

Review
Implant Science



Biomarkers associated with periodontitis and peri-implantitis: a systematic review

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ABSTRACT

Purpose: The pathology of peri-implantitis is still not fully understood and there have been recent challenges to the consensus on its aetiology and pathology, especially in comparison with periodontitis. The assessment of biomarkers allows a comparison of the pathology of these diseases. The aim of this systematic review was to answer the research question: “Is there a difference in the biomarkers associated with peri-implantitis compared with periodontitis in adult humans?”

Methods: Electronic databases were searched and screened, and a manual search was also undertaken. The inclusion criteria were adults with peri-implantitis who had been compared to adults with periodontitis with the outcome of biomarkers assessed via biopsies or crevicular fluid samples in primary or secondary care settings, as recorded in case-control, case series and retrospective, prospective and cross-sectional observational studies. Two reviewers independently screened titles and abstracts and assessed full text articles for eligibility and inclusion. Both reviewers independently extracted data and assessed risk of bias. Differences in biomarker levels were the primary outcome and a narrative review was undertaken due to the heterogeneity of studies.

Results: In total, 2,374 articles were identified in the search, of which 111 full-text articles were assessed for eligibility and 13 were included in the qualitative synthesis. Five of the 13 included studies were deemed to be at high risk of bias, with the others having moderate risk. All studies were cross-sectional and performed at university hospitals. Nine of the 13 included studies found significant differences in the levels of biomarkers or their ratios between peri-implantitis and periodontitis. Four of the studies found no significant differences.

Conclusions: Within the limitations of the included studies, it appears that there may be a difference in biomarker levels and ratios between peri-implantitis and periodontitis, suggesting that these disease processes are somewhat distinct.

Keywords: Biomarkers; Cytokines; Peri-implantitis; Periodontitis

INTRODUCTION

The prevalence of peri-implantitis has been reported to be 10%–30% of implants and 20% of cases [1]. Various treatment approaches have been advocated, and the consensus in the

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

literature echoes the management of periodontitis [2]. Management remains unpredictable, however, with success rates at 12 months ranging from 0% to 100% of patients and from 75% to 93% of implants [3].

Much of the aetiology and pathogenesis of peri-implant disease is currently acknowledged to be similar to periodontitis [4]. However, in contrast to periodontitis, peri-implantitis lesions show a poorer vascular supply, a lack of connective tissue encapsulation of large inflammatory cell infiltrates, and a differing cell profile with high numbers of B cells, osteoclasts and neutrophils [5]. The genetic signatures of soft tissue biopsies from periodontitis and peri-implantitis lesions also differ [6,7]. This suggests that peri-implantitis has a similar aetiopathogenesis to periodontitis, but also notable differences; its progression seems to be faster and more aggressive [5]. A consensus exists among the periodontal community regarding the aetiology and pathogenesis of peri-implantitis; however, some groups have challenged this consensus, albeit with limited evidence [8-10].

Biomarkers are quantifiable disease characteristics that can include any factor aiding a diagnosis [11]. Biomarkers in periodontitis and peri-implantitis can be collected via biopsy or peri-implant sulcular fluid (PISF) and gingival crevicular fluid (GCF) and are then measured by immunoassay [12,13]. Cytokines, chemokines and other biologic mediators are involved in regulating peri-implant and periodontal conditions, proving their use as diagnostic and prognostic tools [14-17].

Given the variable predictability and potential invasiveness of peri-implantitis management, an understanding of the underlying pathophysiology is relevant, as an early diagnosis may help to prevent more serious aspects of the disease and morbidity associated with its treatment [3,18].

The purpose of this study was to systematically search the relevant literature for studies investigating and comparing biomarkers associated with periodontitis and peri-implantitis. The focussed question was, “In adult humans (population), is there a difference in the biomarkers (primary outcome) associated with untreated peri-implantitis compared with untreated periodontitis (comparator) in primary and secondary care (setting) assessed via observational studies?”

MATERIALS AND METHODS

Protocol and eligibility criteria

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and workflow and was registered in the PROSPERO database (registration number: CRD42018089685) [19].

Inclusion criteria

The inclusion criteria were purposefully left broad in order to achieve a sensitive approach due to the relatively low number of articles expected from scoping searches.

- Population: adults with peri-implantitis, defined according to the VIII European Workshop of Periodontology [20]
- Intervention: none

- Comparator: adults with periodontitis
- Outcomes: biomarkers from biopsies or PISF compared with GCF
- Setting: primary and secondary care settings
- Study design: case-control, case series, and retrospective, prospective and cross-sectional observational studies

Exclusion criteria

- Systematic reviews or meta-analyses; however, these were read to obtain general information and to identify further studies
- Studies not directly comparing periodontitis and peri-implantitis
- Implants or mini-implants related to orthodontics
- Extra-oral or zygomatic implants
- Animal or in vitro studies
- Articles not in the English language
- Case reports

These criteria were used both during the identification/screening (phase 1) and eligibility (phase 2) stages.

