4 ± 5.9	0.19	0.065
BMI (kg/m²)	23.7 ± 1.5	23.3 ± 1.4	23.5 ± 1.2	0.13	0.879

Note: **Values are *mean ± SD. BMI:* body mass index. Analysis via One-way ANOVA*; p >* *0.*05 indicates non-significance *(NS)***

The descriptive statistics, including means and standard deviations (Mean ± SD) for all outcome measures (6MWT, Fatigue Severity Scale, Urea levels, Creatinine levels, and Mini-Cog test) pre- and post-intervention across the three groups, are presented in Table 2. Within-group comparisons showed significant improvements in the aerobic (Group A) and active range of motion (Group B) groups across most parameters (p < 0.05), while the control group (Group C) showed no statistically significant changes over time.

Table 2. Mean and standard deviation (Mean ± SD) of outcome measures pre- and post-training across groups (A, B, and C)

Variables		**Aerobic Group A X ± SD**	**Active range of motion Group B X ± SD**	**Control Group C X ± SD**
6MWT *(meters)*	**Pre-training**	**279.7 ± 30.4**	**281.3 ± 43.9**	**279.2 ± 32.5**
	Post-training	**361.74 ± 48.59**	**319.13 ± 44.5**	**261.30 ± 57.5**
	Within-group comparisons	**P<0.05**	**P<0.05**	**P=0.069**

Creatinine Levels ***(mg/dl)***	**Pre-training**	**10.84 ± 0.36**	**10.82 ± 0.32**	**10.83 ± 0.55**
	Post-training	**10.40 ± 0.39**	**10.62 ± 0.32**	**10.80 ± 0.55**
	Within-group comparisons	**P<0.05**	**P<0.05**	**P=0.520**
Mini-Cog Test ***(scores)***	**Pre-training**	**3.70 ± 1.15**	**3.70 ± 1.15**	**3.47 ± 0.96**
	Post-training	**4.65 ± 0.99**	**4.57 ± 0.86**	**3.75 ± 1.03**
	Within-group comparisons	**P<0.05**	**P<0.05**	**P=0.065**
Fatigue Severity Scale ***(scores)***	**Pre-training**	**30.96 ± 4.11**	**31.22 ± 5.18**	**30.48 ± 4.0**
	Post-training	**16.30 ± 4.16**	**22.61 ± 4.08**	**31.43 ± 5.94**
	Within-group comparisons	**P<0.05**	**P<0.05**	**P=0.87**
Urea Levels ***(mg/dl)***	**Pre-training**	**68.91 ± 4.89**	**67.61 ± 7.08**	**69.65 ± 6.16**
	Post-training	**63.52 ± 5.48**	**64.52 ± 7.19**	**69.43 ± 6.**
	Within-group comparisons	**P<0.05**	**P<0.05**	**P=0.990**

$\overline{X}$: Mean, SD: Standard deviation, p-value: Probability value

The baseline-to-post-intervention percentage of changes, statistical interaction values, and partial eta squared (η_p^2). effect sizes for all parameters are comprehensively detailed in Table 3. Furthermore, these divergent clinical trends and interaction effects across the five dependent variables are visually summarized in the multi-panel graph (Figure 2).

The doubly multivariate repeated measures MANOVA revealed significant Time × Group interaction effects across all evaluated clinical and biochemical outcomes ($p < 0.05$). Post-hoc pairwise comparisons indicated that the Aerobic Exercise Group (Group A) achieved the most substantial improvements across all variables, followed by the Active Range of Motion Group (Group B), while the Control Group (Group C) exhibited no significant changes over time.

Table 3. Combined baseline-to-post intervention percentage of changes and MANOVA main interaction effects across groups.

Variables	**Group A (Aerobic) % of Change**	**Group B (Active Free) % of Change**	**Control Group C % of Change**	**MANOVA Interaction (Time×Group)** ***F*-value**	***p*-value**	**Effect Size (η_p^2)**
6MWT *(meters)*	29.34 % ↑	13.44 % ↑	6.41% (NS)	22.91	<0.001	0.25
Fatigue Severity Scale *(scores)*	47.36 % ↓	27.60 % ↓	3.12% (NS)	57.61	<0.001	0.45
Urea Levels *(mg/dl)*	7.82 % ↓	4.57% ↓	0.32% (NS)	5.77	0.005	0.09
Creatinine Levels *(mg/dl)*	4.05 % ↓	1.85% ↓	2.12% (NS)	6.32	0.003	0.11

