

STUDY PROTOCOL

Association of Metrnl Expression With IL-1 β and TNF- α in Patients With Peri-Implantitis: Potential as a Novel Biomarker

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IRB Approval: Atatürk University Non-Interventional Clinical Research Ethics Committee (Approval No. 758)

1. Background and Rationale

Peri-implantitis is a biofilm-associated inflammatory disease characterized by inflammation of the peri-implant mucosa and progressive loss of supporting bone. Although clinical and radiographic parameters — including probing depth, bleeding on probing, suppuration, and radiographic bone loss — are central to diagnosis, these measures primarily reflect established tissue changes and may not fully characterize the underlying local immune-inflammatory response. Analysis of biomarkers in peri-implant crevicular fluid (PICF) may therefore provide complementary information about the biological processes associated with peri-implant health and disease.

Meteorin-like protein (Metrl) is an immunoregulatory protein involved in inflammatory regulation, macrophage polarization, and tissue repair. Experimental and clinical evidence suggests that Metrl may interact with both pro-inflammatory and anti-inflammatory pathways. However, its possible role in peri-implantitis has not been sufficiently investigated.

This observational study will include individuals with peri-implantitis and individuals with healthy peri-implant tissues. Participants will be classified according to clinical and radiographic findings. Clinical periodontal and peri-implant parameters will be recorded to characterize the study groups. PICF samples will be collected from selected implant sites, and the concentrations of Metrl, interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-10 (IL-10) will be analyzed.

Study hypothesis: Metrl levels differ between peri-implant health and peri-implantitis and are associated with the local inflammatory cytokine profile.

2. Objectives

2.1 Primary Objective

To compare Metrl concentrations in peri-implant crevicular fluid between the peri-implantitis group and the peri-implant health group.

2.2 Secondary Objectives

- To compare IL-1 β , TNF- α , and IL-10 concentrations in PICF between the two groups.
- To evaluate the correlation between Metrl and IL-1 β , TNF- α , and IL-10 concentrations, and with clinical parameters (PI, BOP, CAL, PD, age).
- To evaluate the discriminative ability (diagnostic performance) of Metrl in distinguishing peri-implantitis from peri-implant health using ROC curve analysis.

3. Study Design

Observational, case-control study with a cross-sectional time perspective. No biospecimens will be retained beyond the analyses specified in this protocol. Sampling method: non-probability (consecutive) sampling.

Two study groups:

- Peri-Implantitis Group — individuals diagnosed with peri-implantitis based on clinical and radiographic criteria.
- Peri-Implant Health Group — individuals with clinically and radiographically healthy peri-implant tissues.

One implant site is sampled per participant; no tooth (natural dentition) samples are collected.

4. Study Population and Eligibility

4.1 Inclusion Criteria

- Individuals aged 18 years or older.
- Individuals without systemic disease.
- Individuals with at least one healthy implant or one implant affected by peri-implantitis.
- At least 1 year elapsed since placement of the prosthetic restoration on the relevant implant.

4.2 Exclusion Criteria

- Pregnant or lactating individuals.
- Current smokers.
- Use of antibiotics or corticosteroids within the previous 6 months.
- Presence of an implant-supported removable prosthesis.
- Periodontal or peri-implant treatment within the previous 6 months.

4.3 Setting

Department of Periodontology, Faculty of Dentistry, Atatürk University, Erzurum, Türkiye.

5. Sample Size Determination

Sample size determination was based on the study reported by Sağlam et al., which found an effect size of approximately Cohen's $d = 0.50$, interpreted as a medium effect. Based on comparison of the mean difference between two independent groups, a power analysis conducted using G*Power 3.1.9.7 ($\alpha = 0.05$, power $[1-\beta] = 0.80$, two-tailed test) indicated that a minimum of 32 sample units per group was required.

The studies by Guarnieri et al. and Gündoğar & Uzunkaya, which evaluated PICF biomarker levels comparing peri-implant health and peri-implantitis, were considered as supportive methodological literature for the study design (Guarnieri, Reda, et al., 2024; Gündoğar & Uzunkaya, 2021).

Accordingly, a total of 68 implant sites were included in the study: 34 in the peri-implant health group and 34 in the peri-implantitis group.

6. Clinical and Laboratory Procedures

6.1 Clinical Parameters

The following clinical variables are recorded for each participant: gender, age, plaque index (PI), bleeding on probing (BOP), clinical attachment level (CAL), and probing depth (PD).

6.2 PICF Sample Collection and Biomarker Analysis

Peri-implant crevicular fluid is collected from the selected implant site per participant. Metnrl, IL-1 β , TNF- α , and IL-10 concentrations are quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China), according to the manufacturer's instructions. Metnrl is expressed in ng/mL; IL-1 β , TNF- α , and IL-10 are expressed in pg/mL.

7. Outcome Measures

7.1 Primary Outcome

Metnrl concentration in PICEF, compared between the peri-implantitis and peri-implant health groups.

7.2 Secondary Outcomes

- IL-1 β concentration in PICEF, compared between groups.
- TNF- α concentration in PICEF, compared between groups.
- IL-10 concentration in PICEF, compared between groups.

7.3 Pre-specified Exploratory Outcomes

- Correlation between Metnrl and IL-1 β concentrations in PICEF.
- Correlation between Metnrl and TNF- α concentrations in PICEF.
- Correlation between Metnrl and IL-10 concentrations in PICEF.
- Area under the ROC curve (AUC) for Metnrl in distinguishing peri-implantitis from peri-implant health.

8. Ethical Considerations

The study was approved by the Atatürk University Non-Interventional Clinical Research Ethics Committee (Atatürk University Faculty of Medicine), Approval No. 758. The study is not FDA-regulated (not a drug or device trial; no IND/IDE). Data Monitoring Committee: not applicable.

9. Study Contacts

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