Information sources and search

The present study took place between September 2017 and August 2018. A sensitive search was conducted in consultation with a university librarian. An electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase was undertaken in March 2018 utilising specific search strategies in relation to each database. Monthly alerts were set up for new studies meeting the search criteria. The search was aimed at studies published between 1995 and August 2018. The grey literature was searched via Open Grey (<http://www.opengrey.eu/>), dissertations and theses were searched through the ProQuest Dissertation & Theses Database, and conference abstracts were searched through BIOSIS Web of Science and Zetoc (<http://zetoc.jisc.ac.uk/>). A manual search was also conducted of selected journals. The bibliographies of the studies included for full-text screening were searched.

Colleagues with an interest in the topic were consulted regarding further literature. The authors of included studies were contacted requesting information on additional published or unpublished research. If they did not reply after 4 weeks a second email was sent; however, this had no bearing on study selection.

Data collection and analysis

Phase 1 (screening) involved 2 reviewers (Amardip Singh Kalsi [ASK] and Federico Moreno [FM]) independently screening the list of titles and abstracts. The full texts of any studies deemed relevant by either reviewer were sourced. Phase 2 (eligibility) involved screening of the full texts for the inclusion criteria by ASK and FM. A record of all full texts sourced was kept and populated with reasons for exclusion. A discussion of the decision regarding inclusion of the first 10 papers was undertaken to calibrate the reviewers. When the reviewers disagreed, a decision was made via discussion. When consensus was not possible, Haralampos Petridis (HP) made the decision. Inter-reviewer agreement was calculated via kappa statistics. A database form was constructed and filled in directly by ASK upon assessing each study, with FM as a second reviewer. If possible, a meta-analysis was planned to compare the types and frequency of biomarkers associated with peri-implantitis and

periodontitis. If this was not possible due to variability between studies, data were planned to be extracted and tabulated from each study, with reference to each study's characteristics and risk of bias. A narrative analysis to explore the relationships among studies would subsequently be performed, with the aid of appropriate tables and graphs.

Assessment of risk of bias and quality

As all studies were cross-sectional, the Appraisal tool for Cross-Sectional Studies (AXIS) was utilised since no Scottish Intercollegiate Guidelines Network checklist was available [21]. Each included study was assessed for risk of bias by ASK and FM using a database mimicking this form.

Dealing with missing data and heterogeneity

An attempt was made to contact the primary author of potential included studies to retrieve any missing data via email. If the author could not be contacted, then the study was excluded from the review if there was no other way of extracting the relevant data. If data were published in a purely graphical format and the authors did not respond, PlotDigitizer 2.6.8 (<http://plotdigitizer.sourceforge.net/>) was utilised to extract exact values where possible.

RESULTS

Quantity of research available

As shown in Figure 1, 2,374 articles were returned from the search, of which 13 met the inclusion criteria [6,7,22-32]. No meta-analysis was performed due to methodological and biomarker heterogeneity.

Where data were missing from studies or it was unclear whether the study assessed periodontitis and peri-implantitis, emails were sent to the corresponding authors. Initial emails were sent from 21 to 25 July 2018. Seven authors were contacted and 1 responded. Where data were present only in graphical format without exact values, an attempt was made to contact the authors. In the 2 studies where no response was received, data were extracted from the graphs utilising PlotDigitizer [6,24].

Inter-reviewer agreement

Agreement between the reviewers (ASK and FM) was good, with kappa scores of 0.94 for phase 1 screening and 0.84 for phase 2 eligibility. All disagreements were resolved through discussion and the need for the third reviewer did not arise.

Risk of bias

The risk of bias assessment for the included studies is summarised in Table 1. All studies showed some signs of bias. Five of the 13 included studies were deemed to be at high risk of bias, with the remaining at a moderate risk. The sample size was justified in 4 studies and selection was unclear in 8 studies. None of the studies adequately assessed risk or confounding factors to ensure that the periodontitis and peri-implantitis groups were both comparable. Six of the studies failed to adequately describe basic data. Eight of the studies reported receiving sources of funding.

Narrative synthesis

The study characteristics are summarised in Table 2. The numbers recorded in Table 2 relate to the patients assessed who had peri-implantitis or periodontitis. A number of studies also

