Received: 22 November 2023 | Revised: 26 March 2024 | Accepted: 22 April 2024

DOI: 10.1111/jcpe.13996

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

Are periodontitis and psoriasis associated? A pre-clinical murine model

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Abstract

Aim: To investigate the bidirectional influence between periodontitis and psoriasis, using the respective experimental models of ligature- and imiquimod-induced diseases on murine models.

Materials and Methods: Thirty-two C57/BL6J mice were randomly allocated to four experimental groups: control (P− Pso−), ligature-induced periodontitis (P+ Pso−), imiquimod-induced psoriasis (P− Pso+) and periodontitis and psoriasis (P+ Pso+). Samples (maxilla, dorsal skin and blood) were harvested immediately after death. Measures of periodontitis (distance between the cemento-enamel junction and alveolar bone crest [CEJ–ABC] and the number of osteoclasts) and psoriasis (epidermal thickness and infiltrate cell [/0.03mm^2]) severity as well as systemic inflammation (IL-6, IL-17A, TNF-α) were collected.

Results: The P+ Pso+ group exhibited the most severe experimental periodontitis and psoriasis, with the highest values of CEJ–ABC, number of osteoclasts, epidermal thickness and infiltrate cells in the dorsal skin, as well as the highest blood cytokine concentration. The P+ Pso− group presented with higher cell infiltrate (/0.03mm^2) compared to the control group (p <.05), while the P− Pso+ group showed substantially higher alveolar bone loss (CEJ–ABC) than the control group (p <.05).

Conclusions: Experimental periodontitis may initiate and maintain psoriasiform skin inflammation and, vice versa, experimental psoriasis may contribute to the onset of periodontitis. In a combined model of the diseases, we propose a bidirectional association between periodontitis and psoriasis via systemic inflammation.

KEYWORDS
periodontal diseases, periodontal therapy, psoriasis, skin diseases

Clinical Relevance

Scientific rationale for study: Periodontitis and psoriasis share many risk factors and aetiopathogenetic pathways. The epidemiological evidence on their association is still conflicting.

Principal findings: Periodontitis may initiate and maintain psoriasiform skin inflammation and, vice versa, psoriasis may contribute to the onset of periodontitis. A possible bidirectional association between periodontitis and psoriasis driven by a common host inflammatory response is proposed. This is the first study addressing a mechanistic question on the potential association between periodontitis and psoriasiform skin inflammation.
Practical implications: Teamwork between dermatologists and periodontists could help achieve an early diagnosis and treatment of both diseases, and thus ameliorate the life-long management of both periodontitis and psoriasis.

1 | INTRODUCTION

Periodontitis is an inflammatory disease triggered by a dysbiotic biofilm in the oral cavity and affecting the soft and hard tissues around teeth (Tonetti et al., 2018). It is a chronic disease, usually extending over decades of an individual's life; its clinical manifestation is characterized by gingival inflammation with associated alveolar bone loss which, if left untreated, can ultimately lead to tooth loss. Periodontitis is a highly prevalent disease affecting around 750 million people worldwide (between the ages 15 and 99 years) (Frencken et al., 2017): the disease has also been linked to social inequality and poor quality of life of the patients (Ferreira et al., 2017). A large body of evidence has underlined how the inflammatory burden of periodontitis goes well beyond the oral cavity, thus affecting systemic health either through bacterial translocation from the oral cavity to the blood stream or through the induction of a state of low-grade systemic inflammation (LGSI) (Hajishengallis & Chavakis, 2021). Other inflammatory non-communicable diseases (NCDs) have been identified as comorbidities of periodontitis, such as diabetes, cardiovascular diseases and metabolic syndrome (Baima et al., 2022; Botelho et al., 2022; Czesnikiewicz-Guzik et al., 2019; D'Aiuto et al., 2018; Marruganti, Baima, et al., 2023; Marruganti, Suvan, & D'Aiuto, 2023). Similarly, psoriasis, as a source of LGSI, has been associated with a vast range of NCDs including periodontitis (Baurecht et al., 2022; Boehncke, 2018; Patrick et al., 2021; Takeshita et al., 2017; Zhang et al., 2022). Despite the conflicting results obtained from available epidemiological evidence, periodontitis and psoriasis share numerous risk factors and many etiopathogenetic pathways. However, little evidence is available on the mechanisms by which periodontitis might influence the physiopathology of psoriasis, and vice versa. Ligature placement around the molars is one of the most commonly used experimental models to mimic the local and systemic effects of periodontitis (Marchesan et al., 2018), while the topical application of imiquimod (IMQ) cream has increasingly been used as an acute psoriasiform murine model (Swindell et al., 2017). Indeed, the immunomodulating effects of IMQ were found to be able to elicit at a local level the typical psoriasis-like dermatitis, including erythema, scaling, keratinocyte proliferation with acanthosis and proliferation and a T-cell-based dermal infiltrate, and at a systemic level the induction of IL-17/IL-23 axis cytokines and T-lymphocyte production (Swindell et al., 2017). The aim of this pre-clinical investigation was to ascertain whether a bidirectional relationship exists between ligature-induced periodontitis and IMQ-induced psoriasiform skin inflammation and to explore its underpinning biological mechanisms.

2 | MATERIALS AND METHODS

A pre-clinical study was designed according to the modified ARRIVE guidelines for pre-clinical research (Vignoletti & Abrahamsson, 2012) and following the European Union regulations (European Communities Council Directive 86/609/EEC). The protocol was carried out at the Toscana Life Sciences (Siena, Italy) animal facilities and was approved by the local Animal Welfare Body and the Italian Ministry of Health (468/2021-PR).

