Clinical therapeutic effects of combined diacerein and glucosamine in the treatment of osteoarthritis
A protocol for systematic review and meta-analysis

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Abstract
Background: Osteoarthritis (OA) has been identified as a common musculoskeletal condition. As a chronic condition, OA adversely impact the hip and knee joints. Surgical treatment for hip and knee osteoarthritis is associated with high financial and long recovery processes. Therefore, patients are continually searching for alternative methods of treatment. Diacerein is regarded as symptom-modifying, slow-acting drug that could most likely change the disease structure of OA. The present systematic review protocol explains methods utilized to evaluate the clinical therapeutic effects of combining diacerein and glucosamine to treat OA.

Methods: The authors will conduct a search for randomized controlled trials comparing diacerein plus glucosamine with diacerein alone, glucosamine alone, or another treatment in patients with OA. The search will be done in the following online-based databases: EMBASE, MEDLINE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, and WanFang Database. All related RCTs included from inception to September 29, 2021 are included. Two authors will independently conduct data abstraction and quality assessment, and the comparative analysis will compare the results. The present meta-analysis will be performed with the RevMan software (version 5.3), where the results will be expressed as relative risk, mean differences, or standardized mean differences with 95% confidence intervals.

Results: This study will be conducted to evaluate the clinical therapeutic effects of combined diacerein and glucosamine in the treatment of OA.

Conclusion: The summary presented in the study will ascertain whether diacerein plus glucosamine intervention is an efficient and feasible method of treatment for OA patients.

Trial registration number: 10.17605/OSF.IO/VHPZC

Abbreviations: AEs = adverse effects/events, NSAIDs = non-steroidal anti-inflammatory drugs, OA = osteoarthritis, RCTs = randomized controlled trials.

Keywords: diacerein, efficacy, glucosamine, meta, osteoarthritis

1. Introduction

Osteoarthritis (OA) is prevalent among the elderly population. It is a progressive and chronic musculoskeletal condition.1,2 Initially, OA patients experience deterioration in the cartilage resulting in inflammation and destruction of the joints surround-
It has been reported that combining diacerein with another treatment exhibited higher effectiveness when treating OA patients. Thus, it is crucial to perform a meta-analysis on the clinical therapeutic effects of combining diacerein and glucosamine in the treatment of OA.

2. Methods

The present protocol is registered on the Open Science Framework (OSF, https://osf.io/), the registration number is 10.17605/OSF.IO/VHPZC. The development of the protocol will follow the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P).[14]

2.1. Ethics and dissemination

Since the systematic evaluation does not collect patient information and uses the data from published research papers, the proposed meta-analysis will not need an ethics approval and informed consent of patients.

2.2. Eligible criteria for study selection

2.2.1. Types of studies. Only randomized controlled trials (RCTs) of diacerein plus glucosamine in treating OA patients are considered.

2.2.2. Types of participants. All participants with OA are included, there are no restrictions for age, sex, country, and educational background.

2.2.3. Types of interventions. This study includes diacerein plus glucosamine to provide a detailed description of its clinical therapeutic effects on OA patients. Studies that are interfered with diacerein alone, glucosamine alone, no treatment, placebo, or other traditional drugs are considered as control groups.

2.2.4. Types of outcome measures. The primary outcomes include physical function, pain, Lequesne index, radiographic outcomes (radiologic differences in the width of the joint space or narrowing in millimeters, and alternative radiographic standards), collective number of negative effects/events (AEs), and serious AEs. The minor outcomes include quality of life, requirement for joint surgery or arthroscopy, requirement for concomitant medications for number of fatalities, pain relief, and specific AEs.

2.3. Search methods for the identification of studies

2.3.1. Electronic searches. The authors will conduct a search for all RCTs that compared diacerein plus glucosamine with diacerein alone, glucosamine alone, or another treatment in patients with OA. The search will be done in the following online-based databases: EMBASE, MEDLINE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, and WanFang Database. All related RCTs included from inception to September 29, 2021 are included. The authors will use the following key terms for searching: osteoarthritis, OA, diacerein, glucosamine, pain, function, score, grade, motion.

2.3.2. Searching other resources. The authors will search the reference lists of the eligible studies to find additional trials. Since there are several international nutraceutical companies in the chondroitin market, it was deemed that contacting each one to gain unpublished data would not be feasible. This study will not include any search conference proceedings or specific journals, as defined.

2.4. Data collection and analysis

2.4.1. Selection of studies. Pre-determined criteria will be adopted to identify potentially eligible trials. A pair of authors will autonomously evaluate the methods sections in all identified trials based on the pre-determined assessment criteria. All disagreements will first be resolved by consensus. For unresolved disagreements, a third independent author’s opinion would be considered.

