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The Role of Interleukin-23 and Interleukin-17 in Peri-Implant Crevicular Fluid of Subjects With Peri-Implant Disease: A Systematic Review

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ABSTRACT

Background: Activation of the IL-23/IL-17 cytokine axis could trigger peri-implant bone loss. The aim of this review was to analyze whether in people with peri-implantitis (PI) and peri-implant mucositis (PM) the concentrations of the interleukin-23 and interleukin-17 in peri-implant crevicular fluid (PICF) are elevated compared to people with healthy dental implants (HDI).

Methodology: The protocol of this study was registered in OSF (ID: 10.17605/OSF.IO/U8NBQ) and followed PRISMA guidelines. PECO criteria were used to formulate the research question. A search strategy was performed using PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar until November 15, 2024. A rigorous evaluation was performed, and the JBI tool was used to assess the quality of the cross-sectional and case–control studies.

Results: Fourteen observational studies were included in this study, with a total of 587 participants carrying 601 dental implants. The control group was represented by 252 healthy implants, while the exposure group was represented by 113 implants with PM and 236 implants with peri-implantitis. The age range of the subjects varied from 40.8 to 68.6 years, with a mean age ± standard deviation of 53.9 ± 9.9 years. The concentration of the IL-23/IL-17 cytokine axis and isoforms (IL-17E

Abbreviations: AAP, American Academy of Periodontology; APCs, antigen-presenting cells; *DIs*, dental implants; EFP, European Federation of Periodontology; ELISA, enzyme-linked immunosorbent assay; GCF, gingival crevicular fluid; HDI, health dental implant; IFN-γ, interferon gamma; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-15, interleukin 15; IL-16, interleukin 16; IL-17, interleukin 17; IL-17E, interleukin 17E; IL-17F, interleukin 17F; *IL-1β*, interleukin- 1 beta; IL-2, interleukin 2; IL-23, interleukin 23; IL-23R, interleukin 23 receptor; IL-2Rα, interleukin 2 receptor alpha; IL-3, interleukin 3; IL-4, interleukin 4; IL-5, interleukin 5; *IL-6*, interleukin 6; *IL-8*, interleukin 8; IL-9, interleukin 9; LPS, lipopolysaccharides; *MMP-13*, matrix metalloprotease 13; MMP-2, matrix metalloprotease 2; *MMP-8*, matrix metalloprotease 8; *MMP-9*, matrix metalloprotease 9; PD, periodontal disease; *PE*, Peri-implantitis; *PICF*, Peri-implant crevicular fluid; *PIDs*, Peri-implant diseases; *PM*, Peri-implant mucositis; *RANKL*, receptor activator of nuclear factor-κB ligand; Th, helper T cells; *TNF-α*, tumor necrosis factor-alpha; Treg, regulatory T cells.

and IL-17F) was higher in subjects with peri-implant disease compared to the healthy population. Most of the studies (92.8%) showed moderate quality.

Conclusions: The concentrations of cytokines IL-23, IL-17, and IL-17E in PICF were higher in PI-affected dental implants, followed by PM-affected dental implants compared to HDI.

1 | Background

Peri-implant diseases (PIDs) include peri-implant mucositis (PM) and peri-implantitis (PI) [1]. It is estimated that PIDs affect approximately one in five people carrying dental implants (DIs) [2]. The prevalence of PM ranges from 23.9% to 88% in patients and from 9.7% to 81% at the DI level [3]. It corresponds to a reversible condition, which is mainly associated with the accumulation of bacterial plaque pathogens (such as *Prevotella* spp., *Treponema denticola* and *Tanerella forsythia*) [4] around the DIs, which generates an immunoinflammatory response of the surrounding tissue [5]. If PM is not treated, it can progress to PI, in which the persistence of a polymicrobial dysbiosis (major increase in orange/red complex species) [6] induces an exacerbated response, producing bone loss and consequently loss of DIs [7]. This represents a significant economic burden for the individual [1, 2], as well as negatively affecting their quality of life [8] The prevalence of PI is lower (8.9%–45% in patients and 4.8%–23% at the DI level); however, the increase in cases in recent years is due to its popularity and the high demand for treatment with these devices and implant-supported prostheses [9].

Conventionally, the diagnosis of PIDs is usually clinical and through radiographic examination [10]; however, prediction and early detection, as well as monitoring and/or follow-up of PIDs, remain a challenge [11].

Analysis of proteins involved in bone metabolism, oxidative stress, peri-implant connective tissue turnover, and cytokines present in both peri-implant crevicular fluid (PICF) and saliva can provide evidence on the dynamics of the immunoinflammatory process in PIDs [12]. In this regard, it has been shown that the levels of soluble ligand of receptor activator of nuclear factor-κB, receptor activator of nuclear factor-κB ligand (RANKL), matrix metalloprotease 2 (MMP-2), MMP-8, MMP-9, MMP-13, myeloperoxidase, malondialdehyde, elastase activity, alkaline phosphatase, cross-linked N-telopeptides of type 1 collagen, procalcitonin, TNF superfamily member 12, interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α) are elevated in subjects with PI compared to healthy dental implant (HDI) carriers [13–18].

In particular, proinflammatory cytokines have the potential to activate the IL-23/IL-17 axis, which induces peri-implant bone loss [19].

Our previous work on the use of these markers in gingival crevicular fluid (GCF) of subjects with periodontal disease (PD) revealed that there is an increase in the levels of both molecules in individuals with gingivitis and periodontitis compared to the healthy population [20]; thus, with the present systematic review, we hypothesized that IL-23/IL-17 axis concentrations in PICF are elevated mainly in subjects with PE, followed by individuals with PM compared to HDI. Therefore, the aim of this review was to verify whether in people with PI and PM the concentrations of the IL-23/IL-17 cytokine axis, including its receptors and isoforms, are elevated compared to people carrying HDI.

2 | Materials and Methods

2.1 | Protocol

The study protocol was adapted according to PRISMA guidelines [21], and to ensure the transparency and rigor of the process, it was registered in OSF (ID: 10.17605/OSF.IO/U8NBQ).

2.2 | Focused Question

The clinical research question was constructed according to the PECO strategy:

- (P) Population: Subjects with DIs.
- (E) Exposure: Subjects with PM and PI.
- (C) Comparison: Subjects carrying HDI.
- (O) Outcome: Levels of IL-23 and IL-17 in PICF.