2.1 | Study design

Thirty-two male C57/BL6J mice (Charles River Laboratories, Calco, Italy) (20–30 g) aged 8–12 weeks were kept in constant conditions and with ad libitum feeding for 7 days before the experiments (acclimation) (Figure 1). Mice were randomly allocated to four experimental groups ($n = 8$) resulting from the different combinations of induction of periodontitis (P) and psoriasis (Pso): (a) control group (P− Pso−); (b) periodontitis (P+ Pso−); (c) psoriasis (P− Pso+); (d) periodontitis and psoriasis (P+ Pso+).

2.1.1 | Ligature-induced periodontitis model

Mice were subjected to anaesthesia by intraperitoneal injection of a mixture containing 66.7 mg/kg of ketamine and 6.7 mg/kg of xylazine. Sterile silk sutures (5–0) were then ligated around the right second (M2) and third (M3) maxillary molars and kept in place for 14 days (Marchesan et al., 2018).

2.1.2 | Imiquimod-induced psoriasis model

Each mouse received a topical dose of 62.5 mg of commercially available 5% IMQ cream (Aldara; 3 M Pharmaceuticals; Maplewood, MN, USA) on their shaved dorsal skin for five consecutive days (van der Fits et al., 2009).

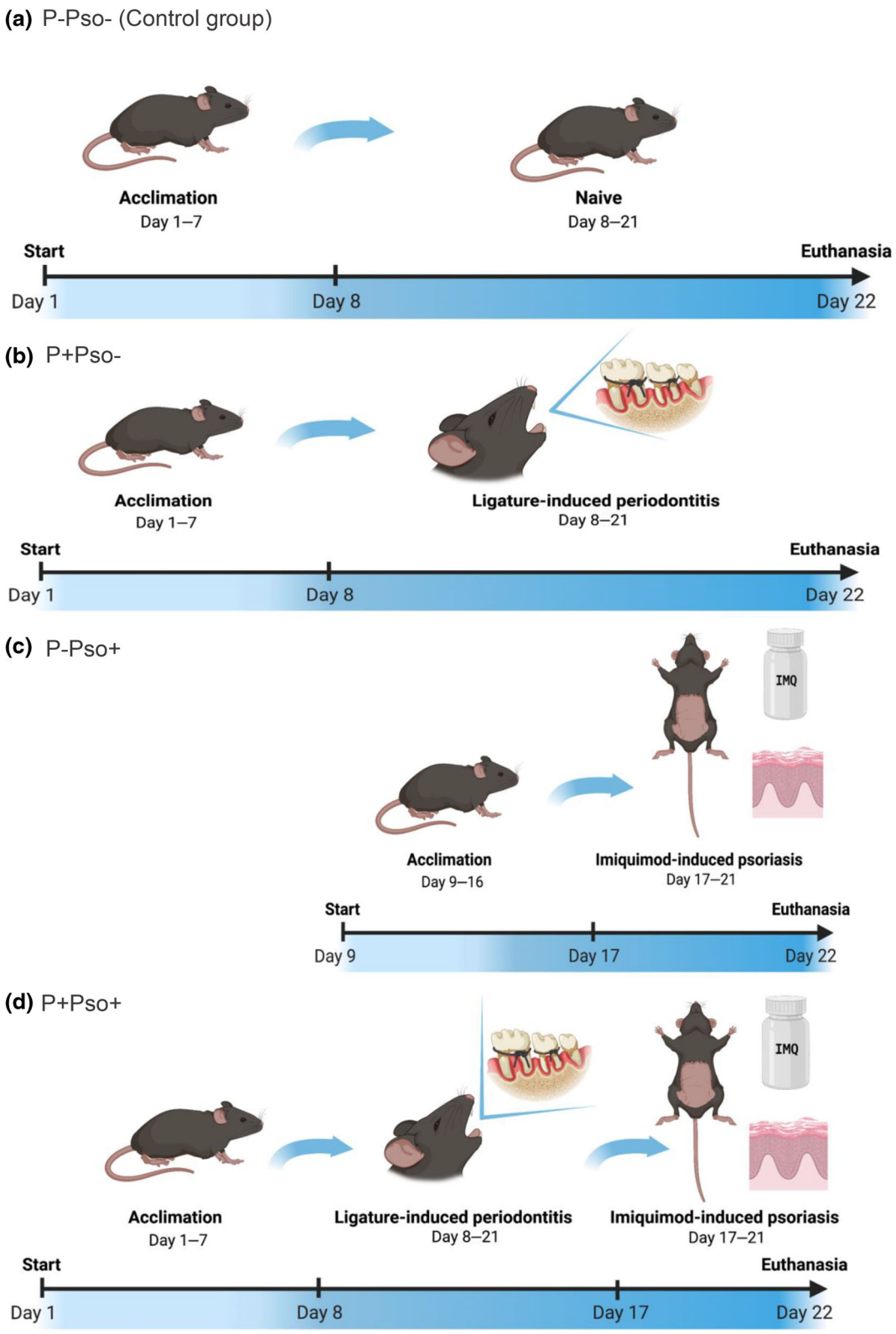

FIGURE 1 Flowchart describing the experimental phases for each group (a–d; figure created with BioRender.com). IMQ, imiquimod.