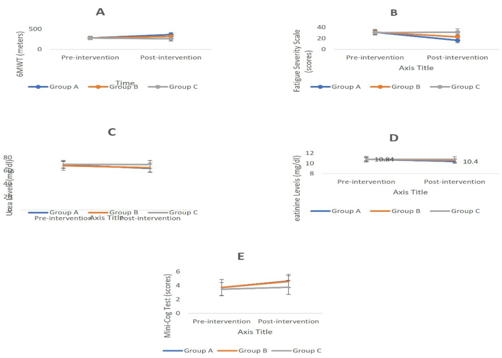

Figure 2. Multi-panel line graphs illustrating pre- to post-intervention trends and error bars (SD) across the three groups for: (A) Six-Minute Walk Test (6MWT), (B) Fatigue Severity Scale (FSS), (C) Urea Levels, (D) Creatinine Levels, and (E) Mini-Cog Test.

yields a 36-meter gain, (p = 0.0001, 10.3% in the 6MWT), and improves timed up-and-go scores.

Our results strongly align with the landmark multicenter study by **Anding-Rost et al.,**[17] which analyzed a large cohort of 917 hemodialysis patients (exercise group, n = 446; usual care group, n = 471). At the 12-month follow-up, they reported a highly significant functional improvement in the 6minute walk test, with the exercise group achieving a 37.5-meter gain (95% CI: 14.7 to 60.4) over the usual care group. This substantial increase in a large-scale population further confirms the clinical efficacy of intradialytic training in countering uremic physical deconditioning.

The critical role of protocol design is highlighted when contrasting our results with **Keles et al.**[18] the significant improvement in the 6MWT in our study demonstrates the efficacy of the 8-week intradialytic aerobic program. In contrast, a similar 8-week study reported no significant change in functional capacity (p = 0.627, n = 30). This discrepancy despite identical durations could be due to exercise specificity; while the other study used a combined aerobic-resistance protocol, our focused aerobic training was likely more efficient in inducing the precise cardiovascular adaptations needed to improve walking distance within a short timeframe.

This disparity underscores the efficacy of our supervised, progressive-intensity design (Borg RPE 12–14), which successfully pushed patients past their cardiovascular adaptation thresholds, unlike the lower-intensity, self-regulated sessions in previous literature. Meanwhile, the significant 13.44% improvement in Group B matches the findings of **Shetty et al.,**[19] who observed significant

Mini-Cog Test *(scores)*	25.90% ↑	22.10% ↑	3.50% (NS)	9.72	<0.001	0.13

***Note*: ↑ indicates an increase; ↓ indicates a decrease. 6MWT: 6-minute walk test; MANOVA: multivariate analysis of variance; NS: non-significant; *F*-value: variance ratio (statistical test value for interaction); *p*-value: probability value (statistical significance); η_p^2: partial eta squared (effect size measure). Statistical significance was set at *p* < 0.05**

Discussion

The findings of the current study demonstrate that both 8-week intradialytic interventions (aerobic exercise and active free ROM exercises) significantly enhance functional capacity and cognitive performance in maintenance hemodialysis patients. However, Group A demonstrated a distinct clinical and statistical advantage over Group B, exhibiting a markedly higher percentage of improvement across all evaluated physical, cognitive, and biochemical parameters.

Functional Capacity and Endurance Adaptation

The robust 29.34% increase in the 6MWT distance achieved by the Aerobic Exercise Group (Group A) nearly doubled the 13.44% improvement observed in the Active Free ROM Group (Group B). From a physiological standpoint, chronic uremia induces skeletal muscle atrophy, capillary rarefaction, and mitochondrial dysfunction, severely limiting oxygen transport and peripheral utilization. The continuous, cyclical muscular demand of aerobic pedaling counters this maladaptation by enhancing peak oxygen consumption (VO_2 peak) and optimizing lower-limb muscle oxygen extraction.

This is strongly supported by **Chae et al.,**[15] who reported a statistically significant 11.41% increase in the (6MWD) (p = 0.006) among 16 participants. In their protocol, the walking distance improved from 333 meters at pre-exercise to 371 meters post-intervention, yielding a substantial 38-meter functional gain**.** Furthermore, our findings align with **Hazarika et al.**,[16] who demonstrated that a structured, short-term intradialytic cycle ergometry program at a moderate intensity (Borg RPE 12–14) significantly enhances functional mobility, effective, and low-cost strategy to alleviate fatigue and improve functional performance.

