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Relationship between osteonecrosis and antiphospholipid antibodies in patients with systemic lupus erythematosus: a systematic review protocol

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ABSTRACT

Introduction Osteonecrosis (ON) is characterised by the destruction of the normal blood supply to the bone tissue. ON is the main cause of disability in patients with systemic lupus erythematosus (SLE). Studies have reported the existence of many risk factors for SLE complicated by ON, including the use of high-dose glucocorticoids and high disease activity. The correlation between antiphospholipid antibodies (aPLs) and ON in SLE has been controversial. We aim to conduct a systematic review of the literature related to SLE, aseptic ON and aPLs, to provide a reference for the clinical screening of high-risk patients and for early prevention.

Methods and analysis The following six databases will be searched: MEDLINE/PubMed, Embase, Web of Science, Chinese Biomedical Literature Database, Wan-Fang Database and China National Knowledge Infrastructure. The database searches will not be restricted by date. Case–control studies, cohort studies or observational studies that compare aPLs between SLE patients with and without ON will be considered eligible. Articles published in English and Chinese will be included. Two researchers will independently perform the processes of study selection, data extraction and study quality assessment. The Newcastle–Ottawa Quality Assessment Scale will be used to assess the quality of the retrieved studies. A meta-analysis will be performed after screening the studies. Data will be analysed using ORs for dichotomous data.

Ethics and dissemination Ethical approval is not required because this systematic review will use published data. The systematic review will be electronically disseminated through a peer-reviewed publication or conference presentations.

PROSPERO registration number CRD42020209637.

Strengths and limitations of this study

- This study will systematically report the relationship among systemic lupus erythematosus, aseptic osteonecrosis and different antiphospholipid antibodies, to provide a reference for the clinical screening of high-risk patients and for early prevention.
- The quality of the studies will be carefully assessed using the Newcastle–Ottawa Quality Assessment Scale.
- Different study designs may cause considerable heterogeneity, which could limit the generation of convincing conclusions.

INTRODUCTION

Osteonecrosis (ON) is characterised by the destruction of the normal blood supply to the bone tissue for various reasons, leading to the collapse of the bone structure and causing joint pain and loss of function. The commonly affected parts are the femoral head and knee joints.[1] ON is the main cause of disability in patients with systemic lupus erythematosus (SLE), seriously affecting their quality of life.[2] The use of high-dose glucocorticoids is a definite, but not the only, risk factor for ON. Studies have reported the existence of other risk factors for SLE complicated by ON.[3 4] Antiphospholipid antibodies (aPLs) include lupus anticoagulant (LA), anticardiolipin (ACL) and anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies, which are closely related to thrombus formation.[5] The correlation between aPLs and ON in SLE has been controversial. On the basis of the previous findings and the fact that no meta-analysis has been conducted, we aim to conduct a meta-analysis of the literature related to SLE, aseptic ON and aPLs to provide a reference for the clinical screening of high-risk patients and for early prevention.

METHODS AND ANALYSIS

The protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews). We will conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for the development of the systematic review.

Research question

This systematic review aims to answer the following question: What is the relationship between aPLs and ON in SLE? We only explore the relationship between the positive rate of aPLs and ON, not involving the titre of aPLs.

Patient and public involvement

No patients will be involved.

Criteria for inclusion of studies in this review

Types of studies

Observational, case–control, cohort and cross-sectional studies will be included. Case reports and cases series (with fewer than five patients) will be excluded.

Types of participants

Patients with SLE will be included without age limitations. Studies related to aPLs in SLE combined with aseptic ON published in English or Chinese will be included. Cases should have clear diagnostic criteria. The diagnosis of SLE should have been made according to the 1982 revised American Rheumatism Association criteria, 1997 American College of Rheumatology classification criteria, Systemic Lupus International Collaborating Clinics classification criteria or 2019 SLE European League Against Rheumatism/American College of Rheumatology classification criteria. ON should have been radiologically confirmed using plain radiography, bone scans, MRI or tomography. Patients with other rheumatologic diseases, including Takayasu arteritis, rheumatoid arthritis and ankylosing spondylitis, will be excluded. Patients with other types of ON, such as traumatic ON and infectious ON, will be excluded.

Types of outcome assessments

Studies should provide clear regulations on the sample size. Each article must provide the OR and 95% CI for positivity of any aPL.