Do subjects with PIDs (PI and PM) have differences in interleukin-23 and interleukin-17 concentrations in PICF compared to individuals carrying HDI?

2.3 | Eligibility Criteria

Inclusion criteria were observational clinical studies (cross-sectional and case–control) in English, analyzing IL-23 and IL-17 concentrations in PICF by ELISA and/or bead-based multiplex assay in individuals with PM, PI, and subjects carrying HDI. Studies evaluating the concentrations of these molecules in any other tissue and/or biofluid of special interest such as gingiva (gingival tissue biopsies), saliva, rinses, serum, and blood plasma were excluded. Those studies that evaluated subjects < 18 years of age, as well as the presence of any pre-existing comorbidity (cardiovascular, neurological, genetic, gastric, allergic, and neoplastic diseases), with previous periodontal and/or peri-implant therapy, use of medications such as anti-plaque rinses, antibiotics, bisphosphonates, anti-inflammatory and/or immunosuppressants in the last 6 months prior to the study performed, as well as pregnant or lactating women and subjects with orthodontic appliances were excluded. Finally, studies in animal models and/or cell lines of any type, posters, abstracts, editorials, letters to the editor, short communications, master's or doctoral theses, systematic reviews, narratives, and meta-analyses were also excluded.

2.4 | Literature Search

Two investigators (M.A.A.-S. and J.S.B.-R.) conducted the literature search individually and blindly in five databases (PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar) until November 15, 2024. Table 1 shows the search strategy, together with the filters used to obtain the records. The keywords: "Interleukin 23," "IL-23," "Interleukin 17," "IL-17," "Biomarkers," "PICF," "Peri-implant Crevicular Fluid," "Peri-implant Disease," "Peri-implant Mucositis," and "Peri-implantitis," were used together with the Boolean operators ["AND"] and ["OR"] for the construction of the search strategy. Also, bibliographic references were searched in the different types of existing reviews related to the central research topic. In addition, a manual search was conducted in Journals related to the area of oral implantology such as *Clinical Oral Implants Research*, *Journal of Prosthodontics-Implant Esthetic and Reconstructive Dentistry*, *Clinical Implant Dentistry and Related Research*, *International Journal of Oral Implantology*, *International Journal of Implant Dentistry*, *International Journal of Oral & Maxillofacial Implants*, *Journal of Periodontal and Implant Science*, *Journal of Oral Implantology*, and *Implantologie* from April 1993 to October 2024 in search of potentially eligible articles. At each step, a third reviewer (A.H.) was consulted in case of disagreement.

2.5 | Data Selection and Extraction

After the electronic searches, the results were compiled in a single library, and duplicates were eliminated. Next, R.R.-M. and S.M.L.-M. independently and blindly performed the first phase of screening, assessing titles and abstracts and applying eligibility criteria to each result reviewed through the Rayyan platform (Rayyan | Home; accessed November 20, 2024). Studies that were included after this phase were then searched and analyzed in full text, and a new screening process was performed, justifying the inclusion and exclusion criteria. After this process, the resulting eligible studies were included in the systematic review, and data extraction was initiated.

For data extraction from the included articles, a previously prepared Excel (Microsoft) spreadsheet format was used, and variables were extracted individually and blinded by M.A.A.-S. and R.R.-M. For each study, the most representative variables on the characteristics of the studies were compiled and expressed in chronological order (Tables 2 and 3) according to the date of publication, such as (I) data of the first author, (II) the year of publication, (III) the country where the research was carried out, (IV) the type of study, (V) the ethical approval of the study, as well as (VI) the journal where the article was published. According to the description of the study population, we analyzed the (VII) eligibility criteria (inclusion/exclusion), (VIII) gender, (IX) age, (X) number of participants with HDI (which would be equivalent to the control group [CG]), (XI) number of participants with DIs affected by PM and PI (exposure group [EG]), as well as (XII) total sample size. The type of classification according to the analysis of PIDs used for the definition of EG and CG, the peri-implant criteria used, the clinical parameters evaluated, the collection of PICF, the methodology used for their conservation and storage, the method of immunoassay (processing), the type of cytokine evaluated (IL-23/IL-17 axis), receptors or isoforms, the units of measurement: pg/mL, pg/site, ng/dL, and log 10 (numerical data) in both study groups (represented as mean ± standard deviation or median), the *p*-value, and the results and main conclusions.

2.6 | Quality Assessment

Two members of the team (M.A.A.-S. and A.H.) carried out the quality assessment process of the observational studies included in the present review individually and blindly. For this purpose, the Joanna Briggs Institute (JBI) critical appraisal tool (https://jbi.global/critical-appraisal-tools; accessed December 10, 2024)

TABLE 1 | Search strategy employed.

Data base	Search strategy	Results
PubMed	(((“Dental Implant” OR “Dental Implants, Mini” OR “Implant, Dental” OR “Implants, Dental”)) AND ((“Peri-implant disease” OR “Peri implantitis” OR “Periimplantitis” OR “Peri-implant mucositis”))) AND ((“Cytokines” OR “Interleukin 23” OR “IL-23” OR “Interleukin-17” OR “IL-17”))	40
Scopus	TITLE-ABS-KEY(“Dental Implant” OR “Dental Implants, Mini” OR “Implant, Dental” OR “Implants, Dental”) AND TITLE-ABS-KEY (“Peri-implant disease” OR “Peri implantitis” OR “Periimplantitis” OR “Peri-implant mucositis”) AND TITLE-ABS-KEY(“Cytokines” OR “Interleukin 23” OR “IL-23” OR “Interleukin-17” OR “IL-17”)	195
ScienceDirect	(“Dental Implant” OR “Dental Implants” AND “Periimplantitis” OR “Peri-implant mucositis” AND “Interleukin 23” OR “IL-23” OR “Interleukin-17” OR “IL-17”)	277
Web of Science	((ALL=((“Dental Implant” OR “Dental Implants, Mini” OR “Implant, Dental” OR “Implants, Dental”))) AND ALL=((“Peri-implant disease” OR “Peri implantitis” OR “Periimplantitis” OR “Peri-implant mucositis”))) AND ALL=(((“Cytokines” OR “Interleukin 23” OR “IL-23” OR “Interleukin-17” OR “IL-17”))	46
Google Scholar	(“Dental Implant” OR “Dental Implants” AND “Periimplantitis” OR “Peri-implant mucositis” AND “Interleukin 23” OR “IL-23” OR “Interleukin-17” OR “IL-17”)	480

TABLE 2 | Baseline characteristics of included studies in this systematic review.