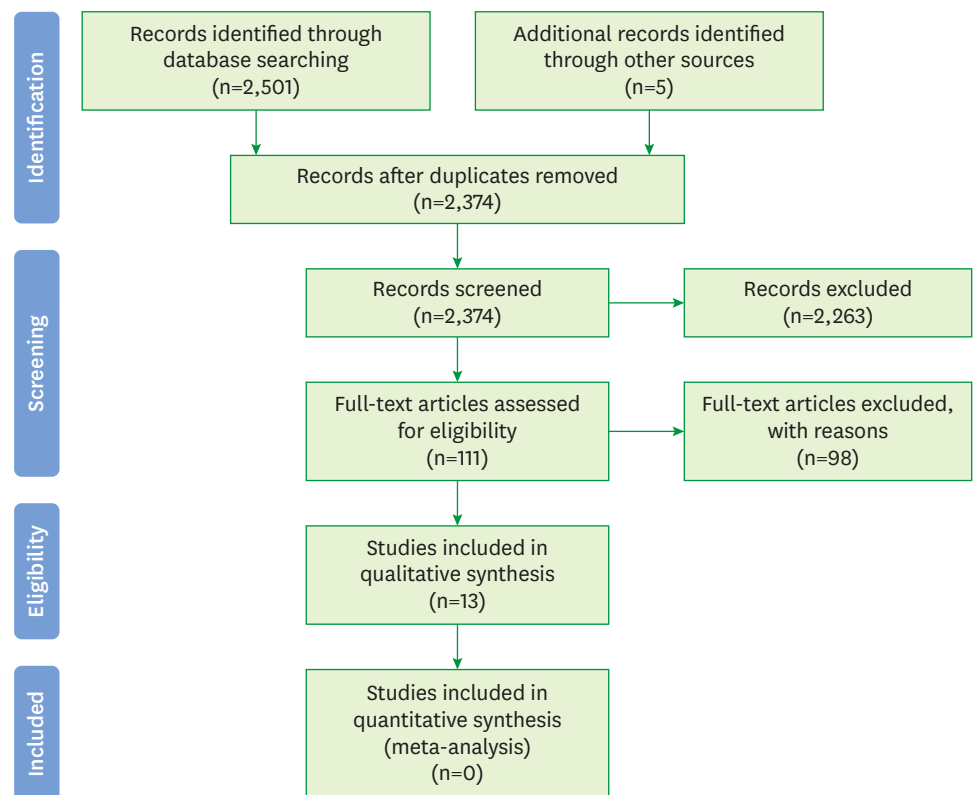


Figure 1. Flow diagram summarising the search strategy.

assessed other groups that were not included in the present study, and hence those numbers were not included. The findings of the studies are summarised in Tables 3 and 4, where studies are grouped by their method of taking samples. Two of the articles were written by similar authors within 1 year of each other, but the cohorts of patients assessed were different [28,29].

The studies were published between 2000 and 2017 across Europe, Asia, North and South America and Turkey. All studies were cross-sectional and performed at university hospitals. The number of patients included in the studies varied from 12 to 135. The study with 135 participants did show a significant difference in biomarker levels between peri-implantitis and periodontitis [6]. Only 1 study compared biomarkers within patients suffering from both periodontitis and peri-implantitis; this study showed that there was no difference, but the number of participants was low (n=15) [24]. In 2 studies, it was unclear whether the diseases had been treated or not [26,28]. The definitions for peri-implantitis and periodontitis were heterogeneous, as were the inclusion and exclusion criteria. All studies assessed chronic periodontitis except for 1 study, which had separate groups for both chronic and aggressive periodontitis [25], and 4 others that did not report the classification [7,22,26,27]. Amongst all of the studies, very little was reported regarding implant systems, techniques, staging, type of restoration, time since loading, symptoms and extent of disease. The included studies focussed on a range of biomarkers, and 1 assessed the transcriptome [7]. That study found a significant difference, in that immune system-associated pathways predominated in peri-implantitis whereas apoptosis and proliferation-associated pathways predominated in periodontitis. They found that only a single transcript was significantly regulated in both diseases.

Table 1. Risk of bias assessment

Study	Becker et al. [7]	Buffoli et al. [22]	Ghigli et al. [23]	Gürlek et al. [24]	Luo et al. [25]	Ma et al. [26]	Nomura et al. [27]	Rakic et al. [28]	Rakić et al. [29]	Teixeira et al. [30]	Venza et al. [6]	Xu et al. [31]	Yamalik et al. [32]
Clear aims/objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design appropriate for the stated aim(s)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justification	No	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No
Target/reference population clearly defined?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample representative of target/reference population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Selection process likely to represent target/reference population	Unknown	Unknown	No	No	Unknown	Unknown	Unknown	Yes	Yes	Yes	Yes	Yes	Unknown
Variables appropriate to study aims	No	No	No	No	No	No	No	No	No	No	No	No	No
Variables measured correctly and trialled/piloted/published previously	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clear method to determine statistical significance	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods sufficiently described to enable repeat	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Basic data adequately described	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No
Results internally consistent	Yes	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results for the analyses described in the methods presented	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Authors' discussions and conclusions justified by the results	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Limitations of the study discussed	Yes	No	Yes	No	No	No	No	No	No	Yes	No	Yes	No
Funding sources or conflicts of interest	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Ethical approval/consent of participants	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall risk of bias rating	High	High	Moderate	Moderate	High	High	High	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Table 2. Study characteristics

