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Effect of intra-dialytic physical exercise on depression in prevalent hemodialysis patients

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Abstract

Background: Depression is associated with morbidity, death, diminished quality of life, decreased longevity, and even suicidal ideation in hemodialysis patients. Intra-dialytic exercise is considered as integral component of the clinical care management of hemodialysis patients as it improves hemodialysis effectiveness, reducing systemic inflammation, increasing exercise tolerance, decreasing depression and improving quality of life. The objective of this study was to assess the effect of intra-dialytic physical exercise on depression and physical activity in prevalent hemodialysis patients. This prospective cohort research comprised 50 hemodialysis patients maintained on regular hemodialysis 3 times/week with duration since starting dialysis (1–5 years), not practicing any previous physical activity, suffering from depressive symptoms, not maintained on antidepressants and separated into two groups: group I underwent intra-dialytic exercise for 3 months and group II was matched in age and gender but did not undertake any exercise.

Results: Hamilton depression rating scale was significantly decreased in group I after completing the exercise program compared to baseline ($P=0.000$), while there was no significant change in group II. Serum tumor necrosis factor alpha significantly decreased in group I compared to baseline ($P=0.000$), while there was no significant change in group II. A positive correlation was found between serum tumor necrosis factor alpha and Hamilton depression rating scale ($r=0.676$), ($P=0.000$). Physical activity tests; 6-min walk test, rapid assessment of physical activity and peak volume of oxygen consumption were significantly improved in group I compared to baseline ($P=0.000$), while there was no statistically significant difference in group II. Serum phosphorus and parathyroid hormone levels were significantly decreased in group I compared to baseline ($P<0.01$), while urea reduction ratio was significantly increased in group I compared to baseline ($P=0.000$), but there was no significant change in group II.

Conclusions: Intra-dialysis exercise can improve depression and physical performance in hemodialysis patients. As positive correlation was found between serum tumor necrosis factor alpha and Hamilton depression rating scale, so tumor necrosis factor alpha may be considered as marker of depression in hemodialysis patients. Intra-dialytic exercise can improve dialysis efficacy by improving urea reduction ratio.

Keywords: Intra-dialytic exercise, Depression, Hemodialysis, Serum tumor necrosis factor alpha, Quality of life, Hemodialysis effectiveness, Exercise tolerance, Systemic inflammation, Physical activity, Hamilton depression rating scale

Background

Depression is an emotional state characterized by somatic and cognitive symptoms including feelings of sadness, worthlessness, sleeplessness, loss of appetite and

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sexual desires, and interest in usual activities. A clinical diagnosis of depression is performed when symptoms of depression become persistent for more than 2 weeks [1]. Patients with mood disorders often have imbalances in specific neurotransmitters as norepinephrine and serotonin [2]. Depression is linked to abnormal activity in several regions of the brain as prefrontal cortex. Decreased activity of prefrontal cortex causes inhibition of control on negative emotions leading to more negative mood condition [3]. Depression is also associated with increased amygdala activity [4], Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has been well-described in mood disorders [5]. High cortisol level which increased during stress is associated with depression [6]. Cortisol increases activity of amygdala and decreases activity of prefrontal cortex which leading to depression [7]. Depression can be triggered by cognitive vulnerability and stressful life events [8]. Cognitive theories of depression posit that depression is triggered by negative thoughts, interpretations, self-evaluations, and expectations [7]. It has long been considered that stressful life can trigger depression, and several studies have supported this conclusion [9]. Hopelessness theory is another cognitive theory of depression which postulates that a particular style of negative thinking causing sense of hopelessness which will lead then to depression [10].

Chronic kidney disease is a worldwide issue, with up to 90% of patients diagnosed with end stage renal disease (ESRD) receiving hemodialysis (HD) on a regular basis as renal replacement treatment. Patients with ESRD have decreased physical function and activity due to muscle wasting, decreased visceral protein storage, and decreased physical function due to uremic myopathy and neuropathy [11]. Dialysis alters patients' interactions with their immediate surroundings, their capacity to execute social roles, their willingness to submit to fixed days and hours of treatment and recurring hospitalization [12]. Depression is the commonest psychological problem in HD patients [13]. The incidence of depression among HD patients is between 20 and 60% [14].

Several factors can cause depression in HD patients, such as physical and emotional stress, functional limitations, dependence on HD procedure, problems related to dialysis access and unsuitable economic conditions [15]. HD patients experience various changes and disabilities in their life as diet and fluid restrictions, physical and cognitive deterioration and inability to perform prior roles or activities which increase liability to depression [16]. HD patients have high levels of depression and anxiety which may be associated with increased levels of inflammatory mediators [17], ventromedial prefrontal cortex activity [18], changes in components of the tryptophan–kynurenine metabolic response to inflammation [19] and brain hypoxia which is a common complication in HD patients causing neuronal abnormalities and depression [20]. The inflammatory theory of depression takes into account immunological hyperactivation and dysregulated cytokine production as factors in the pathophysiology of depression in HD patients [21]. Chronic inflammatory condition is common among patients with ESRD [22]. Inflammation and oxidative stress through production of pro-inflammatory cytokines as tumor necrosis factor-α (TNF-α) plays an important role in the pathogenesis of depression [23]. Chronic inflammatory condition in HD patients accelerates atherosclerosis causing cerebrovascular disease which affects mood regulatory function of the brain as lesions close to frontal lobe and left basal ganglia which have been associated with depression [24].

