Journal of Taibah University Medical Sciences (2023) 18(3), 512–525

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Review Article

The effectiveness of intradialytic exercise in ameliorating fatigue symptoms in patients with chronic kidney failure undergoing hemodialysis: A systematic literature review and meta-analysis

Astri Zeini Wahida, S.Kep., Ners., M.Kep [a], Hotma Rumahorbo, S.Kp, M.Epid [b,*] and Murtiningsih, S.Kp., M.Kep., Sp.Mat [c]

[a] *Sekolah Tinggi Ilmu Kesehatan Sukabumi, Indonesia*
[b] *Politeknik Kesehatan Bandung, Indonesia*
[c] *Universitas Jenderal Achmad Yani Cimahi, Indonesia*

Received 16 July 2022; revised 30 October 2022; accepted 19 November 2022; Available online 29 November 2022

المخلص

أهداف البحث: غسيل الكلى في المرضى الذين يعانون من الفشل الكلوي المزمن هو خيار تدخل آخر غير زرع الكلى. في عام 2019، أصبح الفشل الكلوي المزمن السبب الرئيسي السادس للوفاة في العالم. في إندونيسيا، هناك زيادة في حالات الفشل الكلوي كل عام، والتي تحتل المرتبة العاشرة بين أكبر أسباب الوفاة. استنادا إلى الأبحاث الصحية الأساسية في عام 2018، كان معدل انتشار الفشل الكلوي المزمن 3.4٪، وخضع 19.3٪ من المرضى الذين تبلغ أعمارهم 15 عاما فأكثر لغسيل الكلى. حللت هذه الدراسة فعالية التمرين داخل التحلل على أعراض التعب لدى مرضى الفشل الكلوي المزمن الذين يخضعون لغسيل الكلى من حيث نوع التمرين، ومدته، ووقته، وتواتره.

طرق البحث: تم فحص واستخلاص جميع المقالات ذات النصوص الكاملة المناسبة والمؤهلة المنشورة بين يناير 2010 وأكتوبر 2021 من "بوبميد" و "سكوبس" و "بروكويست" و "ساينس دايركت" و "كروسريف" و غوغل العلمي وقاعدة بيانات جارودا. البحث والتكنولوجيا والمراجعة النقدية. استعرض مؤلفان مستقلان خطر التحيز باستخدام نموذج معهد جوانا بريجز. تم إجراء تحليل البيانات نوعيا للحصول على لمحة عامة عن خصائص التمرين داخل التحليل وكميا باستخدام التحليل التلوي.

النتائج: أظهر بحثنا أن التمرين داخل التحلل وجد أنه فعال في تقليل التعب في مجموعة التدخل بنسبة 81 ٪. كان نوع التمارين داخل الانحل التي كان لها أكبر حجم تأثير هو التمارين الهوائية (146٪)؛ كانت مدة التمرين داخل التحلل مع حجم التأثير الأكثر أهمية< 20 دقيقة (100٪)؛ كان وقت التمرين داخل التحلل مع حجم التأثير الأكثر أهمية هو أول ساعتين (127٪)؛ التكرار أقل من 12 جلسة كان لها أكبر تأثير حجم (120٪).

الاستنتاجات: تعتبر التمارين الهوائية، التي تدوم أكثر من 20 دقيقة، في أول ساعتين من غسيل الكلى، وبتكرار أقل من 12 جلسة، من خصائص التمارين داخل التحلل التي تعتبر فعالة في التغلب على التعب.

الكلمات المفتاحية: التعب؛ الفشل الكلوي المزمن؛ غسيل الكلى؛ تمرين داخل التحلل؛ التحليل التلوي

Abstract

Objective: Hemodialysis in patients with chronic kidney failure is an intervention serving as an alternative to kidney transplantation. In 2019, chronic kidney failure became the world's 6th leading cause of death. In Indonesia, kidney failure has an increasing number of cases every year and is the 10th highest cause of death. According to basic health research in 2018, the prevalence of chronic kidney failure was 3.4%, and 19.3% of patients 15 years of age and older underwent hemodialysis. This study analyzed the effectiveness of intradialytic exercise in ameliorating fatigue symptoms in patients with chronic kidney failure undergoing hemodialysis, in terms of exercise type, duration, time, and frequency.

Methods: All appropriate and eligible full-text articles published between January 2010 and October 2021 were screened and extracted from the databases PubMed, Scopus, ProQuest, Science Direct, CrossRef, Google Scholar, and Garuda Database for Research and Technology. The articles were critically reviewed, and two

* Corresponding address: Politeknik Kesehatan Bandung, Jl. Pajajaran No.56, Pasir Kaliki, Kec. Cicendo, Bandung, 40171, West Java, Indonesia.

E-mail: hotma_rumahorbo@yahoo.com (H. Rumahorbo)

Peer review under responsibility of Taibah University.

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1658-3612

https://doi.org/10.1016/j.jtumed.2022.11.004

independent authors reviewed the risk of bias by using the JBI form. Data analysis was performed qualitatively to obtain an overview of the characteristics of intradialytic exercise and quantitatively through meta-analysis.

Results: Intradialytic exercise was found to effectively decrease fatigue by 81% in the intervention group. The most significant effect sizes were as follows: type of intradialytic exercise: aerobic exercise (146%); duration of intradialytic exercise: >20 min (100%); time of intradialytic exercise: first 2 h (127%); and exercise frequency: <12 sessions (120%).

Conclusion: The characteristics of intradialytic exercise that are considered effective in ameliorating fatigue are aerobic exercise lasting >20 min and performed in the first 2 h of hemodialysis, with a frequency of <12 sessions.

Keywords: Chronic kidney failure; Fatigue; Hemodialysis; Intradialytic exercise; Meta-analysis

Introduction

Chronic kidney disease (CKD) is one of the leading causes of global morbidity and mortality. In the 2019 Global Burden of Disease study, CKD was among the top ten risks associated with the highest number of deaths worldwide, with a death toll of 3.16 million deaths.[1,2] Basic health research data have indicated a 19.1% increase in the proportion of CKD from 2013 to 2018.[3,4]

CKD is a broad and progressive medical condition. After a continued decline in kidney function, the disease eventually reaches a life-threatening stage known as end stage renal disease (ESRD). Patients with ESRD require treatment with renal replacement therapy to live[5,6]. Hemodialysis (HD), continuous ambulatory peritoneal dialysis, and kidney transplantation are the three main modalities of renal replacement therapy,[7] among which HD is the most common type performed in Indonesia.[3]

HD is used to remove fluids and waste products, such as nitrogen and other toxic substances, from the body, because the kidneys cannot perform these functions.[8] HD uses three working principles—diffusion, osmosis, and ultrafiltration—to clear substances that are not needed by the body from the blood.[9]

HD does not cure kidney disease but is a kidney replacement therapy. After optimization, it cannot surpass the performance of healthy kidneys.[10] Consequently, patients who have undergone routine HD can still experience symptoms due to inadequate diffusion, osmosis, and ultrafiltration processes.[11]

