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EFFECTIVENESS OF INTRADIALYTIC EXERCISES ON HEMODIALYSIS OUTCOMES: A META-ANALYSIS

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Abstract

Introduction:
Chronic kidney disease (CKD) has emerged as a prominent global health concern with prevalence rate ranging from 9.1% to 13.4% worldwide and 12.5% to 31.5% in Pakistan. Exercise in Hemodialysis (HD) has made significant progress in the last couple of years including resistance exercises (RE), aerobic exercises (AE) and combination exercise (CE) but still numerous questions are still unanswered.

Objective:
To determine the effectiveness of Intradialytic exercises (IDE) on HD outcomes.

Methods:
This meta-analysis was done as per PRISMA and PEDro guidelines. Data based searching was done after extraction of literature through PubMed, Embrace, and Cochrane. The methodological quality of the eligible studies was assessed. Outcome measures include Dialysis adequacy (KT/V) with a reliability of 0.98, Body mass index (BMI) with a reliability of 0.95 and HD duration

Result:
The meta-analysis of six Randomized controlled trials (RCTs) involving 293 participants showed that IDE have a little impact on BMI with SMD of 0.0691, 95% Confidence Interval [-0.1602; 0.2984], and a p-value of 0.59 and HD duration with SMD of -0.1673, 95% Confidence Interval [-0.3968; 0.0622] and a p-value of 0.1532. Meanwhile, for KT/V, IDE show a statistically significant positive effect on KT/V with SMD of 0.6458, 95% confidence interval [- 0.0264; 1.3179] with P Value 0.05, suggesting improved HD outcomes.

Conclusion:
Intradialytic exercise appears to improve KT/V; however, its effects on other clinical outcomes, including BMI and HD, remain inconclusive. These findings are limited by heterogeneity and small sample sizes, highlighting the need for larger, high-quality randomized controlled trials

CHAPTER 1

1 INTRODUCTION

1.1 Background

Every day in hospitals, when the loud sound of ambulance sirens, prompt healthcare workers to question: Is this another arrival of a chronic kidney patient, either through direct admission or due to complications associated with kidney issues, further complicating their lives? From there, the journey continues to the intensive care unit (ICU), where chronic kidney patients encounter daily challenges involving morbidity, mortality, and the severity of their condition (1). The interventions and support provided in the intensive care setting significantly influences the lives of not only the patient but family too especially in terms of expenses incurred (2).

With documented prevalence rates, CKD has become a major global health concern, ranging from 9.1% to 13.4% worldwide (3). In Pakistan, the prevalence is significantly high, ranging from 12.5% to 31.5% (4), which underwent dialysis procedure and dies within three months of dialysis initiation (5) with reported mortality of dialysis patients around 45% (6). It is estimated that CKD will rise by 2040, to the fifth leading cause of mortality globally, making it one of the largest increment in any chief source of mortality (7). These statistics underscore the need for enhanced understanding, management, and prevention strategies for kidney-related complications, both locally and on a global scale (7).

Alterations to the kidneys composition and functionality as a result of multiple factors characterize CKD (8). CKD is an illness that advances over time into end-stage renal disease (ESRD) which significantly affects the Quality of life (QOL) and also increase the mortality rates (9).

Renal replacement therapy (RRT) includes dialysis and kidney transplantation that is usually necessary for the survival of ESRD patients, which is caused by CKD (10). The three primary form of dialysis are mentioned below:

- HD
- Peritoneal dialysis (PD)
- Continuous renal replacement therapy (CRRT)

Dialysis causes a number of psychological and physical stressors, such as nutrient loss, abnormal protein catabolism, and an inflammatory response that increases the possibility of sarcopenia in patients undergoing HD, resulting in physical decline, decreased muscle mass and strength (11).An increased possibility of death is associated with reduced physical activity, in accord with both objective measurements and self-reported evaluations (12). Hence, the current researches strongly provide evidence regarding improvement in patient outcomes by engaging dialysis patient in physical activity or gradually increasing their level of physical activity (13). Still in dialysis clinics the execution of exercise programs is not up to the mark and patient compliance is low.

It is practical to incorporate exercise during dialysis session into routine clinical practice (14), but maintaining it calls for ongoing help from the medical staff and physiotherapists (PT). PT evaluate the physical functioning and restrictions in order to design an exercise regimen for individual patients as well as inspire and instruct the staff and patients with the goal of bringing into being an "exercise culture" in Denmark. (15).

Exercise provides benefit to the ones by enhancing muscle tissue adaptation, promoting myogenesis, regeneration of skeletal muscle and myostatin mRNA activity regulation (16).Muscular strength, solute elimination, peak oxygen consumption (VO2 peak), intradialytic protein synthesis, nutritional status, QOL and KT/V can all be enhanced by IDE (17). Greatest effects of exercise were noted after 6 months in intradialytic patients who had done high intensity, supervised training and cycling exercise (17). According to Kidney Disease Improving Global Outcome (KDIGO) guideline, exercise regime for patients with CKD includes exercise performance 5 times a week for 30 mins per day keeping in mind the toleration level and cardiovascular health of these patients (18). The American College of Sports Medicine (ACSM) guidelines recommends CKD patients to initially start the exercise with low intensity such as 10-15 mins with intensity gradually increasing (19).

Exercise can generally be categorized into three types that fall under this classification: (1) RE better known as strength training, typically prescribed for increasing muscle size and strength; (2) AE which is rhythmic and repetitive in nature, uses large group of muscles and is commonly recommended to improve endurance; (3) CE, that includes both the RE and AE. While RE is thought to be better than other types of exercise for increasing power, muscular mass and strength, it is usually clear that AE is the best option for increasing cardiovascular fitness. Consequently, integrating both AE and RE is expected to have added beneficial effects (21).

Various researches recommend incorporating HD patients into resistance training (20-25). One research specifically recommends focusing on resistance training for the arm with the arteriovenous fistula (AVF) (20). Exercises using dumbbells, resistance bands, weight machines and free weights were considered as the most frequently suggested types (20-24, 26). The recommendations of RE were categorized based on the individual's level of functioning (24). However, recommendations in regard to the intensity, duration and time may vary for RE. The 10-15 reps of one set inside the limits of 60-75% of one repetition maximum (RM) was most commonly proclaimed repetition count (21-23, 25). Few publications suggest a lesser number of repetitions (5-10 repetitions) (24, 26). For low-functioning individuals, 1-2 sets of 6-10 repetitions are recommended, while high-functioning individuals are advised to do 2-3 sets of 12-15 repetitions (24). However, intensity levels are not specified in these recommendations (24). Home-based RE are also recommended, with an intensity as advised by the healthcare provider for 3 times/week with 5-10 reps (26).