2.4.2. Data extraction and management. We will use an electronic form to extract crucial content, and then it will be filled by 2 authors autonomously. The content include first and corresponding author, inception time, trial designate, features of patients, intercessions, duration, outcomes, adverse impacts, and other specific information. Disagreements shall be solved via group discussion or by consulting with seniors. However, if the authors do not reach a consensus, the respective authors of the studies will be contacted to obtain additional details and further verification.

2.4.3. Assessment of risk of bias in included studies. Two independent authors shall assess the bias risk associated with each trial included with the Cochrane Collaboration assessment recommendations. The primary criteria applied in measuring the risk of bias include blinding presence, allocation concealment, random sequence generation, partial outcome data, and selective outcome reporting.[15] The bias risk of each study was assessed under each criterion using the following standard: low bias risk, high bias risk, or unclear bias risk. Disagreements shall be resolved through a group discussion or by consulting seniors.

2.4.4. Measures of treatment effect. Continuous data will be represented using the mean differences, or standardized mean differences with 95% confidence intervals when evaluating the treatment effect, under which a similar method or measure scale are adopted. For dichotomous data, the relative risk with 95% confidence interval will be used to estimate the treatment effect.

2.4.5. Assessment of heterogeneity. The authors will qualitatively assess the inconsistency in pooled estimates by adopting the I² statistic. It will illustrate the variability percentage in effect estimates that originate from heterogeneity instead of the sampling error.[15]

2.4.6. Assessment of reporting biases. A funnel plot will be employed to determine the publication bias if there are >10 eligible studies for inclusion. [16]

2.4.7. Sensitivity analysis. In order to ascertain the robustness of the conclusions, we will conduct a sensitivity analysis according to the following criteria: sample size, qualities of heterogeneity, and statistical model (random-effects or fixed-effects model).

3. Discussion

To the best knowledge of the authors, this meta-analysis is the first to assess the clinical therapeutic effects of using combined diacerein and glucosamine to treat OA. Indeed, similar articles discuss the issue. However, they did not include non-RCT studies, they also did not include papers written in different
languages. Therefore, the results of the present study will contribute to the literature and fill the gap in research. Besides, it will provide reference for clinical practice.

Author contributions

Conceptualization: Fei Wang, Wei-Xing Shi, Jie Chen, Kang He, Wei Fang.
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References

[1] Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthritis Cartilage 2021.
[2] Summanen M, Ukkola Vuoti L, Kurki S, Tuominen S, Madanat R. The burden of hip and knee osteoarthritis in Finnish occupational healthcare. BMC Musculoskelet Disord 2021;22:501.
[3] Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965–73.
[4] Shah N, Jadidi S, Bajaj P. Correction: a review of non-surgical pain management in osteoarthritis. Cureus 2021;13:e45.
[5] Seah KTM, Rammanohar J, Sutton J, To K, Khan WS. The effectiveness of anti-nerve growth factor monoclonal antibodies in the management of pain in osteoarthritis of the hip and knee: a PRISMA systematic review and meta-analysis. Pain Med 2021;22:1185–204.
[6] Sakellariou G, Conaghan PG, Zhang W, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017;76:1484–94.
[7] Louthrenoo W, Nilganuwong S, Aksaranugraha S, Asavatanabodee P, Saengnipanthkul S. The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study. Osteoarthritis Cartilage 2007;15:605–14.
[8] Steinecker-Frohnsiwer B, Kaltenegger H, Weigl L, et al. Pharmacological treatment with diacerein combined with mechanical stimulation affects the expression of growth factors in human chondrocytes. Biochem Biophys Rep 2017;11:154–60.
[9] da Silva MD, Cical-Filho FJ, Winkelmann-Duarte EC, et al. Diacerein reduces joint damage, pain behavior and inhibits transient receptor potential vanilloid 1, matrix metalloproteinase and glial cells in rat spinal cord. Int J Rheum Dis 2017;20:1337–49.
[10] de Isla NG, Stoltz JF. In vitro inhibition of IL-1beta catabolic effects on cartilage: a mechanism involved on diacerein anti-OA properties. Bioreheology 2008;45:433–8.
[11] Kongthavonskul J, Anothaisintawee T, McEvoy M, Attia J, Woratarnap P, Thakkinstian A. Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis. Eur J Med Res 2015;20:24.
[12] Pavella K, Bruyère O, Cooper C, et al. Diacerein: benefits, risks and place in the management of osteoarthritis. An opinion-based report from the ESCEO. Drugs Aging 2016;33:75–85.
[13] Hermann W, Lambova S, Muller-Ladner U. Current treatment options for osteoarthritis. Curr Rheumatol Rev 2018;14:108–16.
[14] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[15] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[16] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.