Alvarez et al.[12] have found that fatigue is the most common symptom experienced by patients undergoing HD (62%), and is followed by cramps (44%), and hypotension (42%). Cervantes et al.[13] have also reported that fatigue is the most frequent symptom (87%), and is followed by pain (64%). Prolonged fatigue symptoms negatively affect patients with ESRD, e.g., through decreasing productivity, sleep quality, and quality of life.[14]

The cause of physical fatigue in patients with ESRD remains multifactorial and unclear. However, physical fatigue is generally associated with disruption of the energy system in the body, mitochondrial dysfunction, and minimal physical activity resulting in muscle wasting and decreased muscle strength. These symptoms are associated with long periods of bed rest in each phase of HD and a feeling of weakness that makes patients less physically active, thus resulting in muscle atrophy.[15]

Therefore, interventions are needed to decrease fatigue, improve energy metabolism, decrease the intensity of prolonged bed rest, and minimize muscle atrophy in patients receiving HD. Exercise is recommended to ameliorate fatigue.

Studies on the effectiveness of intradialytic exercise on the symptoms of fatigue in patients with CKD undergoing HD have not clearly described the patterns of exercise effectiveness. Various types of intradialytic exercises have been implemented to ameliorate fatigue. The frequency of exercise also widely varies, from as few as four sessions to as long as 8 months. The type of fatigue subjected to interventions must be studied further so that the effectiveness of intradialytic exercise against each type of fatigue can be described. Moreover, the exercise duration and time must be assessed to identify patterns of intradialytic exercise in effectively ameliorating fatigue symptoms. Several studies have performed systematic literature reviews and meta-analyses of effectiveness of exercise in patients receiving HD, such as studies of intradialytic exercise[16,17] and fatigue in patients receiving HD.[18,19] However, this research has not directly linked intradialytic exercise to symptoms of fatigue or examined the effectiveness of intradialytic exercise in detail, according to the characteristics of the exercise performed. Therefore, this analysis was aimed at investigating studies examining the effectiveness of intradialytic exercise according to the type of exercise, duration, time, and frequency of exercise, to provide the specifications of effective exercise. Experimental designs including RCT and quasi-experimental designs were used to eliminate bias and serve as a basis for the literature review. The following research questions were asked:

1. Which type of intradialytic exercise is most often used to treat fatigue in patients with CKD undergoing HD?
2. What duration of intradialytic exercise is used most often?
3. What intradialytic exercise time is most often chosen?
4. What intradialytic exercise frequency is used most often?
5. What is the effectiveness of intradialytic exercise in ameliorating symptoms of fatigue in patients with chronic renal failure undergoing HD?
6. What is the effectiveness of different types of intradialytic exercise?
7. What is the effectiveness of different intradialytic exercise durations?
8. What is the effectiveness of different timings of intradialytic exercise?
9. What is the effectiveness of different frequencies of intradialytic exercise?

Materials and Methods

Formulation of the problem

This systematic literature review and meta-analysis was conducted to analyze and integrate the effects of intradialytic exercise in ameliorating symptoms of fatigue in patients with chronic kidney failure undergoing HD. The systematic literature review and meta-analysis stages were based on "A step by step guide for conducting a systematic review and meta-analysis with simulation data",[20] a representative research guide for conducting systematic reviews and meta-analyses. The stages consisted of determining research questions, validating ideas, determining inclusion and exclusion criteria, determining search strategies, conducting database searches, screening literature, extracting data, and performing statistical analysis.

To analyze the effects of intradialytic exercise on symptomatic relief of fatigue in patients with chronic kidney failure undergoing HD, we based the study selection criteria in the meta-analysis on population, intervention, comparison, and outcome (PICO):

1. Population (P): Adult patients with chronic kidney failure undergoing HD
2. Intervention (I): Intradialytic exercise
3. Comparison (C): Another group or comparison group that did not receive intradialytic exercise
4. Outcome (O): Type, duration, execution time, and frequency of intradialytic exercise
5. Study design (S): Randomized controlled trials and quasi-experimental studies

Study search and selection strategies

A systematic search was performed on the Garuda Ristekdikti, CrossRef, Scopus, PubMed, Google Scholar, ProQuest, and Science Direct databases. PubMed standard subject/keyword indexing, i.e., Medical Subject Headings (MeSH), was used to determine search keywords and identify synonyms or related terms for "chronic kidney failure," "HD," "intradialytic exercise," and "fatigue." The search was formulated as follows:

1. "HD OR Hemofiltration OR Dialysis OR HD*"
2. "CKD OR Chronic Failure OR ESRD OR End Stage Renal Disease OR Chronic Kidney Failure"
3. "Intradialytic exercise OR Intradialytic Exercise OR Physical Exercise OR Exercise"
4. "Fatigue OR Weakness OR Tired OR Exhaustion OR Fatigue OR Fatigue"
5. AND (2) AND (3) AND (4)

The literature was selected on the basis of the following inclusion criteria: publication in 2010–2021, original research, RCT or quasi-experimental design, and availability of full text. The selected literature was added to Mendeley reference management and subsequently underwent three forms of screening: duplication screening; title and abstract screening; and full-text screening. To avoid bias and to ensure that all literature was identified, we also conducted manual searches of the reference lists in the literature and then tracked the citations.

Literature quality assessment

The literature that passed the screening stage was assessed for quality with the Joanna Briggs Institute (JBI) checklist form for RCT and quasi-experimental designs as the appraisal tool. After a screening stage, an assessment of literature quality was performed by two independent evaluators who filled out the JBI checklist. If the evaluator responded "yes" on the assessment sheet, a score of 1 was assigned, whereas, if the evaluator responded "no" or "not clear" on the assessment sheet, a score of 0 was assigned. Afterward, the score for each article was calculated as a percentage (number of scores/total questions × 100) with core criteria >75% of the literature is considered feasible.[21] For RCT studies, the quality was assessed on the basis of (1) random allocation; (2) allocation concealment; (3) participant homogeneity; (4) participant blinding; (5) treatment administrator blinding; (6) assessor blinding; (7) similarity of the interventions received; (8) adequate follow-up; (9) group analysis; (10) measurement between groups; (11) measurement reliability; (12) accuracy of analysis; and (13) design suitability. For quasi-experimental research studies, the assessors identified feasibility on the basis of: (1) clarity of cause and effect; (2) participant homogeneity; (3) similarity of the interventions received; (4) identification of the control group; (5) repeated measurements; (6) adequate follow-up; (7) measurement similarity (8) measurement reliability; and (9) accuracy of statistical analysis. After the quality assessment stage, data extraction and analysis were performed. To evaluate the quality of methods in experimental controlled studies, we assessed the risk of bias (ROB) for RCT and non-RCT studies,[22,23] on the basis of the following seven items: random sequencing, allocation concealment, blinding of participants and personnel, blinding to outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item was scored as low, high, or uncertain.[24] Inconsistent items were reconciled through rigorous discussion and review of the original text.