2.1.3 | Tissue specimens

At the end of the study period (Day 22; Figure 1), mice were euthanized by inhalation of 3.5% isoflurane and cervical dislocation. Samples of maxillae, dorsal skin and blood were harvested immediately after death. Blood samples were collected by cardiac puncture, which were then anti-coagulated with ethylenediaminetetraacetic acid (EDTA, 1% w:v; 1 vol. EDTA per 50 vol. blood) and centrifuged for

15 min at room temperature to obtain the plasma. In addition, the mandible was removed from the skull, and the dorsal skin was collected. All specimens, except the dorsal skin, were stored at −80°C.

2.2 | Study outcomes

2.2.1 | Alveolar bone loss

After euthanasia, palatal tissue samples were fixed in 4% paraformaldehyde (PFA)/phosphate-buffered saline (pH 7.4) for 24 h and examined using micro-computed tomography (micro-CT) for high-resolution scans (SkyScan 1172 Micro-CT, Bruker, Billerica, MA, USA) and image reconstruction (NRecon, Bruker). Segmentation was then applied using commercial software (Mimics 20.0, Materialize, Ann Arbor, MI, USA) to visualize the whole palatal tissue through 3D rendering. The CEJ–ABC distance was measured by a single previously calibrated examiner. Examiner calibration was performed on two non-study samples (eight sites per tooth), which was considered satisfactory only when an agreement in at least 95% of measurements (with a maximum of 0.05 mm difference) was recorded. The intra-rater agreement resulted in ICC = 0.98 (p =.0001). For each tooth (M2 and M3), eight measurements from the CEJ to the bone level were taken from the sagittal view (CEJ–ABC). Four measurements were taken for the mesial peak (MB1, MB2, MP1, MP2) and four for the distal peak (DB1, DB2, DP1, DP2) of each molar, progressively moving from the buccal aspect to the palatal aspect to map the whole interproximal bone profile. The CEJ–ABC distance in millimetres was used as a measure of alveolar bone loss. For each animal, the mean of the measurements taken for M2 and M3 was used as the CEJ–ABC distance. Higher values of CEJ–ABC distance indicate more alveolar bone loss. Moreover, bone volume analysis was performed on each sample, limiting the volume of interest (VOI) between the M2 and M3 and manually excluding the palatal bone. In order to do that, all the high-quality stl files generated from micro-CT segmentation were imported into Geomagic Qualify Studio 12 (3D Systems) and manually cut. This step was meant to reduce the effect on the anatomical variables that occur between samples, such as the different root morphology. After that, all holes were closed with a straight-surface algorithm and normals were fixed. Volume calculation was achieved through the homonymous function available in the software (Geomagic Qualify Studio 12, 3D Systems) and expressed as bone volume/total volume (%).

2.2.2 | Histological outcomes

Palatal tissues: Maxillae samples were demineralized and embedded in paraffin; 4-µm-thick sagittal sections were made around the region of interest (M2–M3) for histological and immunohistochemical analysis performed by one calibrated examiner who was blinded to the group allocation. In addition, osteoclasts were stained with the tartrate-resistant acid phosphatase kit (TRAP; 387A-1KTF; Sigma Chemical Co.) following the manufacturer's instructions, with haematoxylin Gill 3 (Sigma-Aldrich) counterstaining. For every sample, four fields of 1.13 mm^2 each (corresponding to ×20 magnification each) were identified, and the concentration of osteoclasts was calculated as the number of TRAP-positive multi-nucleated cells for each field. For each animal, the average concentration in the four fields was calculated.

Dorsal skin: Mice were perfused with 4% PFA, and, after the harvest, the dorsal skin was fixed in 10% neutral-buffered formalin and then processed and embedded in paraffin blocks. Samples were then cut into 4-µm-thick sections using a rotary microtome and stained with haematoxylin and eosin (H&E; Muto Pure Chemicals Co., Ltd.; Tokyo; Japan). Stained sections were observed using a digital microscope (OMAX 40×-2500× LED, ZEISS, Germany). Epidermal thickness was assessed as epidermal area (µm^2)/basal membrane length (µm) measured in two different fields, each covering 1.13 mm^2 for each sample; then the mean value was considered (Ju et al., 2019). The inflammatory infiltrate in the dermis was quantified and expressed as the number of infiltrated cells (/0.03 mm^2). The entire mice skin was sampled and included in the evaluation. All the acquisitions, measurements and histological analyses were made through the digital microscope software (ZEN Blue 3.4 software, ZEISS, Germany). Each measurement was taken twice by a single examiner who was blinded to group allocation, and the mean value was considered.

2.2.3 | Systemic inflammation

The production of IL-6, IL17A and TNF-α were assessed by Luminex immunoassay in blood sera (Luminex Assays, Thermo Fisher Scientific, Waltham, MA). Analytes were detected (Bio-Plex pro mouse cytokine group 1, BioRad, Hercules, CA) and then analysed using Bio-Plex technology following the manufacturer's instructions (Bio-Plex Magpix Multiplex Reader, BioRad). Cytokine concentrations (pg/ml) were calculated in duplicate based on the standard curve in each plate and analysed using the appropriate software (Bio-Plex Manager 6.2, BioRad). Intra-and inter-assay coefficient of variations were all <6%.