In contrast to resistance training, AE for dialysis patients is also recommended by various researches (20, 22, 23, 25). Common recommended examples of AE include walking, running, swimming, and cycling. Individuals should be engaged in AE for 20–60 minutes per day (23, 26) to 180 minutes weekly, or 15 to 45 minutes for each HD session, according to the guidelines (64). The level of intensity recommended for AE varied significantly across researches. Some studies suggest moderate intensity (i.e. 40–60% of maximum oxygen consumption (VO2 max) (19, 23) or 10-12 (21) / 11-13 (19, 23) / 12-13 (19) / 11-16 (25, 26) on the Borg scale. Those involved in AE have reported increased exercise capacity measured by VO2 max (12).Generally, recommended AE was three to five times weekly, although the suggestions given may differ. For instance, one research incorporates wide range of guidelines for frequency that ranged from daily to as frequently as possible (26) while another gave more specific recommendations, providing evidence of doing exercise one to two times weekly (25); two times weekly on days when dialysis is not performed; thrice a week when dialysis is performed (21, 22); three to five times weekly on most days (23).

On contrary, there is limited detail or recommendations regarding flexibility exercises in the researches. In the studies that do discuss flexibility, the recommendations vary from trunk twists, standing elbow-to-knee, lateral bends activities for patients who have high functionality to stretching of arm for patients in wheelchair (21).The ACSM guidelines provide extensive recommendations for flexibility (19) which provide evidence of static stretches of each joint for 60 seconds and contractions of 3-6 seconds followed by ten to thirty seconds of maximum voluntary contraction at 20-75%. Duration of 10 mins is considered suitable for flexibility exercises (19, 25).

For HD patients engaging in IDE, certain precautions are recommended. Some studies suggest exercising within the first 2 hours of dialysis (19, 23), as this may lower the risk of hypotension (68). However, conflicting advice exists, with another research proposing that late IDE could actually help alleviate hypotension in specific cases. The ACSM advises against exercising immediately after HD treatment due to the heightened risk of hypotension (19).

Numerous conditions have been identified as contraindications (CI) to exercise, including individuals with an unstable cardiovascular status, uncontrolled arrhythmias and hypertension (HTN) (19, 22, 25). However, there appears to be a lack of clear guidance about the appropriateness of exercise for those with comorbidities. This include individuals receiving dialysis who have pulmonary embolism (PE)/infarction, unstable angina, severe pulmonary hypertension, deep vein thrombosis (DVT), heart failure (HF), severe and symptomatic aortic stenosis, aortic/aneurysmal dissection, or severe retinopathy. Acute inflammation or infection, such as pericarditis, myocarditis, and endocarditis, were considered a hindrance to exercise in two researches (19, 22). A certain research recommended that exercise is contraindicated in the presence of fever (26). So, it is crucial to have a greater understanding about the efficacy of various IDE modalities to determine the effectual and suitable exercise regimen individually for patients undergoing dialysis (27).

Exercise in HD has made significant progress in the last couple of years, but still numerous questions are still unanswered. Regarding effectiveness, while some recent RCTs have yielded disappointing results (18, 28), others have uncovered previously unacknowledged cardiovascular advantages (29-31) and enhancement in outcomes reported by the patient including Restless leg syndrome (RLS), cramping and tiredness (32). Despite low implementation rates globally, various countries are incorporating exercise regimen in dialysis units on a wide scale (33), suggesting that such programs are practical and probably cost-effective (34). However, numerous policy measures are required to improve implementation (35).The durability of structured exercise programs for HD patients and approach to PT are both ongoing challenges for dialysis units. Discrepancies and limited guidelines make it difficult for dialysis physicians to encourage patient's physical activity (36).

The evidence provided by Vogiatzaki et al., (2022) (37) demonstrated that there was a considerable improvement in kt/v of exercise group doing IDE in comparison to control group. Yabe et al., (2021)(16) in their study found that there is an improvement in overall physical function in the exercise group in comparison to the control group. In contrast, Lucas et al., (2018) (38) revealed that intradialytic aerobic training (IAT) showed significant reduction in BMI. Study by Hema et al., (2022)(39) stated that average kt/v showed variation as it increase from 1.42 to 1.61 by eight week while kt/v score of control group remained constant at the end of week 8. On contrary, Sunki etal., (2022)(40) demonstrate that there was notable increment in the exercise group's kt/v. Study done by Hoda et al., (2022)(41) showed that there was a major improvement in the kt/v of exercise group by 20.18%.

Multiple studies have been conducted on IDEs. Yet their words are questions that are IDE safe to perform in HD patients, providing better outcome. So, in this meta-analysis, one aims to determine the effectiveness of IDE on HD outcomes.

1.2 Significance of the problem

This study aims to establish clinical practice guidelines regarding the implementation of IDE in HD patients and well define the PT's role in nephrology unit. This study also shows that how IDE plays a key role in reducing mortality rate, improving QOL and an early return to function and recovery. This meta-analysis will provide evidence of accurate and precise data and also recommends that IDE are effective in HD patients.

1.3 Objective of the study

- To determine the effectiveness of IDE on HD outcomes.

1.4 Hypothesis

Null Hypothesis (H_0)

H_0: IDE has no statistically significant difference on HD outcomes.

Alternate Hypothesis (H_1)

H_1: IDE has a statistically significant impact on HD outcomes.

1.5 Operational Definitions

1. IDE:

Exercise training carried out during HD sessions with the goal of improving the patient's strength and endurance and, consequently, addressing a variety of physiological and psychological characteristics is known as IDE (36).

2. HD outcomes:

HD outcomes are the quantifiable effects or results of HD therapy for individuals suffering from renal failure. These outcomes encompass various aspects including KT/V, BMI and HD duration (42).

3. Kt/v:

Kt/v is an assessment parameter to check the efficacy of HD session. It observes the effective elimination of clearance K (specific solute) in a patient (with a fixed volume of distribution V for the solute observed) (43). It is being used as an outcome measure in this meta-analysis with a reliability of 0.98 (44).

4. BMI:

BMI classifies people into groups such as overweight and obese, is a measure of a person's height or weight (45). With a reliability of 0.95, it is used as an outcome measure in this meta-analysis. (46).

5. HD duration:

It is the time taken to remove waste and other fluids from blood. The duration can range from 3 to 8 hours per session and this process usually occurs thrice a week (47).

CHAPTER 2

2 Review of Literature

1. Evidence provided by Vogiatzaki et al., (2022) is a RCT in which thirty-four ESRD patients were shortlisted to undergo maintenance HD for a minimum of six months, three days a week for four hours every session. Kt/V and Urea reduction ratio (URR) is considerably increased due to physical performance which is measured by six minute walk test (6MWT) as a result of exercise training. Main limitation of the study includes the use of rate of perceived exertion (RPE) scale, instead of the measurement of oxygen uptake relative to individual VO2 max as a more suitable objective measure and small number of participants. More studies on this topic with large sample size is recommended to evaluate the efficacy of IDE in HD patients (37).
2. Yabe et al., (2021) study consists of 101 individuals in total that were enrolled in this randomized controlled parallel study. Short physical performance battery (SPPB) score was used as a measure for outcome assessment. Certain restraints of the study include the use of single-center design; the results might not be entirely generalizable. Secondly, there might have been execution and observer biases in this study because patients and evaluators could not be blinded. Lastly, the recommendations include that future researches should be done by including QOL as major assessment tool (16).
3. The study of Lucas et al., (2018) concluded that HD was used to treat study participants in this RCT. IAT considerably increased performance in the 6MWT and significantly reduced BMI. Regarding the limitations of the research, it is essential to draw attention to the fact that the study participants did not follow a strict diet plan. Lastly, the results' discussion provides limited data due to lack of previous researches including IAT (38).
4. Study conducted by Hema et al., (2022) shows that participants of treatment group were involved in IDE sessions for 30 mins per week besides accepting standard care. Participants of control group only received normal care. The treatment group showed significant reduction in tiredness and marked increase in URR and KT/V; on the other hand, control group did not experience any change in these variables. Weakness of the study includes that the participants and researchers were not blinded due to the type of intervention and also the exercises were modified so that the patient can do it during dialysis session. The weaknesses may affect the outcomes of the study. Recommendations of the study include blinding of participants and researcher (39).
5. Sunki et al., (2022) study concluded that this RCT was conducted three times a week for 40 to 70 minutes using an ergometer ride, along with one education session. Results were evaluated through the Short Form-36 questionnaire (SF-36), Kt/V urea, SPPB. Limitations of the study include recruiting patients from single HD center. Secondly, risk of biasness is increased by small improvement in Mental component score (MCS) score. With the use of small sample size factorial statistics were excluded from study. Recommendations for

future studies include going for a multicenter approach by modifying duration, intensity and time of IAT (40).