Data extraction

Data extraction was performed on the literature that passed the quality assessment on the basis of the research questions. The data were extracted independently in the form of study characteristics and intradialytic exercise characteristics, according to the type of exercise, duration of exercise, time of exercise, frequency of exercise, and effectiveness of intradialytic exercise in ameliorating symptoms of fatigue in patients with chronic kidney failure undergoing HD. The descriptive summary of the study is presented in Table 1.

Data analysis

Both qualitative and quantitative analyses were conducted. Qualitative analysis was performed to assess the effectiveness of the intradialytic exercises according to the narrative indicated by the literature, by extracting data associated on characteristics of intradialytic exercise, including type, duration, time, and frequency. Quantitative analysis was performed through meta-analysis of data means, standard deviations, and total samples from each study. Meta-analysis calculations were performed in Review Manager 5.4 software. Continuous data were analyzed with standardized mean difference (SMD) and 95% confidence intervals (CI). Heterogeneity among studies was tested with chi-square and I-square (I^2) tests. If the I^2 value was less than 50%, and the value was greater than 0.05, the meta-analysis was not considered statistically homogeneous.[22] SMD was calculated with a fixed effect model or a random effect model depending on the heterogeneity of the results. A meta-analysis of the effectiveness of intradialytic exercise on fatigue between the exercise and control groups was performed. In addition, subgroup analysis was used to identify the effectiveness of intradialytic exercise in alleviating fatigue symptoms, according to exercise type, duration, execution time, and frequency.

Results

Selection process

A total of 820 articles were obtained from literature searches: 92 articles from PubMed, 124 articles from Google Scholar, 86 articles from Science Direct, 98 articles from Scopus, 161 articles from CrossRef, 149 articles from ProQuest, and 110 articles from Garuda. The initial selection was performed by filtering articles by year of publication (2010–2021), article type (original research), and accessibility (full text); 178 articles remained. Furthermore, screening for duplicate articles on the basis of the similarity of title, author, and year of publication returned 106 articles, thus leaving 72 articles. These 72 articles underwent title and abstract screening; 24 articles were excluded, and 48 articles remained.

A total of 23 articles were further excluded because they did not describe the type (3 articles), duration (7 articles), implementation time (9 articles), or frequency of intradialytic exercise (4 articles), thus leaving 25 articles. Those articles then underwent quality assessment of eligibility for data analysis. Of the 25 articles, 10 did not use continuous data so that used categories; the remaining 15 articles were eligible for meta-analysis. The flow of the study selection process is presented in Figure 1.

Descriptive summary of the selected literature

The characteristics of the studies are shown in Table 1. Among the 25 studies, 7 were from India, 23 were from the continent of Asia, and 15 used quasi-experimental designs. The measurement instrument most often used to observe fatigue symptoms was the Multidimensional Fatigue Inventory Scale (MFI), in 5 studies, and the most common research sample size was >50 respondents. Although in-depth analysis of the differences in the instruments was not conducted, we considered the type of fatigue assessed on the basis of each instrument used to examine the symptoms of physical and psychological fatigue. However, this aspect is a limitation of this study, and future research may consider the homogeneity of instruments.

Literature quality evaluation

The results of the bias risk analysis are shown in Figure 2. The risk of bias was identified by using ROB with seven assessment items. A total of 100% of the studies had low ROB regarding random sequence generation. A total of 13.3% of the studies had an uncertain ROB regarding the concealment of allocation, and 6.6% had a high ROB with respect to limitations in respondent allocation. Regarding the blinding of study participants and personnel, 53.3% had a low ROB. In the blinded outcome assessment, 20% had a low ROB, whereas 6.6% had a high ROB because the assessors were not blinded. In terms of incomplete outcome data, 6.6% had high ROB due to dropout; in terms of selective outcome reporting, 100% had a low ROB. No other sources of bias were identified.

Effectiveness of intradialytic exercises in ameliorating fatigue in general

A total of 15 studies were included in the meta-analysis. The forest plot of the effectiveness of intradialytic exercise on fatigue is shown in Figure 2. Because high heterogeneity was found ($I^2 = 90\%$, $P < 0.00001$), a random effect model was used. Intradialytic exercise significantly decreased fatigue symptoms in patients with chronic kidney failure undergoing HD (SMD −0.81, 95% CI −1.13 to −0.49, $P < 0.00001$). The forest plot is shown in Figure 3. Sensitivity analysis indicated that the results did not change and therefore were stable and reliable.

Intradialytic exercise was considered effective in decreasing fatigue, on the basis of the results of a systematic literature review and meta-analysis, in which one study suggested that exercise decreases fatigue in adults undergoing HD.[18] In addition, a meta-analysis supported our findings, suggesting that intradialytic exercise affects fatigue in patients receiving HD (SMD = −0.85, Z = 4.77, $P < 0.00001$).[19]

Intradialytic exercise functions by optimizing the formation and use of energy, and physical exercise is tailored to each patient's condition.[16,18] In addition, exercise can train the body in energy use, increase blood flow to muscles, and increase capillary surface area, thereby increasing the transfer of urea and toxins from tissues to blood vessels.[23,29] Additionally, exercise helps the body efficiently deliver oxygen to the muscles, improves overall circulation, decreases blood pressure, and releases metabolic waste products that inhibit energy form such as lactic acid.[19,49]

In intradialytic exercise, the patient performs exercise while undergoing HD. The effects are positive because patients with chronic kidney failure regain new kidney function that would not have been obtained in the absence of HD, and the risk of accumulation of metabolic products due to physical exercise is minimized by the HD process. These positive effects are supported by studies showing that intradialytic exercise increases Kt/V-urea and creatinine clearance during dialysis.[27]