2.3 | Data analyses

All analyses were performed using a statistical software (Stata, release 17, StataCorp LLC, College Station, TX) setting the significance level at 5%. The sample size calculation was based on the primary outcome measure: CEJ–ABC (mm). The coexistence of periodontitis and psoriasis was hypothesized to result in double the amount of bone loss (CEJ–ABC = 1 mm) compared to the reference group of animals affected only by periodontitis (CEJ–ABC = 0.5 mm). Considering the mean CEJ–ABC value in the control group (0.1 mm), the resulting sample size, with a power of 80% and an alfa error of 0.05, was eight animals per group (n = 32) (Marchesan et al., 2018; Queiroz-Junior et al., 2012). Variables are presented as means and standard deviation (SD) or medians and interquartile range (IQR). ANOVA and post hoc Tukey's tests were used for intergroup and pairwise comparisons if variables were normally distributed, while the Kruskal–Wallis and post hoc Dunn's tests were used as nonparametric equivalent tests.

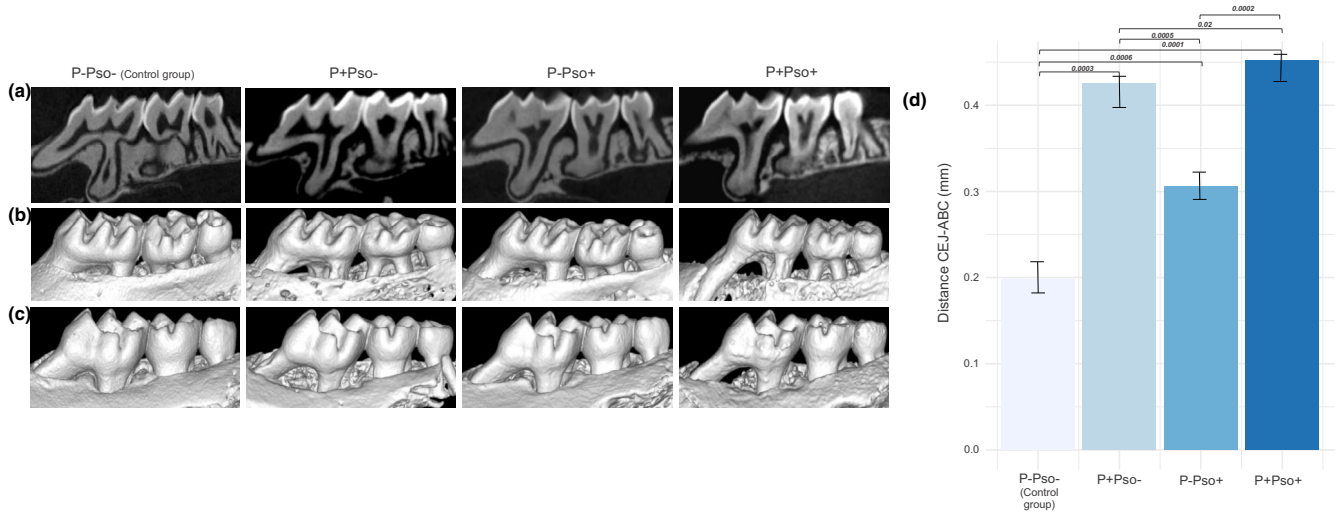

FIGURE 2 Representative bidimensional (a) and sagittal 3D views of the maxillary molars for each group on the buccal (b) and palatal (c) sides. (d) Histogram showing the mean distance between the cemento-enamel junction and the alveolar bone crest for each group (error bars indicate 95% confidence intervals).

3 | RESULTS

3.1 | Study sample

A total of eight animals were allocated to each experimental group ($N = 32$). Two mice died before the induction of periodontitis during the administration of anaesthesia required to place the ligatures, resulting in seven animals for each P+ Pso− and P+ Pso+ groups. The final sample analysed included 30 animals.

3.2 | Alveolar bone levels

Fourteen days after ligatures placement, the control group (P− Pso−) presented the lowest mean value of the CEJ–ABC distance (0.2 ± 0.04 mm) when compared to the other groups, while the P+ Pso+ group presented the highest value (0.5 ± 0.06 mm), with a statistically significant difference when compared to the P+ Pso− group (0.4 ± 0.04 mm) (p <.001). In addition, all P+ groups exhibited greater CEJ–ABC distances when compared to P− groups, respectively; the P− Pso+ group (0.3 ± 0.03 mm) showed a statistically significant greater CEJ–ABC distance than the control group (p =.006) (Figure 2). Bone volume analyses reported consistent results, with the control group (P− Pso−) showing the highest mean value and the P+ Pso+ showing the lowest mean value of bone volume (Figure S1).

3.3 | Histological outcomes

3.3.1 | Palatal tissues

All P+ groups showed increased bone resorption compared to P− groups (Figure 3). The lowest number of osteoclasts was recorded in the control group (0.7 ± 0.9), while the highest was in the P+ Pso+ group (8.0 ± 1.3). All P+ groups showed a statistically significant higher number of osteoclasts than the P− groups (p < .01). However, the P− Pso+ group (4.0 ± 2.2) presented a higher number of osteoclasts than the control group, even though the difference was not statistically significant (Figure 3).

3.3.2 | Dorsal skin

The lowest value of epidermal thickness was recorded in the control group (85.5 ± 24.9 mm), while the highest was in the P+ Pso+ group (315.2 ± 36.7 mm) (Figure 4). All Pso+ groups presented statistically significant increased epidermal thickening compared to Pso− groups (p <.01). The P+ Pso− group (159.6 ± 55.9 mm) had the highest mean value of epidermal thickness when compared to the control group, but the difference was not statistically significant (Figure 4e).

