

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of intradialytic exercise in hemodialysis patients: a systematic review and Meta-analysis
AUTHORS	Pu, Jiang; Jiang, Zheng; Wu, Weihua; Li, Li; Zhang, Liling; Li, Ying; Liu, Qi; Ou, Santao

VERSION 1 – REVIEW

REVIEWER	Neil Smart University of New England, Australia
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	<p>METHODS Search >6months out of date.</p> <p>The TESTEX tool by Smart et al. far superior to JADAD for assessing bias in exercise training studies, this reviewer strongly suggests use of TESTEX here.</p> <p>What determines whether heterogeneity is substantial? If heterogeneity was considered unsubstantial was a random effects model really used? The convention is to use a fixed effects model if heterogeneity is low and only use a random effects if heterogeneity is high.</p> <p>How is it possible to eliminate heterogeneity, please expand on this as readers would like to learn how this is done.</p> <p>RESULTS Mean JADAD is not that helpful a median score would be more useful.</p> <p>What are the units for MD of peak VO₂? Is it METS? Please also provide unit for other MD measures eg SBP</p> <p>Avoid using 'didn't' better to say did not.</p> <p>Page 12 I am uncertain why an I squared value has been provided for 'biochemical examinations' when this would entail a range of markers eg phosphate, creatinine etc.' so one value is insufficient please report them all. Similarly please report all lipid values.</p> <p>Why does cardiac function suddenly appear when it is not listed as an outcome in methods, please remove it. Also what are the units? A MD of 61 cannot be ejection fraction so it cannot be that cardiac function is reported here.</p> <p>Where are results for albumin etc.?</p>
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	<p>The events analysis is futile as only 2 studies reported and event prevalence is negligible.</p> <p>DISCUSSION It is good that clinical meaning of kt/v is discussed but the MD reduction of 0.07 does not really add context as we need to know where patients ended after exercise to relate to mortality and other outcomes.</p> <p>Relate peak VO₂, PCS, MCS to knowledge of clinically meaningful reductions eg is 4.11 change in VO₂(units????) meaningful or not?</p>
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REVIEWER	Dr Gordon McGregor Coventry University, University Hospital Coventr
REVIEW RETURNED	31-Dec-2017

GENERAL COMMENTS	<p>The authors present a systematic review and meta-analysis aimed at assessing the efficacy and safety of intra-dialytic exercise (IDE). Thank you for the opportunity to review.</p> <p>This form of exercise training is increasingly popular both clinically and in research and, therefore, the topic is of considerable interest and asks relevant questions. There is real potential for IDE to favourably influence clinical outcomes.</p> <p>Writing style would benefit from improvement in places but is generally ok– there are spelling mistakes, and inappropriate wording: p.4 line 5 (efficiency), p.5 line 26 (unconformable), line 41 (better sleep), line 47 (introdialytic), p.6 line 36 (literature data), p.13line 43 (efficiency)</p> <p>The authors state that there is a lack of evidence supporting efficacy and safety of IDE – however, this is not strictly true – the authors should reference other major recent studies and reviews/meta-analyses. They should more convincingly justify the need for this particular review/meta-analysis to be conducted and what it aims to add to the literature.</p> <p>In the introduction, the authors discuss an isolated case of simultaneous bilateral quadriceps tendon rupture as an important indicator of the danger of IDE. This seems a little odd. One case of this in all the thousands of hours performed does not seem relevant. Safety concerns during IDE are more related to hypotension and other cardiovascular sequelae. This should be the focus.</p> <p>Methodology seems appropriate and the study is well conducted, adhering to the PRISMA guidelines and using Cochrane software. Inclusion/exclusion of trials is suitable. However, it does not appear to have been registered with a designated registry. Statistical review is also recommended to ensure appropriate application of meta-analytical techniques etc.</p> <p>Results are reasonably well presented and described, however, there appears to be a major problem with the Forest plots. They seem to indicate that improvements in VO₂ peak, Kt/V, 6MWT etc favour control (not exercise). Presumably a data input error?</p>
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	<p>VO2 peak is one of the main outcome of interest, however, it is not stated anywhere in the paper how this was measured/estimated. This should be included and discussed as it is a very important determinant of this measure.</p> <p>Depression – overview description of which tools/questionnaires were used should be included in the manuscript</p> <p>Cardiac function is mentioned a number of times, but it is not distinguished how this was measured and what parameters were used. This is very important. Also cardiac function is not followed through in the discussion. There is no explanation of the data, appraisal of the results or any discussion of the relevance to clinical outcomes.</p> <p>Exercise interventions – there should be a more thorough appraisal of the interventions included. Significant heterogeneity is described, but the relevance of this should be further explored and discussed. Also, do any of the papers mention fidelity – ie what was adherence/compliance like and how able were participants to complete the intended intervention.</p> <p>The authors conclude that IDE is safe - this may be overstated given that 12 trials did not report adverse events (as identified by the authors). This conclusion should be reconsidered or better justified</p> <p>The final sentence of the conclusion is perhaps a little bold. Current data and this review do not suggest reduced mortality with IDE. Although this is possible, it is highly speculative and should be removed or reworded to better reflect this.</p>
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REVIEWER	Neri A Alvarez-Villalobos Universidad Autonoma de Nuevo Leon, Subdireccion de Investigación
REVIEW RETURNED	28-Feb-2018

