INPLASY PROTOCOL

To cite: Wang et al. Vitamin D for inflammation biomarkers in coronary artery disease: a protocol for systematic review and meta-analysis. Inplasy protocol 202060072. doi: 10.37766/inplasy2020.6.0072

Received: 20 June 2020

Published: 20 June 2020

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Support: **National Natural Science Found**

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

Conflicts of interest:
None.

Vitamin D for inflammation biomarkers in coronary artery disease: a protocol for systematic review and meta-analysis

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Review question / Objective: **Participants: All patients must meet the CAD diagnostic criteria established by the American College of Cardiology/American Heart Association. Interventions: Patients in the experimental group should be treated with VD or VD plus conventional medicine, such as statin, aspirin, b-blockers, et al. The patients in control group should be treated with VD placebo or VD placebo plus the same conventional medicine. Outcomes: Primary outcomes. Inflammation biomarkers of peripheral blood include CRP, IL-2, IL-6 and IL-10; Secondary outcomes. Triglyceride, total cholesterol, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol, blood pressure and adverse effects. Types of studies: All the clinical randomized controlled trials of VD for CAD will be included in the review.**
Condition being studied: **Coronary artery disease (CAD) is a clinically common coronary heart disease. Vitamin D (VD) might be beneficial in CAD patients through its favorable effects on inflammation biomarkers. This study was performed to examine the effects of VD supplementation on inflammatory markers in CAD patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 June 2020 and was last updated on 20 June 2020 (registration number INPLASY202060072).

INTRODUCTION

Review question / Objective: **Participants: All patients must meet the CAD diagnostic criteria established by the American College of Cardiology/American Heart Association. Interventions: Patients in the experimental group should be treated with VD or VD plus conventional medicine, such as statin, aspirin, b-blockers, et al. The patients in control group should be treated with VD placebo or VD placebo plus the**

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Condition being studied: Coronary artery disease (CAD) is a clinically common coronary heart disease. Vitamin D (VD) might be beneficial in CAD patients through its favorable effects on inflammation biomarkers. This study was performed to examine the effects of VD supplementation on inflammatory markers in CAD patients.

METHODS

Participant or population: Coronary artery disease patients.

Intervention: VD or VD plus conventional medicine, such as statin, aspirin, b-blockers, et al.

Comparator: VD placebo or VD placebo plus the same conventional medicine.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: Participants: All patients must meet the CAD diagnostic criteria established by the American College of Cardiology/American Heart Association. There will be no limitations of countries, ages, gender and comorbidity. Patients with acute myocardial infarction, myocarditis, uncontrolled chronic diseases, mental illness or related drug allergy will be excluded. Addtionally, patiens who consume VD supplements within the past 3 months will also be excluded. will be excluded. Interventions: Patients in the experimental group should be treated with VD or VD plus conventional medicine, such as statin, aspirin, -blockers, et al. The patients in control group should be treated with VD placebo or VD placebo plus the same conventional medicine. It will not be limited to VD doses and courses. Outcomes: Primary outcomes. Inflammation biomarkers of peripheral blood include CRP, IL-2, IL-6 and IL-10; Secondary outcomes. Triglyceride, total cholesterol, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol, blood pressure and adverse effects Types of studies. All the clinical randomized controlled trials of VD for CAD will be included in the review.

Information sources: We will search the following electronic databases, including PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese Biological and Medical database, VIP, and Wanfang Database. The search time limit is from the database inception to June 2020. In addition, we will also manually search for the relevant journals, conference articles, dissertations and unpublished researches to avoid missing grey literature. Two investigators (YFZ and JW) will search for the potential studies according to the methods independently.

Main outcome(s): Inflammation biomarkers of peripheral blood include CRP, IL-2, IL-6 and IL-10.

Data management: Two researchers (NZ and MJM) will independently use Review Manager (Revman, version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software to extract literature data. A third research member (PL) will detect data consistency and check the final database. If the data of included study are uncertain, lost or in the form that not extractable, we will email the authors of the study to request for an affirmation. The data extraction contents are as follows: Common information: title, first author, corresponding author, publishing time and contact information. Study designs: article type, sample size, baseline balance, randomized method, blinding method, data loss and analysis and selective reporting. Participants: region, ethnicity, age, male/female ratio, diagnostic criteria, combined

disease and duration of illness. Intervention: treatment period, treatment frequency, drug dosage, combined drugs, details about the control group and follow-up. Outcomes: main observation indicators (inflammation biomarkers of peripheral blood include CRP, IL-2, IL-6 and IL-10) and secondary observation indicators (triglyceride, total cholesterol, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol and blood pressure) and adverse effects. Others: sources of funding, ethics audit.

Quality assessment / Risk of bias analysis: Two independent reviewers (NZ and MJM) will use the Cochrane Collaboration's tool to assess the methodological quality and risk of bias. The assessment contains seven dimensions: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other issues. Each bias divides into low, unclear and high level according to the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.3). The inconsistencies cannot be resolved in this review will search consensus for a third author (PL) as required. Or else, we will consult with the Cochrane Professional Group for final resolution.

Strategy of data synthesis: We will use Chi-squared test to conclude the homogeneity of included studies. I2 statistic >50% suggests significant heterogeneity of the test (using a random effect model), and I2 statistic <50% suggests that there is no statistical heterogeneity or heterogeneity is small relatively (using a fixed effect model). If there is significant clinical heterogeneity, firstly we will check the raw data in the studies. Next, the sensitivity analysis or subgroup analysis will be used to find the cause of heterogeneity. If it is unable to judge the source of heterogeneity, we will choose descriptive analysis.

Subgroup analysis: We will perform subgroup analysis to measure the heterogeneity of the researches as following reasons: (1) Clinical consideration: different age, sex and race; different VD dosage and VD form; different treatment course (2) Methodology consideration: tests with unclear or high risks of bias.

Sensibility analysis: If possible low-quality studies are included, we will perform the sensitivity analysis. This is a key method mainly used to evaluate the robustness and reliability of the combined meta-analysis results. The method is eliminating each included article, or changing the inclusion and exclusion criteria or removing some types of articles.

Language: English.

Country(ies) involved: China.

Keywords: coronary artery disease; Vitamin D; inflammation biomarkers; review.

Contributions of each author:
Author 1 - Yiru Wang - Assessment of heterogeneity and reporting bias, sensitivity analysis, grading the quality of evidence, writing – original draft.
Author 2 - Yifan Zhang - Search for the potential studies.
Author 3 - Jing Wei - Search for the potential studies.
Author 4 - Wenting Du - Search for the included studies.
Author 5 - Jie Ding - Search for the included studies.
Author 6 - Yiyi Zhang - Assessment of heterogeneity and reporting bias, sensitivity analysis.
Author 7 - Na Zhang - Data extraction and synthesis, risk of bias assessment.
Author 8 - Meijiao Mao - Data extraction and synthesis, risk of bias assessment.
Author 9 - Ping Liu - Conceptualization, grading the quality of evidence.