Authors/year	Country	Study design	Ethics	Journal	Inclusion criteria	Exclusion criteria	Sex M[a]/ F[e]	Age	*N* HI	*N* PM	*N* PE	*N* (total)
Malmqvist et al. (2024) [22]	Sweden	Cross-sectional	Yes	Clin Exp Immunol	HI and PE subjects	Metabolic diseases, and use of anti-inflammatory and antibiotics	10/29	68.6	24	—	15	39
Talib et al. (2024) [23]	Iraq	Cross-sectional	Yes	BDJ Open	HI and PE subjects	Metabolic diseases, and use of anti-inflammatory and antibiotics	29/16	40.8	30	—	15	45
Dutra et al. (2023) [24]	Brazil	Case–control	Yes	J Clin Periodontol	HI and PM subjects	Metabolic diseases, and use of anti-inflammatory and antibiotics, pregnant, breast feeding	4/16	43.4	10	10	—	20
Chaparro et al. (2022) [25]	Chile	Cross-sectional	Yes	IJMS	HI, PM and PE subjects	Metabolic diseases, and use of anti-inflammatory and antibiotics	7/12	67.7	7	2	10	19
Song et al. (2022) [26]	China	Cross-sectional	Yes	J Clin Med	HI and PE subjects	Previous periodontal or peri-implant therapy, metabolic diseases, use of anti-inflammatory, and antibiotics, pregnant, breast feeding, smokers and mental illness, non-compliant patients	8/6	56.1	14	—	14	14
Gleiznys et al. (2021) [27]	Lithuanian	Cross-sectional	Yes	Med Sci Monit	HI and PM subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding, and smokers	NR	63.1	30	30	—	60
Milinkovic et al. (2021) [28]	Serbia	Cross-sectional	Yes	Clin Oral Implants Res	HI, PM and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory antibiotics, and oral anti-plaque mouthwash, pregnant, breast feeding, drugs and alcohol	55/75	47.5	27	34	27	88

(Continues)

TABLE 2 | (Continued)

Authors/year	Country	Study design	Ethics	Journal	Inclusion criteria	Exclusion criteria	Sex M[a]/ F[e]	Age	*N* HI	*N* PM	*N* PE	*N* (total)
Farhad et al. (2019) [29]	Iran	Case–control	Yes	Int J Prev Med	HI, PM and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding, smokers and alcohol	22/29	48.2	17	17	17	51
Gao et al. (2018) [30]	China	Cross-sectional	Yes	Medicine	HI and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding, and smokers	43/37	44.1	40	—	40	80
Teixeira et al. (2017) [31]	Brazil	Cross-sectional	Yes	Clin Oral Implants Res	PM and PE subjects	Previous peri-implant therapy, use of anti-inflammatory and antibiotics, pregnant, breast feeding and smokers	9/15	59.8	—	10	14	24
Zani et al. (2016) [32]	Brazil	Cross-sectional	Yes	J Clin Periodontol	PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, and pregnant	34/6	57.5	14	—	26	40
Severino et al. (2016) [33]	Brazil	Cross-sectional	Yes	Arch Oral Biol	HI, PM and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding and smokers	13/32	65.6	10	10	20	40
Darabi et al. (2013) [34]	Iran	Case–control	Yes	Iran J Allergy Asthma Immunol	HI and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding and smokers	17/25	42.6	18	—	24	42
Severino et al. (2011) [35]	Brazil	Cross-sectional	Yes	Arch Oral Biol	HI and PE subjects	Previous peri-implant therapy, metabolic diseases, use of anti-inflammatory and antibiotics, pregnant, breast feeding and smokers	14/11	49.8	11	—	14	25

Note: Age is represented with mean or range.
Abbreviations: F[e], female; HI, health implant; M[a], male; NR, not reported; PE, peri-implantitis; PM, peri-implant mucositis.

TABLE 3 | Characteristics of IL-23/IL-17 cytokine axis in peri-implant crevicular fluid of subjects with peri-implant disease and control group.

Authors/ year	Classification	Peri-implant criteria	Clinical parameters assessment	PICF collection	Methodology	Technique/ Cytokine	Value CG	Value EG	*p*	Results and conclusions
Malmqvist et al. (2024) [22]	2017 EFP/AAP	PE: PD ≥6 mm, RBL ≥3 mm	BOP, SU, PD, RBL	Perio papers ×30 s	ET and kept −80°C	Multiplexed bead immunoassay (R&D Systems)/ IL-23/IL-17	NR	NR	<0.05	↑ IL-23 levels in group with PE compared to HI
Talib et al. (2024) [23]	NR	NR	GI, PI, PD, BOP	Perio papers ×30 s	ET with 0.5 mL PBS, centrifuged at 3000 rpm for 10 min/kept −80°C	ELISA/IL-23	120.0 ± 13.03 pg/mL	609.1 ± 17.1 pg/mL	0.0001	↑ IL-23 levels in group with PE compared to HI
Dutra et al. (2023) [24]	2017 EFP/AAP	PM: PD >4 mm CAL >5 mm	PD, GR	Perio papers ×30 s	ET and kept −20°C	Multiplexed fluorescent bead-bead immunoassay (Millipore Corporation)/ IL-17	NR	NR	<0.05	↑ IL-17 levels in group with HI compared to PM
Chaparro et al. (2022) [25]	2017 EFP/AAP	NR	PD, CAL, BOP, TM, SU	Perio papers ×30 s	ET with 0.6 mL PBS, and PIC, centrifuged at 12,000× *g* for 5 min/kept −80°C	ELISA/IL-23	70.16 ng/mL	193.42 ng/mL 134.905 ng/mL	NR	↑ IL-23 levels in groups with PM and PE compared to HI
Song et al. (2022) [26]	2017 EFP/AAP	PE: MBL ≥3 mm and PD ≥6 mm	PI, GI, PD, BOP, MBL, KGW	Paper points ×4 min	ET and kept −80°C	ELISA/IL-17A and IL-17E	3.7(3–4.4) pg/mL 9.8 (9.5–10.6) pg/mL	10.5(6.6–25) pg/mL 11.8(10.8–13.7) pg/mL	0.002 0.048	↑ IL-17 levels in group with PE compared to HI
Gleiznys et al. (2021) [27]	2008 Sixth EWP	PM: PD, MB 0–3 mm, without SU or RBL	PI, PD, MB	Capillary tube ×30 s	ET with 0.2 mL PBS, and 0.01 mL of PIC, centrifuged at 3000 *g* for 5 min/kept −70°C	ELISA/IL-17	1.87 pg/mL	17.94 pg/mL	0.001	↑ IL-17 levels in group with PM compared to HI