GENERAL COMMENTS	<p>Page 9 row 29-31 they say: when heterogeneity was not substantial or obvious clinical heterogeneity was eliminated and the random effects model was used to combine the data. I suppose they should say: when heterogeneity was not substantial or obvious clinical heterogeneity was eliminated and the fixed effects model was used to combine the data.</p> <p>Albumin levels should be reported with mean differences and not with SMD. Due to Mg/dl or mmol/dl can be changed instead standardized the results. The same for cholesterol and phosphorus levels.</p> <p>Page 12 Row 44 they say: No significant heterogeneity was found [SMD=0.01,95%CI(0.29,0.31), P=0.95;Fig. 6B] They should include a heterogeneity value and confidence interval is wrong (it should include the negative sign).</p> <p>Page 29: Geovana 2016, is included in the table of page 29 but that study is not included in the references.</p>
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VERSION 1 – AUTHOR RESPONSE

Replies to Reviewer 1

Specific Comments

1. METHODS

Search >6months out of date.

Response: Thank you for your suggestion. We have updated our searching to March 2018, and the included studies based on searching results remain unchanged. I will continuously pay attention to this issue. Thank you for your suggestion.

The TESTEX tool by Smart et al. far superior to JADAD for assessing bias in exercise training studies, this reviewer strongly suggests use of TESTEX here.

Response: Thank you for your suggestion. The use of TESTEX tool may improve our analysis. However, Jadad score is also a widely recognized quality assessment tool. We will try to use TESTEX in the future if we conduct further study in the future.

2.What determines whether heterogeneity is substantial? If heterogeneity was considered unsubstantial was a random effects model really used? The convention is to use a fixed effects model if heterogeneity is low and only use a random effects if heterogeneity is high.

Response: Thank you for your suggestion. We have revised the corresponding text in the text (page 9 line16, page 9 line20).

3. eliminate heterogeneity, please expand on this as readers would like to learn how this is done.

Response: Thank you for your suggestion. We have revised the corresponding text in the revised text.

4.RESULTS

Mean JADAD is not that helpful a median score would be more useful.

Response: Thank you for your suggestion. We have revised the corresponding text in the revised text page10 line13-16).

5.What are the units for MD of peak VO₂? Is it METS? Please also provide unit for other MD measures eg SBP

Response: Thank you for your suggestion. We have provided the unit for all MD measures mentioned in the text (page 11 line 12-13, page 13 line 2, page 13 line 11-12, line21-22).

6. Avoid using 'didn't' better to say did not.

Page 12 I am uncertain why an I squared value has been provided for 'biochemical examinations' when this would entail a range of markers eg phosphate, creatinine etc.' so one value is insufficient please report them all. Similarly please report all lipid values.

Response: Thank you for the suggestion. We have revised the text by changing 'biochemical examinations' to 'serum phosphorus', and changing 'blood lipid' to 'cholesterol' (page 13 line 11-12).

7. Why does cardiac function suddenly appear when it is not listed as an outcome in methods, please remove it. Also what are the units? A MD of 61 cannot be ejection fraction so it cannot be that cardiac function is reported here.

Response: Thank you for the suggestion. We have removed the phrase 'cardiac function' and replaced that with 'physical performance' (page 14 line 2, line 5-6).

8.Where are results for albumin etc.?

Response: The results of albumin have been provided in the first paragraph of the section 'Secondary outcomes' (page 13 line 6-9).

9.The events analysis is futile as only 2 studies reported and event prevalence is negligible.

Response: Thank you for your suggestion. We have revised the conclusion which is more accurate in describing the safety issue (page17 line 11-14, page19 line 6).

10.DISCUSSION

It is good that clinical meaning of kt/v is discussed but the MD reduction of 0.07 does not really add context as we need to know where patients ended after exercise to relate to mortality and other outcomes.

