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ORIGINAL ARTICLE

Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: a systematic review and meta-analysis

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ABSTRACT

Background. Intradialytic cycling (IDC), delivered during haemodialysis (HD), has the potential to improve many health issues. This systematic review and meta-analysis examine the evidence on the effects of IDC on exercise capacity, quality of life (QoL), physical function and cardiovascular health.

Methods. Twenty-four databases were searched alongside Internet and hand searching, and consultation with experts. Eligibility criteria were cluster randomized, randomized and quasi-randomized controlled trials (RCTs) of IDC versus usual care in prevalent adult HD patients. Primary outcome measures were exercise capacity (VO_2 peak and field tests) and QoL. Secondary measures were cardiac and physical function.

Results. Thirteen RCTs were eligible. Eight provided data for use in meta-analyses, which indicated no significant change in VO_2 peak (mean difference, MD 1.19 mL/kg/min, 95% confidence interval −1.15 to 3.52, P = 0.3), physical (mean change, MC 1.97, −8.27 to 12.22, P = 0.7) or mental component (MC 3.37, −7.94 to 14.68, P = 0.6) summary scores of the Medical Outcomes Short Form 36, pulse wave velocity (MD −0.57 m/s, −1.55 to 0.41, P = 0.4), systolic (MD −2.28 mmHg, −14.46 to 9.90, P = 0.7) or diastolic blood pressure (MD 2.25 mmHg, −3.01 to 7.50, P = 0.4) following IDC. IDC, however, leads to an improvement in performance on the 6-min walk test (MD 87.84 m, 39.60–136.09, P = 0.0004). All included studies were considered to have high risk of bias.

Conclusions. There is insufficient evidence demonstrating whether cycling exercise during HD improves patient outcomes. High-quality, adequately powered RCTs of IDC are required.

Keywords: ESRD, exercise, haemodialysis, meta-analysis, systematic reviews

INTRODUCTION

The incidence and prevalence of end-stage renal disease (ESRD) requiring dialysis is increasing, with the majority of patients undertaking haemodialysis (HD) [1]. These patients have significantly increased morbidity and mortality, with cardiovascular disease as the leading cause of death [2]. Skeletal muscle catabolism, malnutrition, anaemia, uraemia, chronic inflammation, comorbidities and physical inactivity, together with 'enforced' sedentary time during HD [3] contribute to a reduction in exercise and functional capacity that are associated with disability [4], increased healthcare utilization [5] and reduced quality of life (QoL) [6].

Exercise interventions have the potential to target several of these issues. The majority of previous reviews have examined the effects of exercise in general within the HD population [7–10]. 'Intradialytic exercise' (an umbrella term covering a range of heterogeneous exercise interventions delivered during HD) is, however, often advocated due to greater adherence rates [11]. Recent systematic reviews indicate that intradialytic exercise can significantly improve exercise capacity [12], physical QoL [12, 13] and blood pressure (BP) [13], but the interventions used include a range of different components. In choosing to review methods of exercise delivery rather than the specific type of intervention undertaken, clinicians and policymakers lack clear information on which specific modes of intradialytic exercise are most beneficial, hampering the translation of research evidence into practice.

As intradialytic exercise delivered solely by means of a cycle ergometer (intradialytic cycling, IDC) is most commonly done within clinical practice [14], the aim of this review is to provide an up-to date synthesis of available evidence comparing the effects of IDC versus usual care on exercise capacity, QoL, physical function and cardiovascular health in HD patients.

MATERIALS AND METHODS

Protocol registration and eligibility criteria

A pre-specified protocol was published on PROSPERO (www.crd.york.ac.uk/PROSPERO identifier CRD42016030006 (28 February 2018, date last accessed)). Eligibility criteria included cluster randomized, randomized and quasi-randomized controlled trials (RCTs) of prevalent HD patients. Trials in which it was possible to elucidate the direct effects of IDC training were included; studies of acute responses to a single bout of IDC were excluded. Control groups were defined as those who received usual care HD, for 4 h thrice weekly, not receiving any form of exercise intervention, counselling or education. Primary outcome measures included: exercise capacity measured by VO_2 peak; treadmill or field tests [e.g. 6-min walk test (6MWT) or Incremental Shuttle Walk Test (ISWT) and QoL using validated measures]. Secondary outcome measures included: cardiac (echocardiogram, BP and pulse wave velocity) and physical function determined using a range of measures (STS5, Sit to Stand 5; STS30, Sit to Stand 30; STS60, Sit to Stand 60; NSRI, North Staffordshire Royal Infirmary Walk Test; TUAG, Timed Up and Go Test).

Study identification

To identify existing relevant trials and systematic reviews, the pre-specified databases, in addition to the NIHR (National Institute of Health Research) Centre for Reviews and Dissemination Database, SciELO (Scientific Electronic Library Online), OAIster (Open Archives Initiative), SCOPUS, BASE (Bielefeld Academic Search Engine) and Open Grey, were searched from inception to March 2017, supplemented with Internet searching until 4 July 2017, hand searching reference lists and consultation with experts. No restrictions were placed upon publication, language status or year of publication. Search terms were adapted to database requirements and the full search strategy for the MEDLINE database is shown in Supplementary data, Item S1.

Study selection, data extraction and risk of bias assessment

Search results were managed using Refworks (ProQuest, Ann Arbour, MI, USA). Duplicate citations were removed, and the remaining citations screened against eligibility criteria. Titles and abstracts deemed not to meet these criteria were excluded. For the remaining citations, full-text articles were assessed for eligibility by H.M.L.Y., D.S.M. and M.P.M.G.B.. Disagreements were resolved by discussion with recourse to a fourth reviewer if needed.

Data from eligible studies were extracted by one reviewer and checked by another, using a template based upon the Cochrane collaboration tool. Information relating to study design, population, intervention, usual care control, outcomes and adverse events were recorded. Where multiple reports originated from a single study, comparison of the key characteristics was done using tables and were only included, as a single study, if they reported relevant outcomes to avoid overstating results. Where missing data were encountered, original authors were contacted.

Reviewers independently assessed study quality according to the Cochrane Risk of Bias assessment tool. Risk of bias for RCTs was assessed as high, low or unclear across five domains [15]. The overall risk of bias was determined using the following criteria: (i) low risk of bias (all criteria graded adequate), (ii) moderate risk of bias (one criterion graded inadequate or two unclear) and (iii) high risk of bias (more than one criterion graded inadequate or more than two unclear).