Search methods for identification of studies

The search strategy will be applied according to the Cochrane Handbook guidelines.[6] The following six databases will be searched from their inception through 26 December 2020: MEDLINE/PubMed, Embase, Web of Science, Chinese Biomedical Literature Database, WanFang Database and China National Knowledge Infrastructure. The keywords will include the following: “Systemic lupus erythematosus”, “Lupus Erythematosus Disseminatus”, “Libman-Sacks Disease”, “Libman Sacks Disease”, “Osteonecrosis”, “Bone Necrosis”, “Avascular Necrosis of Bone”, “Bone Avascular Necrosis”, “Kienbock Disease”, “Kienboeck’s Disease”, “kienboecks disease”, “Aseptic Necrosis of Bone” and “Bone Aseptic Necrosis.” The strategy for searching the PubMed database is shown in table 1. This search strategy will also be applied to the other electronic databases.

Table 1 Search strategy used in the PubMed database

No.	Search items
1	Systemic lupus erythematosus
2	Lupus Erythematosus Disseminatus
3	Libman-Sacks Disease
4	Libman Sacks Disease
5	or 1–4
6	Osteonecrosis
7	Bone Necrosis
8	Avascular Necrosis of Bone
9	Bone Avascular Necrosis
10	Kienbock Disease
11	Kienboeck’s Disease
12	kienboecks disease
13	Aseptic Necrosis of Bone
14	Bone Aseptic Necrosis
15	or 6–14
16	5 and 15

This search strategy will be modified as required for other electronic databases.

Screening and data collection

The titles and abstracts will be screened by two authors. Any disagreement during the selection of studies will be discussed and decided by a third author. The details of the selection process are shown in the flowchart in figure 1. The results will be screened by checking the titles and abstracts of the articles. Studies pertaining to ON, SLE and aPLs will be included. Studies that compare the positive rate of aPLs between ON and non-ON groups will be included.

Quality assessment and data extraction

The quality of the included studies will be assessed using the Newcastle–Ottawa Quality Assessment Scale. Scores between 7 and the maximum of 9 will be defined as high quality; scores between 4 and 6 will be defined as intermediate quality and scores between 1 and 3 will be defined as low quality. Two authors will independently extract the following data: general information (name, country, year of publication, title of the study, authors’ publication details, number of patients, and mean age and range), study characteristics and follow-up periods (from the measurement of the antibodies to the onset of ON, from the measurement of the antibodies to the end of follow-up, from the onset of ON to the end of follow-up). All searched studies will be imported to EndNote software, which can assist the reviewers in managing data and screening for duplicate publications. The data will subsequently be entered into Stata V.11.0 software for analysis. Any disagreement will be discussed and finally decided by a third author.

Analysis methods

Raw numerical data will be extracted from the studies. A meta-analysis will be performed, if possible, using Stata V.11.0 software. Before combining the statistics, tests for heterogeneity will be conducted. If p>0.1, the