Response: Thank you for your suggestion. Since all studies included failed to examine the influence of intradialytic exercise on patient mortality, we can not analyze the mortality rate after the prescribed exercise, which has been mentioned in the manuscript. However, we explained in the revised manuscript that Kt/V was found to inversely correlate with the mortality of patients on maintenance hemodialysis. Based on this assumption, we proposed that intradialytic exercise might lower mortality through increasing Kt/V.

11. Relate peak VO₂, PCS, MCS to knowledge of clinically meaningful reductions eg is 4.11 change in VO₂(units????) meaningful or not?

Response: Thank you for your suggestion. We have added the discussion about VO₂ in the revised discussion section. PCS and MCS are the physical and mental self-rating levels of patients' quality of life; the higher the scores are, the better their quality of life will be (page 15 line 20-21 to page 16 line1-6).

Replies to Reviewer 2

1. Writing style would benefit from improvement in places but is generally ok– there are spelling mistakes, and inappropriate wording: p.4 line 5 (efficiency), p.5 line 26 (unconformable), line 41 (better sleep), line 47 (introdialytic), p.6 line 36 (literature data), p.13line 43 (efficiency)

Response: We have corrected all the spelling mistakes and inappropriate wordings in the revised manuscript.

2.The authors state that there is a lack of evidence supporting efficacy and safety of IDE – however, this is not strictly true – the authors should reference other major recent studies and reviews/meta-analyses. They should more convincingly justify the need for this particular review/meta-analysis to be conducted and what it aims to add to the literature.

Response: Thank you for the suggestion. We have made revisions in the corresponding areas in the revised manuscript. Please refer to page 6 line 9-21.

3. In the introduction, the authors discuss an isolated case of simultaneous bilateral quadriceps tendon rupture as an important indicator of the danger of IDE. This seems a little odd. One case of this in all the thousands of hours performed does not seem relevant. Safety concerns during IDE are more related to hypotension and other cardiovascular sequelae. This should be the focus.

Response: Thank you for the suggestion. We have made revisions in the corresponding areas in the revised manuscript. Please refer to page 6 line 5.

4.Methodology seems appropriate and the study is well conducted, adhering to the PRISMA guidelines and using Cochrane software. Inclusion/exclusion of trials is suitable. However, it does not appear to have been registered with a designated registry. Statistical review is also recommended to ensure appropriate application of meta-analytical techniques etc.

Response: Thank you for the comment. We will follow your instructions in our work in the future.

5. Results are reasonably well presented and described, however, there appears to be a major problem with the Forest plots. They seem to indicate that improvements in VO₂ peak, Kt/V, 6MWT etc favour control (not exercise). Presumably a data input error?

Response: Thank you for the suggestion. We have amended our figure to clarify our intent. Please refer to figures 3,4,7.

6. VO₂ peak is one of the main outcome of interest, however, it is not stated anywhere in the paper how this was measured/estimated. This should be included and discussed as it is a very important determinant of this measure

Response: Thank you for the suggestion. We have added relevant discussion in the revised manuscript. Please refer to page 15 line 20 to page 16 line 6.

7. Depression – overview description of which tools/questionnaires were used should be included in the manuscript

Response: Thank you for the suggestion. We have added the descriptions about depression assessment tools used in the included studies, such as Self-rating Depression Scale, Beck Depression Inventory, and The Hospital Anxiety and Depression Scale, in the revised discussion section. Please refer to page 16 lines 13-20.

8. Cardiac function is mentioned a number of times, but it is not distinguished how this was measured and what parameters were used. This is very important. Also cardiac function is not followed through in the discussion. There is no explanation of the data, appraisal of the results or any discussion of the relevance to clinical outcomes.

Response: Thank you for the suggestion. We have removed the phrase “cardiac function” from the manuscript.

9. Exercise interventions – there should be a more thorough appraisal of the interventions included. Significant heterogeneity is described, but the relevance of this should be further explored and discussed. Also, do any of the papers mention fidelity – ie what was adherence/compliance like and how able were participants to complete the intended intervention.

Response: Thank you for the suggestion. We have discussed the results of different exercise prescriptions in the revised manuscript. Please refer to page 17 line 11-14, page 18 line 15. With regard to the issue of patient compliance to the prescribed interventions, we believed that the compliance was good, since the exercise program was implemented during dialysis under the supervision of caring staff.

10. The authors conclude that IDE is safe - this may be overstated given that 12 trials did not report adverse events (as identified by the authors). This conclusion should be reconsidered or better justified

Response: Thank you for the suggestion. We have revised the conclusion which is more accurate in describing the safety issue (page 17 line 11-14, page 19 line 6)

11. The final sentence of the conclusion is perhaps a little bold. Current data and this review do not suggest reduced mortality with IDE. Although this is possible, it is highly speculative and should be removed or reworded to better reflect this.