Statistical analysis

Descriptive statistics were used to study characteristics of included studies. Where means and standard deviation (SD) were neither reported nor available from study authors [16, 17], they were estimated from medians and interquartile ranges [18] or SD was calculated from standard error [19, 20]. Only data from the first period within crossover trials were used to reduce the potential influence of carry-over.

All outcomes were treated as continuous data and interpreted as mean differences. Analysis was primarily based upon final values. In circumstances of baseline imbalances between groups, analysis was based on changes from baseline [15]. Statistical heterogeneity was assessed with the I^2 test, which describes the percentage of variation across studies above that attributed to chance [21]. Heterogeneity was considered unimportant for I^2-values up to 40% [15]. RevMan 5.3 software was used to undertake meta-analyses. Data pertaining to similar outcome measures were pooled (with participant as the unit of analysis) in a meta-analysis, using a random effects model, which assumes that the observed estimates of treatment effect vary across studies due to within- and between-study variance [22, 23]. Pre-planned subgroup and sensitivity were not possible due to the limited number of studies available for meta-analysis and all studies being classified as high risk of bias, respectively.

RESULTS

Search results and study characteristics

Figure 1 provides a flow diagram of included studies: search results identified 1269 citations after duplicates were removed. Thirteen studies were eligible for inclusion after screening of titles, abstracts and full text articles. A table detailing the excluded studies can be found in Supplementary data, Item S2. Due to inadequate reporting of group sizes, results and wide heterogeneity of measures, only eight trials provided information for use in meta-analyses [17, 19, 20, 24–28].

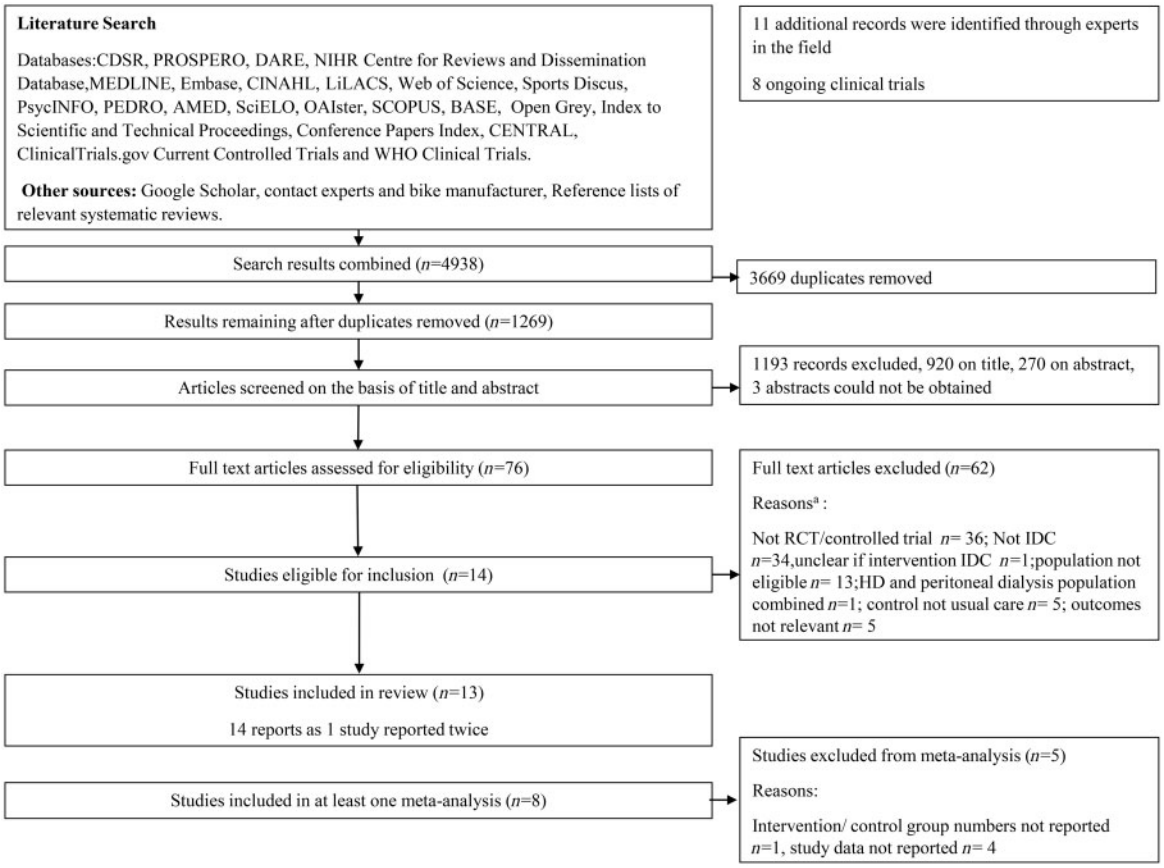

FIGURE 1: Flow diagram of study selection. [a]Some studies excluded for multiple reasons.

Supplementary data, Item S3 provides a summary of the characteristics of included trials. Included trials were published between 1995 and 2016 in English. Twelve were individually randomized [17, 19, 20, 24–33], and one cluster randomized [16]. Twelve used a parallel group design and one a crossover design [17]. All trials measured outcomes at baseline and at the end of the intervention [16, 17, 19, 20, 24–33]; of these, two also measured outcomes at an interim time point [27, 33]. Only one study included longer follow-up, 1 month post-intervention [28]. In total, 369 patients were randomized to receive IDC ($n = 190$) or usual care ($n = 179$) with sample sizes ranging from 18 to 49.

Characteristics of IDC

Full reporting of the IDC intervention was lacking in several studies, and the characteristics of IDC interventions ranged widely between studies. Five studies did not provide information regarding the mode of IDC training used [17, 24, 26, 29, 30, 32], four provided continuous training [19, 20, 27, 31], two interval training [16, 33] and two a combination [25, 28]. Mean duration of exercise training was 14 weeks (range 6–26). In all but one study, where patients exercised twice a week [16], they were encouraged to exercise at each HD session. The mean duration of each planned bout of training was 31 min (range 20–45) and a majority required patients to exercise at a moderate intensity [19, 20, 24–27, 29, 33]. Actual levels of concordance were difficult to ascertain, as only four studies reported adherence level [17, 25, 26, 28, 29] and only three summarized the amount of exercise achieved [17, 26, 29, 33]. Where reported, mean adherence rates were 81%. Only five trials reported on adverse events [16, 17, 25–27, 29], of which four reported no events [16, 17, 25, 27] and one no 'significant complications' [26, 29]. Exercise training was provided by researchers in three studies [20, 25, 27], 'physical activity experts' in one study [19] and HD staff in another [17]. One study reported the intervention being provided by medical and nursing staff, but it was unclear whether these were attached to the trial or the HD unit [31]. Seven studies did not report who was delivering the intervention [16, 24, 26, 28–30, 32, 33].