From a qualitative analysis, the dermal inflammatory infiltrate was characterized mainly by lymphocytes and granulocytes for the P+ Pso+ and P− Pso+ groups, and mainly by lymphocytes for the P+ Pso− group. The control group presented with the lowest number of cell infiltrate (2.2 ± 0.9) among the groups. The P+ Pso+ group of animals had the highest number of cells (42.1 ± 7.3), even statistically significantly greater than those in the P− Pso+ group (24.3 ± 17.1) (p =.03). All Pso+ groups showed statistically significantly larger inflammatory infiltrates when compared to Pso− groups, with the exception of the P+ Pso− group animals (4.5 ± 0.5) (p <.05) (Figure 4f).

3.4 | Systemic inflammation

All experimental groups (P+ Pso−, P− Pso+, P+ Pso+) exhibited statistically significant higher concentrations of IL-6, IL-17A and TNF-α than the control group (p <.05). IL-6, IL-17A and TNF-α reached their

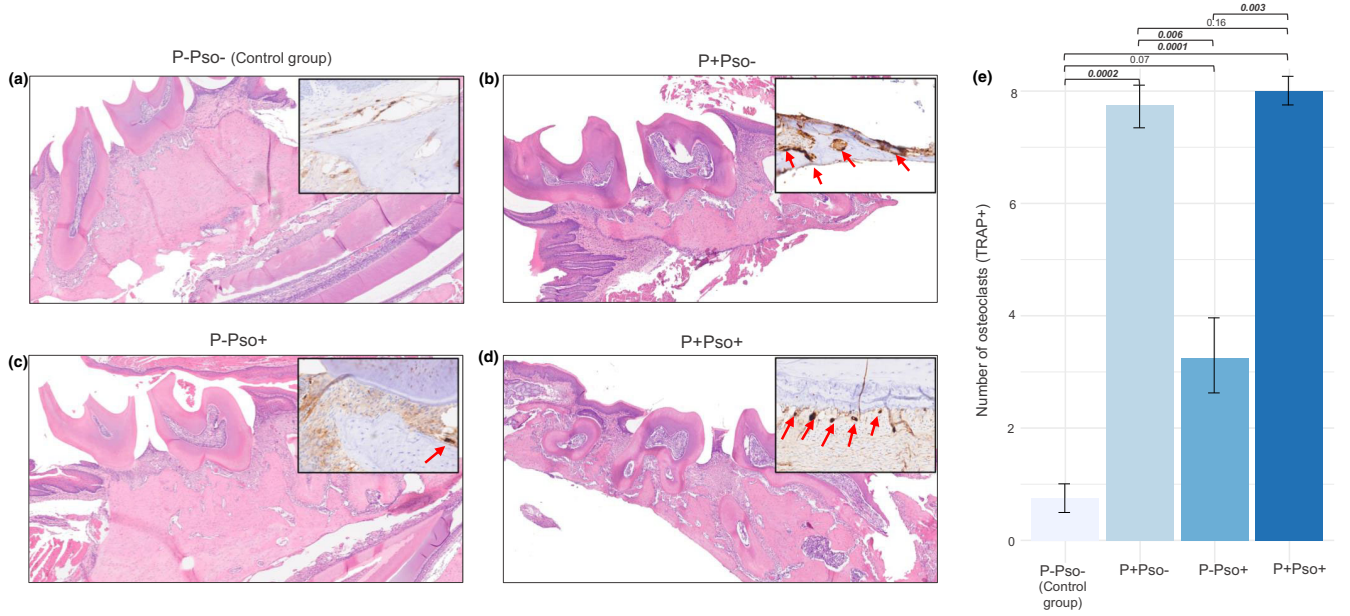

FIGURE 3 Representative haematoxylin and eosin-stained sections of gingival tissues for each group (a–d: ×100 magnification), with detail of representative immunohistochemical TRAP-stained sections. (e) Histogram showing the average number of osteoclasts (TRAP+ multinucleated cells) identified at ×20 magnification for each group (error bars indicate 95% confidence intervals).

highest levels in the P+ Pso+ group, while their lowest concentrations were recorded for the control group. The P+ Pso+ group had statistically significant higher levels of IL-6 and IL-17A when compared to the P− Pso+ and P+ Pso− groups (p <.05). Similar trends were observed for TNF-α levels, but differences were not statistically significant (p >.05; Figure 5).

4 | DISCUSSION

A combined model of experimental periodontitis and psoriasis resulted in synergistic effects of alveolar bone loss and skin inflammation when compared to the control group. Experimental periodontitis was partially associated with increased inflammation of the otherwise-healthy dorsal skin, as shown by the tendency towards increased epidermal thickening and inflammatory infiltrate, thus suggesting that periodontitis may potentially trigger psoriasiform skin inflammation. In this experiment, the combination of periodontitis and psoriasis (P+ Pso+) demonstrated the most severe manifestations of both diseases, namely the highest amount of alveolar bone loss and number of osteoclasts in the periodontium, and the highest amount of epidermal thickening and inflammatory infiltrate of the dorsal skin. Moreover, circulating levels of inflammatory biomarkers further increased when the two diseases were combined. This experiment suggests common pathways that could link two common inflammatory diseases in humans.