Depression plays an important role in progression of chronic medical illness as patients fail compliance on medications and preventive measures [25]. Depression may contribute to the development of chronic kidney disease via adverse health risk behaviors, such as smoking, sedentary habits and obesity [24]. HD patients may commit suicide more easily through noncompliance with dialysis, medications, dietary indiscretion or disruption of their vascular access [26]. Depression can affects social interactions, work, reduces the motivation of patients to do physical rehabilitation and preventing most patients from returning to their original jobs [27].

Physical activity is defined as any muscle contraction resulting in an energy metabolism above basal metabolic rate. Exercise training is any physical activity that is planned, structured, performed repeatedly, and specifically aimed at improving the physical fitness [28]. Physical activity is regarded as safe and practical among HD patients [14]. Intra-dialytic exercise (IDE) is described as exercise training done during an HD session to improve the patient's strength and endurance, hence improving different physiological and psychological characteristics [29]. Different exercise modalities have been studied, but IDE is considered the best approach, because adherence of patients to this modality is higher than other modalities [30]. IDE is typically done during the first 2 h of HD session. The most popular example of intra-dialytic exercise training involves placing a cycle ergometer in front of the treatment chair or at the foot of a bed [31]. Exercise programs must be tailored to physical capacity and comorbidities of each patient. This is the main way for a correct and safe implementation of physical activity in ESRD patients. Nephrologists should lead a team of specialists and professionals including cardiologist, physiotherapist, exercise physiologists, renal dieticians and nurses [31].

All patients need to be assessed by physiotherapist to ensure exercise safety. Pre-exercise criteria should be

fulfilled before exercise is approved, such as targeted ultrafiltration rate < 13 ml/h/kg, blood pressure < 180/100 or > 100/50 mm Hg, resting heart rate < 100 beats/min, no hospitalization or illness within the last week. Hemoglobin (HB) to be at least 9 g/dl, Blood glucose level is controlled (between 126 and 252 mg/dl), Oxygen saturation levels should be above 90% at rest and above 88% during exercise, cardiac patients are sent for stress testing to ensure safety during exercise, If a patient misses the previous HD session, no exercise is allowed as missing HD can cause symptoms of volume overload and hyperkalemia, patients with recurrent hyperkalemia may need 30 min of HD before starting exercise and patients with intra-dialytic hypotension need long duration of cool-down. All patients should have their feet elevated immediately after ending of exercise [32].

The Renal Association Clinical Practice Guideline on Hemodialysis recommended that once patients became familiar with IDE they should be encouraged to continue exercise on non-dialysis days [33].

Exercise plays an important role in maintaining and improving muscle and physical function. Improvements in physical function explain a possible neural mechanism that supposed positive effects of exercise on depressive symptoms [34].

This study investigated the importance of intra-dialytic physical exercise and its effect on depression, physical performance and dialysis adequacy in prevalent hemodialysis patients.

Methods

Fifty adult ESRD patients (18–50 years) on regular HD 3 times/week for at least 1 year, taking into account duration since commencing dialysis (1–5 years), no previous physical activity, suffering from depressive symptoms, and not on antidepressant therapy. They were separated into two groups: group I, 25 patients who stayed on the usual IDE programme for 3 months and group II, 25 patients who did not conduct any intra-dialytic exercise.

In the years 2020 and 2021, 50 patients were chosen from dialysis unit. We excluded patients with unstable cardiac conditions, such as angina, decompensated congestive heart failure and uncontrolled arrhythmias, physical restrictions that would interfere with using the ergometer, motor skill disorders, prior renal transplant recipients, and those with severe hyperparathyroidism (PTH > 800 Pg/ml). Patients with comorbid psychiatric conditions rather than depression, past history of depression and patients receiving any previous or recent antidepressant therapy had been excluded from our study.

A multidisciplinary team evaluated group I study participants' fitness for physical activity throughout the dialysis session. Patients in group II received HD with the same conditions but did not exercise, lasting 4 h with a blood flow > 250 ml/min and a dialysate flow of 500 ml/min on a high flux dialyzer. In all groups, patients were instructed to refrain from eating or drinking anything during HD while continuing to take their antidiabetic or antihypertensive medications, calcium, and vitamin D supplements.

Patients were subjected to full medical history taking including socio-demographic history (age, gender, residence and marital status), etiology of ESRD, duration of HD and other comorbidities in predefined data sheets, full clinical examination including musculo-skeletal, neurological and cardiac examination with doing Electrocardiogram (ECG) at baseline and after the exercise program, anthropometric measures: calculation of body mass index by dividing dry body weight (kg) by the squared height (m^2), laboratory investigations including urea reduction ratio (URR), calcium (Ca), phosphorus (PO_4), parathyroid hormone (PTH), thyroid function tests, hemoglobin (HB), iron study, and serum tumor necrosis factor alpha (TNF-α) measured by enzyme linked immune-sorbent assay (ELISA) were all calculated from blood samples taken at baseline and 3 months after the IDE program.

Evaluation of physical performance included Rapid Assessment of Physical activity (RAPA) (9-items), a valid measure of physical activity for use in clinical practice. RAPA evaluates a wide range of physical activity levels, from sedentary to vigorous activity, as well as strength and flexibility training. Each question has a (Yes) or (No) option. The score ranges from 1 to 7, a score of 6–7 points is considered (active), 4–5 points as (suboptimal active), and ≤ 3 points is defined as (sedentary) to (under-active regular-light activities) [35], and six-min walk test (6MWT) is a secure tool for assessment of the cardiorespiratory system and used to assess aerobic capacity and endurance. The distance covered over a time of 6 min is used as the outcome by which to compare changes in performance capacity [36]. Exercise capacity evaluated by peak volume of oxygen consumption ($peakVO_2$) using six-min walk distance (6MWD) which is obtained using the equation: Estimated Mean $PeakVO_2 = 4.948 + (0.023 \times 6MWD)$ [37].