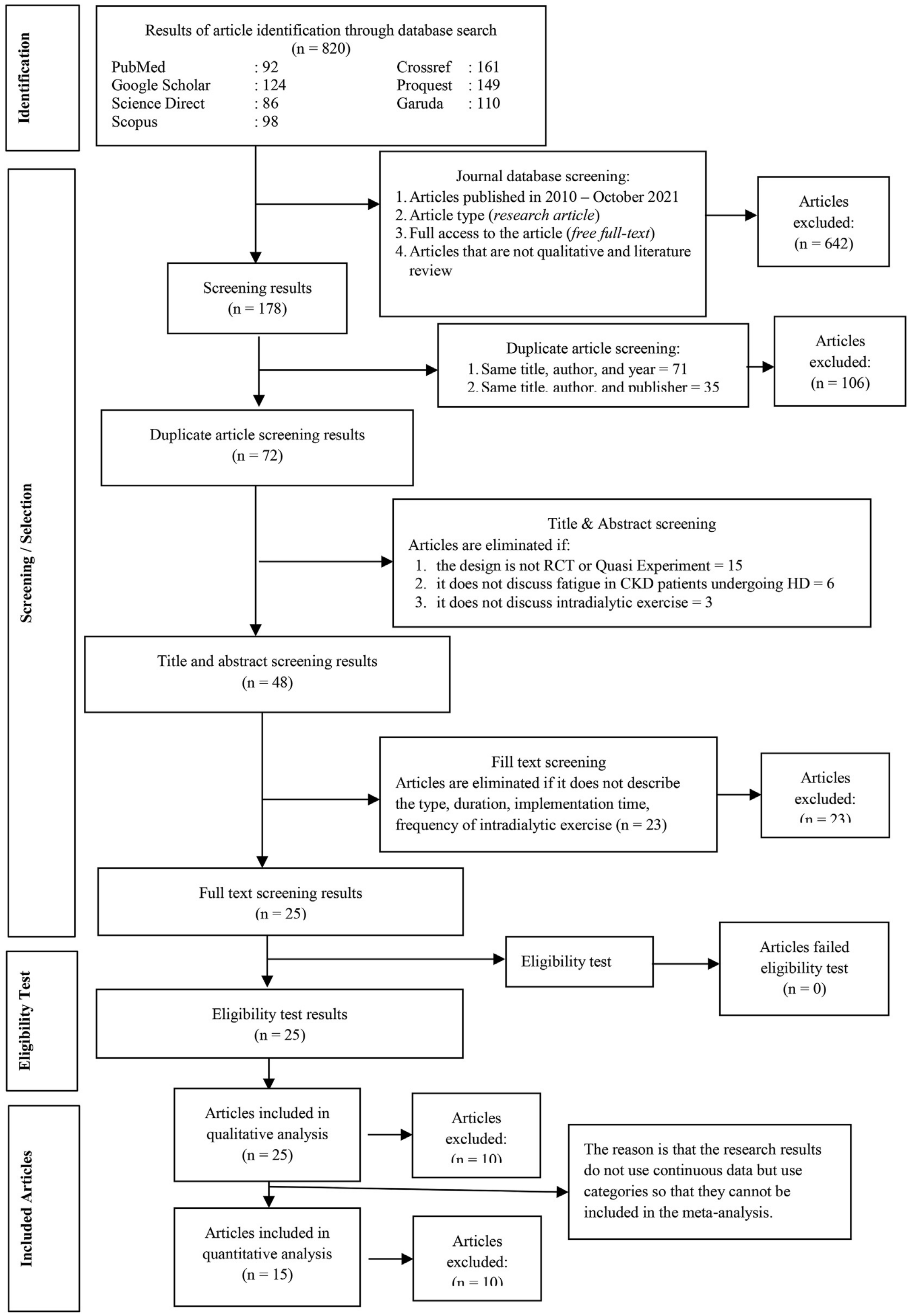

Figure 1: PRISMA flowchart: Results of research article searching and screening.

Effectiveness of intradialytic exercise types

Four types of intradialytic exercise were used: flexibility exercise, aerobic exercise, strengthening exercise, and combination exercise. Flexibility exercise was the intradialytic exercise type most often used for ameliorating fatigue (9 of 25 studies). The heterogeneity test results indicated that the four types of exercise had high heterogeneity (AE: $I^2 = 94\%$, SE: $I^2 = 74\%$, FE: $I^2 = 87\%$, and CE: $I^2 = 90\%$); therefore, a random effect model was used. The effectiveness of

Table 1: Characteristics of the studies.

No	Researcher (Year)	Country	Research Design	Sample Size	Research Instrument	Fatigue Measurement	Type of Intradialytic Exercise	Duration of Intradialytic Exercise	Implementation Time of Intradialytic Exercise	Frequency of Intradialytic Exercise	Outcome
1.	Chang et al. (2010)[25]	Taiwan	RCT	42 respondents	PFS (Piper Fatigue Scale)	15 min after intradialytic exercise	Flexibility exercise	30 min	First hour of the hemodialysis (HD) session	3 × per week for 4 weeks (12 sessions)	Intradialytic exercise at this frequency was effective in decreasing fatigue in patients with chronic kidney disease (CKD).
2.	Maniam et al. (2014)[26]	Singapore	Quasi-experimental with control group	55 respondents	FACIT (Functional Assessment of Chronic Illness Therapy)	After hemodialysis session	Combination (flexibility and strengthening exercise)	30–40 min	2 h after HD start	3 × per week for 12 weeks (36 sessions)	Intradialytic exercise at low to moderate intensity had a significant effect on decreasing fatigue in the control group compared with the intervention group.
3.	Mathew et al. (2014)[27]	India	Quasi-experimental	40 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After intradialytic exercise	Strengthening exercise	30 min	Unspecified	2 × per week	Intradialytic exercise was effective in decreasing fatigue in dialysis patients with t count values (12.71 and 24.45), larger than the t table value ($t39 = 1.69$) at the 0.05 significance level.
4.	Motedayen et al. (2014)[28]	Iran	RCT	66 respondents	FSS (Fatigue Severity scale)	1 h after HD	Combination exercise (flexibility and strengthening exercise)	20 min	First 2 h of the HD session	2 × per week for 2 months (16 sessions)	Fatigue scores decreased significantly from the start until 2 months after the intervention in the experimental group.
5.	Wu et al. (2014)[29]	Taiwan	Quasi-experimental	172 respondents	Hemodialysis Patient Fatigue Scale	After intradialytic exercise	Strengthening exercise	10 min	During HD session	3 × per week for 8 weeks (24 sessions)	Exercise conducted 3 times/week for 2 months significantly decreased fatigue in patients receiving HD.
6.	Soliman, (2015)[30]	Egypt	RCT	30 respondents	Iowa Fatigue Scale	After intradialytic exercise	Flexibility exercise	15 min	First 2 h of the HD session	3 × per week for 4 weeks or 1 month (12 sessions)	After 8 weeks of intradialytic range of motion exercises, a significant decrease was observed in the fatigue level, phosphate serum, and potassium, calcium, urea, creatinine, whereas a slight increase was observed in hemoglobin level.
7.	Amini et al. (2016)[31]	Iran	RCT	67 respondents	PFS (Piper Fatigue Scale)	After dialysis session	Aerobic exercise	30–40 min	First hour of the HD session	2 × per week for 8 weeks (16 sessions)	Aerobic intradialytic exercise affected fatigue in patients with chronic kidney failure undergoing hemodialysis.
8.	Makiyah et al. (2017)[32]	Indonesia	RCT	32 respondents	PFS (Piper Fatigue Scale)	After intradialytic exercise	Flexibility exercise	20 min	During HD session	2 × per week for 4 weeks (8 sessions)	Exercise affected fatigue in patients with chronic kidney failure undergoing hemodialysis.
9.	Sakitri et al. (2018)[33]	Indonesia	Quasi-experimental	32 respondents	PFS (Piper Fatigue Scale)	After intradialytic exercise	Strengthening exercise	20 min	First hour of the HD session	3 × per week for 16 weeks (48 sessions)	Intradialytic exercise was effective in decreasing fatigue in patients receiving hemodialysis.
10.	Ibrahim et al. (2018)[34]	Egypt	Quasi-experimental	100 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After intradialytic exercise	Aerobic exercise	40 min	First 2 h of the HD session	3 × per week for 4 weeks (12 sessions)	Intradialytic exercise affected fatigue, hemoglobin levels, and