This is the first study to address a mechanistic question on the potential association between periodontitis and psoriasiform skin inflammation. There is little experimental evidence linking periodontitis and psoriasis, and the clinical epidemiological evidence has resulted in conflicting results (Baurecht et al., 2022; Zhang et al., 2022).

The models adopted in this study successfully resulted in periodontitis and psoriasiform skin inflammation (psoriasis) (Abe & Hajishengallis, 2013; Marchesan et al., 2018; Swindell et al., 2017). The combined induction of periodontitis and psoriasis (P+ Pso+) led to greater alveolar bone loss and both clinically and histologically confirmed skin inflammation.

An interesting finding from the present study is that experimental psoriasis was associated with an increased number of osteoclasts and alveolar bone loss in an otherwise-healthy periodontium, suggesting that psoriasis may trigger the onset of periodontitis. There is sufficient clinical evidence suggesting that patients affected by psoriasis exhibit a systemic host response characterized by increased serum cytokine, C-reactive protein (CRP) levels and numbers of Th1 and Th17 cells (Christophers & van de Kerkhof, 2019). The increase in specific levels of cytokines, such as IL-17A, TNF-α and IL-6, as shown in this experiment, was shown to potentially promote the onset of periodontitis via the recruitment and stimulation of other immune cells (e.g., neutrophils) and the synthesis of metalloproteinases causing periodontal tissue destruction (Huang et al., 2021; Pink et al., 2015). Moreover, the systemic inflammatory effects of psoriasis have been associated with inflammation-induced endothelial dysfunction (Boehncke, 2018) as well as increased insulin resistance (Patrick et al., 2021), both of which were previously shown to exert a negative influence on the periodontium (Botelho et al., 2022).

Several mechanisms may underlie the association between periodontitis and psoriasis (Figure 6). Recent evidence has shown that a specific skin microbiome can activate the innate immune system and result in the pathogenesis of psoriasis (Fry et al., 2013); an additional microbial trigger could originate from the gut lining (Rademaker et al., 2019), which seems to have an altered permeability in patients

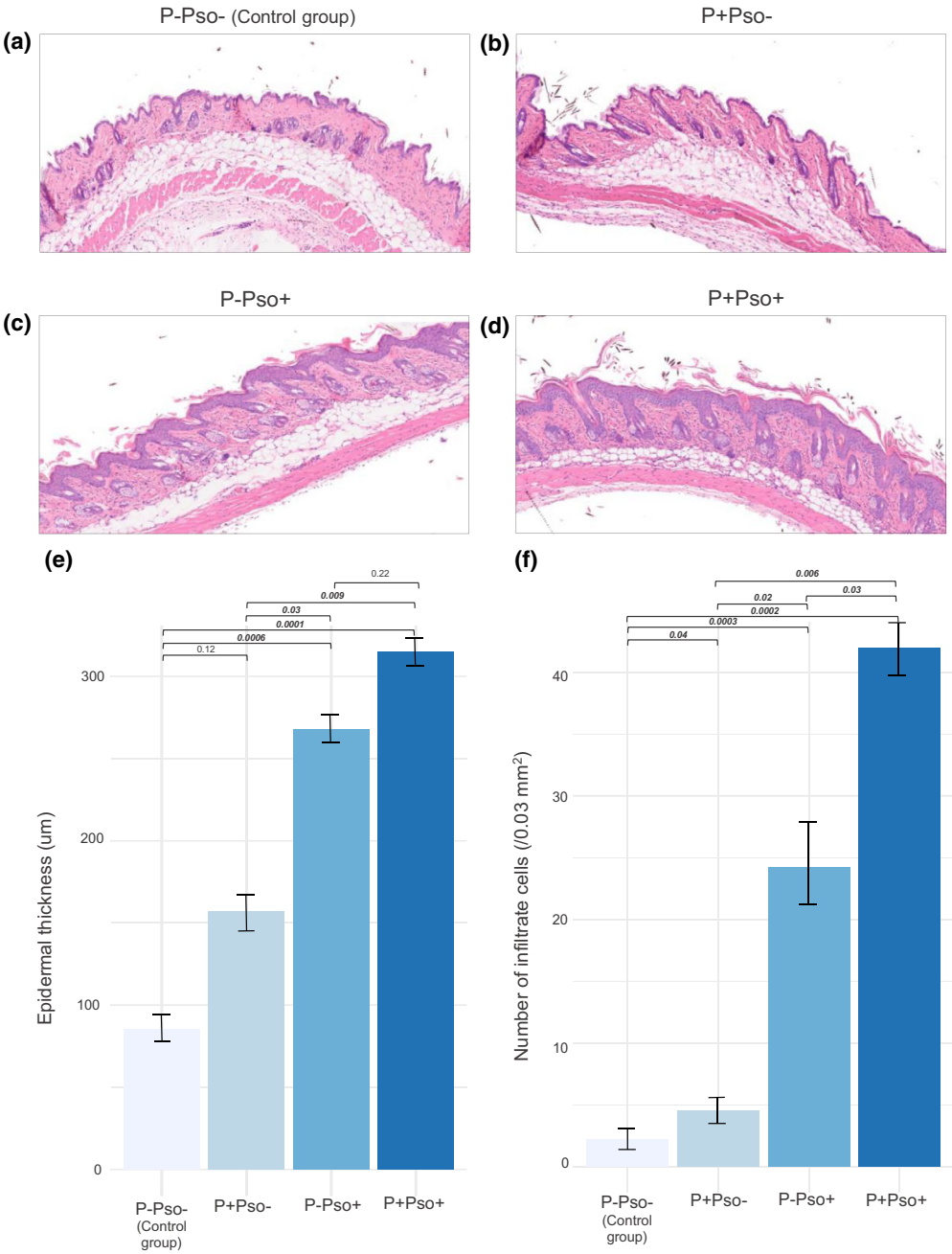

FIGURE 4 Representative haematoxylin and eosin-stained dorsal skin sections for each group (a–d). (e) Histogram showing the mean epidermal thickness and (f) the number of infiltrate cells for each group (error bars indicate 95% confidence intervals).