6. Study conducted by Hoda et al., (2022) included that the patient's age range of both genders, was 55 to 65. Borg's RPE scale, which ranges from 9 to 11 in this scale, is the basis for prescribing exercise intensity. Intradialytic leg exercises combined with upper limb range of motion (ROM) exercises showed significant increase in post treatment Kt/v and also had positive impact on QOL in physical health. This study showed that combining two exercises reduced creatinine with increasing kt/v (41).

7. Clarkson et al., (2019) study is a systematic review that incorporated exercise interventions such as resistance, aerobic, mixed, or alternative forms of progressive exercise. The review included strong evidences regarding benefit of exercise, still there a chance of risk of biasness in certain of the studies. Specifically, participant and staff blinding, concealment, and randomization were causes for concern. A large number of studies were disqualified from this analysis because they lacked a control group or used non-randomized participant assignment (12).

8. A study conducted by Zelko et al., (2022) consists of 48 participants who finished the study's follow-up. Hand-held dynamometer was used as a measurement of maximal isometric contraction force providing good inter-rater reliability and accuracy. Restrictions on investigation include patient allocation which was determined by the location of the dialysis center. This leads to variations in baseline BMI, kt/v, albumin, and calcium levels which may have altered the results. Furthermore, recommendations of the study include concealment of the study's group allocation (48).

9. Evidence provided by Thangarasa et al., (2018) included the main patient focused outcomes of interest, consisting of physical performance (6MWT, activity of daily living (ADL), stair climbing capacity, and sit-to- stand (STS) test), tiredness, and QOL in this meta-analysis and systematic review. Secondary outcomes of one study include blood pressure (BP), lipid profile, and dietary measurements. Drawback of the study consists of restriction in ability to conclude data by the diversity of the studies' exercise regimens, research designs, and patient characteristics (49).

10. Rodrigo et al., (2020) study is a RCT that short listed patients who had ESRD. Patients who were excluded from the study had a history of coronary artery disease (CAD), being admitted to an ICU, being unable to exercise due to musculoskeletal limitations. 6MWT was used to assess functional capacity. Gaps in the study for future researches include assessing the intervention in other populations, using extensive interventions, long-term follow-up, and varying exercise volumes (50).

CHAPTER 3

3 Methodology

3.1 Study Design

The study design for this research was a meta-analysis. This design was crucial because the goal is to synthesize and analyze data from multiple studies on the effectiveness of IDE on HD outcomes. The goal of meta-analysis was to merge results from various studies to draw broader conclusions about the topic, paving a way for clinical practice guidelines.

3.2 Study Setting

It involved extensive search of studies from sources which are mentioned above. The studies included in this meta-analysis involved HD patients (both inpatient and outpatient) in dialysis unit.

3.3 Study Duration

The total duration for this meta-analysis was 9 month that lasted from 6th march 2024 to 13th November 2024. This duration involved:

- Literature search (exploring databases regarding the relevant topic): 6th March 2024 to 14th March 2024
- Topic selection: 15th March 2024
- Screening (assess the eligibility based on RCTs outcome measures): 16th March 2024 to 25th March 2024
- Drafting and Writing: 26th March 2024 to

5th May 2024

- Synopsis Approval: 30th May 2024
- Data extraction and duplicates removal: 12th May 2024 to 20th June 2024
- Data Analysis and Interpretation: 20th August 2024 to 5th October 2024
- Discussion and Conclusion write up: 8th October 2024 to 20th October 2024
- Final report of Meta-analysis: 13th November 2024

3.4 Search strategy

Data based searching was done after extraction of literature through PubMed, Embrace, and Cochrane. To keep the data accurate and valid, the quality of methodology was assessed in all RCTs through Preferred reporting items for systematic reviews and meta-analysis (PRISMA), Physiotherapy Evidence Database (PEDro) scale, Crow critical appraisal tool (CCAT) and Cochrane risk of bias assessment tool. To concise researches from generalized searching Boolean operators were used. The research initially included keywords like IDE, HD outcomes, kt/v, BMI and HD duration. To be more precise and accurate with the searches one used Boolean operators that combined Medical Subject Headings (Mesh) with Keywords which included 'IDE' AND 'HD outcomes', 'HD' NOT 'PD', 'IDE' AND 'HD patients', 'IDE' OR 'Intradialytic Training', 'HD outcomes AND HD patients', 'IDE' NOT 'Stretching exercise', 'HD patients' NOT 'Kidney transplant patients'.

3.5 Inclusion Criteria

Studies who met the criteria mentioned below were selected for the meta-analysis:

- Participants must be actively receiving HD with a minimum of 6 months to 2 years.
- Age group >18
- Conducted in between 2018 to 2024.
- The study must be published in a peer-reviewed journal or reputable academic source.
- All studies need to be RCTs.
- Studies that are published in English language and have full text articles available.
- Studies involving HD patients with CKD.
- RCTs comparing IDE to usual and conventional care.

3.6 Exclusion Criteria

Excluded studies were:

- RCTs not reporting similar outcome measures
- All those studies that include HD patients with:
  - Mental illness
  - DVT
  - Recent event of stroke
  - Cognitive impairment
  - Amputation of lower limb
  - Unable to feel his or her own legs due to the presence of severe polyneuropathy
  - Conditions like vision impairment or blindness that can compromise the safety of patients during exercise
  - The goal of undergoing HD due to any cause other than CKD.

3.7 Assessment of methodological quality

PRISMA, PEDro scale, CCAT, and Cochrane risk of bias assessment tool were used to investigate the study's methodological quality and to evaluate the degree to which the study had address bias in the design, conduct and analysis.

3.8 Outcome measures

Data collection tools for this meta-analysis included a standardized form for extracting data. Key information was recorded from each study; study design, sample size, patient demographics, IDEs intervention, and outcome measures such as BMI, HD duration and KT/V.

3.9 Data collection instrument

Data abstraction and quality evaluation were performed through inclusion exclusion criteria, guided by developed uniform protocol. Summary of data mining was done to ensure data precision by combining author, year of publication, country, groups of interventions, and outcome measures to ensure that data collected from each study is reliable and consistent to enhance the accuracy and validity of the study.