Conversely, **Figueiredo et al.**[23]reported that intradialytic aerobic exercise did not cause a significant between-group reduction in fatigue. This contrast is likely due to the different assessment tools utilized; our study used the Fatigue Severity Scale (FSS), which focuses strictly on the physical impact of fatigue, while **Figueiredo et al** used the Modified Fatigue Impact Scale (MFIS). The MFIS is a multidimensional tool that measures cognitive and psychosocial fatigue alongside physical symptoms. Because exercise primarily improves physical capacity, its positive effects were likely masked by the unchanged psychological scores in their multidimensional scale.

The 27.60% reduction in fatigue observed in our active free ROM group is consistently supported by a robust body of clinical evidence. Recently, **Nesnawy et al.**[24] demonstrated that structured intradialytic leg exercises elicit highly statistically significant reductions in overall fatigue scores ($p < 0.001$). This aligns with the findings of **Malini et al.,**[25] who demonstrated a 9.6% decline in fatigue specifically utilizing an intradialytic ROM protocol. This localized benefit stems from enhanced musculoskeletal comfort and the disruption of prolonged intradialytic sedentary cycles, which directly alleviates physical exhaustion. Furthermore, contemporary literature exhibits a consistent consensus regarding the therapeutic benefits of active ROM exercises, establishing low-intensity structured movement, as an evidence-based, safe strategy for intradialytic fatigue management.

Optimization of Metabolic Adequacy and Solute Clearance

Biochemically, Group A demonstrated superior clearance efficiency for uremic toxins, reducing serum urea by 7.82% and creatinine by 4.05%, outperforming Group B's modest reductions of 4.57% and 1.85%, respectively. This dual metabolic optimization and the clinical value of structured aerobic training are strongly substantiated by the recent randomized controlled trial conducted by **Karkousha et al.**[26] in their comparative framework, an intradialytic stationary cycling protocol (n=15) sustained at 60% of maximum heart rate induced statistically significant improvements in the urea reduction rate (URR) ($p < 0.05$). Mechanistically, active muscle contractions induce systemic vasodilation and expand perfusion to skeletal muscle beds. This drives a significant kinetic fluid shift from intracellular to extracellular compartments, maximizing improvements in 6MWT (9.98%, p<0.001). This peripheral gain is primarily achieved by alleviating joint stiffness and enhancing localized tissue perfusion, which improves basic mobility. However, as noted by **Ren et al.**[20] in their network meta-analysis, range of motion (ROM) exercises alone do not induce statistically significant improvements in the 6MWT distance. Unlike aerobic exercise (AE) which drives the central cardiovascular adaptations needed to enhance walking capacity, ROM protocols primarily target local joint flexibility, making them less effective for expanding functional walking distance on their own.

Pathophysiological Mechanisms of Fatigue Management

Subjective fatigue profiles revealed a highly significant advantage for the aerobic intervention, with Group A showing a 47.36% reduction in FSS scores compared to a 27.60% reduction in Group B. In the aerobic cohort, this substantial relief closely reflects the findings of **Lakshmi et al.,**[21] who documented a 21.0% fatigue reduction ($p < 0.001$, $n = 148$) using intradialytic cycling**.** This benefit is biochemically driven by the exercise-induced upregulation of Brain-Derived Neurotrophic Factor (BDNF) and the concurrent suppression of pro-inflammatory cytokines like Interleukin-6 (IL-6), which collectively optimize mitochondrial efficiency and downregulate central fatigue perception during the dialysis session.

Furthermore, these positive outcomes align seamlessly with contemporary large-scale evidence by **Zou et al.**[22]Their comprehensive meta-analysis encompassing 31 randomized controlled trials with 1,365 maintenance hemodialysis patients confirmed that intradialytic exercise significantly diminishes fatigue severity, yielding a highly significant pooled effect size ($SMD = -0.47$, 95% CI: -0.72 to -0.23, $p = 0.0001$). On a molecular scale, this collective amelioration is largely driven by exercise-induced muscle oxidative phosphorylation, optimization of mitochondrial structures, and enhanced systemic blood circulation, which altogether counteract chronic physical exhaustion.