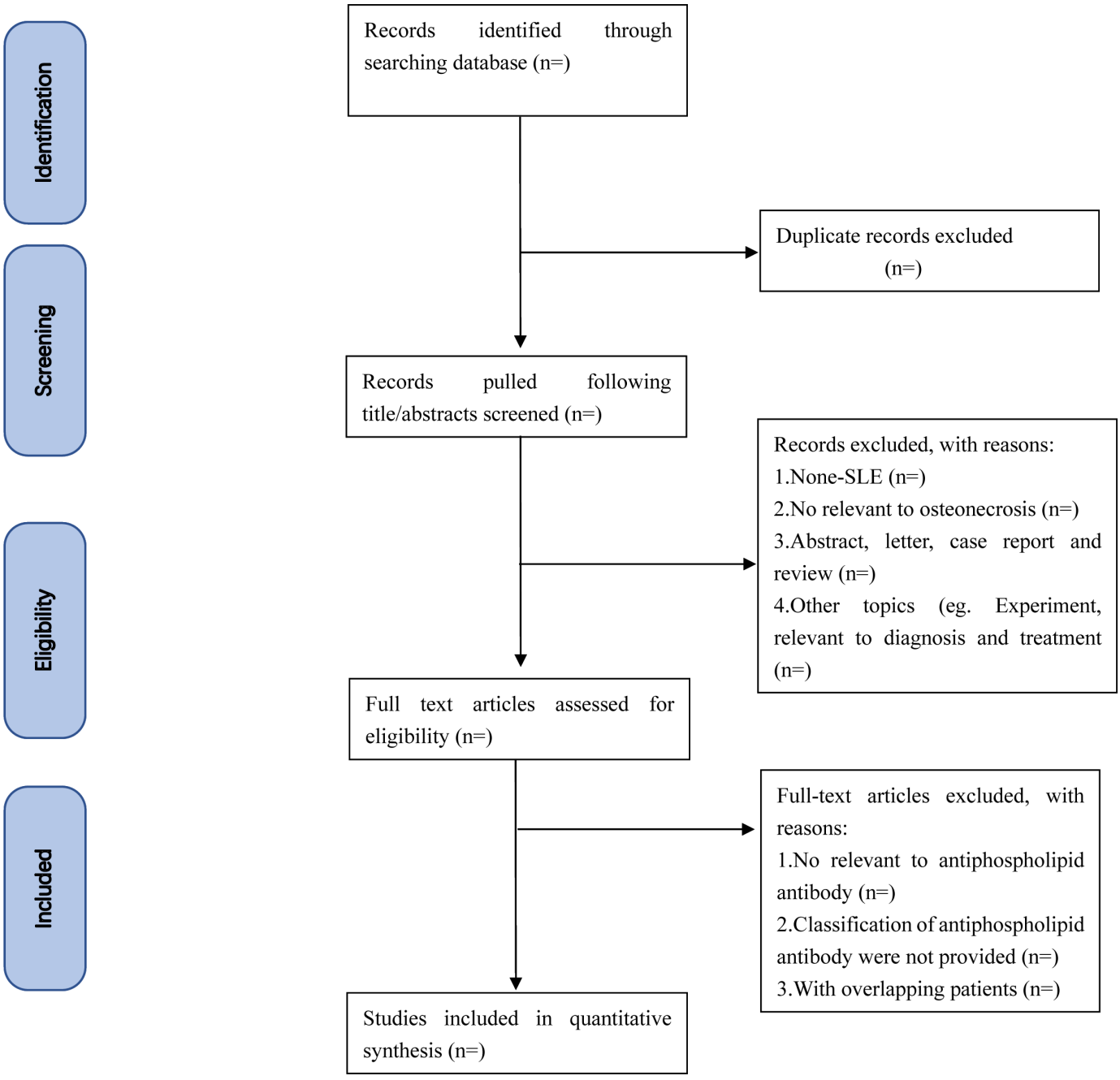

Figure 1 Study flow diagram. SLE, systemic lupus erythematosus.

fixed-effects model will be used to combine the data. If p<0.1, the DerSimonian and Laird random-effect model will be used. The reasons for heterogeneity will be analysed, and subgroup analysis will be performed. The subgroup analysis will be performed according to the study design, country of origin of the participants, age of the participants and sample size, if necessary. The results will be expressed as ORs with 95% CIs. Two of the authors will independently assess the studies and perform adjustments for risk of bias. Harbord's modified test and funnel plots will be used to assess reporting biases.

Because our search will include studies across different settings, other factors such as glucocorticoid use or hyperlipidaemia may confound the independent effect of aPLs on ON in SLE. To exclude the independent effect, we will distinguish between descriptive studies and those that adjusted for independent effects.

We hope to complete the entire study by the end of May 2021.

DISCUSSION

aPLs include LA, ACL and β2GP1. The correlation between ON and aPLs in patients with SLE was first proposed by Asherson. Since then, many studies have investigated this association. However, the results have been inconsistent and inconclusive.[7 8] Therefore, we aim

to review the literature and to perform a meta-analysis to derive more precise results.

Previous studies have shown that ACL, anti-β2GP1 and LA antibodies are highly related to thrombosis.[9 10] Immune complexes and aPLs in patients with SLE are important factors that cause blood coagulation.[11] At present, it is believed that ON is a comprehensive result of metabolic and local factors affecting blood supply.[12 13] Meanwhile, thrombosis is a risk factor for ON.[14 15]

The primary objective of this systematic review is to evaluate the correlation between ON and aPLs in patients with SLE. We will conduct qualitative and quantitative analyses of the overall data of each study to determine the relationship between aPLs and ON in patients with SLE and, consequently, to provide a reference for the clinical screening of high-risk patients and for early prevention.

In conclusion, this will be the first systematic review to assess the association between aPLs and ON in patients with SLE. The findings from this review might clarify the current issues on aPLs and ON in SLE, and may help experts and clinicians reach a consensus and develop guidelines to minimise problems and optimise patient outcomes.

Ethics and dissemination

Ethical approval and patient consent are not required because the results of this systematic review will be disseminated through publication in a peer-reviewed journal and presented at a relevant conference. The data used in this systematic review will not contain individual patient data. The study commenced at 26 December 2020, and its expected completion date is the end of May 2021. This study aims at reporting the relationship among SLE, aseptic ON and different aPLs, to provide a reference for the clinical screening of high-risk patients and for early prevention.

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Contributors WQJ prepared the first draft. CZH designed the systematic review protocol and reviewed and revised the first draft. ZM designed the search strategy and will perform the search. LJW and ZM will be included in the study screening to extract data and assess the risk of bias in the included studies. GF, ZSL and CZH will dispute disagreements between reviewers. LH will analyse and interpret the data.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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