Exercise program included patient education and psychological support; all patients received education on importance of exercise and physical activity, how to monitor their physical exertion, and when to stop exercise. Exercise was in the form of aerobic cycling exercise in the first 2 h of dialysis session using pedal exerciser that was placed in front of the patient's chair and patient pedaled while sitting upright. Exercise program has been divided into 2 phases: 1st phase was a conditioning phase (4 weeks) and 2nd phase was a progressive aerobic

endurance exercise phase (8 weeks). Each exercise session consisted of three basic parts: (a) warming-up part: the patient started the exercise session with 10 min low intensity exercise at low speed of cycling. (b) Main part (active part): started with 10 min cycling at the level of speed obtained at warm-up part in conditioning phase and increased gradually in the later phase up to 30 min cycling, and (c) Final part (cooling down): 5 min of relaxation and breathing exercise.

Patients were observed for heart rate, blood pressure, and symptoms of exhaustion during the exercise sessions. If there was severe physical exhaustion, chest discomfort, vertigo, pallor, tachycardia, hypotension, or hypertension, exercise had to be stopped.

Severity of depressive symptoms were assessed by Hamilton depression rating scale 17 items (HDRS17) at baseline and after completing of exercise program by assistance of trained psychiatrist under complete confidential status, HDRS used to quantify symptoms severity (HDRS < 7 [none], HDRS 7–17 [mild], HDRS 18–24 [moderate], and HDRS ≥ 25 [severe]). HDRS, the most widely used clinician-administered depression assessment scale, has promising psychometric properties making it a good tool to use for the diagnosis of patients with depression [38]. HDRS served as the gold standard for evaluating depression. It is the most frequently used clinician-administered depression evaluation scale. The original version of the survey (HDRS17) has 17 items that discuss recent depressive symptoms. The administration takes 20 to 30 min, and the rating is clinician-rated. The main goal is to evaluate the intensity and evolution of depression symptoms [39].

Data were gathered, edited, coded, and put into IBM SPSS version 23 of the Statistical Package for Social Science. When the data were parametric, they were displayed as means, standard deviations, and ranges; when they were non-parametric, they were displayed as medians and interquartile ranges (IQR). Qualitative variables were displayed as numbers and percentages. When the predicted count in a particular cell was less than 5, the groups were compared using the Chi-square test and/or Fisher exact test. The Independent *t* test was used to compare two independent groups with quantitative data and a parametric distribution, whereas the Mann–Whitney test was used with a non-parametric distribution. When comparing two paired groups with quantitative data and a parametric distribution, the Paired *t* test was used, whereas the Wilcoxon Rank test was used for non-parametric distributions. The correlation between two numerical parameters within the same group was evaluated using Spearman correlation coefficients. Univariate and Multivariate linear regression analysis was used to find out significant predictors of TNF-α, depression (HDRS) and physical performance (6MWT, RAPA and peakVO_2) in cases. A "*P* value" of less than or equal 0.05 was considered statistically significant.

Results

Our study included 31 (62%) females and 19 (38%) males. The mean of age was 36.92 ± 7.97 years in group I and 39.88 ± 6.96 years in group II. ECG has been done for both groups and revealed that it was normal at baseline and it did not show any changes at the end of the study. This study showed no significant difference between group I and group II regarding demographic data, chronic diseases (diabetes and hypertension) and duration of ESRD, ($P > 0.05$). The 2 groups had no statistically significant difference regarding baseline studied parameters, such as serum TNF-α, HDRS, bone profile (Ca, PO_4, PTH), URR, HB and physical activity tests (6MWT, RAPA and peak VO_2), $P > 0.05$.

In group I, we found that there was highly statistically significant difference at baseline and after exercise program regarding serum TNF-α, HDRS, PO_4, PTH, URR ($P < 0.001$) and physical performance tests (6MWT, RAPA and Peak VO_2), ($P < 0.001$). While there was no statistically significant difference regarding Ca, HB, transferrin saturation (T. sat.) and thyroid stimulating hormone (TSH), ($P > 0.05$) as in Table 1 which shows that there was highly statistically significant difference before and after IDE in group I regarding serum TNF-α, PO_4, PTH, URR and physical performance tests (6MWT, RAPA and peak VO_2).

On the other hand, in group II, after 3 months without doing any exercise, we found that 6MWT and RAPA decreased, while PTH increased, but there was no statistically significant difference regarding TNF-α, HDRS, Ca, PO_4, URR, HB and peak VO_2 as in Table 2 which shows that there was statistically significant difference at start and end of the study in group II regarding 6MWT, RAPA and PTH, while there was no significant difference between start and end of the study without IDE in group II regarding serum TNF-α, Ca, PO_4, URR, HB, TSH, HDRS and peak VO_2.