(*continued on next page*)

Table 1 (*continued*)

No	Researcher (Year)	Country	Research Design	Sample Size	Research Instrument	Fatigue Measurement	Type of Intradialytic Exercise	Duration of Intradialytic Exercise	Implementation Time of Intradialytic Exercise	Frequency of Intradialytic Exercise	Outcome
											blood pressure in patients receiving hemodialysis.
11.	Merline et al. (2018)[35]	India	Quasi-experimental	34 respondents	Iowa Fatigue Scale	After intradialytic exercise	Combination exercise (flexibility and strengthening exercise	15 min	First hour of the HD session	2 × per week for 4 weeks	A statistically significant difference in the level of fatigue was observed between pre- and post-intradialytic exercise.
12.	Neethu et al. (2018)[36]	India	Quasi-experimental	30 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After intradialytic exercise	Strengthening exercise	30 min	First 2 h of the HD session	2 × per week for 2 weeks (4 sessions)	A significant difference was observed in the level of fatigue between the experimental and control groups after intradialytic exercise ($t = 6.88$, $p = 0.001$). A significant difference in the level of fatigue was observed in the experimental group before and after intradialytic exercise ($t = 12.58$, $p = 0.001$).
13.	Sankari, (2018)[37]	India	RCT	60 respondents	FSS (Fatigue Severity scale)	After dialysis session	Aerobic exercise	20 min	During HD session	14 sessions	Aerobic exercise had a significant effect in decreasing fatigue levels and increasing ADL in patients undergoing hemodialysis.
14.	Kulkarni et al. (2018)[38]	India	Quasi-experimental	150 respondents	FSS (Fatigue Severity scale)	After intradialytic exercise	Flexibility exercise	15 min	First 2 h of the HD session	3 sessions	The average decrease in fatigue score in the experimental group was significantly greater than that in the control group.
15.	Amilia et al. (2019)[39]	Indonesia	Quasi-experimental	32 respondents	Chalder Fatigue Scale	After dialysis session	Strengthening exercise	30 min	During HD session	2 × per week for 4 weeks (8 sessions)	Intradialytic exercise decreased fatigue levels in patients with ESRD undergoing hemodialysis.
16.	Elhameed et al. (2019)[40]	Egypt	RCT	62 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After intradialytic exercise	Flexibility exercise	10−15 min	30 min after HD start within the first 2 h of the HD session	3 × per week for 36 weeks or 9 months (78 sessions)	Implementation of the exercise program effectively decreased fatigue and depression in patients undergoing hemodialysis in the study group.
17.	Kim et al. (2019)[41]	Korea	RCT	85 respondents	PFS (Piper Fatigue Scale)	After dialysis session	Flexibility exercise	25 min	2 h after HD start	3 × per week for 8 weeks (24 sessions)	Exercise intervention significantly decreased fatigue in patients receiving hemodialysis and significantly increased positive psychological mode.
18.	Wilkinson et al. (2019)[42]	England	RCT	36 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After dialysis session	Combination (aerobic and resistance exercise)	30 min	During HD session	3 × per week for 12 weeks (36 sessions)	Exercise decreased the number of reported fatigue symptoms by 17% and had a beneficial effect on fatigue.

19.	Albadry et al. (2020)[43]	Egypt	Quasi-experimental	60 respondents	FSS (Fatigue Severity scale)	After dialysis session	Combination exercise (aerobic and strengthening exercise)	20 min	1 h after HD start	5 sessions	A significant difference was observed in the total score of the fatigue severity scale before and after the implementation of the intradialytic exercise.
20.	Chandralekha et al. (2020)[44]	India	Quasi-experimental	60 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After intradialytic exercise	Flexibility exercise	30 min	2 h after HD start	3 × per week for 3 weeks (9 sessions)	Most clients undergoing hemodialysis experienced moderate to severe fatigue, and intradialytic stretching exercise decreased fatigue.
21.	Djamaludin et al. (2020)[45]	Indonesia	Quasi-experimental	17 respondents	FSS (Fatigue Severity scale)	After intradialytic exercise	Strengthening exercise	30 min	Second hour of the HD session	8 sessions	A significant decrease in fatigue was observed in patients receiving hemodialysis who performed intradialytic exercise.
22.	Mol et al. (2020)[46]	India	Quasi-experimental	60 respondents	FACIT (Functional Assessment of Chronic Illness Therapy)	After intradialytic exercise	Flexibility exercise	40 min	First hour of the HD session	1 × per week for 4 weeks (4 sessions)	Ergometric intradialytic exercise once per week for 4 weeks effectively decreased fatigue in patients with CKD undergoing hemodialysis.
23.	Salehi et al. (2020)[47]	Iran	RCT	54 respondents	MFI (Multidimensional Fatigue Inventory Scale)	After dialysis session	Aerobic exercise	20 min	During HD session	2 × per week for 4 weeks or 1 month (8 sessions)	Intradialytic exercise on a mini-bicycle twice per week for 1 month did not have a significant effect in decreasing fatigue in patients undergoing hemodialysis.
24.	Grigoriou et al. (2021)[48]	England	Quasi-experimental	20 respondents	FSS (Fatigue Severity scale)	1 h after the dialysis session	Combination exercise (aerobic exercise and strengthening exercise)	60−80 min	During HD session	3 × per week for 9 weeks	Patients reported feeling better during the post-dialysis hours after 9 months of intradialytic exercise. In addition, exercise increased scores of cognitive function ($p = 0.037$), vitality ($p = 0.05$), depression ($p = 0.000$), and fatigue ($p = 0.039$).
25.	Muliani et al. (2021)[23]	Indonesia	Quasi-experimental	20 respondents	FACIT (Functional Assessment of Chronic Illness Therapy)	After dialysis session	Flexibility exercise	15 min	During HD session	2 × per week for 8 weeks (16 sessions)	The pre-test average value was 25.70, and the post-test was 30.75, thus indicating an increase in fatigue scores, with $p < 0.001$ indicating an effect of intradialytic exercise.

