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# Immune regulation and tissue remodeling mediators of EG: systematic review

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**ADMINISTRATIVE INFORMATION**

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**Review Stage at time of this submission -** Data extraction.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2023120050

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2023 and was last updated on 12 December 2023.

## INTRODUCTION

**Review question / Objective** This study aims to investigate the changes of immune regulation and tissue remodeling mediators in gingival crevicular fluid (GCF) before and during experimental gingivitis. Also, the secondary aims of this proposed systemic review is to investigate the differences of these mediators in full-mouth (FM) or partial-mouth stent (PM) design.

**Rationale** Experimental gingivitis has been utilized to explore the periodontal tissue responses towards bacterial challenges, including immune regulation and bacterial community shifting. Researchers use two different experimental designs to induce experimental gingivitis in healthy human subjects, full mouth and stent designs. The impacts of these designs on the outcomes of immune regulation and tissue remodeling mediators in gingival crevicular fluid (GCF) remain unknown.

**Condition being studied** Systemic healthy patients with peri-health who volunteer for the induction of experimental gingivitis using either full-mouth or partial-mouth oral hygiene refraining.

## METHODS

**Search strategy** • PubMed:
("experimental gingivitis"[tiab:~2] OR "experimentally gingivitis"[tiab:~2]) NOT (Animals[Mesh] NOT Humans[Mesh])
• Embase:
(experimental* NEAR/2 gingivitis) NOT ('animal'/exp NOT 'human'/exp)
o There was only one conference abstract, but if you want to exclude it you can add NOT

([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)
• Web of Science:
(TS=(experimental* NEAR/3 gingivitis)) AND DT=(Article OR Early Access OR Correction).

**Participant or population** Healthy patients with periodontal health.

**Intervention** Induction of experimental gingivitis either using either FM or PM designs.

**Comparator** Same patient in baseline, i.e. healthy periodontium (day 0).

**Study designs to be included** Randomized controlled trials or clinical controlled trials.

**Eligibility criteria** (1)The studies should be published in English. (2).The study should evaluate the immune regulation and tissue remodeling mediators in gingival crevicular fluid before and after (>=14 days of inflammation) the induction of experimental gingivitis (3).≥ 10 human participants with age more or equal to 18 year old. (4) The study should report outcomes of immune regulation and tissue remodeling mediators (5).The length of induction phase of experimental gingivitis should be more or equal to 14 days.

**Information sources** A search was conducted for studies published from January 1960 to June 2023 in several electronic databases, including MEDLINE (PubMed), EMBASE, Web of Science, and ClinicalTrials.gov., using above-mentioned search strategy. Moreover, the additional search was performed in the following journals: Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research, and Journal of Dental Research. Finally, the reference lists of identified articles were screened to find additional articles that might fit the selection criteria.

**Main outcome(s)** Value changes of GCF mediators.

**Additional outcome(s)** Clinical parameters, including bleeding on probing, plaque index, and gingival index.

**Data management** The titles and abstracts of all retrieved articles are independently screened by two authors (Y.H, H.L). The full texts of potentially qualifying articles are reviewed. Any disagreement between the two authors is resolved by discussion. If the identified studies had multiple groups of subjects, only those groups fitting the selection criteria described above are included. Data are independently extracted by the two authors (Y.H, H.L) with a specially designed form on Covidence platform and the accuracy was confirmed by a third reviewer (R.D). The authors of potentially qualifying articles are contacted if there was unclear information that needed clarification.

**Quality assessment / Risk of bias analysis** The Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2)6 and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)7 tools will be used to assess quality of randomized controlled trials (RCT) and non- randomized controlled trials (NRCT) respectively. The quality assessment will be conducted by two authors (Y.H, H.L) independently and the agreement between the two authors was evaluated using the kappa statistic.

**Strategy of data synthesis** Extracted data will be summarized in evidence tables to detect differences in study characteristics and quantify the body of evidence. The Metainsight tool (V3.1.13) (Owen et al., 2019) will be used for evidence synthesis based on the R package netmeta (Rücker et al., 2017). Frequentist models for meta-analysis and NMA will be used if the meta-analysis is feasible.

**Subgroup analysis** The impact of stress, age, and systemic status will be analyzed only in direct comparison.

**Sensitivity analysis** The primary data analysis was conducted where data from original studies will be included based on a per-protocol (PP) approach. A sensitivity analysis will be conducted using an Intention-to-Treat (ITT) approach.

**Language restriction** English.

**Country(ies) involved** United State of America/ University of Washington, Seattle, WA.

**Keywords** experimental gingivitis, tissue remodeling, immune regulation.

**Contributions of each author**
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