In comparison between group I and group II at end of the study we found that there was statistically significant difference regarding serum TNF-α and HDRS ($P < 0.001$), PO_4, PTH and URR ($P < 0.05$). In addition, significant difference was found between the two groups regarding physical activity tests (6MWT, RAPA and peak VO_2), $P < 0.001$. While, there was no statistically significant difference regarding serum Ca and HB level as in Table 3 which shows that there was highly statistically significant difference between group I and group II at end of the study regarding serum TNF-α, HDRS and physical exercise tests (6MWT, RAPA and peak VO_2), there was statistically significant difference between

Table 1 Comparison of laboratory tests, physical activity tests and HDRS scores before and after exercise in group I

	Group I		Test value	*P* value
	Before	After		
TNF-α (pg/ml)				
Mean ± SD	109.88 ± 46.80	46.24 ± 14.66	7.883•	0.000
Range	32–200	20–79		
Ca (mg/dl)				
Mean ± SD	8.43 ± 0.61	8.36 ± 0.65	1.026•	0.315
Range	7.5–9.5	7.3–9.3		
PO_4 (mg/dl)				
Mean ± SD	5.46 ± 0.89	4.36 ± 0.90	5.352•	0.000
Range	4.1–7.5	2.8–6		
PTH (pg/ml)				
Mean ± SD	466.60 ± 176.68	402.00 ± 140.98	2.900•	0.008
Range	99–770	140–620		
URR %				
Mean ± SD	72.40 ± 8.47	76.23 ± 7.48	− 4.655•	0.000
Range	61–90	65–90		
HB (g/dl)				
Mean ± SD	9.41 ± 1.13	9.55 ± 0.92	− 0.990•	0.332
Range	7.5–13	8–12.7		
T. sat. %				
Mean ± SD	33.74 ± 8.89	31.39 ± 8.26	1.645•	0.113
Range	18–51	12.6–48		
TSH (mu/l)				
Mean ± SD	1.56 ± 0.34	1.46 ± 0.33	2.042•	0.052
Range	1–2.3	0.9–2.1		
HDRS				
Mean ± SD	17.56 ± 4.21	10.40 ± 3.25	10.310•	0.000
Range	11–26	5–18		
6MWT (m)				
Mean ± SD	217.68 ± 37.40	253.04 ± 42.48	− 15.413•	0.000
Range	153–285	177–343		
RAPA				
Median (IQR)	2 (2–2)	3 (3–3)	− 4.134≠	0.000
Range	1–3	1–4		
PeakVO_2 (ml/(kg min)				
Mean ± SD	9.91 ± 0.88	10.72 ± 0.98	− 15.828•	0.000
Range	8.4–11.5	9–12.8		

TNF-α: tumor necrosis factor alpha, Ca: calcium, PO_4: phosphorus, PTH: parathyroid hormone, URR: urea reduction ratio, HB: hemoglobin, T. sat.: transferrin saturation, TSH: Thyroid Stimulation Hormone, HDRS: Hamilton Depression Rating Scale, 6MWT: six-min walk test, RAPA: rapid assessment of physical activity, peak volume of oxygen consumption (peak VO_2)

•: Paired *t* test; ≠: Wilcoxon Rank test; *P* value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

Table 2 Comparison between baseline values and values at end of the study in control group (group II) without doing IDE

	Group II (control group)		Test value	*P* value
	Start of the study	End of the study		
TNF-α (pg/ml)				
Mean ± SD	91.64 ± 29.38	87.24 ± 23.95	1.059•	0.300
Range	49–155	48–137		
Ca (mg/dl)				
Mean ± SD	8.31 ± 0.58	8.40 ± 0.45	− 1.137•	0.267
Range	7.2–9.5	7.7–9.3		
PO_4 (mg/dl)				
Mean ± SD	5.30 ± 1.08	5.08 ± 1.30	1.014•	0.321
Range	2.9–7	2.6–6.7		
PTH (pg/ml)				
Mean ± SD	460.08 ± 135.00	482.96 ± 131.46	− 2.359•	0.027
Range	269–752	300–770		
URR %				
Mean ± SD	73.48 ± 6.39	72.08 ± 6.66	1.421•	0.168
Range	64–88	61.5–90.2		
HB (g/dl)				
Mean ± SD	9.64 ± 0.86	9.56 ± 0.77	1.151•	0.261
Range	7.9–10.8	8–10.7		
T. sat. %				
Mean ± SD	30.82 ± 5.64	31.55 ± 6.18	− 0.635•	0.531
Range	18.5–44	16.8–42		
TSH (mu/l)				
Mean ± SD	1.46 ± 0.56	1.48 ± 0.54	− 0.316•	0.755
Range	0.5–2.6	0.5–2.5		
HDRS				
Mean ± SD	15.64 ± 5.15	16.16 ± 3.95	− 0.923•	0.365
Range	9–26	8–23		
6MWT (min)				
Mean ± SD	209.60 ± 35.19	204.72 ± 41.13	2.640•	0.014
Range	155 – 283	142 – 283		
RAPA				
Median (IQR)	2 (1–2)	1 (1–2)	− 2.333≠	0.020
Range	1–3	1–3		
Peak VO_2 (kg min)				
Mean ± SD	9.72 ± 0.81	9.66 ± 0.87	1.592•	0.124
Range	8.5–11.4	8.2–11.4		

TNF-α: tumor necrosis factor alpha, Ca: calcium, PO_4: phosphorus, PTH: parathyroid hormone, URR: urea reduction ratio, HB: hemoglobin, T. sat.: transferrin saturation, TSH: Thyroid Stimulation Hormone, HDRS: Hamilton depression rating scale, 6MWT: six-min walk test, RAPA: rapid assessment of physical activity, Peak VO_2: peak volume of oxygen consumption

P value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

•: Paired *t* test; ≠: Wilcoxon Rank test

Table 3 Comparison between group I and group II at the end of the study as regard the studied parameters