(Continues)

TABLE 3 | (Continued)

Authors/ year	Classification	Peri-implant criteria	Clinical parameters assessment	PICF collection	Methodology	Technique/ Cytokine	Value CG	Value EG	*p*	Results and conclusions
Milinkovic et al. (2021) [28]	2017 EFP/AAP	PM: BOP and SU PE: PD ≥ 6 mm RBL ≥ 3 mm	PI, BOP, SU, PD	Paper strips × 30 s	ET with RNA stabilization solution refrigerated overnight (2°C–8°C), after which the solution removed and kept −80°C	ELISA/IL-17	NR	NR	0.001	↑ IL-17 levels in groups with PE and PM compared to HI
Farhad et al. (2019) [29]	2013 Ninth EWP	PM: PD ≤ 4 mm PE: PD > 4 mm	PD, BOP	Paper points × 4 min	ET and kept −70°C	ELISA/IL-17	5.8 ± 0.5 ng/dL	57.7 ± 14.6 ng/dL 19.9 ± 10.3 ng/dL	0.001	↑ IL-17 levels in groups with PM and PE compared to HI
Gao et al. (2018) [30]	Guidelines for Periodontal Disease, USA	NR	BOP, PD, RBL	Paper tip × 30 s	ET and kept −80°C	Multiplex Immunoassay/ IL-17A	23.59 pg/mL 24.93 pg/mL	19.81 pg/mL 21.44 pg/mL	> 0.05	↑ IL-17A levels in groups with HI compared to PE
Teixeira et al. (2017) [31]	2013 AAP	PM: Clinically inflamed sites PE: RBL	PI, PD, CAL, BOP	Perio papers × 30 s	ET with 0.2 mL PBS, and 0.01 mL of PIC, centrifuged al 3000 *g* for 5 min/kept −70°C	Multiplex assay/ IL-17A, IL-17F, IL-23	NR	NR	> 0.05	No significant differences
Zani et al. (2016) [32]	NR	PE: PD > 4 mm and RBL ≥ 2 mm	PD, CAL, BOP, SU	Perio papers × 1–2 min	ET and kept −80°C	Multiplexed bead immunoassay (Luminex)/IL-17	0.27 ± 0.27 $\log_{10}$	0.50 ± 0.33 $\log_{10}$	0.0100	↑ IL-17 levels in group with PE compared to HI
Severino et al. (2016) [33]	NR	PM: PD 0–3 mm PE: MB and PD > 3 mm	PI, PD and MB	Perio papers × 30 s	ET with 0.25 mL PBS, and PIC/ kept −70°C	ELISA IL-17	NR	NR	0.02	↑ IL-17 levels in group with PM and PE compared to HI

(Continues)

TABLE 3 | (Continued)

Authors/year	Classification	Peri-implant criteria	Clinical parameters assessment	PICF collection	Methodology	Technique/Cytokine	Value CG	Value EG	*p*	Results and conclusions
Darabi et al. (2013) [34]	NR	NR	PD, BOP, SU	Paper cons #30 10 s	EP with 0.20 mL PBS/kept −70°C	ELISA IL-17	14.5 ± 8.9 pg/site	19.7 ± 16.0 pg/site	0.016	↑ IL-17 levels in group with PE compared to HI
Severino et al. (2011) [35]	NR	PE: PD > 3 mm	MB, PD, SU	Perio paper × 30 s	ET with 0.25 mL PBS, and PIC/kept −70°C	ELISA IL-17	NR	NR	> 0.05	↑ IL-17 levels in group with PE compared to HI

Abbreviations: ↑, increased; AAP, American Academy of Periodontology; BOP, bleeding on probing; CG, control group; EFP, European Federation of Periodontology; EG, exposure group; ET, Eppendorf tubes; EWP, European Workshop on Periodontology; GI, gingival index; GR, gingival recession; HI, health implant; IL-17, interleukin 17; IL-23, interleukin 23; KGW, keratinized gingival width; MB, marginal bleeding; MBL, marginal bone loss; NR, not reported; PBS, phosphate buffer saline; PD, probing deep; PE, Peri-implantitis; PI, plaque index; PIC, protease inhibitor cocktail; PM, Peri-implant mucositis; RBL, radiographic bone loss; SU, suppuration; TM, Tooth mobility.

was used for both cross-sectional studies (8 items) and case–control studies (10 items). The evaluation criteria were rated "yes," "no," "unclear," or "not applicable." Each criterion rated as "yes" scored one point, while other values were considered as zero; subsequently, the total score for each study was calculated and summed [36–38]. The scoring forms were as follows: (I) a score < 3 = low quality; (II) a score of 4–6 = moderate quality, and (III) a score > 7 = high quality.

3 | Results

3.1 | Study Selection

Initially, the databases queried yielded a total of 1039 articles including PubMed ($n = 40$ records), Scopus ($n = 195$ records), ScienceDirect ($n = 277$ records), WoS ($n = 46$ records), and Google Scholar ($n = 480$ records). While, in the manual search, one more article related to the central theme of this research was found. In the identification phase, 153 duplicates were discarded. Subsequently, in the screening phase and based on the title and abstract, 866 studies were excluded, giving a total of 20 potentially eligible records. After full-text review of the remaining articles, six articles were excluded (thesis $n = 1$; systematic review $n = 1$; in vitro study $n = 1$; use of other methodologies $n = 1$; cytokine analysis in other biofluids $n = 1$; comparison of cytokines in GCF vs. PICF from healthy implants $n = 1$). Finally, 14 articles were selected for qualitative analysis [22–35] (Figure 1).