Risk of bias assessment

Risk of bias summaries for all included studies are provided in Table 1. All studies were rated as high risk of bias, primarily due to insufficient reporting. Only one study provided the information required to assess bias across all domains and was judged to be of high risk in all [25].

Effect of IDC

Exercise capacity. Nine studies reported outcomes related to exercise capacity. Five studies measured VO_2 peak [16, 19, 26–28]; however, it was not possible to include VO_2 data from the cluster RCT in meta-analyses due to inadequate reporting [16]. One study used maximum work capacity, measured in watts [33]. Three studies used the 6MWT [19, 25, 31] and one the ISWT [20], both field tests of exercise capacity. Four studies including 85 participants provided VO_2 peak data appropriate

Table 1. Risk of bias for included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data	Reporting bias	Other bias	Overall risk
Carmack *et al.* [28]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	High risk
de Lima *et al.* [32]	High risk	Low risk	Unclear	Unclear	Unclear	Low risk	High risk	High risk	High risk
Giannaki *et al.* [24]	Unclear	Unclear	Unclear	Unclear	High risk	Low risk	Unclear	Low risk	High risk
Groussard *et al.* [19]	Unclear	Unclear	High risk	High risk	High risk	Low risk	Unclear	Low risk	High risk
Koh *et al.* [25]	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Liao *et al.* [31]	Unclear	Unclear	High risk	High risk	High risk	Low risk	High risk	Low risk	High risk
Momeni *et al.* [30]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	High risk
Moug *et al.* [16]	Unclear	High risk	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	High risk
Painter *et al.* [27]	Low risk	Unclear	Unclear	Unclear	High risk	Unclear	High risk	Low risk	High risk
Parsons *et al.* [33]	Low risk	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	Low risk	High risk
Reboredo *et al.* [26, 29]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	High risk	High risk
Toussaint *et al.* [17]	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk	High risk
Wilund *et al.* [20]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	High risk	High risk	High risk

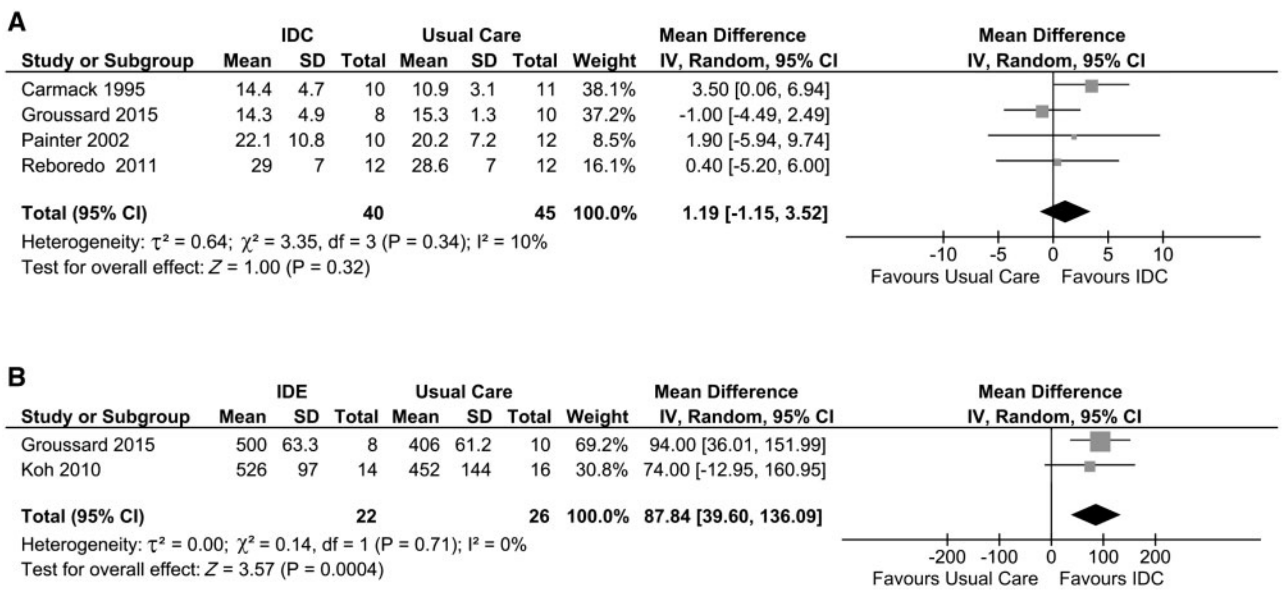

FIGURE 2: Forest plot comparing IDC with usual care on VO_2 peak (**A**) and the 6MWT (**B**).

for meta-analysis. A non-significant improvement of 1.19 ml/kg/min [95% confidence interval (CI) −1.15 to 3.52, P = 0.3, Figure 2A] was observed immediately following IDC compared with usual care [19, 26–28]. Statistical heterogeneity was low $I^2 = 10\%$. The study that reported maximal work capacity also reported no significant difference between IDC and usual care [33].

Two of the three studies that assessed 6MWT provided sufficient information to pool results [19, 25]. These trials included 48 participants and demonstrated a statistically significant improvement of 87.84 m (39.60–136.09, P = 0.0004, Figure 2B) in favour of IDC. There was no evidence of statistical heterogeneity ($I^2 = 0\%$). The study excluded from synthesis also suggested a significant improvement in the IDC group ($P < 0.05$) [31]. Only one included study assessed ISWT [20] whereby a statistically significant 15% (P = 0.03) improvement in distance walked was observed in the IDC group.

Quality of life. The Medical Outcomes Short Form 36 (SF-36) tool reports QoL as physical (PCS) and mental component scores (MCS) [34]. Two studies with a total of 52 participants reported the effect of IDC on PCS and MCS. Due to baseline imbalances between groups for one of the two included studies [25], both PCS and MCS summary for the SF-36 were assessed as change from baseline scores. Of these studies, only one reported mean change and SD [24]. For the remaining other study [25], we used a conservative estimated correlation coefficient value of 0.5 [35] to calculate SD of change scores. No statistical differences were observed between IDC and usual care for the PCS (1.97, −8.27 to 12.22, P = 0.7, Figure 3A) or MCS scores (3.37, −7.94 to 14.68, P = 0.6, Figure 3B) of the SF-36. Statistical heterogeneity was not evident for the MCS ($I^2 = 0\%$), and was neglible for the PCS ($I^2 = 18\%$).

