INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Biomarkers Associated with Complex Regional Pain Syndrome in Humans: Protocol for a Systematic Review

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Review question / Objective: **The aim of this systematic review is to explore the pathophysiology of complex regional pain syndrome and what differs between healthy controls and patients with CRPS concerning biomarkers. To this end, the proposed systematic review will answer the following question: 1. Which protein, lipid, or microRNA biomarkers are found in the body fluids or microdialysis fluid in the skin in complex regional pain syndrome (CRPS)?**
Condition being studied: **Complex regional pain syndrome (CRPS) is a disease that develops most often after a trauma to the affected limb. The disease manifests itself as severe pain, allodynia and reduced motor function in the affected limb. However, the symptoms can spread and there are documented cases of when CRPS has spread contra laterally from one limb to another. However the underlying pathophysiology of CRPS is unknown.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 November 2022 and was last updated on 20 November 2022 (registration number INPLASY2022110100).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to explore the pathophysiology of complex regional pain syndrome and what differs between healthy controls and patients with CRPS concerning biomarkers. To this end, the proposed systematic review will answer the following question: 1. Which protein, lipid, or microRNA biomarkers are found in the body fluids or microdialysis fluid in the skin in complex regional pain syndrome (CRPS)?**

Rationale: **The underlying pathophysiology for CRPS is still today unclear. There is no**

consensus on which mediators that are primary or secondary regarding this disease. In addition, it is unsure whether all patients with CRPS share the same pathophysiology. The evidence points toward that CRPS is a multifactorial disease with components associated to inflammation, autoimmunity, neuronal plasticity, autonomous dysregulation, and psychological aspects.
This review will capture the different biomarkers for CRPS and help our understanding on this disease. In addition, this review aims to identify knowledge gaps.

Condition being studied: Complex regional pain syndrome (CRPS) is a disease that develops most often after a trauma to the affected limb. The disease manifests itself as severe pain, allodynia and reduced motor function in the affected limb. However, the symptoms can spread and there are documented cases of when CRPS has spread contra laterally from one limb to another. However the underlying pathophysiology of CRPS is unknown.

METHODS

Search strategy: Both qualitative and quantitative studies will be sought. No study design, date or language limits will be imposed on the search. PubMed, Web of Science and Embase will be searched. The specific search strategies will be created by a Health Sciences Librarian with expertise in systematic review searching. The search strategies will be peer reviewed by a second librarian, not otherwise associated with the project, using the PRESS standard.
As relevant studies are identified, reviewers will check for additional relevant cited and citing articles.
The search strategies for each database are the following:
- For PubMed ("complex regional pain syndromes"[MeSH Terms] OR "complex regional pain syndromes"[All Fields] OR "complex regional pain syndrome"[All Fields]) AND ("biomarker's"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields])
- For Web of Science ("complex regional pain syndrome*" OR CRPS) AND (biomarker* OR "Biologic Marker*")
- For Embase ('complex regional pain syndrome'/exp OR 'complex regional pain syndrome' OR 'complex regional pain syndromes' OR 'pain syndrome, complex region-al') AND ('biological marker'/exp OR 'biological marker' OR 'biological markers' OR 'biomarker' OR 'biomarkers' OR 'marker, biological').

Participant or population: We will include studies examining the general adult human population (18 years or older). We will include studies addressing both adults and children if data provided for adults are reported separately. Studies with established diagnosis of CRPS according to the Budapest Criteria for CRPS (2003) will be included in the systematic review.

Intervention: Patients undergoing various types of procedures, yielding samples for further analysis (blood, saliva, skin (microdialysis), cerebrospinal fluid and other).not applicable.

Comparator: Subjects without chronic pain condition or reference values from healthy controls not applicable.

Study designs to be included: We will include only peer-reviewed original studies.

Eligibility criteria: We will include only peer-reviewed original studies. Articles reported in the English language will be included. Only studies that report potential biomarker candidates for CRPS will be included.

Information sources: Literature search strategies will be developed using medical subject headings (MeSH) and text words related to CRPS and biomarkers. We will search PubMed, Web of Science and Embase. The literature search will be limited to the English language and human subjects.

To ensure literature saturation, we will scan the reference lists of included studies identified through the search.

Main outcome(s): The main outcome for this systematic review will be potential biomarker candidates for complex regional pain syndrome. Additionally outcome will be to identify the knowledge gap in the search of biomarkers of CRPS.

Data management: The references will be exported to EndNote Reference Software. Duplicates will then be removed. We will juxtapose author names in EndNote to avoid double counting.
Then, a blinded and independent process of selection based on title and abstract will be made individually by FW and BG. Next, a thorough analysis of eligible studies will be performed by evaluating full texts. Any excluded study together with the reason of exclusion will be noted in a separate table. When discrepancies will be encountered, we will resolve them by discussion. Neither of the review authors will be blind to the journal titles or to the study authors.

Quality assessment / Risk of bias analysis: To facilitate the assessment of possible risk of bias for each study, we assess the following: I) if the studies included healthy controls, II) sample size, III) methodological procedures and IV) inclusion and exclusion criteria. Disagreement will be resolved by discussion with all review team members.

Strategy of data synthesis: We will summarize the study results and follow the PRISMA guidelines.

Subgroup analysis: Not applicable.

Sensitivity analysis: Not applicable.

Country(ies) involved: Sweden, Germany.

Keywords: CRPS; biomarkers; omics; biofluids.

Contributions of each author:
Author 1 - Bijar Ghafouri - BG is the guarantor, will draft the manuscript, will contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. All authors will read, review, and approve the final version of the manuscript.
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Author 2 - Felix Wilhelm - FW will draft the manuscript, will contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria, developed the search strategy, will read, review, and approve the final version.
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Author 3 - Ann-Kristin Reinhold - RA will contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria, will provided expertise on CRPS , will read, review, and approve the final version of the manuscript.
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