Response: Thank you for the suggestion. The sentence mentioned above (the final sentence of the conclusion) has been removed from the manuscript.

Replies to Reviewer 3

1. Page 9 row 29-31 they say: when heterogeneity was not substantial or obvious clinical heterogeneity was eliminated and the random effects model was used to combine the data.

I suppose they should say: when heterogeneity was not substantial or obvious clinical heterogeneity was eliminated and the fixed effects model was used to combine the data.

Response: Thank you for your insightful suggestion. We have revised the sentences as suggested. Please refer to page9 lines17.

2. Albumin levels should be reported with mean differences and not with SMD. Due to Mg/dl or mmol/dl can be changed instead standardized the results. The same for cholesterol and phosphorus levels.

Response: Due to the differences in the unit of albumin, cholesterol, and phosphorus used in the original reports, deviations of results may arise if we transform all of them into a unified unit, particularly when we extract mean with standard deviations from each study. Therefore, we used SMD for analysis.

3. Page 12 Row 44 they say: No significant heterogeneity was found [SMD=0.01,95%CI(0.29,0.31), P=0.95;Fig. 6B] They should include a heterogeneity value and confidence interval is wrong (it should include the negative sign).

Page 29: Geovana 2016, is included in the table of page 29 but that study is not included in the references.

Response: Thank you for your suggestion. We have revised the manuscript as suggested. Please refer to page 13 lines 9, Table 1 and Figure 6.

VERSION 2 – REVIEW

REVIEWER	Dr Gordon McGregor Coventry University, UK
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	<p>1. The manuscript has certainly been improved further to reviewers' comments, and the overly bold statements have been toned down</p> <p>2. During the revision period, prior to the resubmission of this manuscript, a further important meta-analysis has been published. It is important that the authors include and discuss this, as conclusions are very different to their own. It must be made clear why these two reviews reach different conclusions.</p> <p>Nephrol Dial Transplant. 2018 Mar 28. doi: 10.1093/ndt/gfy045. [Epub ahead of print] 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. Young HML1, March DS1, Graham-Brown MPM1,2, Jones AW3, Curtis F3, Grantham CS1, Churchward DR1, Highton P1,2, Smith AC1, Singh SJ4, Bridle C3, Burton JO1,2.</p> <p>3. In the same vein, the introduction must still be more convincing as to what this paper adds to the existing literature and why it is different from existing reviews. The rationale for undertaking this work must be clearly described</p> <p>4. Pg 5, line 26 – lack of education is an unlikely a prominent reason for low physical activity in this population</p>
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	<p>5. Pg5, line 55 – what does this sentence mean? it is not clear</p> <p>6. Pg 6, line 16 – ‘injuries’ – this is the wrong word</p> <p>7. Pg 14, line 33 – please reconsider the word ‘efficiency’ – it doesn’t seem to quite match the authors point</p> <p>8. Pg. 18, line 13 – this new paragraph, whilst addressing reviewers’ concerns, would benefit from English language editing. There are numerous grammatical errors which make it hard to follow</p>
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REVIEWER	Alvarez-Villalobos Neri Alejandro Universidad Autonoma de Nuevo Leon, Subdireccion de Investigaci3n
REVIEW RETURNED	25-Jun-2018

GENERAL COMMENTS	<p>In row 13 of page 13, the authors mention that twelve studies compare Hb, but they show 13 references. They have to eliminate a reference or authors have to mention that thirteen are the ones that make the comparison of Hb.</p> <p>In row 45 of page 17 is badly written hemodialysis. They wrote hemdialysis</p> <p>Although there is a debate in the use of SMD or MD, in the albumin analysis, I would recommend the use of MD instead of SMD. Studies are reporting in g/dl, and just two articles (Groussard and Hristea) are reporting in g/L that is to say, it is only required to divide between 10 those two values. Moreover, we could maintain the original value of the albumin report. Which in this case seems useful. Something similar happens with cholesterol values. It requires conversion of mmol/l to mg/dl in two studies.</p> <p>In the case of phosphorus, I do not understand the reason for using SMD, I believe that all results are reported with the same units.</p> <p>The authors mention that "resistance exercise and a combination of aerobic and resistance exercise were not studied in the RCTs," but on study characteristics, authors mention that four studies focused on resistance exercise, and seven on a combination of aerobic and resistance exercises. I suggest only mentioning: "due to the heterogeneity of exercise methods in the included studies, we did not perform subgroup analyses."</p> <p>However, these observations do not limit the publication of this article.</p>
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VERSION 2 – AUTHOR RESPONSE

Replies to Reviewer : Dr Gordon McGregorr

1. The manuscript has certainly been improved further to reviewers’ comments, and the overly bold statements have been toned down

Response: Thank you for your comment and the original advice.