Study	Becker et al. [7]	Buffoli et al. [22]	Ghigli et al. [23]	Gürlek et al. [24]	Luo et al. [25]	Ma et al. [26]	Nomura et al. [27]	Rakić et al. [28]	Rakić et al. [29]	Teixeira et al. [30]	Venza et al. [6]	Xu et al. [31]	Yamalik et al. [32]
Country	Germany	Italy	France	Turkey	China	Finland	Japan	Serbia	Serbia	Brazil	Italy	USA	Turkey
Type of study	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional (cohort for healthy implants)	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	NR	Cross-sectional
Setting	University hospital	NR	University hospital	University hospital	University hospital	University hospital	University hospital	University hospital	University hospital	University hospital	University hospital	NR	University hospital
Total study duration	NR	NR	10 mon	8 mon	NR	NR	12 mon	NR	20 mon	NR	2 yr	NR	13 mon
No. of participants	14	12	21	15	54	20	17	45	45	23	135	15	21
No. of male participants	5	NR	NR	8	37	13	NR	39 (including controls)	37 (including controls)	9	NR	7	14 males (including controls)
No. of female participants	9	NR	NR	7	17	7	NR	31 (including controls)	30 (including controls)	14	NR	8	26 females (including controls)
Average age (yr)	Median: 57 for peri-implantitis, 49 for periodontitis	NR	NR	Mean: 54.3 yr	NR	Mean: 64.4 for peri-implantitis, 51.7 for periodontitis	Mean: 61.0±9.1 for peri-implantitis, 56.2±9.2 for periodontitis	Mean: 48 for peri-implantitis, 42 for periodontitis	Mean: 38.8±7.73 (including controls)	Mean: 59.9±3.8 for peri-implantitis, 66.7±8.8 for periodontitis, no significant difference	NR	NR	Mean: 36.15 (including controls)
Age range (yr)	33-71	16-67	NR	48-60	25-68	59-77 for peri-implantitis, 27-71 for periodontitis	NR	33.2-58.6	23-60 (including controls)	-	NR	40-72	20-65 (including controls)
Comparison within/ between patients	Between	Between	Between	Within	Between	Between	Between	Between	Between	Between	Between	Between	Between
Treated or untreated peri-implantitis and periodontitis	Untreated	Both - separate groups	Continued probing depth >4 mm after non-surgical therapy	Untreated	Untreated	NR	Untreated	NR	Untreated	Untreated	Untreated	Untreated	Untreated
Risk factors	Current, quit >5 yr ago or never-smokers. 1 smoker in peri-implantitis group	NR	NR	NR	NR	NR	NR	NR	NR	NR	Diabetes	NR	NR
Chronic and/or aggressive periodontitis	NR	NR	Chronic	Chronic	Chronic and aggressive separate groups	NR	NR	Generalised severe chronic	Generalised severe chronic	Moderate-severe chronic localised	Chronic	Chronic	Chronic

NR: not reported.