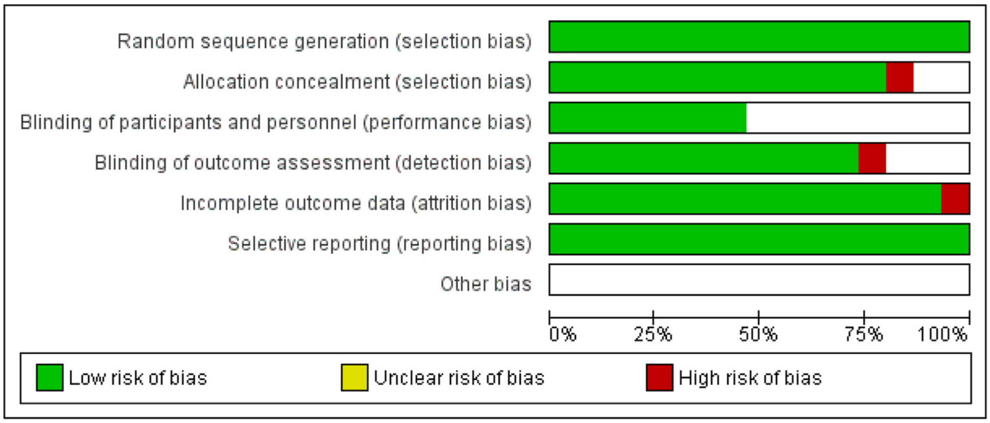

Figure 2: Bias risk analysis results.

intradialytic exercise according to the type of exercise indicated that only three of the four exercises effectively decreased fatigue symptoms: aerobic exercise (SMD −1.46, 95% CI −2.68 to −0.25, P = 0 0.02), strengthening exercise (SMD −0.43, 95% CI −0.71 to −0.15, P = 0.002), and flexibility exercise (SMD −0.90, 95% CI −1.41 to −0.38, P < 0.00001). In contrast, combination exercise did not significantly decrease fatigue. The results of the meta-analysis also demonstrated that aerobic exercise had the largest effect size.

Effectiveness of intradialytic exercise duration

The duration of exercise was divided into two categories: <20 min and >20 min. A total of 13 studies used an exercise duration >20 min. In the heterogeneity test, the two durations had high heterogeneity (<20 min: I^2 = 88% and >20 min I^2 = 90%); therefore, a random effect model was used. The results of the meta-analysis showed that an intradialytic exercise duration >20 min had the largest effect size (SMD −0.65, 95% CI −1.02 to −0.28, P = 0.0006), but a duration <20 min was also considered effective in decreasing symptoms of fatigue (SMD −0.65, 95% CI −1.02 to −0.28, P = 0.0006).

Effectiveness of intradialytic exercise implementation time

The timing of the intradialytic exercise was identified, and three categories of implementation time were identified. Of the 25 studies, 14 applied exercise in the first 2 h of HD. The

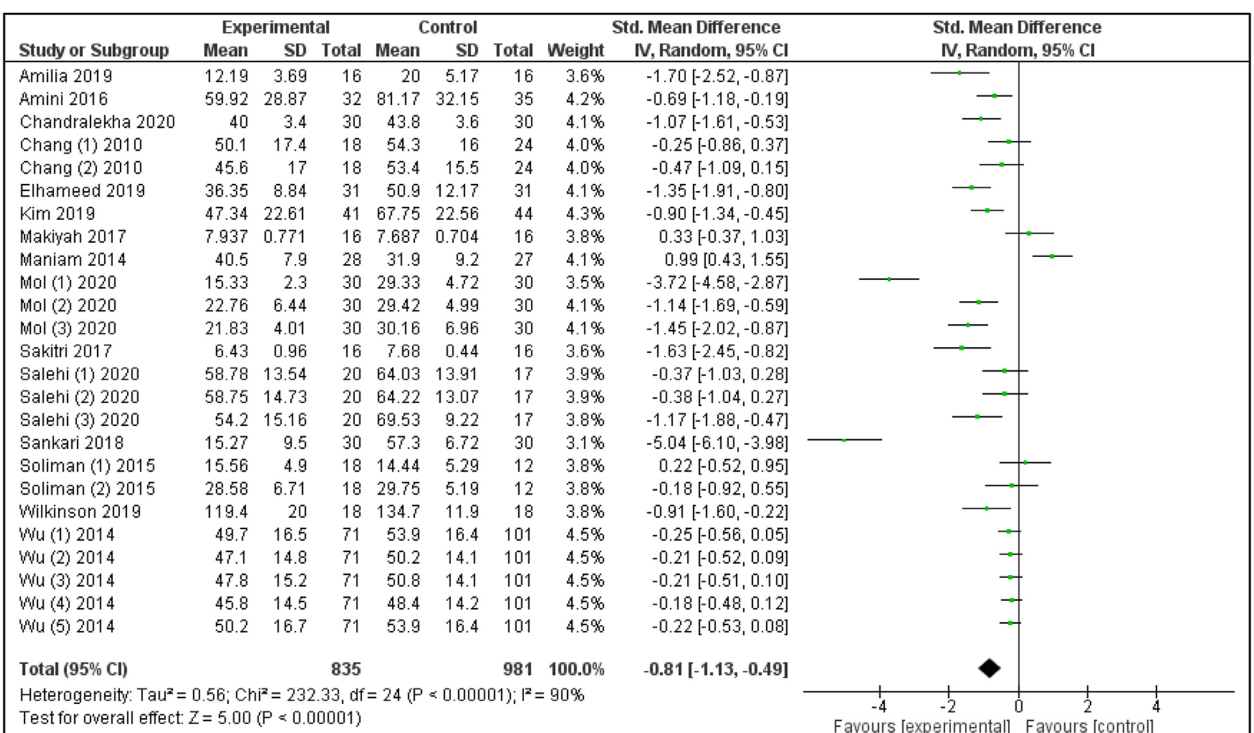

Figure 3: Forest plot of the effects of intradialytic exercise on fatigue.

Table 2: Subcategories of intradialytic exercise.

Category	Classification	Sign	Effect Size	95% CI		I^2 (%)
				Lower	Upper	
Type	Aerobic exercise	P < 0.00001	−1.46	−2.68	−0.25	94%
	Flexibility exercise	P < 0.00001	−0.90	−1.41	−0.38	87%
	Strengthening exercise	P = 0.0008	−0.43	−0.71	−0.15	74%
	Combination exercise	P = 0.96	0.05	−1.81	1.91	94%
Duration	≤20 min	P = 0.0006	−0.65	−1.02	−0.28	88%
	>20 min	P = 0.0005	−1.00	−1.56	−0.43	90%
Implementation Time	First 2 h	P < 0.00001	−1.27	−1.79	−0.74	85%
	>2 h after	P = 0.97	0.04	−1.81	1.89	96%
	Unspecified (during hemodialysis sessions)	P = 0.0008	−0.61	−0.97	−0.25	87%
Frequency	≤12 sessions	P = 0.005	−1.20	−2.04	−0.36	91%
	13−24 sessions	P = 0.0005	−1.10	−1.72	−0.49	89%
	>24 sessions	P = 0.08	−0.25	−0.53	0.03	76%

heterogeneity test results indicated that the exercise times of the first 2 h of HD ($I^2 = 85\%$), >2 h of HD ($I^2 = 96\%$), and unspecified/during HD sessions ($I^2 = 87\%$) had high heterogeneity values. Therefore, a random effects model was used to determine the effect size. The forest plot indicated that only two categories of implementation time significantly decreased fatigue: the first 2 h (SMD −1.27, 95% CI −1.79 to −0.74, P < 0.00001) and unspecified/during the HD session (SMD −0.61, 95% CI −0.97 to −0.25, P < 0.00001). The largest effect size was observed for the first 2 h of the HD session. Meanwhile, an implementation time of >2 h was considered insignificant in decreasing fatigue (SMD 0.04, 95% CI −1.81 to 1.89, P = 0.97).