Cardiac outcomes. Five studies reported cardiovascular outcomes, of these three measured resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) [17, 20, 25], and two measured pulse wave velocity [17, 25]. Three studies recorded findings from echocardiogram [20, 29, 30].

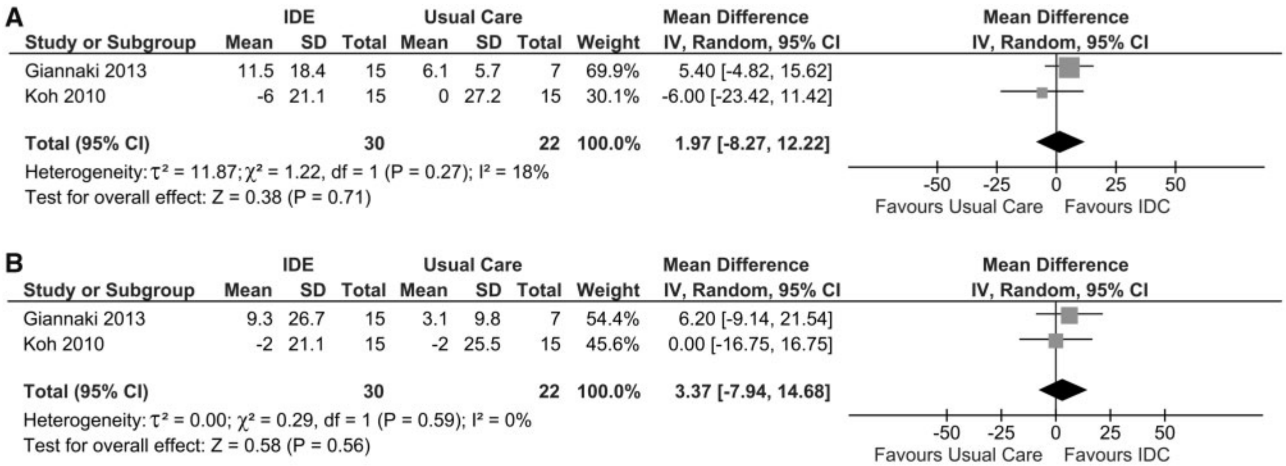

FIGURE 3: Forest plots comparing change in physical (**A**) and mental (**B**) component summary scores of the SF-36 in IDC and usual care.

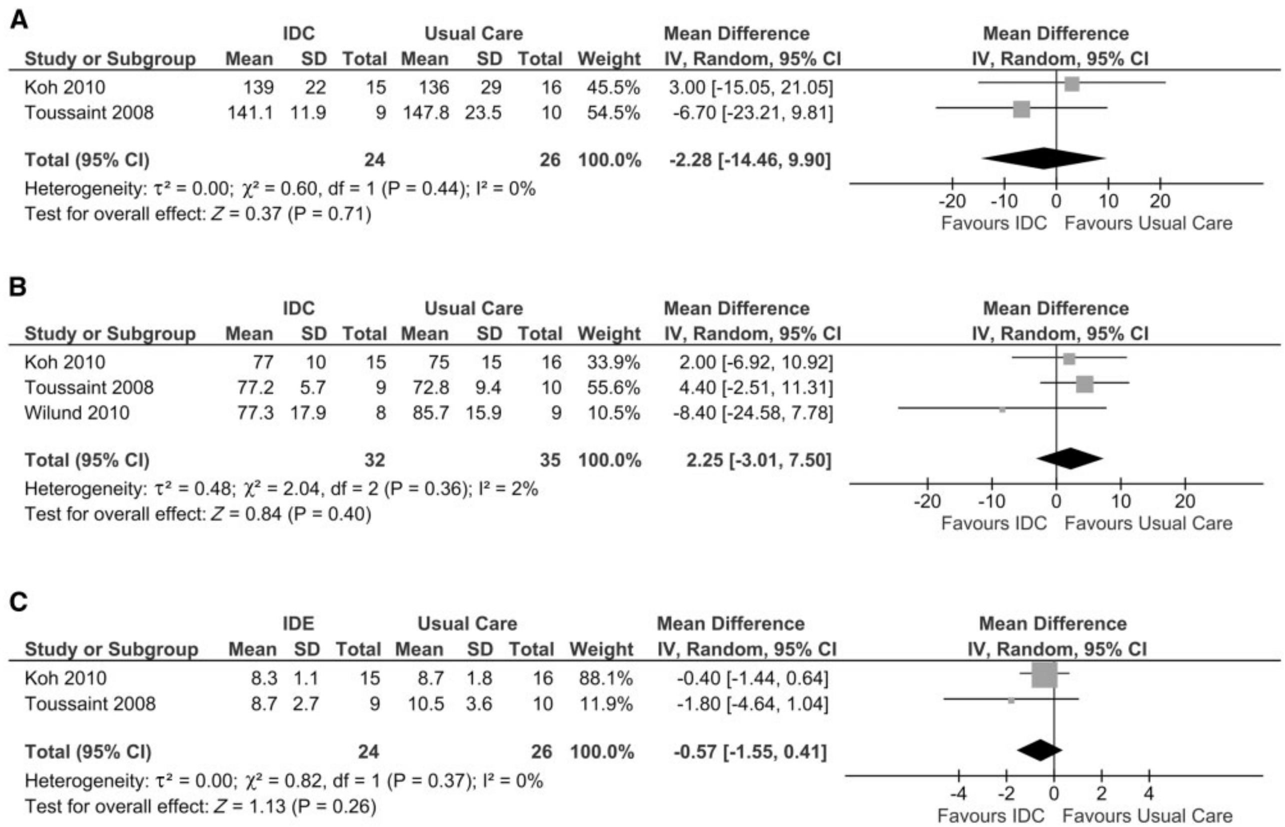

FIGURE 4: Forest plot comparing IDC with usual care on SBP (**A**), DBP (**B**) and pulse wave velocity (**C**).

One trial was excluded from meta-analysis for SBP due to a large baseline difference of 21.4 mmHg between the usual care and IDC groups [20]. This study did not report any significant effect on BP results. Synthesized data from the remaining two trials [17, 25] including 50 participants revealed a non-significant reduction in SBP of −2.28 mmHg with IDC (−14.46 to 9.90, $P = 0.7$, Figure 4A). Synthesized data from three trials including 67 participants demonstrated a non-significant increase of 2.25 mmHg in DBP with IDC (−3.01 to 7.50, $P = 0.4$, Figure 4B). There was no evidence of statistical heterogeneity for the SBP ($I^2 = 0\%$) and negligible heterogeneity for the DBP ($I^2 = 2\%$).