Table 3. Summary of studies assessing biopsies

Study	Becker et al. [7]	Buffoli et al. [22]	Ghighti et al. [23]	Ma et al. [26]	Venza et al. [6]
Biomarkers assessed	Transcripts; apoptosis and proliferation as dominant features	AQP1	IL-1 β , IL-10, IL-17, eotaxin, FGF, G-CSF, GM-CSF, PDGFbb, RANTES, OPG	Cellular fibronectin	TNF- α , IL-6, IL-8, MCP-1, CCRI, CCR2, CCR3, CCR4, CCR5, CXCR1, CXCR2, CXCR3
Type of biomarkers	Transcripts	Tissue homeostasis	Immune-related	Extra-cellular matrix	Immune-related
Concentrations of each biomarker in peri-implantitis sites	Not applicable	<ul style="list-style-type: none"> • 38.06\pm0.84 untreated • 34.74\pm0.68 treated 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> • IL-1β 613.9 (\pm549.5) pg/mL • IL-10 97.7 (\pm63.8) pg/mL • IL-17 114.8 (\pm37.1) pg/mL • Eotaxin 78.3 (\pm11.5) pg/mL • FGF 139.6 (\pm11.5) pg/mL • G-CSF 10.6 (\pm8.1) ng/mL • GM-CSF 122.5 (\pm87.2) pg/mL • PDGFbb 15.5 (\pm6.5) pg/mL • RANTES 681 (\pm545.6) pg/mL • OPG 1.4 (\pm1.2) μg/mL • TIMP-2 14.66\pm6.24 ng/mL 	<p>Median: 26.5% of positive cellular fibronectin staining</p>	<p>Relative expression in healthy patients, patients with diabetes, and patients with poorly controlled diabetes:</p> <ul style="list-style-type: none"> • TNF-α 3.94, 3.98, 4.7 • IL-6 6.21, 6.60, 9.2 • IL-8 6.95, 7.55, 9.81 • MCP-1 3.73, 3.85, 4.34 • CCRI 1.18, 1.18, 1.18 • CCR2 3.20, 3.18, 3.22 • CCR3 1.17, 1.25, 1.26 • CCR4 3.21, 3.26, 3.25 • CCR5 3.48, 3.69, 4.30 • CXCR1 1.18, 1.21, 1.21 • CXCR2 1.21, 1.21, 1.23 • CXCR3 3.39, 3.68, 4.53
Concentrations of each biomarker in periodontitis sites	Not applicable	<ul style="list-style-type: none"> • 33.09\pm0.51 untreated • 27.95\pm0.97 treated 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> • IL-1β 205.5 (\pm156) pg/mL • IL-10 44.5 (\pm23.8) pg/mL • IL-17 92.9 (\pm22.8) pg/mL • Eotaxin 77.9 (\pm8.8) pg/mL • FGF 85.5 (\pm34.5) pg/mL • G-CSF 13.9 (\pm12.7) ng/mL • GM-CSF 149.8 (\pm119.2) pg/mL • PDGFbb 17.3 (\pm10.2) pg/mL • RANTES 994.3 (\pm812.3) pg/mL • OPG 2 (\pm0.9) μg/mL • TIMP-2 9.41 (\pm4.7) ng/mL 	<p>Median: 5.5% of positive cellular fibronectin staining</p>	<p>Relative expression in healthy patients, patients with diabetes, and patients with poorly controlled diabetes:</p> <ul style="list-style-type: none"> • TNF-α 1.17, 1.16, 3.70 • IL-6 4.53, 4.68, 8.94 • IL-8 3.51, 3.72, 8.41 • MCP-1 3.04, 3.19, 3.97 • CCRI 1.10, 1.14, 1.22 • CCR2 3.06, 3.14, 3.51 • CCR3 1.17, 1.19, 1 • CCR4 3.27, 3.20, 3.59 • CCR5 1.20, 1.18, 4.09 • CXCR1 1.12, 1.15, 1.23 • CXCR2 1.12, 1.19, 1.21 • CXCR3 1.18, 1.16, 4.34
Statistically significant difference	Yes	Yes, between all groups (P<0.05)	TIMP-2, IL-10 (on immunohistochemistry only) and RANKL higher in peri-implantitis (P<0.05)	Yes: compared with controls, higher in peri-implantitis and lower in periodontitis	Units=mRNA expression quantified as ratio to β -actin TNF- α , IL-6, IL-8, CCR5 and CXCR3 higher in peri-implantitis
Comments	Only a single transcript was found to be significantly regulated in both periimplantitis and periodontitis: TRIB1 (tribbles homolog 1, Drosophila)	-	-	-	Data taken from figures via PlotDigitizer

AQP1: aquaporin 1, CCR: C-C chemokine receptor, CXCR: CXC chemokine receptor, FGF: fibroblast growth factor, G-CSF: granulocyte colony-stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor, IL: interleukin, MCP: monocyte chemoattractant protein, OPG: osteoprotegerin, PDGF: platelet-derived growth factor, RANKL: receptor activator of nuclear factor kappa- α ligand, RANTES: regulated upon activation, normal T cell expressed and presumably secreted, TIMP: tissue inhibitor of metalloproteinases, TNF: tumor necrosis factor.