3.10 Statistical Analysis

The data analysis procedure included the following:

- Used statistical software RevMan software version 5.4 to conduct the meta-analysis. revman.cochrane.org

- Calculated effect sizes for each study to determine the effectiveness of IDE on HD outcomes in CCU. Using the I^2 statistic, the heterogeneity of the studies was evaluated.

3.11 Ethical considerations

Ethical considerations for this meta-analysis include all studies that had obtained ethical approval and informed consent from participants. In order to sustain objectivity throughout the research process, the authors did not receive any financial encouragement to accommodate IDE as an intervention. This meta-analysis also received no funding from outside which enhances its independence and decreases the chance of biasness. Disclosing any potential conflicts of interest or funding sources that may influence the meta-analysis results. Following ethical guidelines for research and ensuring proper citation of all included studies. (15)

CHAPTER 4

4 Result

4.1 Literature Search

Figure 1 demonstrates the overall study identification process by PRISMA guidelines. Initially, 8,329 articles were extracted from PubMed, Embrace and Cochrane with an additional 1,020 articles found from other sources. Duplicates were removed by further screening down the records to 5,329 articles. Out of these articles, 3,329 records were screened based on their titles and abstracts. Following this screening process, 2,500 articles were omitted for not meeting the criteria of included studies. Further, 829 full-text studies were evaluated for eligibility. However, after relevant study searching that led the exclusion of 249 articles that were not conducted within the time frame of 2018-2024, being in languages other than English, conducted on animals, or having different outcome measures. At last, 255 articles were incorporated in the qualitative synthesis, with only 6 articles meeting the criteria to be included in the quantitative synthesis (Yabe et al., 2021(16); Vogiatzaki et al., 2022(37); Lucas et al., 2018(38); Sunki et al., 2022(40); Hoda et al., 2022(41); Hema et al., 2022(39)) where data from these studies were statistically analyzed.

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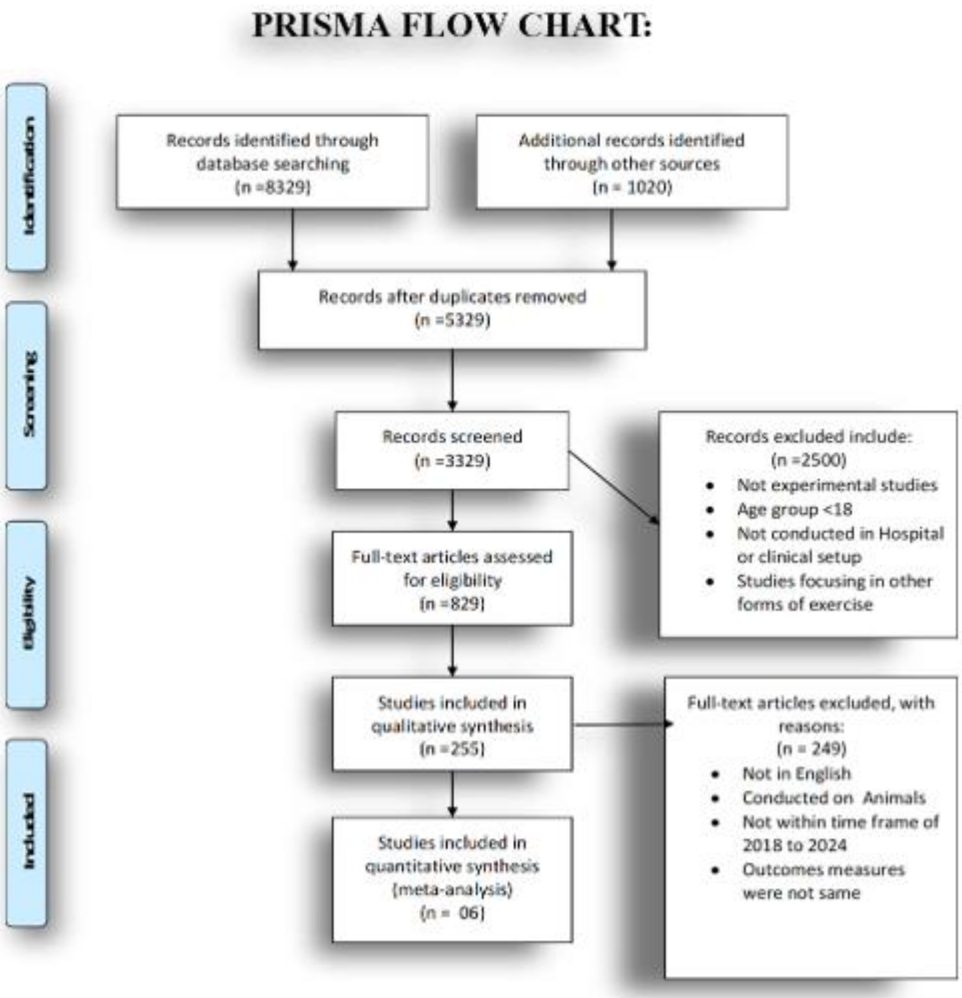

Figure 1: PRISMA flow diagram.

4.2 Study Characteristics

The six articles incorporated in this meta-analysis took place in Japan, Greece, Brazil, Indonesia, Korea and Egypt and were published from 2018-2024. The six qualified studies involved 293 participants with exercise group including 147 participants and control group including 146 participants where the effectiveness of IDE on HD outcomes was assessed based on BMI, KT/V, and HD duration in both the experimental and control group by taking 95% confidence interval for statistical significance. The comprehensive features of the studies incorporated are enumerated in Table 1 and 2.

Table 1 shows the included studies in this meta-analysis based on age, sample size, type of intervention, outcome measures, and main findings, meanwhile the table 2 shows studies based on mean, standard deviation and p value of the outcome measures (BMI, KT/V, HD duration).

NO.	STUDY NAME	STUDY AUTHOR	STUDY YEAR	COUNTRY	AGE	OUTCOME MEASURES	INTERVENTION GROUP	(N)	CONTROL GROUP	(N)
1	Effects of intradialytic exercise for advanced age patients undergoing hemodialysis	Yabe etal., (16)	2021	Japan	>70	Kt/v, BMI, Hemodialysis duration	Tailored exercise training	51	usual care, no instruction to exercise	50
2	The effect of a 6-month intradialytic exercise program on hemodialysis adequacy and body composition	Vogiatzaki etal., (37)	2022	Greece	>18	Kt/v, BMI, Hemodialysis duration	aerobic intradialytic exercise training program	12	Maintain regular life style and refrain from any structured non- or intradialytic exercise program	12
3	Intradialytic aerobic training improves inflammatory markers in patients with chronic kidney disease	Lucas etal., (38)	2018	Brazil	18-65	Kt/v, BMI, Hemodialysis duration	Mechanical cycle ergometer (altmayer, BM 3600)	15	Kept their Usual Daily Routines	15
4	An intradialytic aerobic exercise program ameliorates frailty and improves dialysis adequacy and quality of life among hemodialysis patients	Sunki etal., (40)	2022	Indonesia	>18	Kt/v, BMI, Hemodialysis duration	Intradialytic cycle ergometer exercise program and one educational session	21	Received one educational session	21
5	Combination of Intradialytic Leg Cycling & Upper Limb Range of Motion Exercises on Improving Dialysis Adequacy and Solutes Removal	Hoda etal., (41)	2022	Korea	55-65	Kt/v, BMI, Hemodialysis duration	Intradialytic lower extremities cycling by ergometer and upper limb ROM exercise	23	only upper limb range of motion exercise	23