Synthesized data from two trials measuring pulse wave velocity [17, 25] including 50 participants demonstrated a non-significant improvement of −0.57 m/s (−1.55 to 0.41, $P = 0.4$, Figure 4C) in the IDC group. There was no evidence of statistical heterogeneity ($I^2 = 0\%$). Of the three trials reporting echocardiography measures, two trials including 37 participants provided results for left ventricular mass index (LVMI). However, we deemed meta-analysis inappropriate due to a large, clinically relevant baseline difference between the control and IDC groups of 28.3 g/m^2 in one study [20] and 13.9 g/m^2 in the other [29], respectively. Neither reported any significant difference in LVMI following IDC.

Two studies including 62 patients measured left ventricular ejection fraction (LVEF). These were not included in a meta-analysis due to inadequate reporting of group size in one study [30]. This study saw a significant improvement in LVEF in the IDC group (P = 0.004) [30] whilst the other reported no significant change [29].

Physical function. Three studies reported physical function outcomes. The clinical diversity in outcome measures prevented pooling of results, but inspection of individual studies revealed limited impact of IDC across a range of measures. A single study of 29 participants revealed no statistically significant change in TUAG scores (−0.3 s, −1.39 to 0.77, P = 0.9) between IDC and usual care [25]. Similarly, a single trial of 22 participants that reported a number of function measures observed non-statistically significant improvements in STS5 (−0.57 s, −1.85 to 0.71, P = 0.4), STS30 (0.59 stands, −2.76 to 3.94, P = 0.7), STS60 (0.50 stands, −5.67 to 6.67, P = 0.9), normal gait speed (0.43 s, −0.67 to 1.53, P = 0.5) and fast gait speed (0.08 s, −0.41 to 0.57, P = 0.8) [24]. A baseline difference of 31.98 s between the IDC and control group was noted for the NSRI walk test, but analysis of mean change scores revealed a statisitically significant improvement in the NSRI walk test (−10.2 s, −17.6 to −2.8, P = 0.007) following IDC [24]. Finally, a single trial of 21 participants reported a significant improvement in the number of steps completed in 6 min in the IDC group compared with usual care [32]; however, a clinically relevant baseline imbalance of 15 steps between groups may have influenced these results.

DISCUSSION

Main findings

The results of this systematic review and meta-analysis suggest that IDC can lead to statistically and clinically significantly improvements in exercise capacity measured via field testing, but current evidence demonstrates no statistically significant effect upon VO_2 peak, QoL, BP or arterial stiffness. Due to issues with trial reporting and substantial baseline imbalances in outcome measures between intervention groups and inconsistency in selection of outcome measures across studies, it was not possible to synthesize the effect of IDC on cardiac or physical function. The quality of the included evidence was considered to be at high risk of bias. Based upon this review, there is currently insufficient evidence to support the use of IDC in clinical practice to improve exercise capacity, QoL, cardiac or physical function.

Comparison with previous reviews

Our review, which focussed specifically upon intradialytic aerobic exercise, delivered using a static cycle ergometer, stands predominantly in contrast to previous publications. These reviews have shown significant improvements in exercise capacity [12, 13] physical QoL [12] and BP [13]. These differences may be explained by the inclusion of additional evidence in our data synthesis, the decision of previous reviews to include intradialytic exercise programmes consisting of a range of types of exercises within their meta-analyses or because they included interventions that were not exclusively aerobic training [36, 37] or delivered to HD patients [38] within their subgroup analyses [13].

Implications for practice

Current evidence suggests patients, on average, observe a clinically important improvement of 87 m in the 6MWT after a programme of IDC, although the strength of this conclusion is limited by the high risk of bias within the two included studies [39]. Theoretically, an improvement in field tests of exercise capacity might reasonably be expected to be reflected in improvement in VO_2 peak, given that aerobic capacity contributes towards overall exercise capacity. The contrasting results seen in these two outcomes may be due to the inclusion of greater numbers of different trials within the meta-analysis for VO_2 peak in comparison with that for the 6MWT, other factors known to influence field test performance [5] and the use of different protocols to measure exercise capacity, which can influence the measurement of VO_2 peak, and its sensitivity to change following a programme of exercise [40]. The high prevalence of autonomic dysfunction in many HD patients may also be another reason for the discrepancy between the results of the two outcomes [41]. Autonomic dysfunction can lead to cardiac unresponsiveness, which is in turn associated with poor physical performance. Whilst speculative, it is possible that this may play a more important role during a higher intensity exercise test and therefore, patients may achieve greater improvements in field tests such as the 6MWT, when compared with VO_2 peak. Although, reduced exercise capacity and sedentary behaviour are powerful predictors of mortality in ESRD [4, 42, 43], these results should not be extrapolated, as a causal link between increased exercise capacity through exercise training and decreased mortality has yet to be established. IDC also appeared to have little influence upon cardiovascular outcomes within the current review, although this may reflect a lack of high-quality RCTs rather than evidence of ineffectiveness.

Previous reviews have reported no significant adverse events [9, 12, 13] due to exercise training, citing these as evidence of safety. In the current review, eight trials failed to report information on adverse events and those which did only provided limited information. Therefore, it is difficult to make a clear judgement about the safety of IDC. A recent study of IDC noted a significant drop in BP 1 h post-exercise, with no reported adverse events [44]. Given the association between asymptomatic intradialytic hypotension and adverse outcomes [45, 46], further research is needed to confirm that IDC is not associated with subclinical adverse events, or to provide clinicians with information about groups of patients for whom intradialytic exercise is not appropriate.