2. During the revision period, prior to the resubmission of this manuscript, a further important meta-analysis has been published. It is important that the authors include and discuss this, as conclusions are very different to their own. It must be made clear why these two reviews reach different conclusions.

Nephrol Dial Transplant. 2018 Mar 28. doi: 10.1093/ndt/gfy045. [Epub ahead of print]

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.

Young HML1, March DS1, Graham-Brown MPM1,2, Jones AW3, Curtis F3, Grantham CS1, Churchward DR1, Highton P1,2, Smith AC1, Singh SJ4, Bridle C3, Burton JO1,2.

Response: Thank you for the suggestion. We have compared the findings in the reference (Young et al., 2018) with ours' and discussed in the revised manuscript. Please refer to page 18, line 4 to 8.

Indeed, there is a recent meta-analysis published by Young et al., in which intra-dialytic exercise failed to improve VO₂ and blood pressure. These findings are not inconsistent with ours. This is possibly because our study enrolled studies involving aerobic exercise, resistance exercise, or their combination; while the study of Young et al. only included studies of aerobic exercise.

3. In the same vein, the introduction must still be more convincing as to what this paper adds to the existing literature and why it is different from existing reviews. The rationale for undertaking this work must be clearly described

Response: Thank you for your suggestion. There is a controversy whether intra-dialytic exercise is beneficial and safe for those receiving hemodialysis, and results from prior meta-analysis studies are inconsistent with limited randomized controlled trials (RCTs) included. Owing to the emergence of new evidence from recent RCTs, we believe that an updated meta-analysis is necessary to answer these unsolved questions.

4. Pg 5, line 26 – lack of education is an unlikely a prominent reason for low physical activity in this population

Response: Thank you for your advice. We have deleted the sentence from the revised manuscript.

5. Pg5, line 55 – what does this sentence mean? it is not clear

Response: Thank you for the comment. We have revised the highlighted sentence.

6. Pg 6, line 16 – 'injuries' – this is the wrong word

Response: We have revised the word to "injury".

7. Pg 14, line 33 – please reconsider the word ‘efficiency’ – it doesn’t seem to quite match the authors point

Response: Thank you for your suggestion. We have changed the word “efficiency” to “efficacy”.

8. Pg. 18, line 13 – this new paragraph, whilst addressing reviewers’ concerns, would benefit from English language editing. There are numerous grammatical errors which make it hard to follow

Response: Thank you for the suggestion. We have revised this paragraph according to your suggestion.

Replies to Reviewer 3 Alvarez-Villalobos Neri Alejandro

1. In row 13 of page 13, the authors mention that twelve studies compare Hb, but they show 13 references. They have to eliminate a reference or authors have to mention that thirteen are the ones that make the comparison of Hb.

Response: Thank you for your suggestion. We have removed the original reference NO.15 from our manuscript.

2. In row 45 of page 17 is badly written hemodialysis. They wrote hemdialysis

Response: Thank you for your suggestion. We have amended the word “hemdialysis” in the sentence.

3. Although there is a debate in the use of SMD or MD, in the albumin analysis, I would recommend the use of MD instead of SMD. Studies are reporting in g/dl, and just two articles (Groussard and Hristea) are reporting in g/L that is to say, it is only required to divide between 10 those two values. Moreover, we could maintain the original value of the albumin report, which in this case seems useful. Something similar happens with cholesterol values. It requires conversion of mmol/l to mg/dl in two studies.

In the case of phosphorus, I do not understand the reason for using SMD, I believe that all results are reported with the same units.

The authors mention that "resistance exercise and a combination of aerobic and resistance exercise were not studied in the RCTs," but on study characteristics, authors mention that four studies focused on resistance exercise, and seven on a combination of aerobic and resistance exercises. I suggest only mentioning: "due to the heterogeneity of exercise methods in the included studies, we did not perform subgroup analyses."

Response: Thank you for your recommendation. As the levels of serum phosphate in several of the studies mentioned were expressed in mmol/L, while others were in mg/dL, we decided to use SMD in this study. We will change to MD in subsequent studies according to your suggestion.

We have mentioned “due to the heterogeneity of exercise methods in the included studies, we did not perform subgroup analyses” in the revised manuscript (page 19, line 9 to 10).