with psoriasis (Sikora et al., 2018). On this basis, we could hypothesize that a systemic bacterial translocation induced by periodontitis (Hajishengallis & Chavakis, 2021) and the reciprocal influence of the mouth–gut microbiome axis (Olsen & Yamazaki, 2019) could result in an immuno-inflammatory response affecting the host tolerance to the skin microbiota (dysbiosis), eventually leading to the pathogenesis of psoriasis. An alternative pathway suggests that the host response induced by periodontitis—characterized by the raised levels of specific cytokines (i.e., IL-6 and IL-17A)—can directly trigger the activation of the innate (e.g., via the NF–kB pathway) and adaptative (e.g., via the differentiation of naïve T-cells into Th17) immune responses, thus altering metabolism of the keratinocytes by increasing their proliferation and loss of differentiation, and facilitating the formation of psoriatic lesions (Cai et al., 2019; Griffiths et al., 2021).

Some limitations should be acknowledged when interpreting these findings, including the lack of assessment of the skin and oral microbiota. Notwithstanding the fact that experimentally induced periodontitis using ligatures may exert a higher degree of trauma to the periodontal tissues (Klausen, 1991) when compared to other experimental models (e.g., oral gavage with *P.gingivalis*), and the ligatures around the molars might not have been stable throughout the whole experimental period (Marchesan et al., 2018), the substantial dental biofilm accumulation, bone loss and robust host inflammatory responses are achieved in a shorter period (de Molon et al., 2016; Hajishengallis & Chavakis, 2021). Male mice were chosen to avoid any

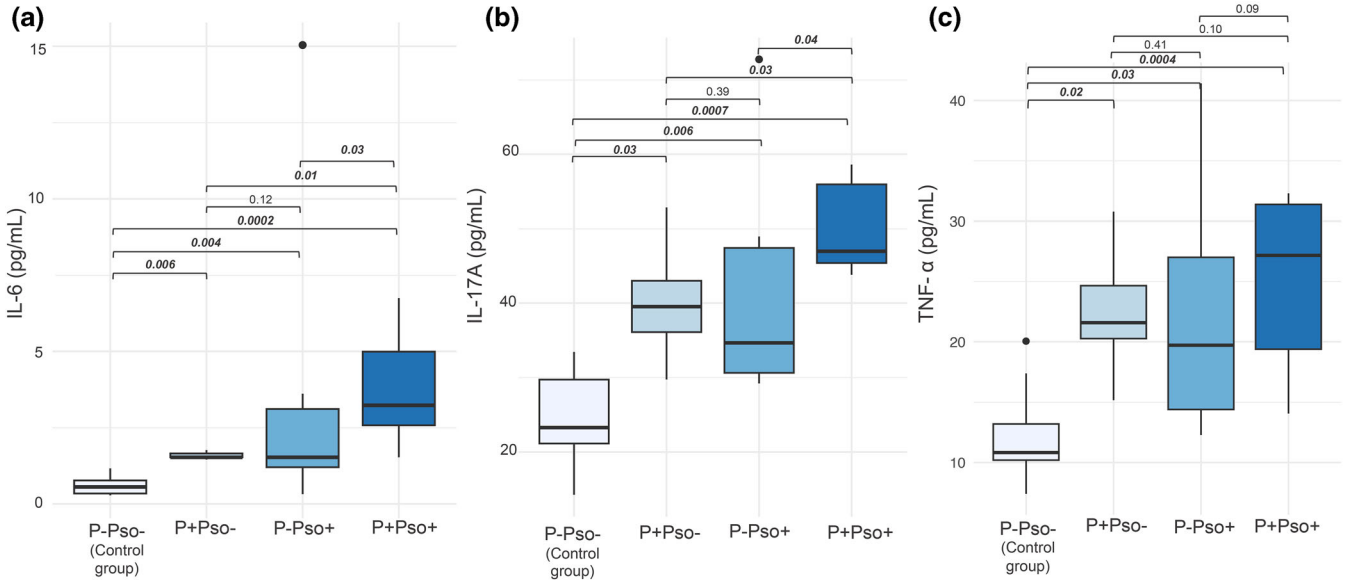

FIGURE 5 Boxplots showing the IL-6, IL-17A and TNF-a levels for each group (boxes and bars indicate the median value and interquartile range, respectively).