Exercise is beneficial across a spectrum of chronic diseases [47] and current Kidney Disease Outcomes Quality Initiative

Table 2. Recommendations for enhancing the reporting, quality and synthesis of clinical trials of IDC

Aim	Methodological limitation	Rationale for inclusion	Potential strategies to address limitation
Improved reporting of trials	Poor reporting of delivery of intervention	Seven studies did not report intervention providers. Four studies reported adherence levels and three summarized amount of exercise data. Five studies did not provide any information regarding the type of IDC training used.	Adhere to CONSORT guidance for the reporting of non-pharmacologic trials [53]; Use TIDieR checklist for intervention reporting [54].
	Poor reporting of study design and trial procedures	All studies were rated as high risk of bias, primarily due to lack of sufficient reporting. Nine trials provided insufficient details and allocation concealment.	Adhere to CONSORT guidance for the reporting of NPTs [55].
	Poor reporting of testing procedures in relation to field testing and patient reported outcomes	Two studies provided no information on the procedures used during field tests. Of those reporting, use of a familiarization test was not reported in one study, and another did not report if tests were conducted on non-HD or HD days or were standardized for follow-up.	Report: Timing of testing in relation to HD treatment; Familiarization procedures; Procedures for collecting patient reported measures; Explicit reporting of standardization of these procedures for follow-up.
	Poor reporting of adverse events	Five trials reported whether any adverse events had occurred. Statements about adverse events lacked detail.	Adhere to CONSORT reporting guidance, including specific guidance for reporting harms [56]; Use of standardized and validated measurement instruments for adverse events, where possible.
	Reporting bias in relation to study results	Selective outcome reporting in five of the studies due to incomplete reporting of outcomes or time points, reporting of only statistically significant outcomes. Only one study had published a protocol paper.	Registration of trials; Publication of protocol paper; Presentation of all data in numerical form, not solely figures; Adherence to CONSORT for NPT [53]; Raw data freely available in repository.
Reduction of bias within trials	Attrition bias	Of the 10 studies providing information about attrition, a mean of 23% (range 6–56%) of participants were lost to follow-up in the IDC group, and 14%, (range 0–56%) in usual care. Only one study reported the use of an intention to treat analysis for their primary outcome measure.	Reduce dropout: Minimize number of visits or integrate into usual care; Allow step-wise withdrawal if unavoidable; Engage a patient involvement group to provide patient perspective on trial procedures; Judicious selection of outcome measures; Feasibility studies prior to full-scale trial. Undertake an intention to treat analysis. Explicitly state the methods used to address missing data.
	Small sample sizes and underpowered studies	Only three studies based their sample sizes on an *a priori* power calculation for their primary outcome. One was unable to recruit the required number of patients. Trials of exercise and rehabilitation can be challenging to deliver and the numbers of patients required to adequately power outcomes may be large depending on the chosen primary outcome measure.	*A priori* power calculation for primary outcome measure for RCTs or report as a feasibility or pilot study, with appropriate outcomes, limitations and conclusions; collaborative, multi-center working to increase sample sizes.
	Lack of blinding of participants and intervention providers	Three studies reported that they were unable to blind participants and personnel, others do not report blinding.	Report blinding explicitly including methods and the fidelity; Where blinding not possible, strategies to reduce bias should be reported;
	Lack of blinding of outcome assessors	Blinding of outcome assessment was reported incompletely in only five studies, all of which were high risk due to explicit lack of blinding or researchers assisting participants to complete QoL questionnaires.	Aim to use blinded outcome assessors where possible; Report blinding explicitly including methods and the fidelity; Where blinding not possible, strategies to reduce bias should be reported.
	Baseline imbalances	Five studies demonstrated large, potentially clinically significant differences between control and IDC groups for baseline LVMI, SBP, the SF-36 and some measures of physical function, although all authors state that these differences were not statistically significant.	Adequate sample sizes and randomization procedures; Identification of important baseline differences *a priori*; Discuss characteristics of important differences in results; Do not use significance testing to determine if baseline imbalances exist.

Continued

Table 2. Continued

Aim	Methodological limitation	Rationale for inclusion	Potential strategies to address limitation
Enhanced synthesis of trial results	Wide heterogeneity of outcome measures	Limited number of outcomes appropriate to combine in meta-analyses.	Use of core outcomes as identified by SONG-HD in addition to outcomes pertinent to the aims of the specific trial [57];
	Discuss clinical significance of results	Individual trials report statistically significant results that seem unlikely to translate to a meaningful benefit for patients.	Report CIs and effect sizes; Comment on the clinical relevance of findings within the results alongside statistical significance; Use MCIDs from other chronic disease populations where they do not exist for HD.

MCID, minimum clinically important difference; SONG-HD, Standardized Outcomes in Nephrology-Haemodialysis; NPTs, non-pharmacologic trials.

guidelines recommend patients with chronic kidney disease to undertake 'an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week' [48]. Expert statements provide more specific guidance [49, 50] and systematic reviews have extolled the benefits of exercise for HD patients [7–10, 12, 13]. These have all led to increasing calls for exercise, particularly intradialytic, to become a routine part of the care of HD patients [13, 51, 52]. The results of this review suggest, however, that the specific effects of IDC are currently unknown, primarily due to the methodological shortcomings of existing trials. Further to this, high-quality, well-reported, RCTs are required. Two such trials, PEDAL (NCT02222402) and CYCLE-HD (ISRCTN11299707) [58], will imminently provide evidence of the ability of intradialytic exercise to influence cardiac function and QoL, which may further inform best practice.

Implications for research

Table 2 outlines several implications for future research that have been highlighted by this review. Unclear reporting was a feature of most IDC trials, and the primary reason for high risk of bias. Evidence presented by unclear trials rarely leads to change in practice or advances in research, because clinicians and policymakers lack confidence in the validity of findings and interventions can rarely be replicated [53, 55]. Whilst we acknowledge that several IDC trials included within this review precede the publication of this guidance, future trials should adhere to both CONsolidated Standards of Reporting Trials (CONSORT) guidance for the reporting of non-pharmacologic trials and use the Template for Intervention Description and Replication (TIDieR) checklist for intervention reporting [53, 54].

Most trials were small, and not powered to detect a true effect [59]. Studies reporting echocardiography and harms are particularly vulnerable to lack of statistical power [60–63]. Lack of blinding, which can influence the participant, intervention provider and outcome assessor behaviour, leading to over-estimation of effect [59, 64, 65], particularly within non-pharmacologic trials [66] and 'per protocol' analysis, which may bias the estimated effects, were also common [64, 67, 68]. Future trials should endeavour to adequately power studies, and aim to report blinding methods and fidelity explicitly [59].

Inconsistent use of a wide range of outcome measures limited meta-analyses, highlighting the need for a core outcome set to be measured and reported in all trials, alongside outcomes relevant to the individual study. Standardized Outcomes in Nephrology (SONG) aims to develop a core set of validated outcomes that reflect the main concerns of key stakeholders, including patients [57]. Thirty-four priority areas have been identified, ∼21 of which may potentially be influenced by exercise interventions. Once standardized outcome measures have been established, better synthesis of studies will be possible, allowing comparisons of different interventions across outcomes [57, 69].