After	Group I $n=25$	Group II $n=25$	Test value	*P* value
TNF-α (pg/ml)				
Mean ± SD	46.24 ± 14.66	87.24 ± 23.95	−7.301•	0.000
Range	20–79	48–137		
Ca (mg/dl)				
Mean ± SD	8.36 ± 0.65	8.40 ± 0.45	−0.229•	0.820
Range	7.3–9.3	7.7–9.3		
PO_4 (mg/dl)				
Mean ± SD	4.36 ± 0.90	5.08 ± 1.30	−2.292•	0.026
Range	2.8–6	2.6–6.7		
PTH (Pg/ml)				
Mean ± SD	402.00 ± 140.98	482.96 ± 131.46	−2.100•	0.041
Range	140–620	300–770		
URR %				
Mean ± SD	76.23 ± 7.48	72.08 ± 6.66	2.071•	0.044
Range	65–90	61.5–90.2		
HB (g/dl)				
Mean ± SD	9.55 ± 0.92	9.56 ± 0.77	−0.017•	0.987
Range	8–12.7	8–10.7		
T. sat. %				
Mean ± SD	31.39 ± 8.26	31.55 ± 6.18	−0.080•	0.937
Range	12.6–48	16.8–42		
TSH (mu/l)				
Mean ± SD	1.46 ± 0.33	1.48 ± 0.54	−0.159•	0.874
Range	0.9–2.1	0.5–2.5		
HDRS				
Mean ± SD	10.4 ± 3.25	16.16 ± 3.95	−5.624•	0.000
Range	5–18	8–23		
6MWT(m)				
Mean ± SD	253.04 ± 42.48	204.72 ± 41.13	4.086•	0.000
Range	177–343	142–283		
RAPA				
Median (IQR)	3 (3–3)	1 (1–2)	−4.836≠	0.000
Range	1–4	1–3		
PeakVO_2 (ml/(kg min)				
Mean ± SD	10.72 ± 0.98	9.66 ± 0.87	4.042•	0.000
Range	9–12.8	8.2–11.4		

•: Independent *t* test; ≠: Mann–Whitney test; *P* value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

TNF-α: tumor necrosis factor alpha, Ca: calcium, PO_4: phosphorus, PTH: parathyroid hormone, URR: urea reduction ratio, HB: hemoglobin, T. sat.: transferrin saturation, TSH: Thyroid stimulation hormone, Hamilton Depression Rating Scale (HDRS), 6MWT: six-min walk test, RAPA: rapid assessment of physical activity, peak VO_2: peak volume of oxygen consumption

group I and group II at end of the study regarding serum PO_4, PTH and URR, while there was no statistically significant difference between group I and group II at end of study regarding serum Ca, HB, T. sat. and TSH level.

In group I, we found at end of the study that 2/25 patients showed remission (HDRS < 7), 9/25 patients showed more than 50% reduction in depressive symptoms and 14/25 patients showed less than 50% reduction in depressive symptoms as in Table 4 which shows that there was statistically significant difference between group I and group II regarding response and improvement in depression symptoms of HDRS at end of the study.

Our study showed that HDRS was significant positively correlated with serum TNF-α, Fig. 1, while significant negatively correlated with URR ($r=-0.245$) and physical activity tests; 6MWT, Fig. 2, RAPA ($r=-0.195$), and peak VO_2 ($r=-0.116$). Serum TNF-α was negatively correlated with URR, Fig. 3, and physical activity tests;

Table 4 Comparison between group I and group II regarding response and improvement in depression symptoms of HDRS at end of the study

Hamilton after IDE	Group I Case $n=25$	Group II Control $n=25$	Test value	*P* value
Remission (HDRS < 7)	2 (8.0%)	0 (0.0%)	25.360*	0.000
Response (Reduction > 50%)	9 (36.0%)	0 (0.0%)		
Reduction < 50%	14 (56.0%)	11 (44.0%)		