6	The Effect of Intradialytic Range of Motion Exercise on Dialysis Adequacy and Fatigue in Hemodialysis Patients	Hema etal., (39)	2022	Egypt	>18	Kt/v, BMI, Hemodialysis duration	Flexibility / Stretching and ROM exercise (such as simulated bike riding) for the upper and lower extremities.	**25**	standard care only	**25**

NO.	STUDY NAME	STUDY YEAR	KT/V	BMI (KG/M2)	HEMODIALYSIS DURATION
1	Yabe etal., (16)	2021	**Mean ± SD: Exercise group** (1.5 ± 0.3) **Control group** (1.5 ± 0.3) **P value:** (0.64)	**Mean ± SD: Exercise group** (21.4 ± 2.6) **Control group** (21.3 ± 2.8) **P value:** (0.82)	**Mean ± SD: Exercise group** (61.9 ± 63) **Control group** (70.9 ± 79.2) **P value:** (0.82)
2	Vogiatzaki etal., (37)	2022	**Mean ± SD: Exercise group** Baseline (1.27 ± 0.05) after 6 months (1.41 ± 0.06*.a) p value (0.01) **Control group** Baseline (1.26 ± 0.04) after 6 months (1.24 ± 0.07) **p value:** (0.26)	**Mean ± SD: Exercise group** (25.8 ± 3.4) **Control group** (25.9 ± 4.0) **P value:** (0.34)	**Mean ± SD: Exercise group** (8.2 ± 4.0) **Control group** (8.5 ± 5.0) **P value:** (0.55)
3	Lucas etal., (38)	2018	**Mean ± SD: Exercise group** (1.2 ± 0.5) **Control group** (1.3 ± 0.3) **P value:** (0.897)	**Mean ± SD: Exercise group** Pre (24.6 ± 3.7) Post (22.9 ± 5.0) **Control group** Pre (23.6 ± 3.4) Post (23.0 ± 4.9) **P value:** (0.001)	**Mean ± SD: Exercise group** (5.2 ± 2.3) **Control group** (5.6 ± 2.9) **P value:** (0.438)

4	Sunki etal., (40)	2022	**Mean ± SD: Exercise group** (1.76 ± 0.30) **Control group** (1.64 ± 0.18) **P value:** (0.13)	**Mean ± SD: Exercise group** Baseline(21.55±2.31) After 12 weeks(21.58 ± 1.98) P value:0.88 **Control group** Baseline(21.68± 3.06) After 12 weeks(21.79± 3.01) **P value:** 0.63	**Mean ± SD: Exercise group** (223.61 ± 17.81) **Control group** (228.10 ± 19.14) **P value:** (0.46)
5	Hoda etal., (41)	2022	**Mean ± SD: Exercise group** Pre (1.09 ± 0.14) Post (1.31 ± 0.13) **P value:** (0.001) **Control group** Pre (1.1 ± 0.24) Post (1.18 ± 0.25) **P value:** (0.006)	**Mean ± SD: Exercise group** (30.21 ± 3.35) **Control group** (29.39 ± 3.15) **P value:** (0.39)	**Mean ± SD: Exercise group** (2.1 ± 0.72) **Control group** (2.28 ± 0.63) **P value:** (0.35)
6	Hema etal., (39)	2022	**Mean ± SD: Exercise group** (1.61 ± 0.22) **Control group** (1.42 ± 0.17) **P value:** (< 0.001)	**Mean ± SD: Exercise group** (23.2 ± 4.1) **Control group** (22.4 ± 3.9) **P value:** (0.364)	**Mean ± SD: Exercise group** (1.7 ± 1.6) **Control group** (2.0 ± 1.9) **P value:** (0.693)

4.3 Risk of bias

The Cochrane Risk of Bias Assessment tool was used to evaluate the six studies methodological quality as shown in figure 2 and 3. The risk of bias for the six RTs was classified as high, low, or unclear.

Cochrane Risk of Biasness

	Random Sequence Generation (Selection Bias)	Allocation concealment (Selection Bias)	Blinding of Participants and personnel (Performance Bias)	Blinding of Outcome Assessments (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Hema et al 2022	+	-	?	+-	+-	?	+
Lucas etal. 2018	+	-	-	-	+-	?	?
Hoda et al 2022	+	+	-	-	+-	+	?
Sunki et al 2022	+	-	-	+-	-	+	+
Vogiatzaki et al 2022	+	-	?	-	-	+	+
Yabe et al 2021	+	+	-	-	-	?	-

