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Support: None.

Review Stage at time of this submission: The review has not yet started.

Conflicts of interest: None.

INTRODUCTION

Review question / Objective: We aim to explore the effects of exercise on inflammation and nutrition in adult patients with chronic kidney disease(CKD) without renal replacement therapy. Condition being studied: Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. Rehabilitation effects of exercise on adults with CKD have been generally recognized; however, the effects of exercise on

Effects of exercise on inflammation and nutrition outcomes in patients with chronic kidney disease: a protocol for systematic review and meta-analysis

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Condition being studied: Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. Rehabilitation effects of exercise on adults with CKD have been generally recognized; however, the effects of exercise on inflammation and nutrition have been underexplored. We aim to explore the effects of exercise on inflammation and nutrition in adult patients with chronic kidney disease(CKD) without renal replacement therapy. This systematic review analyzed the evidence and made recommendations for clinical applications and future research.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 October 2020 and was last updated on 03 February 2021 (registration number INPLASY2020100025).

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METHODS

Search strategy: The literature search will be conducted by two researchers (Lihua Wu & Yu Liu) independently in the form of "back-to back", discrepancies regarding included studies will be discussed and settled by a third reviewer(Mingguan Li). We will use the combination of Medical Subject Headings(MeSH)terms and free text words to complete the literature search strategies, mainly include: 1) "exertion, physical" [MeSH Terms], "exercise" [MeSH Terms], "physical activity" [MeSH Terms], "physical fitness" [MeSH Terms], "resistance training" [MeSH Terms], "aerobic exercise" [MeSH Terms], "exercise training", "exercise therapy", "exercise test", "resistance program", "resistance exercise", "aerobic program", "aerobic training", "endurance exercise", "endurance training", "endurance program", "physical activit*", "physical rehabilitation", 2) " renal insufficiency " [MeSH Terms] , " chronic kidney failure" [MeSH Terms], " renal disease ", " kidney disease ", " renal failure ", " kidney insufficiency "," CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF ". Besides, we will scan the reference lists of included original or relevant reviews to identify additional relevant articles.

Participant or population: All adults (\geq 18 years) with any stage CKD without renal replacement therapy (kidney transplant or dialysis). Studies investigating the effects of regular physical exercise training in adults with acute kidney injury (AKI) and studies in children were excluded.

Intervention: the intervention included one or more modalities of regular exercise

training, such as aerobic exercise, resistance exercise, and combined aerobic exercise and resistance exercise. An exercise program should include intensity, frequency, and duration (\geq 2 months).

Comparator: Control group with usual care or no exercise.

Study designs to be included: Randomized controlled trial (RCT) including combination therapy and monotherapy of exercise will be included.

Eligibility criteria: 1. Patients: All adults (≥ 18 years) with any stage CKD without renal replacement therapy (kidney transplant or dialysis).2. Intervention included one or more modalities of regular exercise training, such as aerobic exercise, resistance exercise, and combined aerobic exercise and resistance exercise. The exercise program should include intensity, frequency, and duration (\geq 2 months). 3. Control group with usual care or no exercise.4. The primary outcomes include: 1)Nutritional measures: Subjective Global Assessment (SGA); albumin; pre-albumin; 2)Systemic inflammation outcomes: serum interleukin 6; C-reactive protein (CRP) level. The secondary outcomes include 1)Nutritional measures: energy intake; protein intake; transferrin; body mass indices (muscle mass, fat mass, body mass index, anthropometric measures - waist circumference, mid-arm circumference, calf circumference; mid-thigh circumference); 2)Systemic inflammation outcomes: tumor necrosis factor-a; 3.Only RCTs will be included.

Information sources: We will comprehensively search the following 9 databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), The Cumulative Index to Nursing & Allied Health Literature (CINAHL), Web of Science, Chinese National Knowledge Infrastructure (CNKI), WANFANE Database, Chinese Scientific and Technological Periodical Database (VIP) and Chinese Biomedical Database (CBM). Ambiguous literature will be manually searched to avoid missing eligible trials. Ongoing registered clinical trials will be searched on the websites of the Chinese clinical trial registry (http:// www.chictr.org.cn/) and international clinical trial registry (http:// clinicaltrials.gov/). Additional trials will be searched by reviewing the reference lists of the retrieved articles, conference proceedings, and gray literature. We will contact the original investigators for more complete details of the study to solve questions about eligibility if necessary.

Main outcome(s): The primary outcomes include: 1)Nutritional measures: Subjective Global Assessment (SGA); albumin; prealbumin; 2)Systemic inflammation outcomes: serum interleukin 6; C-reactive protein (CRP) level.

Additional outcome(s): The secondary outcomes include: 1)Nutritional measures: energy intake; protein intake; transferrin; body mass indices (muscle mass, fat mass, body mass index, anthropometric measures - waist circumference, mid-arm circumference, calf circumference; midthigh circumference); 2)Systemic inflammation outcomes: tumor necrosis factor-a.

Quality assessment / Risk of bias analysis:

The quality of the studies will be assessed by the Cochrane Collaboration. For unclear items in the study, contact the corresponding author for details. The quality assessment will be conducted independently by two researchers (Lihua Wu & Ling Wu). Any disagreement will be resolved by/through discussion with a third reviewer (Mingquan Li).

Strategy of data synthesis: Review Manager 5.4 software, provided by the Cochrane Collaboration www.cochrane.org will be used for data analysis. Binary outcomes will be summarized using odds ratios (ORs) or relative risks (RRs) with a 95% confidence interval (CI) for relative effect. Continuous outcomes will be presented as a mean difference (MD) with 95% CI between groups. Statistical heterogeneity between trials will be analyzed by Q statistic and I2 test. When the heterogeneity test indicated that there was no heterogeneity between the groups (P >.01, I2 <50%), the fixed-effect model was used for combined analysis to We adopted the Dersimonian-Laird inversevariance-weighted random-effects model to pool results, then calculated heterogeneity (P50% =high heterogeneity). When the heterogeneity test indicated that there was no heterogeneity between the aroups (P > .01, I2 < 50%), the fixed-effect model was used for combined analysis. If quantitative synthesis is not appropriate, qualitative analysis will be carried out. Quality of evidence and strength of recommendations will be assessed by the Grading of Recommendations, Assessment, Development, and **Evaluations (GRADE) method.**

Subgroup analysis: Subgroup analysis will be further stratified by the type of intervention and treatment duration when there were sufficient data.

Sensibility analysis: Sensitivity analysis will be performed by changing the effect model, for evaluating whether the results of the meta-analysis are reliable and finding the potential sources of heterogeneity. The funnel plot analyses would be performed to determine potential publication bias if every comparison included more than 10 studies.

Language: English or Chinese articles.

Country(ies) involved: China.

Other relevant information: None.

Keywords: chronic kidney disease, exercise, systematic review.

Dissemination plans: The results will be published in a scientific journal after peerreview and disseminated electronically or in print.

Contributions of each author:

Author 1 - Lihua Wu - drafted the manuscript.

Author 2 - Hongmei Lu - provided statistical expertise.

Author 3 - Ling Wu - contributed to the risk of the bias assessment strategy. Author 4 - Bo Qu - read, provide feedback, and approved the final manuscript. Author 5 - Yu Liu - contributed to the development of the selection criteria. Author 6 - Mingquan Li - designed the study protocol.