Intestinal Microbiota and Active Systemic Lupus Erythematosus: protocol for a systematic review

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Protocol

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Abstract

Background

Systemic Lupus Erythematosus (SLE) is an autoimmune disease, characterized by being multi-systemic and, therefore, reaching various organs and affecting mainly young women. Its pathogenesis comprehends many factors, including the interaction between microbiota and immune system. The aim of this systematic review protocol is to assess the relationship between intestinal microbiota and SLE in activity, highlighting microbiota representative patterns regarding quantity and diversity.

Methods

The systematic review will be carried out using the following databases: Medline via PubMed, Scopus, and EMBASE. Inclusion criteria will be: observational studies (cross-sectional, cohort, and case-control) that analyzed intestinal microbiota composition in patients with SLE, with no restriction of age or sex, which fulfilled the classification criteria of either Systemic Lupus International Collaborating Clinic (SLICC), European League Against Rheumatism (EULAR) or American College of Rheumatology (ACR) and used the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to classify disease in activity or remission. The Downs & Black Scale will be applied to analyze the risk of bias during study selection and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) will be used to assess the quality of the evidence of the selected studies.

Discussion

This review will identify investigation gaps, for better understanding of aspects related to etiopathogenesis and to the inflammatory process during SLE progression.

Systematic review registration

PROSPERO registration: CRD42021229322

Background

Systemic Lupus Erythematosus (SLE) is an autoimmune, chronic, and multi-systemic disease that affects mainly young women (1). This condition has as main feature intolerance to autoantigens (2) resulting in numerous antibodies and inflammatory recruitment of T cells, producing pro-inflammatory cytokines (3).

The cause of SLE is unknown, however its predisposing factors are: (a) genetic, e.g. CSK and IRF7 genes; (b) immune, comprehending the production of B cells that produce antibodies and T cells; and (c) hormonal, related to estrogen increase. Additionally, environmental and/or psychological factors are also triggers, such as sunlight exposure, drugs, intestinal microbiota, Epstein-Barr virus, cytomegalovirus, smoking, sedentary lifestyle, and stress(4–8).

Among the abovementioned factors, intestinal microbiota plays a fundamental role in metabolic function, epithelium barrier maintenance, immune system modulation and homeostasis, as well as protection against infection by pathogenic agents. On the other hand, intestinal balance is preserved by a complex cellular network that acts on the development of innate and adaptive immune response (9).

Therefore, intestinal microbiota may be important on the development and maintenance of SLE symptoms (6). Immune responses against intestinal microorganisms could exacerbate preexistent inflammation and imbalance of intestinal regulating T cells (Treg/Th17), which could attack intestinal microbiota and amplify dysbiosis. This process leads to a vicious cycle in which the disease states continues (9).

In view of that, it is necessary an in-depth study for better understanding the role of intestinal microbiota in SLE etiopathogenesis and activity, focusing on the following questions: (a) does intestinal microbiota present distinctive characteristics, assessed by quantity and diversity, in individuals with SLE in activity?; (b) is there dysbiosis in the microbiota of SLE in activity?; (c) is the pattern of intestinal bacteria different in SLE in activity and SLE in remission?

It is important to highlight that this is the first systematic review study to concentrate on the relationship between microbiota and SLE in activity, being the latter the main outcome. In this context, this paper aims to carry out a systematic review in order to verify whether there is a relationship between intestinal microbiota composition and SLE activity. The hypothesis is that there are representative patterns and dysbiosis in the microbiota composition of individuals with SLE in activity. Moreover, it is believed that individuals with SLE in remission present different patterns.

Methods

This systematic review aims to relate intestinal microbiota to SLE in activity. This study will be conducted and reported in line with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)(10). See Additional file 1 for the completed PRISMA-P checklist. The review will adopt the PECO structure (11) (Population, Exposure, Comparator, and Outcome) recommended for systematic reviews. The PECO structure will be defined as 'P' (individuals with SLE), 'E' (intestinal microbiota composition), 'C' (SLE in remission and healthy control group), and 'O' (SLE in activity).

Eligibility criteria

This review will include observational studies (cross-sectional, cohort, and case-control) which analyzed the intestinal microbiota composition in patients with SLE. Publications concerning cases with SLE, with no restriction of age or sex, which fulfilled the classification criteria of either Systemic Lupus International Collaborating Clinic (SLICC)(12), European League Against Rheumatism (EULAR) or American College of Rheumatology (ACR) (13) and considered the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (14) to classify disease in activity or in remission will be included. Researches that evaluated intestinal microbiota composition in SLE from stool samples, colon tissue or intestinal biopsies through a

method accepted by the scientific community will be considered. There will be no restriction on language and publication year.