3.2 | Quality Analysis

The observational studies evaluated had moderate (13/92.8%) and low (1/7.2%) quality according to the JBI items. Regarding the cross-sectional studies, 100% showed a positive response to items #1, 6, and 8 [22–28, 30–33, 35]. About 91.6% showed a positive response to item #2 [22, 23, 25–28, 30–33, 35], 58.3% showed a positive response to item #3 [24, 27, 28, 31–35], 66.6% showed a positive response to item #4 [22, 24–28, 30, 31], 75% showed a negative response to item #5 [23, 24, 26–28, 30, 31, 33, 35] and 66.6% showed a positive response to item #7 [22, 24–28, 30, 31] (Figure 2). Relative to case–control studies, 100% showed a positive response to items #1, 2, 5, 9, and 10 and a negative response for items #4, 6, 7, and 8 [29, 34]. Farhad et al. [29] showed a positive response to item #3, while Darabi et al. [34] showed a negative response to the same item (Figure 3).

3.3 | Clinical Outcomes

Of the 14 articles analyzed, 12 (85.7%) were cross-sectional studies [22–28, 30–33, 35] and 2 (14.3%) were case–control studies [29, 34]. The most recent article was published in 2024 [29], whereas, the oldest was from 2011 [34]. Most of the studies were published after 2016 [22–33]. The 14 studies were published in 8 different countries [22–35]. Five (35.7%) studies were conducted in Brazil [24, 31–33, 35] two (14.2%) in China [26, 30] and Iran [29, 34] while the rest (7.1%) were conducted in Sweden [22], Iraq [23], Chile [25], Lithuania [27], and Serbia [28] (Table 2).

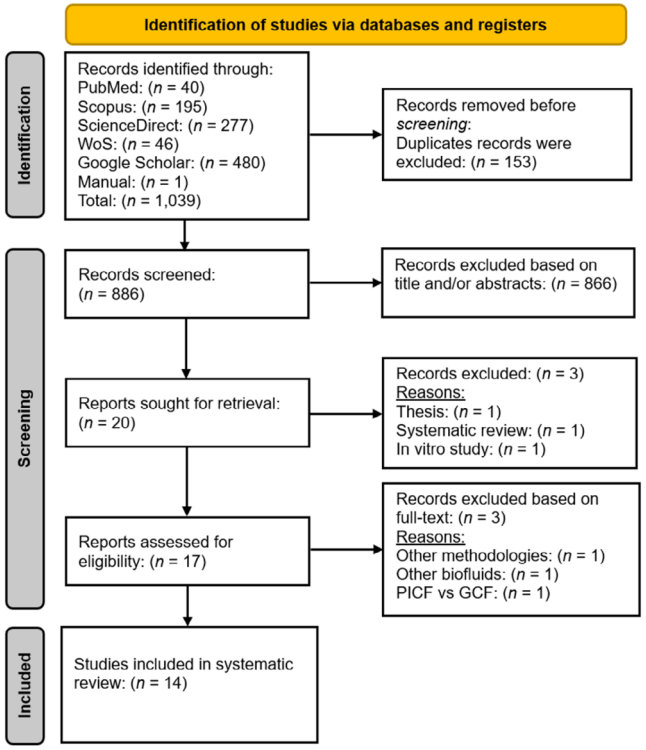

FIGURE 1 | PRISMA flow diagram used in this review. PRISMA, Preferred Reporting Items for Systematic and Meta-Analyses.

The number of subjects varied from 14 to 88 in the included studies, with a total of 587 participants carrying 601 DIs. The CG was represented by 252 healthy implants, while the EG was represented by 113 implants with PM and 236 implants with PI. Of these 45.1% of the participants were male, the other 52.6% were female, and in 2.3% of the cases the sex was not specified [27]. The age range of the subjects varied from 40.8 to 68.6 years, with a mean age ± standard deviation of 53.9 ± 9.9 years [22–35]. The most prevalent exclusion criterion was the presence of any other systemic disease/condition that could be affecting the overall health of the individuals in the study [22–30, 32–35] (Table 2). About 35.7% of the studies used the new classification of periodontal and PIDs (2017 EFP/AAP) [22, 24–26, 28]. The most frequently evaluated clinical parameter was PD [22–35]. A total of 601 PICF samples were taken. In 50% of the cases, PICF samples were collected by using Perio Papers for 30 s [22–25, 31, 33, 35]. And in most cases, the samples were placed in sterile Eppendorf tubes and stored at −80°C [22, 23, 25, 26, 28, 30, 32]. In 64.2% of the cases, the PICF samples were analyzed by ELISA [23, 25–29, 33–35]; the rest (35.8%) were analyzed by multiplex immunoassays [22, 24, 30, 32, 34]. Four (28.5%) studies analyzed IL-23 levels [22, 23, 25, 31], 12 (85.7%) studies analyzed IL-17 levels [22, 24, 26–35], 1 (7.14%) study analyzed IL-17E levels [26], and one more (7.14%) analyzed IL-17F levels [31] (Table 3).

Malmqvist et al. and Talib et al. reported a significant increase in IL-23 levels in implants with PI compared to HDI [22, 23]. Chaparro et al. reported that IL-23 levels were higher in implants with PM, followed by implants with PI compared to HDI [25]. Teixeira et al., on the other hand, found a trend toward increased IL-23 levels in implants with PM compared to implants with PI and HDI [31].

Song et al., Milinkovic et al., Zani et al., Darabi et al., and Severino et al. reported a significant increase in IL-17 levels in implants with PI compared to HDI [26, 28, 32, 34, 35]. Gleiznys et al., Farhad et al., and Severino et al. reported an increase in IL-17 levels in implants with PM compared to HDI [27, 29, 33]. Dutra et al. and Gao et al. reported that IL-17 levels were higher in HDI compared to implants with PI [24] and PM [30]. Also, Song et al. found increased IL-17E levels in implants with PI compared to HDI [26]. Teixeira et al. found no difference in IL-17F levels in PICF from subjects with PID [31].

4 | Discussion

A systematic review was carried out, which evaluated IL-23/IL-17 axis levels in PICF of subjects with PI, PM, and people with HDIs from 14 observational clinical studies that were conducted in eight different countries.