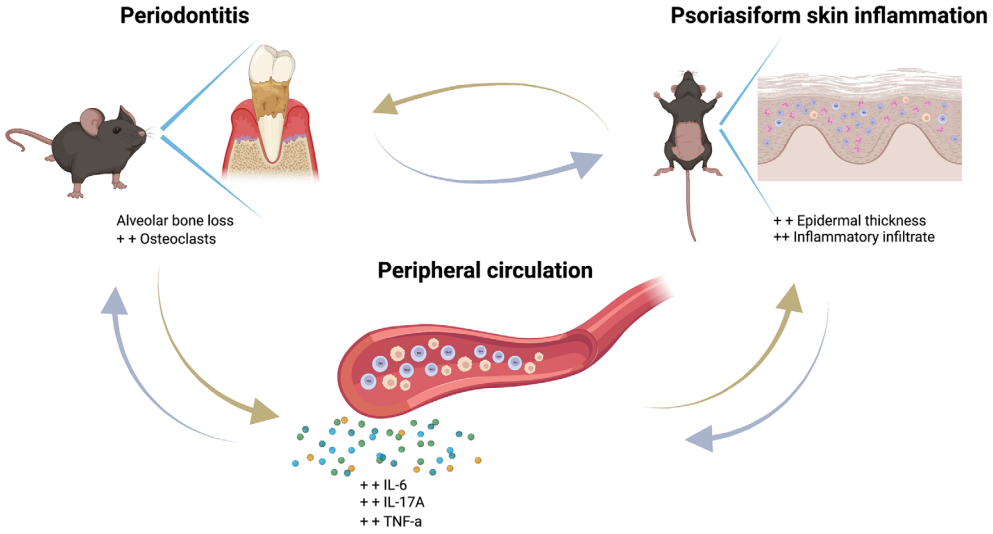

FIGURE 6 Graphical summary of findings (figure created with BioRender.com).

hormonal fluctuation related to periodontitis (Tatakis & Trombelli, 2004). The direct IMQ-induced model of psoriasis was preferred to those previously reported (genetically engineered animals and cytokine injections) in view of its recognized translational potential (Swindell et al., 2017). However, while the IMQ-induced model of psoriasis has been widely used owing to its being the most convenient and repeatable model of psoriasiform skin inflammation, its limitations include the recapitulation of limited aspects of human psoriasis as well as an unintended systemic repercussion due to IMQ ingestion during the experimental period which might have affected the results obtained (Gangwar et al., 2022). In addition, previous evidence showed that IMQ induces epidermal changes limited to the area where the IMQ was applied (Swindell et al., 2017); however, no histological assessments were performed in the Pso+ groups in the skin where the IMQ was not applied. For the experimental models of both periodontitis and psoriasis, the use of knock-out mice instead of ligature- and IMQ-induced periodontitis and psoriasis, respectively, may have produced different results than obtained in this study. However, the repeatability, convenience and cost effectiveness of this combined model of the ligature- and IMQ-induced periodontitis and psoriasis model allowed us to potentially answer our research question. Moreover, other inflammatory markers such as IL-22, leptin and interferon-gamma could have been relevant in assessing the relationship between periodontitis and psoriasis in addition to the measured cytokines. Along the same lines, other histological measures of inflammation, such as neutrophil staining, neutrophil MPO or CD45, could also have been relevant to corroborate the findings obtained. P+ Pso− and P+ Pso+ groups may have been influenced by the general anaesthesia used to place the ligatures, while the P− Pso+ and P+ Pso+ groups may have experienced itchy

skin due to psoriasis induction; nonetheless, any stressors or discomfort have been alleviated using methods of environmental enrichment for the animals (Vachon et al., 2013). However, a rigorous experimental methodology and analyses of the results were adopted by an experienced group studying the development of psoriasis (Gisondi et al., 2022; Talamonti et al., 2020; Trovato et al., 2022).

Evidence from this pre-clinical model suggests that ligature-induced periodontitis may initiate and maintain psoriasiform skin inflammation; and, vice versa, IMQ-induced psoriasis may contribute to the onset of periodontitis. Moreover, the severity of both periodontitis and psoriasis, as well as the levels of systemic inflammatory markers, further increased when the two diseases were combined. Hence, a possible bidirectional association between periodontitis and psoriasis driven by a common host inflammatory response is proposed. These findings are clinically relevant to foster the teamwork between dermatologists and periodontists in order to achieve a successful treatment of both diseases and thus ameliorate the lifelong management of comorbid periodontitis and psoriasis. Further experimental and clinical evidence should be produced to investigate the nature of this association.

AUTHOR CONTRIBUTIONS

C.M. contributed to study conception, study design, data analysis, data collection, and manuscript drafting. C.G. contributed to data analysis, data interpretation, and manuscript drafting. C.F., S.V., E.B., and A.D.R. contributed to setting up the experimental model. E.C. and P.R. contributed to study conception, study design, and manuscript drafting. M.A. and N.S. contributed to micro-CT analyses. A.B. contributed to bone volumetric analyses in micro-CT. C.B. and C.D. contributed to histological analyses. F.F. contributed to cytokine analyses. F.D. contributed to data analysis, data presentation and manuscript drafting. S.G. contributed to study conception, study design, and manuscript drafting.

ACKNOWLEDGEMENTS

The authors would like to thank Prof. Nicola Discepoli for his help during the initial process of study design.

FUNDING INFORMATION

This research received no specific grants from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Marruganti, C., Gaeta, C., Falciani, C., Cinotti, E., Rubegni, P., Alovisi, M., Scotti, N., Baldi, A., Bellan, C., Defraia, C., Fiorino, F., Valensin, S., Bellini, E., De Rosa, A., D'Aiuto, F., & Grandini, S. (2024). Are periodontitis and psoriasis associated? A pre-clinical murine model. *Journal of Clinical Periodontology*, 1–10. https://doi.org/10.1111/jcpe.13996