Table 4. Summary of studies assessing crevicular fluid

Study	Gürlek et al. [24]	Luo et al. [25]	Nomura et al. [27]	Rakic et al. [28]	Rakić et al. [29]	Teixeira et al. [30]	Xu et al. [31]	Yamalik et al. [32]
Biomarkers assessed	SRANKL, OPG, IL-1b, IL-17A, IL-17F, IL-17E, albumin	HMGBl, HMGn2, β-actin, IL-8, TNF-α	TIMP-1, MMP-1, MMP-8, collagenase activity (active), collagenase activity (APMA-activable)	RANK, sRANKL, OPG	RANK	IL-1β, IL-6, IL-4, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33INF-g, sCD40L, TNF-α	Collagenase-2	Cathepsin-K
Type of biomarkers	Immune-related	Immune-related	Extracellular matrix-related	Immune-related	Immune-related	Immune-related	Extracellular matrix-related	Extracellular matrix-related
Concentrations of each biomarker in peri-implantitis sites	<p>Median (second to third quartiles):</p> <ul style="list-style-type: none"> IL-1β 173.59 (99.41-189.91) pg/μL SRANKL 1,130.95 (818.45-1,324) pg/μL OPG 155.38 (47.80-729.08) pg/μL IL-7A 155.10 (53.51-364.63) pg/μL IL-17E 89.37 (40-136.25) pg/μL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> IL-1β 13,845 (±16,314) pg/mL IL-6 16,758 (±8,932) pg/mL OPG 155.38 (47.80-729.08) pg/mL TNF-α 398 (±198) pg/mL HMGBl 9,067 (±1,355) pg/mL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> TIMP-1 6.50 (±9.78) ng/sample MMP-1 1.13 (±1.88) ng/sample MMP-8 4.20 (±4.82) ng/sample TIMP-1/MMP-1+MMP-8 ratio 2.20 (±3.57) Collagenase activity active 4.8 (±2.4)×10⁻¹/sample Collagenase activity APMA-activable 7.6 (±3.3)×10⁻¹/sample 	<p>Mean (95% confidence interval):</p> <ul style="list-style-type: none"> RANK 1,297.39 (1,231.31-3,355.93) pg/mL sRANKL 9.29 (2.19-49.71) pg/mL OPG 18.99 (10.43-68.22) pg/mL sRANKL/OPG ratio 1.01 (0.62-3.46) 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> RANK 1,514.49 pg/mL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> IL-1β 332.7 (±369.8) pg IL-4 0.9 (±1.3) pg IL-6 24.8 (±26.4) pg IL-10 11.0 (±3.6) pg IL-17A 29.2 (±11.9) pg IL-17F 6.7 (±7.9) pg IL-21 22.7 (±7.8) pg IL-22 8.3 (±3.0) pg IL-23 50.0 (±21.0) pg IL-25 2.2 (±0.6) pg IL-31 18.2 (±9.3) pg IL-33 18.0 (±7.1) pg IFN-γ 7.9 (±3.8) pg sCD40L 5.5 (±7.1) pg TNF-α 4.9 (±3.0) pg 	<p>Extracellular matrix-related</p> <ul style="list-style-type: none"> 22.5% lysis of DNP-peptide per μL 14.4% lysis of DNP-peptide per site 	<p>Mean total cathepsin-K activity level: 16.290 units</p>
Concentrations of each biomarker in periodontitis sites	<p>Median (second to third quartiles):</p> <ul style="list-style-type: none"> IL-1β 118.69 (102.37-152.82) pg/μL SRANKL 1,071.43 (773.81-1,190.48) pg/μL OPG 442.23 (155.38-920.32) pg/μL IL-17A 120.27 (56.77-256.78) pg/μL IL-17E 82.50 (53.75-125) pg/μL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> Chronic: IL-1β 6,452 (±2,289) pg/mL IL-6 4,985 (±1,296) pg/mL IL-8 24,503 (±8,756) pg/mL TNF-α 259 (±114) pg/mL HMGBl 18,924 (±9,193) pg/mL Aggressive: IL-1β 7,089 (±3,235) pg/mL IL-6 17,035 (±8,487) pg/mL IL-8 18,214 (±6,102) pg/mL TNF-α 334 (±82) pg/mL HMGBl 17,217 (±2,376) pg/mL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> TIMP-1 13.68 (±9.64) ng/sample MMP-1 0.82 (±0.92) ng/sample MMP-8 4.31 (±2.19) ng/sample TIMP-1/MMP-1+MMP-8 ratio 4.98 (±2.48) Collagenase activity active 6.2 (±4.1)×10⁻¹/sample Collagenase activity APMA-activable 8.8 (±4.0)×10⁻¹/sample 	<p>Mean (95% confidence interval):</p> <ul style="list-style-type: none"> RANK 588.88 (274.32-2,000.83) pg/mL sRANKL 14.75 (5.98-70.59) pg/mL OPG 9.67 (3.14-23.31) pg/mL sRANKL/OPG ratio 1.86 (1.32-7.38) 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> RANK 421.79 pg/mL 	<p>Mean (standard deviation):</p> <ul style="list-style-type: none"> IL-1β 404.9 (±374.2) pg IL-4 2.2 (±2.4) pg IL-6 8.9 (±5.9) pg IL-10 11.5 (±5.5) pg IL-17A 35.2 (±24.3) pg IL-17F 9.1 (±9.7) pg IL-21 24.1 (±13.2) pg IL-22 9.1 (±5.9) pg IL-23 53.1 (±37.3) pg IL-25 2.3 (±1.1) pg IL-31 16.6 (±8.2) pg IL-33 23.6 (±20.7) pg IFN-γ 8.8 (±4.6) pg sCD40L 9.7 (±9.9) pg TNF-α 5.1 (±3.5) pg 	<p>Moderate periodontitis:</p> <ul style="list-style-type: none"> 16.8% lysis of DNP-peptide per μL 8.9% lysis of DNP-peptide per site <p>Severe periodontitis:</p> <ul style="list-style-type: none"> 16.5% lysis of DNP-peptide per μL 15.8% lysis of DNP-peptide per site 	<p>Mean total cathepsin-K activity level: 11.637 units</p>

(continued to the next page)

Table 4. (Continued) Summary of studies assessing crevicular fluid

Study	Gürlek et al. [24]	Luo et al. [25]	Nomura et al. [27]	Rakic et al. [28]	Rakić et al. [29]	Teixeira et al. [30]	Xu et al. [31]	Yamalík et al. [32]
Statistically significant difference	No	No	No except TIMP-1/MMP-1+MMP-8 ratio higher in periodontitis ($P<0.05$ Mann-Whitney <i>U</i> test)	RANK higher in peri-implantitis ($P=0.000$), implantitis lower in peri-implantitis ($P<0.001$), sRANKL/OPG ratio lower in peri-implantitis ($P=0.04$)	RANK higher in peri-implantitis ($P<0.000$), implantitis ($P<0.001$)	No	Higher collagenase-2 in peri-implantitis	No comparison done. No statistical difference between teeth and implants when including control groups
Comments	Data taken from figures via PlotDigitizer. Recorded amounts but not concentrations of IL-17F and IL-17E	-	-	-	-	-	-	Severity of bone loss around dental implants not as distinctive as in teeth group

APMA: aminophenyl mercuric acetate, DNP: dendraoasis natriuretic peptide, HMGB: high mobility group nucleosome-binding, IL: interleukin, INF: interferon, MMP: matrix metalloproteinase, OPG: osteoprotegerin, RANK: receptor activator of nuclear factor kappa-B, sRANKL: soluble receptor activator of nuclear factor kappa-B ligand, TIMP: tissue inhibitor of metalloproteinases, TNF: tumor necrosis factor.