Figure 2: Cochrane Risk of Bias assessment tool

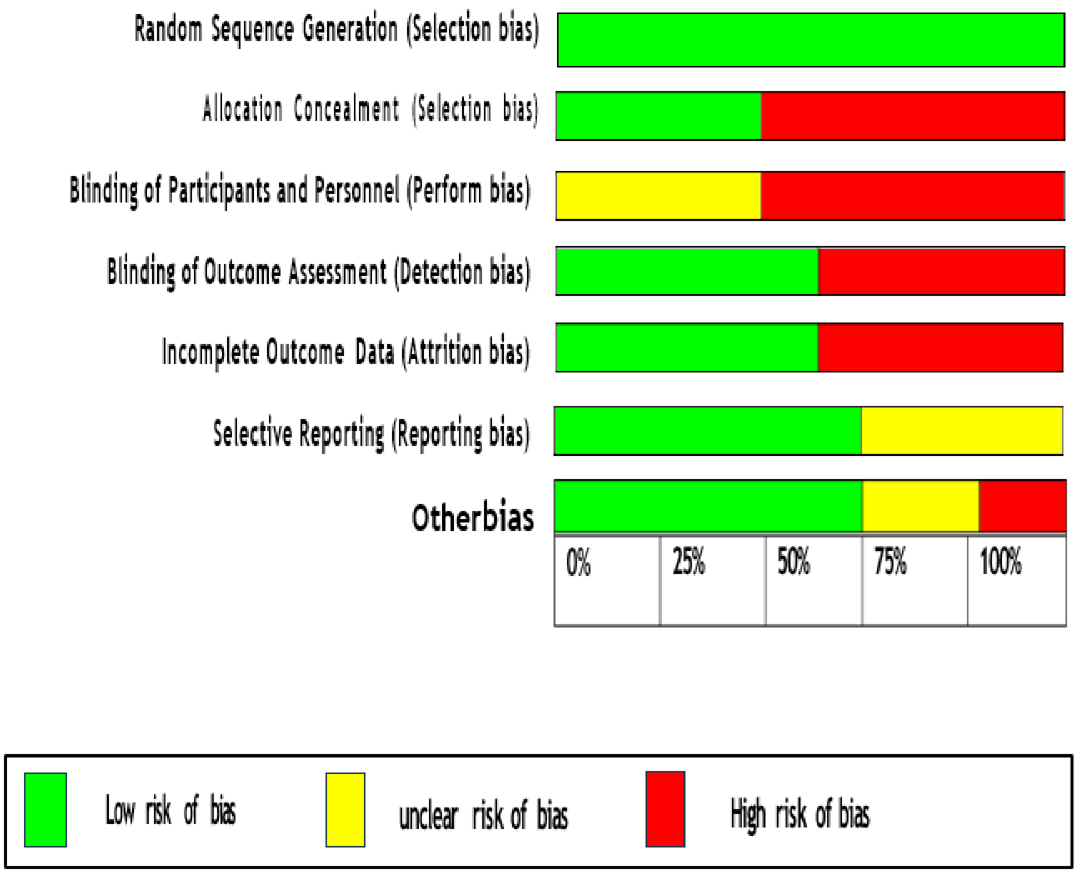

Figure 3: Risk of Bias

4.4 Quality assessment

The quality of the incorporated articles was comprehensively evaluated by using the PRISMA checklist, PEDro scale, and the CCAT. The PRISMA checklist was used to evaluate the comprehensive reporting and transparency of the RCTs, allowing for reliability and accuracy in the methodology and results as shown in table 3. It consists of 23 items encompassing the six stages of RCTs, including: item 1 (Title), item 2 (Abstract), item 3, 4 (Introduction), item 5-15 (methodology), item 16-22 (result) and item 23 (discussion). The table is illustrating the location where the item is reported in the research article.

The methodological accuracy of the RCTs was evaluated using the PEDro scale as displayed in table 4. It assessed the quality of methodology and risk of bias across eleven criteria. The scoring system varies from 0 to 10 points with each criterion donating one point. Criterion 1 is related to external validity and is unscored.. The CCAT was utilized to indicate numerous features of the quality of RCTs over eight categories as demonstrated in table 5. Each category is scored on a scale of 0-5 based on how effectively the study achieves the specifications of each category. The scores of eight categories add up to the total score of 40.

STUDY	ITEM 1	ITEM 2	ITEM 3	ITEM 4	ITEM 5	ITEM 6	ITEM 7	ITEM 8	ITEM 9	ITEM 10A	ITEM 10B	ITEM 11	ITEM 12	ITEM 13A	ITEM 13B	ITEM 13C	ITEM 13D	ITEM 13E	ITEM 13F
Yabe et al.	1	1	2	2	2	2	2	3	4	3	2	3	3	2	2	2	3	2	3
Vogiatzaki et al.	1	1	1	2	4	3	2	2	3	4	6	4	7	6	5	3	3	2	4
Lucas et al.	1	1	1	1	1	2	2	1	2	2	2	3	3	2	2	2	3	2	3
Sunki et al.	1	1	2	2	2	2	2	2	4	6	5	10	10	4	4	2	3	5	5
Hoda et al.	1	1	1	1	1,2	2	2	1	3	5	5	4	2	2	3	2	3	2	3
Hema et al.	1	1	2	2	2	2	3	3	2	7	3	3	7	4	4	3	3	2	4

TABLE: 03 Cont.

STUDY	ITEM 14	ITEM 15	ITEM 16A	ITEM 16B	ITEM 17	ITEM 18	ITEM 19	ITEM 20A	ITEM 20B	ITEM 20C	ITEM 20D	ITEM 21	ITEM 22	ITEM 23A	ITEM 23B	ITEM 23C	ITEM 23D
Yabe et al.	8	2	5	4	5	5	4	4	4	4	4	3	3	4	8	8	7
Vogiatzaki et al.	3	5	5	5	5	7	6	6	5	5	5	7	5	7	9	9	9
Lucas et al.	4	2	3	3	3	5	4	4	4	4	4	3	3	4	5	5	5
Sunki et al.	10	10	9	9	5	10	10	10	9	9	11	10	9	6	11	11	10
Hoda et al.	4	2	3	3	4	5	5	4	4	4	5	3	5	4	5	5	4
Hema et al.	7	7	4	5	3	7	6	6	5	5	5	7	3	6	7	7	7

STUDY	CRITERION 1	CRITERION 2	CRITERION 3	CRITERION 4	CRITERION 5	CRITERION 6	CRITERION 7	CRITERION 8	CRITERION 9	CRITERION 10	CRITERION 11	TOTAL SCORE
Yabe et al.	1	1	1	1	1	1	1	0	1	1	1	10 points
Vogiatzaki et al.	1	1	0	1	1	0	1	0	1	1	1	8 points
Lucas et al.	1	1	0	1	1	1	0	0	1	1	1	8 points
Sunki et al.	1	1	0	1	0	0	0	0	0	1	0	4 points
Hoda et al.	1	1	0	1	0	1	0	1	1	1	0	7 points
Hema et al.	1	1	0	1	1	0	1	0	1	1	1	8 points

STUDY	CATEGORY 1	CATEGORY 2	CATEGORY 3	CATEGORY 4	CATEGORY 5	CATEGORY 6	CATEGORY 7	CATEGORY 8	TOTAL SCORE
Yabe et al.	4/5	2/5	4/5	4/5	3/5	4/5	4/5	3/5	28/40
Vogiatzaki et al.	5/5	2/5	4/5	5/5	3/5	3/5	4/5	3/5	29/40
Lucas et al.	4/5	2/5	4/5	4/5	3/5	4/5	4/5	3/5	28/40
Sunki et al.	4/5	3/5	4/5	5/5	3/5	3/5	4/5	4/5	30/40
Hoda et al.	4/5	4/5	4/5	5/5	3/5	3/5	4/5	3/5	30/40
Hema et al.	4/5	2/5	4/5	5/5	2/5	3/5	4/5	3/5	27/40

4.5 Pooled results:

The result obtained in this meta-analysis was analyzed to assess the effectiveness of IDE on HD outcomes; the result obtained regarding BMI, KT/V, and HD duration is shown in figure 4, 5 and 6.

Data was pooled on the basis of standard mean difference (SMD) using randomized effect model and inverse variance method.

A forest plot is utilized in meta-analysis to show the effect sizes from individual outcome measures alongside the overall pooled estimate.