Limitations

Due to inadequate reporting, two potentially relevant studies were excluded [38, 70]. Additionally, six included trials presented outcome data incompletely [16, 20, 27, 31–33]. Attempts to obtain these data were unsuccessful. The inclusion of these may have provided additional information for meta-analyses, potentially providing larger sample sizes and greater statistical power. The limited number of eligible studies meant it was not possible to assess publication bias or conduct subgroup analyses. Further analyses of specific characteristics of the IDC intervention (e.g. duration of programme, adherence and intensity of exercise) would have provided information on potential reasons for differences in outcomes. Despite the lack of funnel plots, risk of publication bias is minimal, as many included studies reported statistically non-significant results. Unpublished studies with statistically non-significant results may exist, but their addition is not likely to change our conclusions.

CONCLUSIONS

The renal community remains in a position of equipoise regarding IDC, because of a lack of high-quality RCT data. This review highlights the need for adequately powered trials that adhere to published reporting guidance and, as far as possible, take steps to remedy the methodological limitations of trials that have gone before.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

H.M.L.Y., S.J.S., A.C.S. and J.O.B. conceived the study idea. H.M.L.Y. designed the protocol. D.S.M., M.P.M.G.-B., A.W.J., F.C., S.J.S. and C.B. assisted with protocol design. H.M.L.Y. co-ordinated in the review process. H.M.L.Y., D.S.M., M.P.M.G.-B., D.R.C., C.S.G. and P.H. searched for trials. H.M.L.Y., D.S.M., M.P.M.G.-B., D.R.C., C.S.G., P.H. and J.O.B. screened search results. H.M.L.Y., D.S.M., M.P.M.G.-B., S.J.S. and J.O.B. assessed the trials for quality. H.M.L.Y., D.S.M. and M.P.M.G.-B. extracted the data. H.M.L.Y., A.W.J., F.C. and C.B. analysed the data. H.M.L.Y. helped in manuscript preparation. All authors reviewed final manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

REFERENCES

1. US Renal Data System Annual Report. Chapter 1: Incidence, Prevalence, Patient Characteristics, and Treatment Modalities [Internet]; 2017. Available from: https://www.usrds.org/2016/download/v2_c01_IncPrev_16.pdf (28 February 2018, date last accessed)
2. US Renal Data System Annual Report. Chapter 8: Cardiovascular disease in patients with ESRD [Internet]; 2017. Available from: https://www.usrds.org/2016/download/v2_c09_CVD_16.pdf (28 February 2018, date last accessed)
3. Tentori F, Elder SJ, Thumma J *et al.* Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. *Nephrol Dial Transplant* 2010; 25: 3050–3062
4. Sietsema KE, Amato A, Adler SG *et al.* Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int* 2004; 65: 719–724
5. Painter P, Marcus RL. Assessing physical function and physical activity in patients with CKD. *Clin J Am Soc Nephrol* 2013; 8: 861–872
6. Son YJ, Choi KS, Park YR *et al.* Depression, symptoms and the quality of life in patients on hemodialysis for end-stage renal disease. *Am J Nephrol* 2009; 29: 36–42
7. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis* 2014; 64: 383–393
8. Segura-Ortí E. Exercise in haemodialysis patients: a systematic review. *Nefrologia* 2010; 30: 236–246
9. Smart N, Steele M. Exercise training in haemodialysis patients: a systematic review and meta-analysis. *Nephrology* 2011; 16: 626–632
10. Barcellos FC, Santos IS, Umpierre D *et al.* Effects of exercise in the whole spectrum of chronic kidney disease: a systematic review. *Clin Kidney J* 2015; 8: 753–765
11. Konstantinidou E, Koukouvou G, Kouidi E *et al.* Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. *J Rehabil Med* 2002; 34: 40–45
12. Chung Y, Yeh M, Liu Y. Effects of intradialytic exercise on the physical function, depression, and quality of life for hemodialysis patients: a systematic review and meta-analysis of randomized controlled trials. *J Clin Nurs* 2016; 26: 1801–1813
13. Sheng K, Zhang P, Chen L *et al.* Intradialytic exercise in hemodialysis patients: a systematic review and meta-analysis. *Am J Nephrol* 2014; 40: 478–490
14. Greenwood SA, Koufaki P, Rush R *et al.* Exercise counselling practices for patients with chronic kidney disease in the UK: a renal multidisciplinary team perspective. *Nephron Clin Pract* 2014; 128: 67–72
15. Higgins JPT, Green S. (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org (28 February 2018, date last accessed)
16. Moug SJ, Grant S, Creed G *et al.* Exercise during haemodialysis: West of Scotland pilot study. *Scott Med J* 2004; 49: 14–17
17. Toussaint ND, Polkinghorne KR, Kerr PG. Impact of intradialytic exercise on arterial compliance and B-type natriuretic peptide levels in hemodialysis patients. *Hemodial Int* 2008; 12: 254–263
18. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5: 13
19. Groussard C, Rouchon-Isnard M, Coutard C *et al.* Beneficial effects of an intradialytic cycling training program in patients with end-stage kidney disease. *Appl Physiol Nutr Metab* 2015; 40: 550–556
20. Wilund KR, Tomayko EJ, Wu PT *et al.* Intradialytic exercise training reduces oxidative stress and epicardial fat: a pilot study. *Nephrol Dial Transplant* 2010; 25: 2695–2701
21. Higgins JP, Thompson SG, Deeks JJ *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560
22. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011; 342: d549
23. Borenstein M, Hedges LV, Higgins J *et al. Introduction to Meta-analysis*. Chichester: John Wiley and Sons, 2009
24. Giannaki CD, Sakkas GK, Karatzaferi C *et al.* Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. *BMC Nephrol* 2013; 14: 194
25. Koh KP, Fassett RG, Sharman JE *et al.* Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in hemodialysis patients: a randomized pilot study. *Am J Kidney Dis* 2010; 55: 88–99
26. Reboredo MM, Neder JA, Pinheiro BV *et al.* Constant work-rate test to assess the effects of intradialytic aerobic training in mildly impaired patients with end-stage renal disease: a randomized controlled trial. *Arch Phys Med Rehabil* 2011; 92: 2018–2024