Table 5. Summary of narrative synthesis

Summary
<ul style="list-style-type: none"> • Eight of the 13 included studies found significant differences in the level of biomarkers present between peri-implantitis and periodontitis. • Where levels of biomarkers were different, they were higher in peri-implantitis than in periodontitis. • Transcripts were found to be different between peri-implantitis and periodontitis. • Five of the 8 studies deemed to be at the lowest risk of bias found significant differences. • All of the studies assessing biomarkers via biopsies rather than crevicular fluid samples found significant differences. • Four of the 7 studies assessing immune-related biomarkers found significant differences. • Both immune and microbial biomarkers showed similar differences in terms of the trends. • Three of the 4 studies assessing matrix-related biomarkers found significant differences. • The biomarker levels that were significantly different were all inflammatory-related. • Higher levels of biomarkers reflective of extracellular matrix metabolism were generally found in peri-implantitis than in periodontitis. • Biomarkers that act as inflammatory mediators regulating DNA processes (HMGB) and growth factors that can stimulate endothelial cells and hence prevent connective tissue regeneration (FGF, PDGF) showed no differences. • Some differences were found for cytokines and chemokines as inflammatory mediators (interleukins, RANTES, CCR, CXCR, TNF, MCP). • Differences were consistently found across host-derived enzymes for collagen degradation (collagenase, MMP, TIMP, cathepsin), markers of bone homeostasis (OPG, RANK, sRANKL) and markers of tissue homeostasis (aquaporin 1, fibronectin).

CCR: C-C chemokine receptor, CXCR, CXCL chemokine receptor; FGF: fibroblast growth factor, HMGB: high mobility group box, MCP: monocyte chemoattractant protein, MMP: matrix metalloproteinase, OPG: osteoprotegerin, PDGF: platelet-derived growth factor, RANK: receptor activator of nuclear factor kappa-B, RANTES: regulated upon activation, normal T cell expressed and presumably secreted, sRANKL: soluble receptor activator of nuclear factor kappa-B ligand, TIMP: tissue inhibitor of metalloproteinases, TNF: tumor necrosis factor.

Eight of the 13 included studies found significant differences in the levels of biomarkers present between peri-implantitis and periodontitis for transcripts of aquaporin 1, tissue inhibitor of metalloproteinases 2 (TIMP-2), interleukin (IL)-10, receptor activator of nuclear factor kappa-B ligand (RANKL), soluble RANKL (sRANKL), cellular fibronectin, tumor necrosis factor (TNF)-alpha, IL-6, IL-8, C-C chemokine receptor type 5 (CCR5), CXC chemokine receptor 3 (CXCR3) and collagenase-2, as well as the ratios of TIMP-1 to matrix metalloproteinase (MMP-1)+MMP-8 and sRANKL to osteoprotegerin (OPG) [6,7,22,23,26,28,29,31]. When differences in levels of biomarkers were found, they were higher in peri-implantitis than in periodontitis. Two studies did not carry out exact statistical comparisons between these groups, but tested each separately against controls, with 1 reporting a difference [26,32]. An additional study found no significant difference in the levels of biomarkers, but did find a significant difference in the ratio of 2 biomarkers [27].

All of the studies assessing biopsies found significant differences, which could be relevant if biopsies are more sensitive than crevicular fluid samples, as has been reported [33]. Four of the 8 studies assessing crevicular fluids found significant differences.

Four of the 7 studies assessing immune-related biomarkers found significant differences [6,23-25,28-30], as did 3 of the 4 studies assessing matrix-related biomarkers [26,27,31,32].

Of the 8 studies deemed to be at the lowest risk of bias, 6 assessed crevicular fluid and 2 assessed biopsies [6,23-25,28-31]. Five out of these 8 found a significant difference. No studies reported all of the information that was sought for the risk of bias and data extraction tables.

DISCUSSION

This study found some reports of higher levels of inflammatory biomarkers or differences in their ratios in peri-implantitis compared with periodontitis. In the few studies that compared the same biomarkers, the studies that did find a difference appeared to be at lower risk of bias [6,24,27,31]. The level of risk of bias did not appear to relate to the likelihood of a study finding a statistically significant difference or not. Of the 5 studies in which selection met higher standards, 4 found significant differences [6,28,29,31].