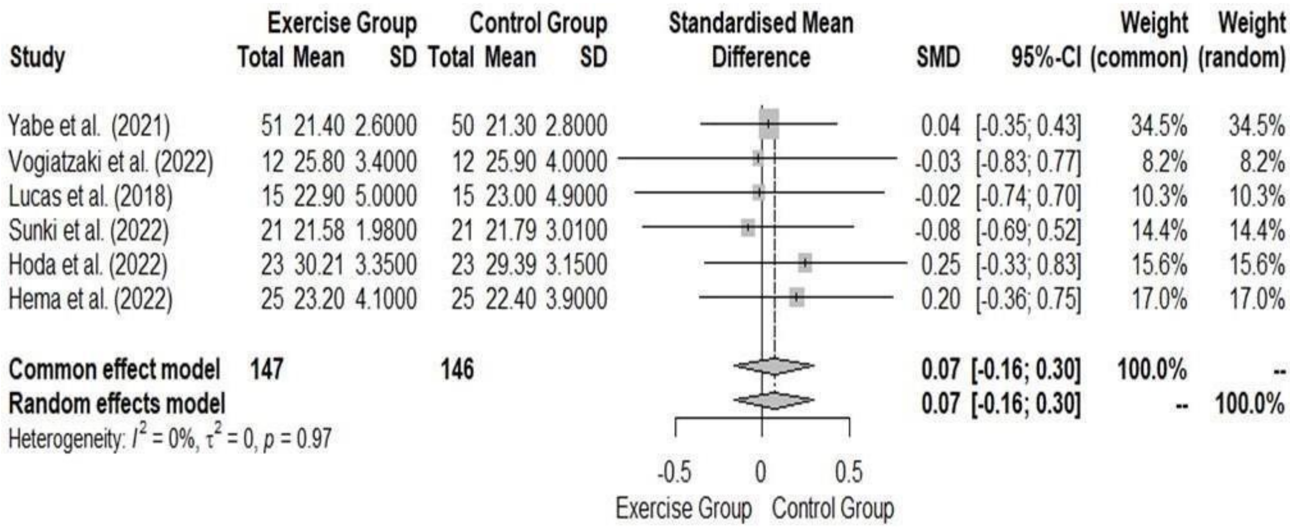

Figure 4: Forest plot BMI

For BMI, the pooled results of the 6 studies showed a slight positive effect of IDE compared to no exercise. The SMD for BMI was 0.0691 with a 95% Confidence Interval [-0.1602; 0.2984], and a p-value of 0.59 according to both the common and random effects models, indicating minimal to no effect among the two groups in terms of BMI. With I² = 0.0% and Tau² = 0 heterogeneity, the studies included show no variability, suggesting consistency across the studies for this outcome. The trend here is relatively neutral, as both the common and random effect models show a very small effect size (SMD = 0.0691).

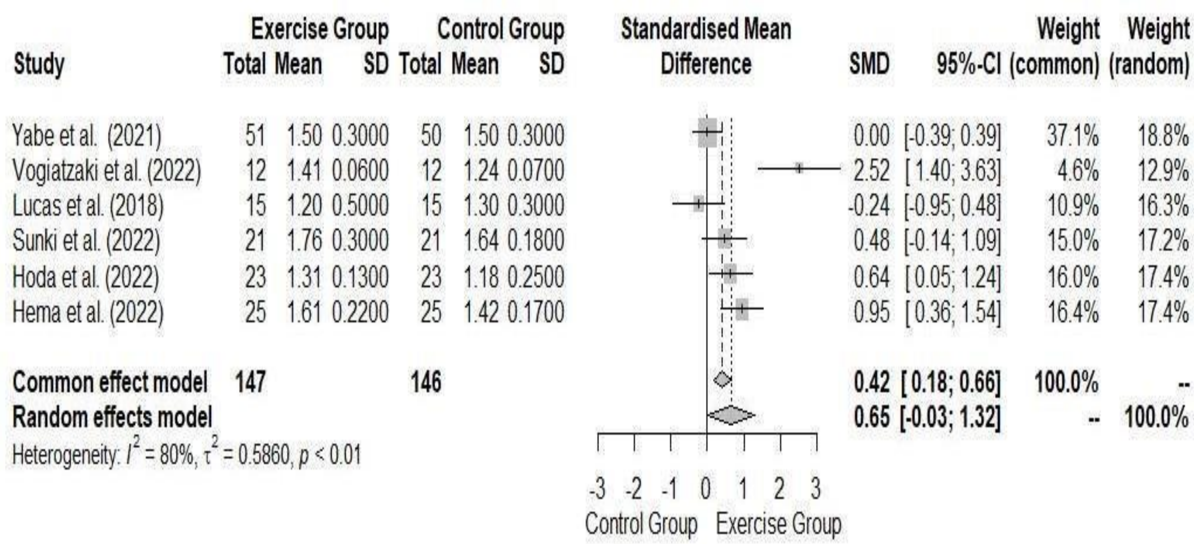

Figure 5: Forest plot KT/V

For KTV, the result revealed that with confidence interval 95%, random effect model was [-0.0264; 1.3179] with P Value 0.05 showing statistically significance in KT/V post IDE in experimental group. The effect size is higher in the random effects model (SMD = 0.6458, 95%-CI). I^2 = 80% and Tau^2 = 0.5860 indicate substantial heterogeneity across studies, suggesting considerable variability in the effect of IDE on KT/V outcomes. KT/V has a clear trend of improvement with IDE, as indicated by a moderate positive effect size. This suggests that IDE are trending toward improving how effectively dialysis clears toxins from the blood, which is a critical outcome for patient health.

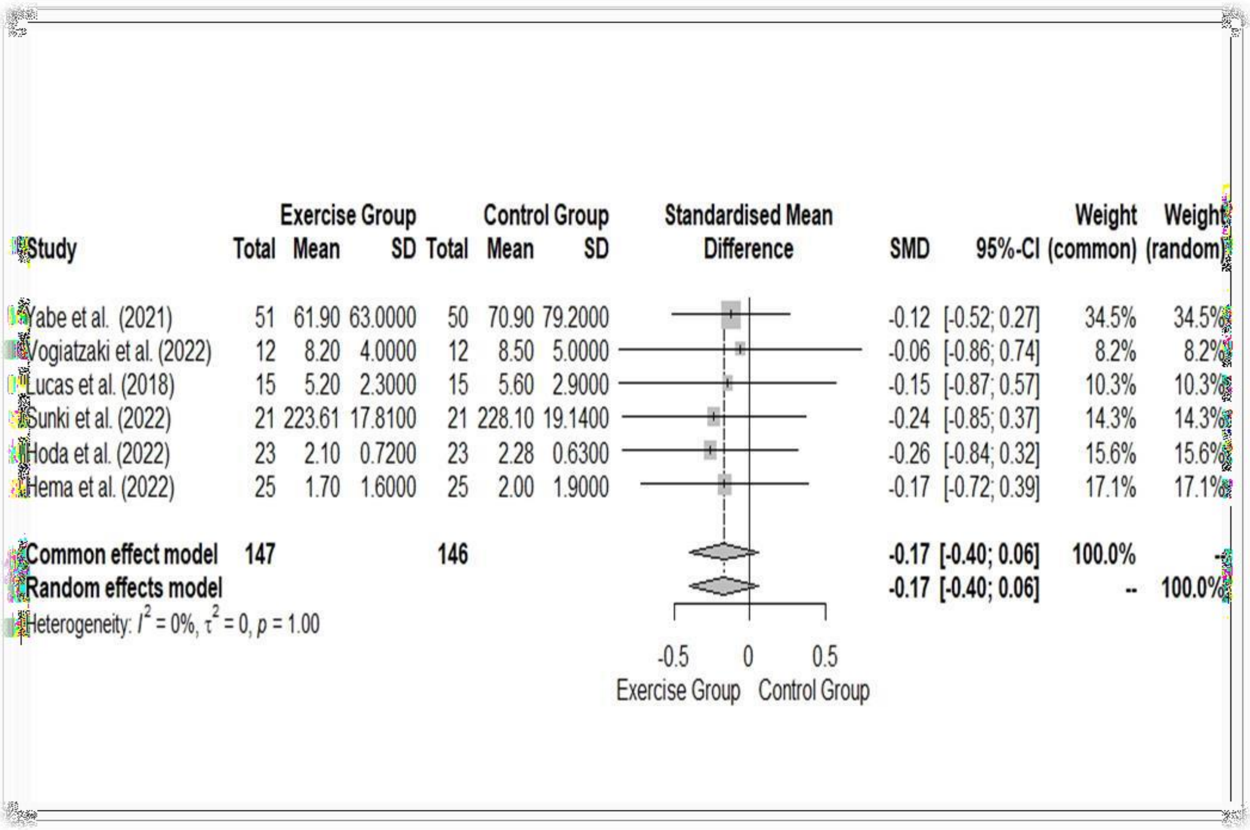

Figure 6: Forest plot HD duration

For HD Duration, the analysis revealed the SMD of -0.1673 with a 95% Confidence Interval [-0.3968; 0.0622] and a p-value of 0.1532. This result suggests a trend towards a reduction in HD duration with IDE, though the finding was not statistically significant. There is no heterogeneity (I^2 = 0%, Tau^2 = 0), indicating that the results are consistent across studies for this outcome. The trend in this outcome points slightly toward a reduction in the duration of dialysis, but the effect is small.

