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Diagnostic and prognostic value of serum/plasma metabolome analyses in Systemic sclerosis: A protocol for literature review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 May 2025 and was last updated on 225 May 2025.

INTRODUCTION

Review question / Objective The aim of this review is to summarize the current state of knowledge on serum or plasma metabolite patterns in SSc patients, to delineate associations with specific phenotypes, and to assess the biomarker potential of metabolomics. In this context, the limitations inherent in metabolomics methodology will be critically discussed, highlighting the need for further research in this field contextual to disease-specific heterogeneity.

Rationale The rationale for this review is the dynamically changing heterogeneous data regarding the current state of knowledge of the SSc-specific metabolome. Furthermore, previous reviews on this topic have not focused on inherent limitations of the methods, which, especially in the context of a highly heterogeneous disease such as SSc, pose several challenges in the interpretation of the current data and for the design of future studies. This represents an important specific knowledge gap.

Condition being studied Systemic sclerosis (SSc) is a life-threatening rheumatic disease characterized by autoimmunity, vasculopathy, and inflammatory fibrosis. The disease presents with heterogeneous clinical symptoms, with interstitial lung disease (ILD) with development of fibrosis, idiopathic and associated pulmonary arterial hypertension (PAH), and cardiac involvement being prognostically significant. In addition to a significant impairment in quality of life, SSc patients' life expectancy decreases by decades. A causal therapeutic approach for SSc patients currently does not exist. Therefore, integrated studies on non-invasive, prognostic and early diagnostic biomarkers remain urgent with the intention to improve treatment and intervene the progression of the disease through a personalized approach. Metabolomics is the comprehensive analytical characterization and large-scale scientific study of small molecules, commonly referred to as metabolites, within an organism, biofluids, cells, or tissues. The immunometabolic characterization of autoimmune diseases contributes to a better understanding of the

underlying inflammatory processes. Consequently, metabolomic analyses in SSc offer promising opportunities to expand our knowledge of pathogenesis, SSc-specific immunometabolism, phenotyping, prognostic characterization, and risk stratification.

METHODS

Search strategy A review of all papers published in English on the topic of metabolome analyses in systemic sclerosis was carried out using the databases PubMed, Scopus, and Web of Science in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA). The search terms/keywords used were (“metabolome”) AND ("systemic sclerosis"), (“metabolome”) AND (“scleroderma”), (“chromatography-mass spectrometry”) AND ("systemic sclerosis"), (“chromatography-mass spectrometry”) AND (“scleroderma”), ("NMR") AND ("systemic sclerosis"), ("NMR") AND (“scleroderma”). No filters were applied. The time span of the publications was 2015 - 2025. Titles and abstracts were first reviewed for topical relevance, followed by a full-text review by the authors independently to ensure only articles that met the predefined inclusion and exclusion criteria were included.

Participant or population Studies that examined adult patients with SSc as their target population, regardless of age, gender, and ethnicity, were included. Studies with a pediatric target population were excluded. Cohort size was irrelevant, and neither the autoantibody profile nor the disease duration or visceral organ manifestations at the time of metabolomic analysis were relevant.

Intervention Not applicable.

Comparator Not applicable for this review.

Study designs to be included Studies design to be included are original research articles with cohort studies and case control studies.

Eligibility criteria The following eligibility criteria are defined for inclusion or exclusion:
Inclusion criteria:
- Original research articles (cohort, case control studies), addressing the human, adult serum or plasma metabolome in SSc published without restriction to a single metabolite and published in English within the last ten years.
- Use of HPLC/UPLC-MS or LC-MS or 1H-NMR.
- SSc diagnosis according to the 2013 American College of Rheumatology and Eu-ropean League Against Rheumatism ACR/EULAR classification criteria.

The exclusion criteria were defined as follows:
- Studies focusing on other biological samples e.g. urine
- In vitro studies.

Information sources The following information sources are used: PubMed, EMBASE, Web of Science, and Scopus.

Main outcome(s) Relevant endpoints for this review are defined as metabolome alterations related to specific SSc phenotypes (cutaneous distribution pattern, visceral organ involvement), correlations with disease activity, and metabolome changes with prognostic significance regarding mortality-determining disease manifestations of interstitial lung disease.

Additional outcome(s) Not applicable.

Data management Two authors will independently conduct a full-text review of the primary literature and transfer the metabolite alterations identified in the studies into an Excel spreadsheet. At the same time, the characteristics of the studied cohorts, including age, gender, cohort size, and sample material, will be recorded and analyzed. Statistical analysis will not be performed as part of the review. Two additional authors will review the data for inconsistencies.

Quality assessment / Risk of bias analysis The quality assessment is based on the QUADOMICS tool.

Strategy of data synthesis The review will provide a qualitative description and subsequent interpretation of the metabolome alterations. A statistical analysis is not planned.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction Only original research articles (cohort, case control studies), published in English will be considered for inclusion.

Country(ies) involved Deutschland.

Other relevant information None.

Keywords metabolomics; metabolome; systemic sclerosis; biomarkers.

Dissemination plans The publication is scheduled for publication in the special issue "Recent Advances in Understanding Systemic Sclerosis" of the journal Sclerosis.

Contributions of each author

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