Ecological studies, case reports or case series, literature reviews, randomized clinical trials, dissertation, thesis and conference summaries, as well as duplicate articles and unavailable data even after contacting the authors will be excluded. Researches in patients with intestinal and metabolic diseases that somehow affect intestinal microbiota, in addition to articles that do not provide measures for microbiota composition will also be excluded.

Databases

Searches will be carried out using the following databases: Medline via PubMed, Scopus, and EMBASE. The search strategy will apply Medical Subject Headings (MeSH) terms in PubMed, Emtree terms in EMBASE, and both terms in Scopus. Relevant keywords about SLE and microbiota will also be used, aiming to encompass all articles on this issue. The search will be adapted for each database. The strategy for PubMed is presented in Table 1.

Review process

The search will be performed by two independent researchers (JRPV and ATOR) and a third senior reviewer (MRF), then articles will be grouped and the duplicated ones will be deleted using Mendeley software. The authors who will participate in the eligibility criteria will be appropriately trained concerning the study inclusion/exclusion criteria and will perform a pilot test to reduce the risk of bias by reading the title and abstract of 5 articles before starting the selection process.

Subsequently, reviewers (JRPV and ATOR) will independently select the articles using Rayyan software (15). Reviewers will read the titles, then the abstracts and, finally, the entire article, according to the eligibility criteria, and so articles will be included. Disagreements about inclusion will be discussed and resolved by the third reviewer (MRF), and agreement between reviewers will be measured using Kappa de Cohen statistic (16). Finally, the studies considered eligible will be included in the systematic review. A flowchart of the planned review process is shown in Figure 1.

Data extraction

Data will be extracted from articles that presented information related to intestinal microbiota and SLE in activity or remission and, then, they will be inserted in a standardized form prepared by the authors. The following aspects were considered: author/year, country where the study was carried out, type of study, participants, microbiota analysis method, disease activity index, and outcomes.

In order to assess the risk of bias, Downs&Black Scale (17) will be used, it consists of an instrument with 27 items, however only 19 items are applicable to observational studies (questions 1–3, 5–7, 9–12, 15–18, 20, 21, 25–27). Each manuscript will receive a punctuation according to the number of items considering the total percentage (0 to 19 points). Low bias risk will be defined for punctuation >70%. The

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)(18) will be applied to assess the quality of the evidence of the selected studies.

Discussion

The main characteristic of this review is to raise an issue that has been insufficiently studied in literature, identifying investigation gaps, and an in-depth study may provide better understanding of aspects related not only to etiopathogenesis but also to the inflammatory process during SLE progression. This may support medical community to elaborate investigation sequences and disease treatment.

Abbreviations

ACR

American College of Rheumatology

EULAR

European League Against Rheumatism

GRADE

Grading of Recommendations, Assessment, Development and Evaluations

MeSH

Medical Subject Headings

PECO

Population, Exposure, Comparator and Outcome

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO

International prospective register of systematic reviews

SLE

Systemic lupus erythematosus

SLEDAI

Systemic Lupus Erythematosus Disease Activity

SLICC

Systemic Lupus International Collaborating Clinic

Declarations

Availability of data and materials

Data sharing is not applicable to this protocol and no datasets were generated or analyzed.

Ethics approval and consent to participate

Ethical approval was not required for this study, as the data used comprises of peer-reviewed publications and information that could identify the subjects of the original studies was not included.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

ATOR and JRP: outline development, protocol writing, contribution to the methodologic aspect. MRF and NAS: manuscript preparation guidance, concept creation and article design (objectives, theme and title). ATOR, JRP, MRF and NAS: reading and approval of the final manuscript.

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Tables

Table 1. Search strategy will be used in Pubmed
1 = "lupus erythematosus, systemic" [MeSH] OR "systemic lupus erythematosus" OR "lupus erythematosus disseminates"
2 = microbiota [MeSH] OR microbiotas OR "microbial community" OR "community, microbial" OR "microbial communities" OR "microbial community composition" OR "community composition, microbial" OR "composition, microbial community" OR "microbial community compositions" OR "microbial community structure" OR "community structure, microbial" OR "microbial community structures" OR microbiome OR microbiomes OR "human microbiome" OR "human microbiomes" OR "microbiome, human".
3 = 1 AND 2

Figures

Figure 1

Flowchart of the selection criteria for the study

Supplementary Files

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