The result showed zero or low heterogeneity which suggests that IDE have a little impact on BMI and HD duration in terms of patient demographics, intervention designs, variation in study design, treatment practices, and follow up duration that may have influenced the observed result. Meanwhile, for KT/V (where high heterogeneity was present) the IDE show a statistically significant positive effect on KT/V, suggesting improved HD outcomes.

CHAPTER 5

5 Discussion

This meta-analysis evaluates the effectiveness of IDE on HD outcomes. A meta-analysis of 6 RCTs found that the IDE ameliorates KT/V, moderately decrease the HD duration, and have a little or no impact on BMI.

KT/V is significantly enhanced by IDE as it ameliorates the flow of blood towards the muscles which facilitates the transport of toxins such as urea and creatinine, to the dialyzer, thereby optimizing toxin clearance. While IDE slightly reduces the duration of HD sessions, this effect is limited by the fixed dialysis protocols set by healthcare providers to ensure adequate toxin removal, independent of physical activity during the session. Additionally, the variability in kidney function, comorbidities, and overall physical health among HD patients influences the duration of HD more significantly than exercise levels. Despite the benefits of IDE, its impact on BMI remains minimal, likely because significant BMI changes typically require prolonged, high-intensity exercise and dietary modifications. HD patients often experience complex metabolic changes and fluid shifts that can obscure BMI alterations, explaining the minimal effect observed.

This meta-analysis supports the growing evidence that IDE improve HD outcomes, particularly in enhancing KT/V. The results are corresponding to previous meta-analysis that examined the impact of effectiveness of IDE on HD outcomes.

5.1 Comparison with existing Research

These results align with previous meta-analyses by Huang et al., (2019)(51), Sheng et al., (2014)(52), Jiang et al., (2019)(53), and Astri et al., (2022)(54) all of which reported significant improvements in KT/V values with IDE (SMD = 0.6458, p = 0.05). According to the studies, IDE improves solute clearance during HD which is important for both treatment effectiveness and patient health.

In contrast, one meta-analysis showed that the effect of IDE on BMI was minimal (SMD = 0.0691, p = 0.59). Evidence provided by Sheng et al., (2014)(52), had similar conclusions, showing insignificant changes in body composition or weight post IDE in HD patients. It recommends that exercise may improve cardiovascular and metabolic parameters but its effect is unnoticeable on body composition especially in short duration interventions.

Regarding HD duration, one study provided evidence of limited impact of IDE on HD session length, consistent with results from Smart and Steele (2011)(55), which also reported no significant reduction in duration of dialysis with exercise interventions. Both studies highlight that while IDE may optimize the HD process by improving toxin clearance, it does not necessarily shorten treatment duration. Variations in exercise type, intensity, and timing may account for this result, indicating a need for more targeted exercise protocols.

Furthermore, numerous meta-analysis indicate the importance of tailored exercise programs. A systematic review conducted by Zelle et al., (2017)(56) highlighted the advantages of tailored exercise programs depending on the cardiovascular health and functional condition of patient. Similar to this, one study also indicate that personalized exercise regimes could boost the effectiveness of IDE in patients undergoing HD.

This meta-analysis shed difference from previous studies (12, 36, 57-60) by addressing limitations through the use of established quality assessment tools such as PRISMA, Cochrane risk of bias, CCAT, and PEDro scale, by focusing specifically on patients who are currently receiving HD, which helps eliminate selection bias towards healthier individuals. Minimize publication bias by incorporating studies published within a defined time frame (2018-2024) and focusing on peer-reviewed articles, supporting for methodological rigor (such as intention-to- treat analysis), combining data from various studies, and demonstrating low heterogeneity for specific outcomes.

5.2 Limitations

The limitations of one meta-analysis were relatively a limited sample size of six studies totaling 293 participants causing their findings not to be generalizable. The geographical and cultural diversity of the included studies introduces variability in healthcare practices, patient characteristics, and intervention protocols, potentially influencing outcomes. High heterogeneity observed in the KT/V outcome (I^2 = 80%) suggests variability in IDE effectiveness on KT/V across studies, which may reduce the reliability of pooled results.

5.3 Strength of the Study

Significant strengths of this meta-analysis include:

- Comprehensive literature search
- Data extraction from multiple studies
- Establishment of clinical practice guidelines
- Inclusion of diverse studies
- Accurate quality assessment
- Used outcome measures that have high reliability (kt/v: 098, BMI: 0.95)
- Thorough statistical analysis
- Comprehensible presentation of results
- Use of recent studies within a time frame of 2018-2024
- Recognition of positive trends.

5.4 Weakness of the Study

The weakness of one meta-analysis is that the study focuses mainly on BMI, KT/V, and HD duration, neglecting other important outcomes like QOL, cardiovascular health, and muscle strength, which are relevant to patient well-being. Varying exercise regimen of the patient (intensity, type and duration) can lead to uneven outcomes, requiring the need of standardization to correlate activities done during dialysis session. Additionally, the exclusion of studies outside the 2018-2024 timeframe and non-English language studies may have led to the missing of potentially valuable research.

CHAPTER 6

6 Conclusion and Recommendations

The study results emphasize that IDE have a significant positive impact on key HD outcomes. One meta-analysis concluded that IDE improves KT/V, also positively influences overall duration of HD treatment sessions and BMI. By incorporating structured exercise programs into the routine of HD patients, healthcare providers can reduce the adverse effects of inactivity or fatigue associated with CKD. Moreover, the implementation of IDE can enhance the patient activity level and adherence to treatment, providing improved HD outcomes. All in all, this meta-analysis supports the inclusion of IDE as an essential part of treatment of HD patients.

The future recommendations involve increasing the sample size by including more studies and participants that may enhance the reliability and generalizability of the findings. To address the heterogeneity in KT/V, future studies should aim to standardize intervention protocols across regions or use subgroup analyses to identify factors influencing outcome variability. Expanding the range of assessed outcomes, such as QOL, cardiovascular health markers, and functional mobility, would provide a more comprehensive understanding of IDE benefits. Additionally, longer follow-up periods would better evaluate the long-term effects of these exercises on HD outcomes. Finally, future research should incorporate a wider patient population regarding age, comorbidities, and HD experience to ensure broader applicability of findings.

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