Owing to the advancements in dental materials science, the utilization of DI therapy has significantly increased within clinical dental practice. This therapy primarily aims to restore masticatory function. Additionally, DIs provide several advantages, including enhanced aesthetics, improved comfort and natural feel, preservation of adjacent teeth, and maintenance of the maxillary bone structure [39].

After implant placement during the wound healing phase, it has been shown that macrophages are responsible for the release of cytokines such as interferon alpha 2, IFN-γ, IL-17, IL-16, IL-15, IL-12, IL-9, IL-6, IL-5, IL-4, IL-3, IL-2Rα, IL-2, and IL-1β when they come into contact with the implant, starting the chronic phase of inflammation. This microenvironment is desirable as it determines the bone remodeling process [40]. The dynamic action of osteoblasts and osteoclasts results in a direct union between the peri-implant bone and the implant surface [41]. It is important to achieve osseointegration to ensure the long-term stability of the implant, which will be reflected in the patient's health. However, because bone tissue undergoes active remodeling influenced by intrinsic and extrinsic factors, it is subject to resorption, leading to what is known as marginal bone loss. Among the factors affecting implant stability, PIDs and the related inflammatory response are the most common challenges [42].

As mentioned earlier, PIDs include PM and PI. Although PIDs are initiated by pathogens found in dental plaque as is the case of PD [43], human biopsy samples have been used to analyze whether the inflammatory reaction in PIDs differs from that in PD [44]. Recently, researchers carried out a single-cell analysis, using biopsies from patients with PIDs, comparing them with subjects with periodontitis and with healthy subjects. Their results suggest a specific immunological environment in PID that could explain differences between PIDs and PD [45]. Another investigation aimed to characterize cell types in gingival samples from subjects with PI compared to healthy samples, concluding that in PI the specific presence of proinflammatory macrophages was observed and that NK cells are more abundant in PI than in healthy samples [46].

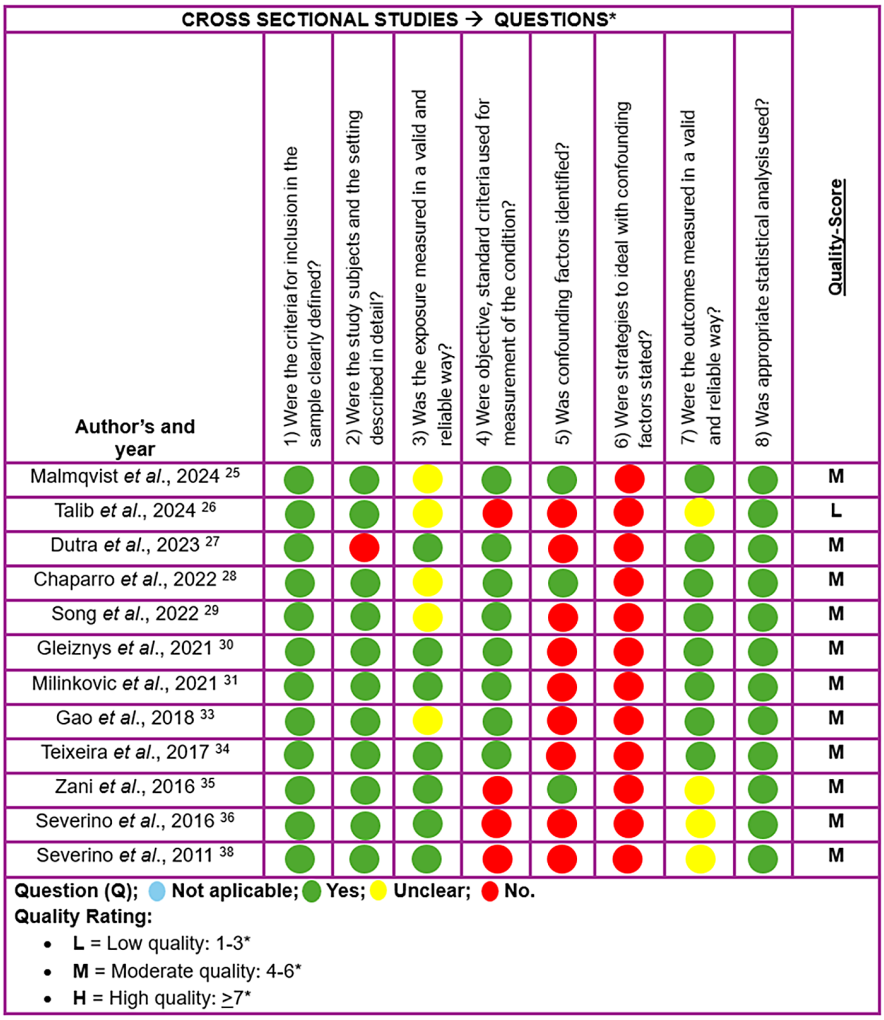

FIGURE 2 | Cross-sectional studies quality evaluation. The asterisk symbols represent scores for low, moderate, and high quality.

The critical factors in the development of PD and PIDs are bacterial colonization and the host response. It has been described that there are differences in the organization and structure of the tissues of gingivitis, periodontitis, and PI; in addition, the microbial species are also distinctive in each of these conditions. Periodontitis lesions are larger and present a higher proportion of macrophages and plasma cells than plaque-induced gingivitis, while PI lesions are larger than periodontitis. All these components determine the discrepancies both in the onset and in the progression of these diseases [47]. At the molecular level, differences have been described in the expression profiles of IncRNA and mRNA in periodontitis and PI, with differences in the distribution and quantity of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 [48].

The colonizing bacteria in PI are anaerobic Gram-negative bacteria, anaerobic Gram-positive bacilli, and Gram-positive bacteria. The lipopolysaccharides (LPS) of the external membrane of Gram-negative bacteria bind to a protein forming a complex that facilitates the transfer of LPS to a Toll-like receptor 4 that is essential for the recognition of LPS by antigen-presenting cells (APCs) with the consequent signal transduction. In turn, these APCs present the antigen to T cells ($CD4^+$) which, once activated, differentiate into effector T cells of the helper T cells: Th1, Th2, regulatory T cells (Treg), and Th17 types [49].