27. Painter P, Moore G, Carlson L *et al*. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *Am J Kidney Dis* 2002; 39: 257–265
28. Carmack CL, Amaral-Melendez M, Boudreaux E *et al*. Exercise as a component of the physical and psychological rehabilitation of hemodialysis patients. *Int J Rehab Health* 1995; 1: 13–23
29. Reboredo MM, Pinheiro BV, Neder JA *et al*. Effects of aerobic training during hemodialysis on heart rate variability and left ventricular function in end-stage renal disease patients. *J Bras Nefrol* 2010; 34: 367–373
30. Momeni A, Nematolahi A, Nasr M. Effect of intradialytic exercise on echocardiographic findings in hemodialysis patients. *Iran J Kidney Dis* 2014; 8: 207–211
31. Liao M, Liu W, Lin F *et al*. Intradialytic aerobic cycling exercise alleviates inflammation and improves endothelial progenitor cell count and bone density in hemodialysis patients. *Medicine* 2016; 95: e4134
32. de Lima MC, Cicotoste CL, Cardoso KS *et al*. Effect of exercise performed during hemodialysis: strength versus aerobic. *Ren Fail* 2013; 35: 697–704
33. Parsons TL, Toffelmire EB, King-van Vlack CE. The effect of an exercise program during hemodialysis on dialysis efficacy, blood pressure and quality of life in end-stage renal disease (ESRD) patients. *Clin Nephrol* 2004; 61: 261–274
34. NMAHP RU, Stirling University. Framework for measuring impact. Sf-36. http://www.measuringimpact.org/s4-sf-36. Updated 2012. [Internet]; 2012. Available from: http://www.measuringimpact.org/s4-sf-36 (25 July 2017, date last accessed)
35. Follmann D, Elliott P, Suh I *et al*. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; 45: 769–773
36. Petraki M, Kouidi E, Grekas D *et al*. Effects of exercise training during hemodialysis on cardiac baroreflex sensitivity. *Clin Nephrol* 2008; 70: 210–219
37. van Vilsteren MC, de Greef MH, Huisman RM *et al*. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in the netherlands: Results of a randomized clinical trial. *Nephrol Dial Transplant* 2005; 20: 141–146
38. Koufaki P, Nash PF, Mercer TH. Assessing the efficacy of exercise training in patients with chronic disease. *Med Sci Sports Exerc* 2002; 34: 1234–1241
39. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017; 23: 377–381
40. Bentley DJ, Newell J, Bishop D. Incremental exercise test design and analysis. *Sports Med* 2007; 37: 575–586
41. Chan CT, Levin NW, Chertow GM *et al*. Determinants of cardiac autonomic dysfunction in ESRD. *Clin J Am Soc Nephrol* 2010; 5: 1821–1827
42. O'Hare AM, Tawney K, Bacchetti P *et al*. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. *Am J Kidney Dis* 2003; 41: 447–454
43. Stack AG, Molony DA, Rives T *et al*. Association of physical activity with mortality in the US dialysis population. *Am J Kidney Dis* 2005; 45: 690–701
44. Dungey M, Bishop NC, Young HM *et al*. The impact of exercising during haemodialysis on blood pressure, markers of cardiac injury and systemic inflammation–preliminary results of a pilot study. *Kidney Blood Press Res* 2015; 40: 593–604
45. Park J, Rhee CM, Sim JJ *et al*. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int* 2013; 84: 795–802
46. Sands JJ, Usvyat LA, Sullivan T *et al*. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. *Hemodial Int* 2014; 18: 415–422
47. Lee I, Shiroma EJ, Lobelo F *et al*. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012; 380: 219–229
48. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney inter.*, Suppl. 2012;2: 337–414. [Internet]; 2012. Available from: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf (28 February 2018, date last accessed)
49. Smart NA, Williams AD, Levinger I *et al*. Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. *J Sci Med Sport* 2013; 16: 406–411
50. Koufaki P, Greenwood S, Painter P *et al*. The BASES expert statement on exercise therapy for people with chronic kidney disease. *J Sports Sci* 2015; 33: 1902–1907
51. Deschamps T. Let's programme exercise during haemodialysis (intradialytic exercise) into the care plan for patients, regardless of age. *Br J Sports Med* 2016; 50: 1357–1358
52. Bennett PN, Capdarest-Arest N, Parker K. The physical deterioration of dialysis patients—Ignored, ill-reported, and ill-treated *Semin Dial*. 2017; 30(5): 409–412
53. Boutron I, Altman DG, Moher D *et al*. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med* 2017; 167: 40–47
54. Hoffmann TC, Glasziou PP, Boutron I *et al*. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; 348: g1687
55. Dechartres A, Trinquart L, Atal I *et al*. Evolution of poor reporting and inadequate methods over time in 20 920 randomised controlled trials included in cochrane reviews: research on research study. *BMJ* 2017; 357
56. Ioannidis JP, Evans SJ, Gøtzsche PC *et al*. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141: 781–788
57. Standardised Outcomes in Nephrology–Haemodialysis. http://songinitiative.org/projects/song-hd/. Updated 2017. Available from: http://songinitiative.org/projects/song-hd/ (25 July 2017, date last accessed)
58. Graham-Brown MP, March DS, Churchward DR, Young HM, Dungey M, Lloyd S, Brunskill NJ, Smith AC, McCann GP, Burton JO. Design and methods of CYCLE-HD: improving cardiovascular health in patients with end stage renal disease using a structured programme of exercise: a randomised control trial. *BMC Nephrol* 2016; 17: 69
59. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002; 359: 696–700
60. Grothues F, Smith GC, Moon JC *et al*. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002; 90: 29–34
61. Stewart GA, Foster J, Cowan M *et al*. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int* 1999; 56: 2248–2253
62. Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Arch Intern Med* 2009; 169: 1737–1739
63. Tsang R, Colley L, Lynd LD. Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials. *J Clin Epidemiol* 2009; 62: 609–616
64. Friedman LM, Furberg C, DeMets DL *et al*. *Fundamentals of Clinical Trials*. 3rd edn. Springer, 1998
65. Nüech E, Reichenbach S, Trelle S *et al*. The importance of allocation concealment and patient blinding in osteoarthritis trials: a meta-epidemiologic study. *Arthritis Rheum* 2009; 61: 1633–1641
66. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS *et al*. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int J Epidemiol* 2014; 43: 1272–1283
67. Nuesch E, Trelle S, Reichenbach S *et al*. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *BMJ* 2009; 339: b3244
68. Abraha I, Cherubini A, Cozzolino F *et al*. Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. *BMJ* 2015; 350: h2445
69. Fish R, Sebag-Montefiore D, Sanders C *et al*. Core outcome research measures in anal cancer. *Colorectal Dis*
70. Akiba T, Matsui N, Shinohara S *et al*. Effects of recombinant human erythropoietin and exercise training on exercise capacity in hemodialysis patients. *Artif Organs* 1995; 19: 1262–1268

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