P value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

HDRS: Hamilton Depression Rating Scale

* Chi-square test

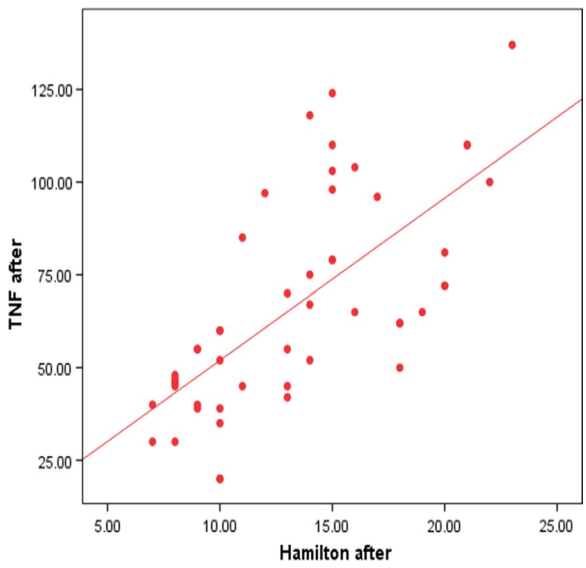

Fig. 1 Positive correlation between TNF-α and HDRS

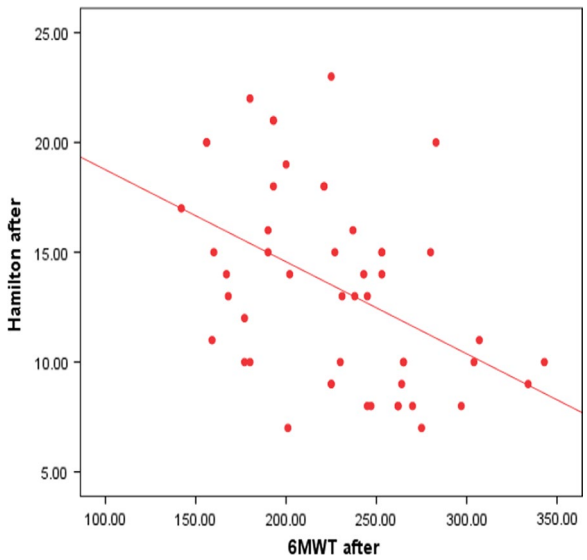

Fig. 2 Negative correlation between HDRS and 6MWT

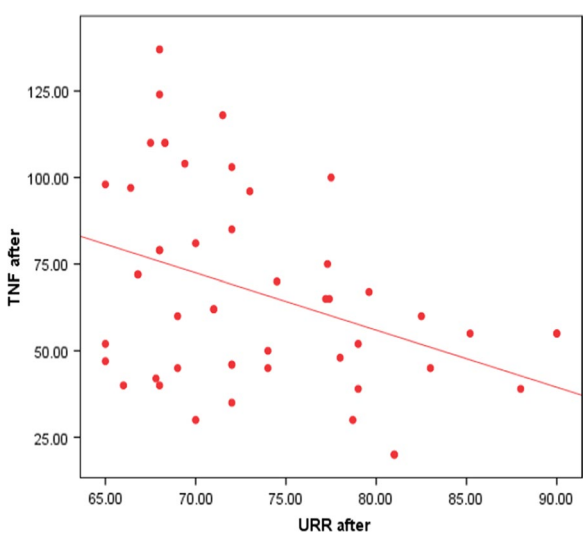

Fig. 3 Negative correlation between TNF-α and URR

6MWT ($r=-0.130$), RAPA ($r=-0.161$) and peakVO_2 ($r=-0.137$). Regarding physical activity tests, 6MWT was positively correlated with RAPA ($r=0.587$) and peakVO_2 ($r=0.999$), while negatively correlated with age ($r=-0.870$) and duration of ESRD ($r=-0.562$) and RAPA was positively correlated with peak VO_2 ($r=0.594$).

By univariate and multivariate linear regression analysis, we found that factors affecting HDRS are serum TNF-α, physical activity tests (6MWT, RAPA, peak VO_2), age and URR, while serum TNF-α is the most significant factor affecting HDRS as in Table 5 which shows that factors affecting HDRS after IDE are TNF-α, 6MWT, RAPA, peak VO_2, age and URR, while serum TNF-α is the only independent factor affecting score of HDRS. We also found that factors affecting serum TNF-α are HDRS, 6MWT, RAPA, peak VO_2, age and URR, while HDRS is the most significant factor affecting serum TNF-α.

We found that factors affecting 6MWT are TNF-α, HDRS, RAPA, peak VO_2, age and duration of ESRD, while peak VO_2 and HDRS are the most significant factors affecting 6MWT as in Table 6 which shows that factors affecting 6MWT after IDE are TNF-α, HDRS, RAPA, peak VO_2, age and duration of ESRD, while peak VO_2 and HDRS are the most significant factors affecting 6MWT. We also found that factors affecting RAPA are TNF-α, HDRS, 6MWT, peak VO_2 and age, while HDRS is the only independent factor affecting RAPA. We also found that factors affecting peak VO_2 are TNF-α, HDRS, 6MWT, RAPA, age and duration of ESRD, while 6MWT is the most significant factor affecting peak VO_2.

Discussion

In the current work, in group I we found that HDRS, serum TNF-α, PO_4 and PTH significantly decreased at end of the study, while physical performance tests (6MWT, RAPA and peak VO_2) and URR significantly increased at end of the study after completing IDE program.

Regarding depression and inflammatory marker, in group I, we found that HDRS was significantly higher before IDE (mean 17.56 ± 4.21) than baseline (mean 10.40 ± 3.25) (P value $=0.000$). This was consistent with a research by Rhee and colleagues [40] that had 22 HD patients participating in IDE for a period of 6 months. According to this study, there was a substantial reduction in depression following the completion of exercise (P 0.05). Serum TNF-α was found significantly higher in group I before IDE (mean 109.88 ± 46.80) than after IDE (mean 46.24 ± 14.66), ($P=0.000$). This was in line with the findings of a research by Dong and colleagues [41] that involved 41 HD patients who were split into two groups: an intervention group (group E, $n=21$) and a control group (group C, $n=20$). Group E got IDE for 12 weeks at a rate of three times per week as part of standard HD therapy, and they found that group E's TNF-α levels dropped more considerably after the intervention than those of group C. In a study by Peres and colleagues [42] on HD patients who performed IDE three times per week for at least 3 months and showed a tendency toward reduction of serum TNF-α at end of the study.