The Th17 cell subtype expresses IL-17, a cytokine that performs functions such as the recruitment of macrophages and neutrophils, thereby stimulating the inflammatory process [50]. There is a determining cytokine for the proliferation of the Th17 cell subtype; IL-23 promotes the proliferation of the Th17 lineage. It is secreted in response to pathogen-associated molecular patterns and damage-associated molecular patterns by dendritic cells and macrophages. Once this cytokine binds to its receptor (IL-23R), expressed on the membrane of Th17 cells, it initiates intracellular signaling that culminates in the translocation of transcription factors that induce the transcription of proinflammatory cytokine genes [51].

It has been described that IL-23 in peri-implant lesions perpetuates chronic inflammation, aggravating the course of the disease [19]. This could be due to the fact that there are also other proinflammatory cytokines that converge in the activation of the IL-23/IL-17 axis, activating and exacerbating the immune response [23] (Figure 4).

CASE-CONTROL STUDIES → QUESTIONS*											
Author's and year	1) Were the groups comparable other than the presence of disease in cases or the absence of disease in	2) Were cases and controls matched appropriately?	3) Were the same criteria used for identification of cases and controls?	4) Was exposure measured in a standard, valid and reliable way?	5) Was exposure measured in the same way for cases and controls?	6) Were confounding factors identified?	7) Were strategies to deal with confounding factors stated?	8) Were outcomes assessed in a standard, valid and reliable way for cases and controls?	9) Was the exposure period of interest long enough to be meaningful?	10) Was appropriate statistical analysis used?	Quality-Score
Farhad *et al.*, 2019 [32]	Yes	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes	Yes	M
Darabi *et al.*, 2013 [37]	Yes	Yes	Unclear	No	Yes	No	No	Unclear	Yes	Yes	M

Question (Q); Not aplicable; Yes; Unclear; No.

Quality Rating:

- **L** = Low quality: 1-3*
- **M** = Moderate quality: 4-6*
- **H** = High quality: ≥7*

FIGURE 3 | Case–control studies quality evaluation. The asterisk symbols represent scores for low, moderate, and high quality.

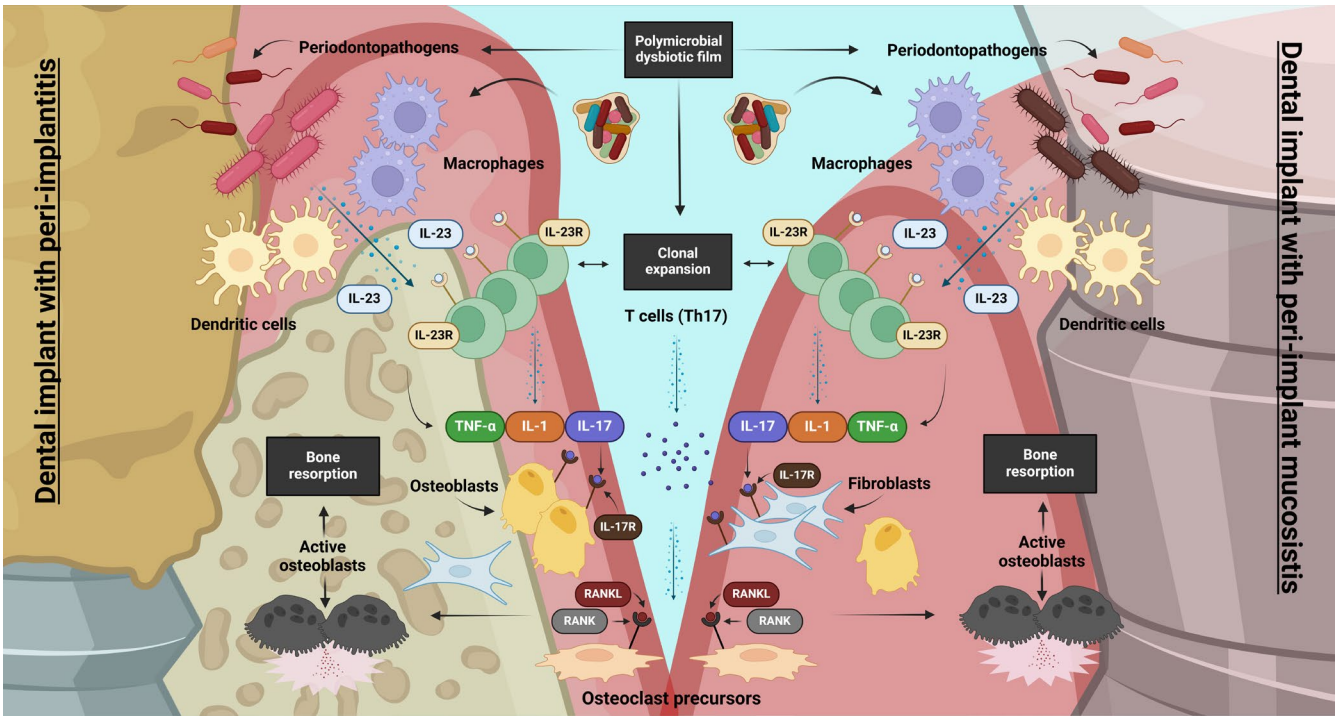

FIGURE 4 | The role of IL-23/IL-17 cytokine axis in peri-implant disease. Created in https://BioRender.com.

As described in the introduction of this paper, PI is the result of unresolved PM in which the inflammatory state is more chronic in PI, the same as that resulting from chronic periodontitis and gingivitis, where the immune response is more exacerbated in chronic periodontitis. In this review, since the diseases are peri-implant, the levels of cytokines in the PICF were considered. This is important to discuss since this exudate could have specific qualities, as it is in contact with materials such as titanium [52].