Effectiveness of intradialytic exercise frequency

The frequency of intradialytic exercise most often applied was <12 sessions (15 of 25 studies). The frequency of exercise was divided into three categories: <12 sessions ($I^2 = 91\%$), 13−24 sessions ($I^2 = 89\%$), and 24 sessions ($I^2 = 76\%$), all of which had high heterogeneity values. The random effect model was used, and a frequency of <12 sessions was considered significant and had the largest effect size (SMD −1.20, 95% CI −2.04 to −0.36, P = 0.005). An exercise frequency of 13−24 sessions was also significant in decreasing fatigue (SMD −1.10, 95% CI −1.72 to −0.49, P < 0.0005), whereas a frequency of >24 sessions was not significant in decreasing fatigue (SMD −0.25, 95% CI −0.53 to −0.03, P = 0.08).

Discussion

The summary of all intradialytic exercise subcategories is presented in Table 2.

The results of this study provide an overview of the specific forms of intradialytic exercises applied, including the type, duration, implementation time, and frequency of exercise. These findings may enable health workers to implement interventions to ameliorate symptoms of fatigue in patients with chronic kidney failure undergoing HD.

The number of studies included in the analysis indicated that research on intradialytic exercise has continued to grow during the past decade, and various benefits of intradialytic exercise have been investigated. This current study focused on assessing the effectiveness of intradialytic exercise on fatigue symptoms.

The meta-analysis of the 15 studies demonstrated that intradialytic exercise was effective in significantly decreasing fatigue symptoms in patients receiving HD, by as much as 81%, in the group that underwent intradialytic exercise compared with the control group. These results are in line with those from a systematic literature review and meta-analysis suggesting that exercise decreases fatigue in adults undergoing HD.[18] In addition, our findings are supported by a meta-analysis suggesting that intradialytic exercise affects fatigue in patients receiving HD (SMD = −0.85, Z = 4.77, P < 0.00001).[19]

Fatigue conditions occur because of a decrease in the body's energy reserves, wherein a disruption of electrical signals from the brain to the muscles decreases energy, owing to ATP deficiency.[23] In addition, the absence of physical activity (sedentary habits) and presence of emotional stress can cause fatigue.[24] In general, interventions for fatigue can optimize the formation and use of energy, and tailor physical exercise to each patient's condition. Physical exercise trains the body in using energy, increases blood flow to muscles, and increases the surface area of capillaries, thereby increasing the transfer of urea and toxins from tissues to blood vessels.[29,31]

Exercise helps the body efficiently deliver oxygen to the muscles, improves overall circulation, decreases blood pressure, and releases metabolic waste products that inhibit energy forms such as lactic acid.[25,38]

The advantage of intradialytic exercise in patients receiving HD, compared with exercise outside the dialytic phase, is that patients with chronic kidney failure regain kidney function that would not be obtained in the absence of HD. The risk of metabolic product accumulation due to physical exercise can be minimized by the HD process, as supported by studies showing that intradialytic exercise increases Kt/V-urea and creatinine clearance during dialysis.[50] In addition, physical exercise can improve muscle health.

Regarding the type of exercise, duration, implementation time, and frequency of intradialytic exercise, our analysis indicated that flexibility exercise was most often used. This finding is probably because flexibility exercise is a simple, safe and effective form of physical exercise in clinical practice modalities for patients undergoing HD, and the exercise program also has low intensity, which is considered safe, is easy to follow by the patients, and does not require special tools.

Distinct significance was found in the results of the meta-analysis of the four exercise types. Aerobic, flexibility, and strengthening exercises significantly decreased fatigue in the experimental group, whereas combination exercise was not statistically significant in decreasing fatigue, although it had an effect size of 5%.

Intradialytic exercises were classified into three types: flexibility exercises, which are light muscle stretching exercises; aerobic exercises, in the form of structured rhythmic movements; and strengthening exercises, which are muscle-strength exercises that can be performed with weights, elastic bands, or the patient's body weight.[24] However, because several studies combined the types of exercise, a new category, combination exercise, was added. This category combined several categories of exercises in series; for example, in combining flexibility with aerobics, flexibility might have been used as a warm-up step, whereas aerobic exercise was the main exercise.

Studies that used combination exercise included those by Maniam, which combined flexibility and strengthening exercises, and Wilkinson et al., which combined flexibility and aerobic exercises.[26,42] Maniam has reported that fatigue symptoms markedly decreased in the control group, possibly because of the characteristics of the respondents in the intervention group, who had a lower GFR and were older than the control group on average. Consequently, the patient's body metabolism was slower, thus affecting the optimization of energy formation.

On the basis of the effect size, among the three types of significant exercises, aerobic exercise had the largest effect size in decreasing fatigue, at 146%. Aerobic exercise has been shown to increase muscle mitochondrial oxidative metabolism and muscle mitochondrial volume, thus maintaining skeletal muscle functionality and integrity.[50] In addition, according to Lesmana et al., at the same intensity and duration, aerobic exercise increases the heart rate more quickly than flexibility or strengthening exercises.[49] An increased heart rate accelerates blood flow to cells and tissues, thereby providing a sufficient supply for cells to increase the intensification of energy production processes.[51] Aerobic exercise performed during HD has been reported to be beneficial as a non-pharmacological intervention that improves cardiorespiratory fitness, maximum oxygen consumption, lower leg muscle strength, nutritional parameters, quality of life, and the functional capacity of the body.[52] In addition, aerobic exercise has been reported to prevent cardiovascular disease, and treat anemia and insulin resistance in patients with chronic kidney failure.[31,32,47] Moreover, aerobic exercise has been associated with a decrease in symptoms of anxiety and depression in patients receiving HD.[26] Therefore, aerobic exercise performs better than other types of exercise in decreasing fatigue symptoms.

An exercise duration >20 min was most frequently used in previous studies. The results of the meta-analysis indicated that an exercise duration >20 min was more effective than a duration of <20 min.