Regarding physical performance tests in group I, we found that 6MWD was substantially higher after IDE (mean 253.04 ± 42.48) than baseline (mean

Table 5 Univariate and multivariate linear regression analysis for factors affecting HDRS after IDE

HDRS	Univariate					Multivariate				
	Unstandardized coefficients		Standardized coefficients	*T*	*P* value	Unstandardized coefficients		Standardized coefficients	*T*	*P* value
	B	S.E	Beta			*B*	S.E	Beta		
TNF-α (Pg/ml)	0.107	0.016	0.685	6.515	**0.000**	0.074	0.019	0.470	3.926	**0.000**
6MWT (m)	−0.041	0.012	−0.441	−3.406	**0.001**	0.154	0.063	1.655	2.437	**0.019**
RAPA	−2.699	0.514	−0.604	−5.254	**0.000**	−1.933	0.716	−0.433	−2.701	**0.010**
Peak VO_2 (ml/(kg min)	−2.011	0.532	−0.479	−3.783	**0.000**	−6.879	2.944	−1.639	−2.337	**0.024**
Age	0.169	0.075	0.311	2.270	**0.028**	−0.050	0.095	−0.092	−0.531	0.598
URR %	−0.228	0.082	−0.373	−2.787	**0.008**	−0.031	0.066	−0.051	−0.470	0.641

HDRS: Hamilton Depression Rating Scale, TNF-α: tumor necrosis factor alpha, 6MWT: six-min walk test, RAPA: rapid assessment of physical activity, peak VO_2: peak volume of oxygen consumption, URR: urea reduction ratio

Bold indicates statistical significance. *P* value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

Table 6 Univariate and multivariate linear regression analysis for factors affecting 6MWT after IDE

6MWT after	Univariate					Multivariate				
	Unstandardized coefficients		Standardized coefficients	*T*	*P* value	Unstandardized coefficients		Standardized coefficients	*t*	*P* value
	B	S.E	Beta			*B*	S.E	Beta		
TNF-α (pg/ml)	−0.713	0.220	−0.424	−3.243	**0.002**	−0.066	0.046	−0.039	−1.433	0.159
HDRS	−4.741	1.392	−0.441	−3.406	**0.001**	0.781	0.317	0.073	2.467	**0.018**
RAPA	38.038	4.222	0.793	9.010	**0.000**	2.714	1.692	0.057	1.604	0.116
Peak VO_2 (kg min)	44.633	0.914	0.990	48.855	**0.000**	44.048	2.120	0.977	20.780	**0.000**
Age	−4.781	0.484	−0.819	−9.883	**0.000**	0.197	0.218	0.034	0.904	0.371
Duration of ESRD	−17.285	6.151	−0.376	−2.810	**0.007**	−1.814	1.103	−0.039	−1.644	0.108

6MWT: six-min walk test, TNF-α: tumor necrosis factor alpha, HDRS: Hamilton Depression Rating Scale, RAPA: rapid assessment of physical activity, peak VO_2: peak volume of oxygen consumption, ESRD: end stage renal disease

Bold indicates statistical significance. *P* value > 0.05: non-significant; *P* value < 0.05: significant; *P* value < 0.01: highly significant

217.68 ± 37.4). This was in line with a study by Liao and colleagues [43] that involved 40 HD patients who were either prescribed a 3-month exercise program (group E, $n = 20$) or were not (group C, $n = 20$). The study revealed that patients in group E had significantly higher 6-MWD after the IDE program compared to their baseline scores (*P* 0.05), but group C did not experience any significant changes in the 6-MWD, RAPA was found much greater in group I following IDE (median 3, IQR 3–3) compared to baseline (median 2, IQR 2–2) and peakVO_2 was substantially higher after IDE (mean 10.72 ± 0.98) compared to baseline (mean 9.91 ± 0.88). This is in line with a research by Huang and colleagues [44] that looked at 677 HD patients and indicated that exercise significantly increased peak VO_2 ($P = 0.0006$). In this study, the intervention group received IDE for 8 weeks. Regardless of exercise duration, intensity, or frequency, patients who performed IDE saw a substantial rise in peakVO_2. PeakVO_2 increased with exercise is considered a sign of enhanced aerobic capacity. Patients with ESRD receiving HD might then increase their activity time due to a decrease in tiredness, abandon a sedentary lifestyle, and finally see a drop in mortality [45]. This was in line with Sheng and colleagues [46] study, which looked at 997 HD patients separated into an IDE group and a control group, and found that IDE significantly increased peak VO_2 and physical performance.

Regarding laboratory results in group I, we found that after IDE serum PO_4 and PTH were significantly decreased (mean 4.36 ± 0.90) and (mean 402 ± 140.98), while URR was significantly increased (mean 76.23 ± 7.48) in comparison with their baseline values, but there was no significant change regarding serum Ca and HB levels after IDE. Our findings were in agreement with study of Abdelnour and colleagues [47] that was conducted on 60 HD patients and revealed that after 3 months of intra-dialytic exercise 3 times/week, significant improvements were seen in both serum PO_4

($P=0.012$) and PTH ($P=0.001$), which significantly decreased after IDE. Our study was also in agreement with study of Makhlough and colleagues [48] which was conducted on 47 HD patients assigned into the exercise group ($n=25$) and the control group ($n=23$). The IDE program was administered to the intervention group three times per week for 2 months, and it was discovered that although serum phosphate levels significantly improved, serum calcium and HB levels remained stable. Our findings were also in agreement with study of Mohseni and colleagues [49] which was conducted on 50 HD patients divided into intervention and control groups. The intervention group received IDE 3 times/week and after 8 weeks, the average score of URR increased by 11% ($P=0.003$) and also in study of Dias and colleagues [50] that revealed that URR was significantly higher in HD sessions with exercise than in HD sessions without exercise ($P=0.02$). A larger flux of circulating toxins and urea from the muscle into circulation and eliminated by dialysis would be diffused by IDE, which was found to increase blood flow and perfusion of muscle tissue and increase surface area [44].

In group II, after 3 months without doing any exercise, we found that 6MWT and RAPA decreased, while PTH increased and this refers to worsening of physical fitness of HD patients who did not undertake any IDE, but there was no statistically significant difference regarding TNF-α, HDRS, Ca, PO_4, URR, HB and peak VO_2.