Osteoimmunology has made considerable progress, with recent reports indicating that marginal bone loss around implants cannot be exclusively attributed to pathogenic bacteria associated with PIDs [40, 49]. It has been reported that factors, such as bone friction, mechanical loading, and chemical agents, among others, induce damage to the outer layer of titanium oxide of the implant; this promotes the release of submicron and nanoscale titanium particles into the surrounding tissues, promoting inflammatory responses and altering immune homeostasis [39]. Since titanium particles are considered foreign bodies by the immune system, macrophages play a decisive role in their elimination. Foreign bodies induce the polarization of macrophages in M1, thus acquiring the proinflammatory profile with the consequent release of cytokines such as IL-1β, IL-6, and TNF [53]. Exposure to transforming growth factor beta, IL-1β, and IL-6 has been described to produce activation of the retinoic acid-related orphan nuclear receptor γt which initiates the differentiation of Th17 cells. Synergistically, TNF and IL-1β increase IL-6 production, facilitating a more pronounced Th17 cell differentiation and subsequently IL-17 expression [19]. It is proposed that the function of IL-23 is the maintenance and survival of Th17 cells because they express the IL-23R receptor once they differentiate from a $CD4^+$ helper T cell [54]. A study focused on evaluating PICF for possible titanium contamination showed statistically significant increases from health to disease in PICF concentrations of IL-1β, IL-6, IL-10, and INF-γ; additionally, Ti was detected in the majority of PICF samples and Ti concentration was positively correlated with IL-1β, IL-2, IL-4, IL-8, IL-13, and INF-γ concentrations [52]. Therefore, the influence of foreign body-induced proinflammatory cytokines should be considered in the onset and exacerbation of PIDs and not only attributed to the bacterial profile, as occurs with periodontal diseases.

The activation of the IL-23/IL-17 axis ultimately leads to the binding of the cytokine IL-17 to its receptor expressed on endothelial cells, chondrocytes, fibroblasts, and osteoclasts among others [55]. Through this interaction, IL-17 promotes the expression of RANKL, which binds to its receptor on the surface of osteoclasts, inducing osteoclastogenesis. Furthermore, the activation of macrophages by IL-17 results in the secretion of TNF and IL-1β, cytokines that play a crucial role in this process [19].

The key to preventing PI lies in addressing and treating PM, as this is often the pre-condition that triggers it. Biomarkers present in PICF are emerging as innovative and effective diagnostic methods in dental implantology [56]. Although some research indicates that there is moderate evidence to determine the efficacy of PICF biomarkers in diagnosing PIDs [57], further research is proposed to lead to the standardization and improvement of methodologies to achieve successful application in clinical contexts [58].

In the present study, 85.7% of the investigations were cross-sectional studies. This design allows the identification of biomarkers associated with health conditions, facilitating the early detection of risks. However, this design does not allow causal relationships to be established.

This work included four investigations carried out in three study groups, HDI, PM, and PI. Only three works [22, 37, 38] showed increased IL-17 levels with a statistically significant difference in the PI and PM groups compared to the HDI group. The work presented by Chaparro et al. [25] showed increased IL-23 levels in the PID groups compared to the HDI group but without a statistically significant difference. These data allow us to understand whether there is an evolutionary action in the different stages of conditions that affect the periodontium and its correlation with cytokine levels since PE represents the most advanced stage of inflammation [47].

On the other hand, this work also includes six investigations in which they measured the levels of cytokines in only two study groups: the PI group and the HDI group [22–27]. Therefore, it is expected that biomarker levels are higher in the PI group. Darabi et al. [34] and Severino et al. [33] found increased levels of IL-17 in the PE group compared to the HDI group, however, only Darabi et al. found statistically significant data. Two studies, meanwhile, measured the isoforms of IL-17A, IL-17E [25] and IL-17A [26]. Interestingly, both found elevated levels of the cytokine, although the work of Gao et al. [30] found a higher concentration in the HDI group although without significant statistical difference. Two other investigations in this category found higher levels of IL-23 in the PI group compared to the HDI group with a statistically significant difference [22, 23]. It is proposed to include in future investigations the action of other cytokines that participate in this axis since, as described above, the fact that there are increases in IL-23 levels does not always correlate with the increase in IL-17 but rather IL-23 participates in the maintenance and survival of Th17 cells [54].

The initial state of inflammation corresponds to PM. Two investigations included the HDI and PM groups [24, 27]. Gleiznys et al. [27] found as expected increased levels of IL-17 in the PM group. Interestingly, the results of Dutra et al. [24] found elevated levels of IL-17 in the HDI group. These results could be attributed to the fact that periodontal tissues are exposed to titanium particles that can induce immune response [40]. It is necessary to design research that evaluates the impact of titanium particles on the immunology of periodontal tissues and to be able to distinguish this effect from the microbial factor.

For their part, the research by Teixeira et al. [31] sought to measure the levels of the IL-17A, IL-17F, and IL-23 isoforms in groups with PM and PI, excluding the HDI group. It is expected that the levels of the proteins would be higher in the PI group compared to the PM group; however, the authors did not find

significant statistical differences. They included a small sample of 24 study subjects; there may not have been enough statistical power. Although, it is also important to consider the genetic variability of the Brazilian population in which the study was conducted.

4.1 | Limitations

The molecular mechanisms of the IL-23/IL-17 axis are well established, and the type of cells that produce these molecules are known, as well as their cellular receptors, target cells, and the responses they trigger. However, little is known about the mechanisms that titanium surfaces can induce in healthy periodontal tissues and that could alter the host's immune response. In addition, aspects such as the genetic variability of each population can influence the levels of cytokines, acting as risk or protection factors in each population.

The research included in this work compares different groups (HDI, PM, PI) but in some cases, they do not include all groups in all studies, which affects the comparative interpretation. As most studies are cross-sectional, it is not possible to determine whether cytokine levels precede or follow the condition, and it is possible that other underlying factors are influencing the results.

4.2 | Future Implications

Based on the results of this study, potential future implications could include the development of new biomarkers that allow for better monitoring of periodontal conditions in both PM and PI. With advances in the field of molecular biology, the development of personalized treatments based on the specific inflammatory profile of each patient or population is possible. Finally, a re-evaluation of the materials used in DIs, given that these can influence the immune response, should be conducted, along with work on developing more biocompatible materials.

5 | Conclusions

According to the studies analyzed, in most of the investigations, it was found that the concentrations of cytokines IL-23, IL-17, and IL-17E in PICF were higher in PI-affected DIs, followed by PM-affected DIs compared to HDI.

Author Contributions

Conceptualization, M.A.A.-S. and J.S.B.-R.; methodology, M.A.A.-S. and A.H.; software, M.A.A.-S.; validation, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; formal analysis, M.A.A.-S., J.S.B.-R, R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; investigation, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; resources, M.A.A.-S. and A.H.; writing – original draft preparation, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; writing – review and editing, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; visualization, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; supervision, M.A.A.-S., J.S.B.-R., R.R.-M., S.M.L.-M., L.-S.E.-V., and A.H.; project administration, M.A.A.-S. and A.H. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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