This reduction in fatigue is also supported by a recent scoping review analyzing randomized controlled trials between 2020 and 2025 which confirmed that complementary non-pharmacological interventions, particularly intradialytic physical exercise, consistently elicit statistically significant reductions in fatigue ($p < 0.05$). These findings reinforce the clinical value of physical therapy as a safe, remarkable 25.90% improvement in Mini-Cog scores. This finding directly aligns with a robust body of contemporary literature; for instance, the comprehensive systematic review by **Mavrommatis et al.**[29] established that structured aerobic exercise during hemodialysis induces significant upgrades in global cognition ($p < 0.05$) and executive domains ($p < 0.001$). Furthermore, our results closely parallel the empirical data reported by **Saputrana et al.,** [30] who evaluated a 12-week intradialytic cycling program and noted a highly significant cognitive improvement ($p < 0.001$) alongside a remarkably large effect size of 1.88.

Taken together, these supportive studies confirm that regular, structured cycling serves as a potent neuroprotective strategy that enhances brain physiology and counteracts dialysis-related cerebral hypoperfusion. Aerobic conditioning enhances cerebral hemodynamics and elevates cardiac output within a safe therapeutic window. This directly increases cerebral perfusion and blood flow velocity, counteracting the transient cognitive "stunning" or silent white matter hypoperfusion caused by rapid fluid removal. This physiological surge upregulates neurotrophic factors (BDNF), promoting hippocampal neurogenesis and accelerating cognitive processing speed.

This rapid and highly significant cognitive enhancement captured in a shorter intervention timeframe is further justified by **Mavrommatis et al.**[29] They emphasized that intradialytic protocols achieve superior clinical efficacy primarily due to exceptional patient adherence, as they strategically exploit the patients' unavoidable captive treatment time within an established routine, thereby maximizing neuroprotective outcomes far more efficiently than home-based designs.

Conversely, this clinical domain is not without controversy, as some large-scale trials report inconsistent outcomes regarding isolated protocols. A prominent example is the recent Interventions Made to Preserve Cognitive Function Trial (IMPCT) multi-center trial conducted by **Ghildayal et al.**,[31] which block-randomized 121 hemodialysis patients. Their findings revealed that after 3 months, an isolated intradialytic foot-peddler exercise arm ($n = 29$) failed to induce any statistically significant changes in executive function compared to standard care. Instead, a significant upgrade in global cognition was strictly conditional upon combining exercise with web-based cognitive tasks (CT+ET arm, MoCA score difference = 2.1, 95% *CI*: 0.4–3.9)**.**

Nevertheless, our study successfully challenged these findings; the substantial dialysis adequacy (Kt/V) and improving solute flux across the dialyzer membrane during ultrafiltration.

Conversely, our positive findings contrast with the recently published trial by **Mohamadizadeh et al.,**[27] who reported non-significant between-group differences in dialysis adequacy and solute clearance parameters following a conservative intradialytic pedaling regimen (n=40). Specifically, their 4-week training protocol failed to elicit any substantial metabolic adjustments, yielding a non-significant post-intervention change in dialysis efficiency (Kt/V; $p = 0.68$) and a marginal, non-significant reduction in blood urea nitrogen levels ($p = 0.74$).

Methodologically, this profound divergence is conclusively explained by the temporal design of the interventions; while our current study utilized a prolonged duration (8 weeks) required for chronic vascular adaptations, the 4-week regimen of **Mohamadizadeh** et al. offered only an acute, short-term stimulus with insufficient session volume (15–20 minutes) to enhance solute transport capacity.

The positive metabolic trajectory tracking in the active free ROM cohort (**Group B**) is conceptually supported by the large-scale data of **Lakshmi et al.**[21] (n=295), which confirmed that structured physical mobilization during dialysis yields highly significant post-test clearance of blood urea and creatinine ($p < 0.001$) compared to completely sedentary routine care (n=147).Mechanistically, this baseline solute clearance is driven by a localized 'muscle pump' effect inherent to repetitive joint kinematics, which mechanically facilitates microvascular perfusion and enhances the movement of low-molecular-weight uremic toxins from the interstitial spaces into the vascular compartment for clearance**.**

In contrast to our significant metabolic findings, **Usui et al.**[28] reported in their crossover RCT involving 16 hemodialysis patients that overall dialysis efficiency was not significantly different between the exercise and non-exercise arms ($p = 0.16$).This discrepancy emphasizes that our structured protocol provided a sufficient therapeutic threshold and cumulative training volume to optimize uremic toxin clearance, whereas alternative training modalities may fail to trigger these favorable metabolic shifts.