In comparison between group I and group II at end of the study, a statistically significant difference was found between both groups regarding serum TNF-α and HDRS ($P<0.001$), PO_4, PTH and URR ($P<0.05$). In addition, significant difference was found between the two groups regarding physical activity tests (6MWT, RAPA and peak VO_2), $P<0.001$. While, there was no statistically significant difference between the two groups regarding serum Ca and HB level.

Regarding improvement of depression and inflammation in HD patients underwent regular IDE, 8% showed complete remission, 36% showed reduction of more than 50% of depressive symptoms which means response to depression treatment and 56% showed reduction of less than 50% of depressive symptoms median (IQR) − 33.33 (− 25 to − 36). HDRS was negatively correlated with physical activity tests (6MWT, RAPA and peak VO_2) which mean that improvement of physical performance by IDE will help in improvement of depression. This was in agreement with study of Zhang and colleagues [51] which was conducted on 72 HD patients and showed that HD patients with depression generally had the most impaired physical performance which was negatively correlated with depression ($r=-0.33$, $P=0.01$). Serum TNF-α was positively correlated with HDRS and that serum TNF-α was the most important factor impacting HDRS ($P=0.000$) in multiple regression analysis suggested that serum TNF-α may be considered as marker of depression in HD patients. This was consistent with a research by Zou and colleagues [21] that found a linear association between TNF-α and the degree of depression as well as that patients with depression had considerably higher levels of TNF-α than controls (P 0.01).

Regarding improvement of physical performance in HD patients underwent regular IDE, we discovered a negative correlation between TNF-α and the results of the 6MWT, RAPA, and peak VO_2 tests following IDE which indicate that decrease in TNF-α and improvement of inflammation with IDE will help improvement of physical performance. This was consistent with a research by Cruz and colleagues [52] that had 30 HD patients, IDE for 12 weeks ($n=15$), and a control group ($n=15$) who continued with their regular daily activities. It was shown that there was a negative association between serum TNF-α and 6MWD following IDE, and that 12 weeks of IDE was adequate to lower serum TNF-α and increase the distance travelled in the 6MWT. In addition, we discovered a favorable correlation between the results of the 6MWT, RAPA, and peakVO_2 physical activity tests. This was consistent with a research by Wai-Kei and colleagues [53] that involved 12 HD patients who received IDE for 3 months. They found that the 6-MWT had a strong positive correlation with peakVO_2, proving that IDE is advantageous to patients in terms of improving 6MWD and, consequently peakVO_2.

Regarding improvement of dialysis adequacy in HD patients underwent regular IDE, it is concluded from our study that URR was negatively correlated with HDRS and serum TNF-α, so IDE can improve depression by increasing URR and decreasing inflammation. Exercise increases the flow of urea and other solutes from the skeletal muscle, allowing for their elimination at the dialyzer membrane. This in turn enhances the blood perfusion between the working muscle and circulation [54]. IDE increases HD effectiveness by boosting cardiac output and muscle vasodilatation, which causes a significant flow of toxins from tissue to the vascular compartment to be cleared by hemodialyzer [50].

Limitations of this work included the limited number of patients and short duration of exercise to show more improving in depressive symptoms, dialysis efficacy and physical performance in HD patients. For the construction of patient exercise system, new studies will be needed to focus on multiple plans for different conditions of patients. In addition, more studies which assess side effects of exercise in HD patients will be needed to provide more evidence for tailoring relevant exercise program.

Conclusions

Intra-dialytic exercise resulted in benefits in terms of improving depression, exercise capacity and HD adequacy in hemodialysis patients. Intra-dialytic exercise reduced HDRS and serum TNF-α, so we can conclude that IDE has the ability to reduce inflammation which is linked to reduction of depressive symptoms in HD patients. Serum TNF-α was positively correlated with HDRS, so we can use serum TNF-α as marker of depression.

IDE can improve depression directly by decrease HDRS and indirectly by improvement of inflammation, physical performance and dialysis adequacy.

IDE can improve physical performance of HD patients directly by improving 6MWT, RAPA and peak VO_2 and indirectly by improving serum TNF-α and HDRS.

IDE is strongly advised for HD patients, since it can improve the sufficiency of the dialysis by increasing URR and decreasing serum phosphorus and PTH.

Given the encouraging results obtained in this study and according to the evidence found in literature, supervised IDE programs should be included as part of HD patients care.

Abbreviations

HPA: Hypothalamic–pituitary–adrenal; HD: Hemodialysis; ESRD: End-stage renal disease; IDE: Intra-dialytic exercise; HDRS: Hamilton depression rating scale; TNF-α: Tumor necrosis factor alpha; 6MWT: Six-min walk test; RAPA: Rapid assessment of physical activity; peak VO_2: Peak volume of oxygen consumption; PTH: Parathyroid hormone; ECG: Electro-cardiogram; 6MWD: Six-min walk distance; URR: Urea reduction ratio; Ca: Calcium; PO_4: Phosphorus; HB: Hemoglobin; ELISA: Enzyme linked immune-sorbent assay; T. sat: Transferrin saturation; TSH: Thyroid stimulating hormone; IQR: Inter quartile range.

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Author contributions

HE: main idea, revised paper; ES: collect clinical data, data analysis, write paper; HH, DF, ESa, MA and ESo had access full responsibility for all data associated with this study; ESa, HH and DF wrote the manuscript. All authors contributed to reviewing and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of the Helsinki. It was approved by the Ethics Committee of Faculty of Medicine, Ain Shams University (FWA 000017585); each participant signed a written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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