Both immune and microbial-associated biomarkers showed similar overall results. The biomarkers that showed a difference between the 2 diseases are all inflammatory-related, which is in line with a bacterial cause for peri-implantitis. Some local risk factors are inherently different than those present around teeth; namely, differences in tissue structure and/or the presence of metallic connections that result in the diffusion of metal particles due to tribocorrosion [34]. This may explain why whilst these biomarkers are also found in periodontitis [35,36], their levels are significantly higher in peri-implantitis. The single study that assessed the transcriptome [7] reported differences relating to microbial and immune responses; however, this was not reflected in any of the remaining studies.

More studies assessing biomarkers related to extracellular matrix metabolism found a difference, unlike studies assessing biomarkers related to the immune system. This might indicate that biomarkers related to extracellular matrix metabolism may be more important in peri-implantitis than in periodontitis. It is unclear whether this difference relates to a lack of connective tissue encapsulation in peri-implantitis.

Biomarkers that act as inflammatory mediators regulating DNA processes (high mobility group box) and growth factors, which can stimulate endothelial cells and hence prevent connective tissue regeneration (fibroblast growth factor, platelet-derived growth factor), showed no differences. Some differences were found with the cytokines and chemokines as inflammatory mediators (ILs, CCL-5, CCR, CXRC, TNF, monocyte chemoattractant protein). Differences were consistently found across host-derived enzymes for collagen degradation (collagenase, MMP, TIMP, cathepsin), markers of bone homeostasis (OPG, RANK, sRANKL) and markers of tissue homeostasis (aquaporin 1, fibronectin). Table 5 presents a summary of the narrative synthesis.

This review adds to other emerging evidence to shed light on the pathology, and hence potential management, of peri-implantitis. Studies that assessed biomarkers and the microbiome in peri-implant mucositis compared with gingivitis also found differences [37-39]. Those studies benefitted from being split-mouth in nature, having baseline assessments and being able to assess the temporal relationship as oral hygiene measures are ceased. Those findings appear to align with this study.

The included studies showed considerable heterogeneity in terms of their definition of peri-implantitis. In 2 studies [26,28], it was unclear whether the patients had undergone any treatment thus far to stabilise the diseases. A breakdown of patients with their clinical scenarios was never provided. Details of the surgical and restorative implant treatment provided were scarce. The numbers included in most studies were low and the sample size was rarely justified. Only one study included more than 100 participants [6] and the majority included fewer than 30. Only one study was carried out within patients [24], while the rest compared separate groups of patients suffering from either one disease process or another. These studies did not attempt to show that the groups were comparable and hence were at a high risk of confounding factors. The selection methods of the studies were often not reported or inadequate, which affected the generalisability of results. Blinding at any stage was very rarely mentioned. Basic data were sometimes not published either in print or online versions of studies, which made it necessary to extract data from graphs. At times the units reported could be unclear. Most studies did not discuss their limitations and received funding from third parties; which could indicate funding and reporting bias [40,41].

The inclusion criteria of the present systematic review could have been broadened to include studies that only assessed peri-implantitis or periodontitis to allow the inclusion of more data. Non-English-language studies were excluded, although there were 3 such studies that would have been eligible for phase 2 screening, which may have improved the amount of data available [42-44]. The risk of bias assessment was carried out utilising the AXIS tool [21]. This is a relatively recent tool that covers the majority of important points; however, it does not give an overall score to classify risk of bias and hence results in a subjective assessment. There was no mention of blinding of assessors in the tool. Most authors did not respond to requests for further information. In 2 studies, PlotDigitizer was utilised to extract exact data from figures [6,24]. This has been reported to be accurate in only 75% of figures [45]. The heterogeneity between studies resulted in the inability to perform a meta-analysis. This meant that reporting bias could not be assessed.

In order to draw conclusions with more confidence, studies with more robust methodology and reporting need to be conducted. It is suggested that all further studies comparing biomarkers between periodontitis and peri-implantitis should include all points from the data extraction and risk of bias forms, in addition to details of selection methods and

attempts to decrease selection bias, blinding of assessors wherever possible, split-mouth studies assessing patients suffering from both periodontitis and peri-implantitis to assess differences in local risk factors and biomarkers, and a breakdown of results by symptoms and severity. In order to assess systemic differences between patients, non-split-mouth studies may also prove useful in the future. Smokers should be classified according to their smoking status and analysed accordingly. Exact figures and units should be reported in the publication along with details of statistical analyses. A power calculation of sample size should be performed at the outset of the study. It should be clearly reported what treatment, if any, participants have undergone prior to biomarker assessment. Longitudinal studies were also lacking from the literature and should be performed in order to assess temporal relationships. A similar systematic review assessing biomarkers in peri-implant mucositis compared with gingivitis could provide additional information on these disease processes, as could one comparing healthy teeth and implants.

Within the limitations of this review, it appears that the majority of evidence points to the possibility of higher biomarker levels in peri-implantitis than in periodontitis, as well as differing biomarker ratios between these diseases.

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