Cognitive Enhancement and the Physical Cognitive Crosstalk

Our study revealed a highly significant cognitive enhancement within the intradialytic cycling cohort (Group A), demonstrating a cognitive rehabilitation, representing a holistic physical-cognitive crosstalk. Mitigating peripheral muscular fatigue and lowering systemic inflammatory cytokines directly alleviates central fatigue perception. As physical exhaustion decreases and systemic oxygenation improves, patients' capacity for cognitive processing and environmental engagement expands. This dual-benefit pathway proves that intradialytic physical exercise does not merely preserve peripheral musculoskeletal function; it acts as an integrated neuroprotective strategy that simultaneously addresses the complex presentation of uremic encephalopathy and physical frailty in end-stage kidney disease.

Limitations

Although the current study provides encouraging evidence for intradialytic aerobic exercise, several limitations should be acknowledged. First, the modest sample size and the 8-week intervention timeframe may restrict long-term generalizations. Additionally, the non-blinded (open-label) design and potential practice effects from repeated cognitive testing could introduce perf ormance or assessment bias. Confoundi-ng factors, such as minor medication adjustments and underlying patient comorbidities, were also not fully controlled. Lastly, as a single-center study, future larger multi-center randomized controlled trials are warranted to confirm these findings. Despite these limitations, the observed clinical benefits underscore the therapeutic value of structured intradialytic training.

practical implications

These findings suggest that incorporating structured intradialytic aerobic exercise into standard hemodialysis care provides substantial clinical utility. Implementing such non-pharmacological programs within dialysis units can effectively optimize both physical functional capacity and cognitive performance in patients with end-stage kidney disease. This underscores the superior therapeutic value of progressive aerobic training over isolated active free range-of-motion exercises, establishing it as a feasible and high-yield rehabilitative strategy during treatment hours.

Conclusions

Intradialytic aerobic exercise proved more effective than active free range-of-motion exercises in enhancing both cognitive function and functional capacity among maintenance hemodialysis patients. While both interventions yielded significant clinical benefits, the aerobic protocol produced distinctly superior outcomes across physical, cognitive, and metabolic parameters. These findings support the strategic integration of structured aerobic training into

25.90% improvement achieved independently by our pure cycling cohort (Group A) indicates that the personalized workload and strict clinical monitoring in our protocol were sufficient to reach the critical physiological threshold required to enhance cognitive performance, even without adjunctive cognitive interventions.

Regarding our intradialytic range of motion cohort (Group B), the findings revealed a highly substantial 22.10% improvement in Mini-Cog scores. This clinical success is conceptually supported by the overarching conclusions of **Mavrommatis et al.**,[29] who emphasized that significant upgrades in global cognition are achievable regardless of exercise modality, provided the protocol is sustained thrice weekly over an extended timeframe. Furthermore, this framework aligns perfectly with the precise statistical data synthesized by **Lee et al.**[32]in their comparative evaluation. They reported that while home-based exercise fails to stimulate cognitive performance (p = 0.78), structured intradialytic interventions yield a significant pooled effect size on cognitive outcomes (SMD = 0.37, 95% CI = 0.13 to 0.60, p = 0.002), driven primarily by enhanced hemodynamic stability and optimized peripheral circulation.

Conversely, the independent efficacy of non-aerobic, low-intensity interventions remains highly controversial in the broader literature. A major piece of evidence is the comprehensive meta-analysis by **Bradshaw et al.**,[33] which pooled 19 trials randomized with 1,160 participants. While confirming the clinical safety of exercise protocols (94 harm events reported in intervention groups versus 83 in controls), their subgroup analysis moderated by exercise type (**χ^2**= 7.62, p = 0.02) revealed that significant positive cognitive effects were strictly confined to aerobic designs (Effect Size = 0.57, 95% CI: 0.21 to 0.93, p = 0.002).

Nevertheless, our study successfully challenged this conservative meta-analytic boundary. The robust 22.10% cognitive upgrade achieved independently by Group B demonstrates that when range of motion exercises are delivered under rigid, one-on-one clinical supervision and executed with continuous engagement, they can successfully cross the critical metabolic threshold required to enhance cognitive alertness. This firmly establishes structured range of motion protocols as a highly potent, effective, and safe therapeutic alternative, particularly for frail hemodialysis patients who exhibit poor tolerance toward strenuous aerobic workloads.

Ultimately, this study highlights a compelling synergy between physical and routine dialysis care to comprehensively optimize physical performance and cognitive health in this population.

Conflicts of Interest

The authors declare no conflict of interest.

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