The duration of exercise is closely associated with the intensity of the exercise performed and the minimum exercise threshold. According to the Centers for Disease Control and Prevention, low to moderate-intensity exercise can have an effect if the heart rate is 50–70% of the maximum heart rate.[41]

Intradialytic exercise generally uses low to moderate-intensity exercise. Therefore, a longer exercise duration can increase the potential for achieving the minimum exercise threshold. In addition, type 1 muscle fibers are used during low to moderate-intensity exercise with long duration and have many mitochondria, which are sites of ATP formation. Consequently, more ATP is produced by the body, thus facilitating energy formation in patients receiving HD who experience a decrease in ATP. Lemoine et al.[53] have reported an increase in phosphate and a significant decrease in ATP during dialysis sessions at the resting phase. In addition, Kestenbaum et al. have suggested that a decrease in intracellular ATP leads to clinical intolerance during dialysis, such as asthenia and muscle weakness, which manifests as symptoms of fatigue.[54] When an exercise reaches the threshold, optimal benefits are obtained by the body, which is associated with the mechanism of exercise that can help improve oxidative phosphorylation of muscles and mitochondrial structure, and increase muscle mass and faster myosin heavy chain isoforms.[55]

Implementation time is also an indicator of effectiveness. The implementation time of intradialytic exercise was divided into three categories: the first 2 h of HD, >2 h of HD, and unspecified (during HD sessions). Previous studies have often applied an implementation time of the first 2 h of HD sessions.

The results of the meta-analysis showed that among the three sub-groups of intradialytic exercise implementation times, the categories that statistically significantly decreased fatigue were the first 2 h and unspecified time. However, the sub-group of >2 h did not show a statistically significant decrease in fatigue. In addition, on the basis of the effect size, intradialytic exercise performed in the first 2 h of HD had the largest effect size in decreasing fatigue, at 127%.

HD is generally administered in 4–5 h. Each phase in the HD process can cause hemodynamic changes in the patient's body. One change that can affect fatigue is intradialytic hypotension, which decreases cardiac output and can lead to symptoms of fatigue.[56] Several studies observing fluctuations in blood pressure during HD sessions have reported a decrease in blood pressure in the first hour to the second hour of HD, then an increase after the second hour until the end of HD.[57–59] This finding indicates that the potential for intradialytic hypotension spans the first hour to the second hour of HD.

Further observations for 6 months, reported by Rhee et al., have indicated a significant decrease in hypotension incidence in patients receiving HD who underwent intradialytic exercise in the first hour of HD.[59] This finding is supported by the hypothesis that exercise increases baroreceptor sensitivity, thus resulting in more effective blood pressure regulation by nerves and stabilizing blood pressure.[49]

The frequency of intradialytic exercise was also examined. The primary frequency of intradialytic exercise used was <12 sessions. However, on the basis of the significance and effect size from the meta-analysis, frequencies of <12 sessions and 13–24 sessions had significant results, whereas the >24 session subgroup showed insignificant results despite having an effect size of 25%. Subsequently, the effect size for the subgroup with exercise frequency <12 sessions was greater than that with an exercise frequency of 13–24 sessions (120% and 110%, respectively).

In summary the subgroup analysis results indicated that the recommended characteristics of intradialytic exercise were aerobic exercise >20 min in duration, with an execution time <2 h and frequency of <12 sessions. This is associated with the characteristics of aerobic exercise, which can increase the heart rate, accelerate blood flow to cells and tissues, and provide sufficient supply of blood to cells and tissues to increase the intensification of the energy production process. An exercise duration >20 min is associated with the minimum threshold of exercise and type 1 muscle fibers, which have many mitochondria and consequently increase ATP production by the body. An implementation time <2 h affects the occurrence of intradialytic hypotension, which can manifest as fatigue. The implementation time can increase the sensitivity of baroreceptors, which can help stabilize blood pressure. As well as a limited frequency of <12 sessions where the frequency of exercise that is performed continuously without any increase in duration or intensity will have results or changes that are not significant.

The exercise frequency is closely associated with the duration and intensity of exercise. Different combinations of frequency, duration, and intensity have different results when applied. In studies using an exercise frequency of <12 sessions, the average low-intensity exercise duration was 15–40 min.

Every physical exercise causes the body's organs to respond to the dose or training load and consequently maintain a stable body balance (i.e., homeostasis).[51] Exercise is a physical stressor that can affect homeostasis; therefore, the application of physical exercise requires measuring the proper dose, including the frequency of exercise. Continuous exercise without any increase in duration or intensity may have insignificant results or changes, as compared with exercise with progressive intensity and duration.[49] Therefore, a frequency of >24 sessions did not significantly ameliorate fatigue symptoms, although it had an effect size of 25%.

The results of the meta-analysis indicated that a frequency of <12 sessions had the largest effect size, possibly because in the initial phase, when the body had not been trained, the body tried to meet energy needs to accelerate energy formation; therefore, ATP formation and the body's metabolism were faster. In addition, the effect of exercise on energy formation was influenced by duration and intensity. A higher exercise frequency does not necessarily have a significant effect on the energy formation in the body, because although the frequency of intradialytic exercise continues for a long time, in a certain period it is necessary to increase the intensity or duration of the exercise.[51]

Different combinations of type, duration, implementation time, and frequency of exercise may have different results. To date, no studies have compared these various exercise combinations. Further research should perform such comparisons to obtain more applicable results.

Conclusion

This research systematically reviewed 25 studies and conducted a meta-analysis of 15 studies on the effectiveness of intradialytic exercise in treating fatigue. The results indicated the characteristics of the application of intradialytic exercise recommended as interventions for ameliorating the fatigue symptoms experienced by patients receiving HD. Aerobic exercise with a duration of <20 min, implemented in the first 2 h of HD, with a frequency of <12 sessions were the recommended characteristics for intradialytic exercise, according to the results of the meta-analysis, on the basis of effect sizes. However, this research has several limitations. First, subgroup analysis of fatigue characteristics and respondent characteristics was not conducted but would have provided more specific information on the effectiveness of intradialytic exercise according to the characteristics of the population. Moreover, the literature search was not performed with assistance from librarians to provide access to potentially inaccessible databases.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This manuscript was approved by the Institutional Review Board at Ahmad Yani University with IRB 09/KEPK/FITKES-UNJANI/II/2022, dated February 21, 2022.

Authors contributions

AZW: Phenomenon identification, research question formulation, article search, data extraction, analysis and interpretation, and report compilation. HR: Phenomenon development, assistance in article search strategies, article quality assessment, and research result discussion. Murtiningsih: Writing systematics correction, article quality evaluation, research result discussion. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgment

We thank H. Iwan Permana for fully supporting our activities, and Mr. Hikmawanto and Mr. Gunawan Irianto, who encouraged the completion of this research.

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How to cite this article: Wahida AZ, Rumahorbo H, Murtiningsih. The effectiveness of intradialytic exercise in ameliorating fatigue symptoms in patients with chronic kidney failure undergoing hemodialysis: A systematic literature review and meta-analysis. J Taibah Univ Med Sc 2023;18(3):512−525.