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Increased of IL-18 levels are associated with periodontitis: a systematic review and meta-analysis

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Abstract

Background The presence of a polymicrobial dysbiotic film in direct and constant contact with periodontal tissues initiates the host immune response. Interleukin 18 (IL-18) triggers up-regulates the production of other proinflammatory cytokines (TNF-α, IL-1β, IL-6), creating a vicious cycle that expands the inflammatory and destructive process in the periodontal tissue. A systematic review and meta-analysis was carried out with the main propose to investigate IL-18 expression in different biological samples from subjects with chronic periodontitis.

Methods The protocol followed PRISMA guidelines and was registered in Open Science Framework (OSF):https://doi.org/10.17605/OSF.IO/BS9GM. A digital search was conducted in the databases PubMed, ScienceDirect, Google Scholar, Web of Science and Dentistry & Oral Sciences Source databases were consulted from March 15th, 2005 to February 10th, 2023. Study quality was assessed using the JBI tool for cross-sectional studies and clinical trials. A meta-analysis was performed using a random/fixed effects model to evaluate the concentration of IL-18 in serum, plasma, saliva, gingival tissue and GCF of exposure group compared to control group.

Results The search strategy provided a total of 3,156 articles, of which 18 investigations met the inclusion criteria and 15 articles were quantitatively analyzed. The total number of patients studied was 1,275 (682 cases and 593 controls). The meta-analysis revealed significantly elevated IL-18 levels of serum, saliva and GCF of subjects with chronic periodontitis compared to healthy subjects (Serum: SMD = 62.73, 95%CI: 25.43-100.03, Z = 3.29, $p = 0.001$*; Saliva: SMD = 243.63, 95%CI: 8.68-478.59, Z = 2.03, $p = 0.042$*; GCF: SMD = 150.26, 95%CI: 56.86-243.66, Z = 3.15, $p = 0.02$*).

Conclusion IL-18 levels in serum, saliva and GCF could have the potential to be used as complementary diagnostic tools to the clinical and radiographic parameters in subjects with periodontitis.

Keywords Interleukin 18, Serum, Plasma, Saliva, Gingival tissue, Gingival crevicular fluid, Periodontitis

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Introduction

Periodontitis is a chronic immunoinflammatory disease and highly prevalent (62,3%) worldwide [1]. Repeated exposure to a polymicrobial dysbiotic biofilm with predominantly Gram-negative anaerobes such as the periodontopathogenic red complex species; *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* [2], along with other environmental (smoking, nutritional deficiencies) [3, 4] and genetic (single nucleotide polymorphisms/SNPs) [5] risk factors are the main cause of periodontitis development and progression [6]. Clinically it is an asymptomatic condition (which is why patients fail to detect it in its early stages) however, depending on the severity of the disease, there are characteristic signs and symptoms such as gingival erythema and edema, excessive accumulation of dentobacterial plaque, supra and subgingival calculus, gingival recession with root exposure, which increases tooth sensitivity and mobility, presence of bleeding and suppuration spontaneously or with minimal stimulus, which is accompanied by halitosis and metallic taste [7]. The most evident radiographic findings are the widening of the periodontal ligament and the characteristic bone loss in different directions (vertical or horizontal) [8]. In severe cases, this leads to extraction or loss of teeth, which has a significant impact on both the economics and oral health-related quality of life of the individual [9].

The gold standard for the diagnosis of periodontitis continues to be periodontal probing that measures some clinical indicators such as probing depth (PD), clinical attachment level (CAL) and bleeding on probing (BOP), along with radiographic evaluation of the bone surface [10]. However, these tools alone are unable to distinguish the onset and progression of the disease, therefore in recent years, researchers are searching for new molecular biomarkers that contribute to early diagnosis, prognosis and can monitor periodontal diseases [11].

The influence of pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) of red complex species stimulate host cells through Toll-like receptors (TLRs) and consequently activate the nuclear factor kappa B (NF-κB) pathway which, up-regulates the expression of genes encoding a variety of cytokines and chemokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 23 (IL-23), interleukin 17 (IL-17), as well as interleukin 18 (IL-18) which play an important role in the immunopathogenesis of periodontitis [12, 13].

IL-18, also called interferon gamma-inducible factor or interleukin 1 gamma, is a proinflammatory cytokine, which is encoded by the *IL18* gene located at 11q23.1 [14]. Initially, it is synthesized as an inactive precursor (pro-IL-18), which is cleaved by caspase 1 and gives rise to a protein in its mature form, consisting of 193 amino acids and with a molecular weight of 22.36 kDa [15]. IL-18 is produced mainly by keratinocytes, gingival fibroblasts, macrophages and dendritic cells [16]. Once released, IL-18 interacts and binds with its receptor (IL-18R). In this way, IL-18 forms a heterodimer together with the α and β chain of the IL-18 receptor (IL-18Rα and IL-18Rβ) and with the accessory chain of the IL-1R co-receptor (IL-1R3), which allows Toll-IL-1 receptor (TIR) domains to approach and recruit MyD88, resulting in NF-κB activation [17]. Therefore, in addition to triggering the production of interferon gamma (IFN-γ) by T helper type 1 (Th1) cells and IL-17 by Th17 cells contributing to the activation of the IL-23/1L-17 axis, it up-regulates the production of other proinflammatory cytokines, creating a vicious cycle that expands the inflammatory and destructive process in gingival tissue [18, 19].

Since IL-18 expression generally increases in any inflammatory condition, numerous studies have reported differences in IL-18 levels in biological samples such as serum, plasma, saliva, gingival tissue, and gingival crevicular fluid (GCF) of subjects with chronic periodontitis compared to periodontally and systemically healthy subjects [20–37]. However, to date, there is no comprehensive systematic review summarizing the findings of previous studies. Therefore, based on the available scientific evidence, the overall aim of the present study was to investigate IL-18 expression in different biological samples from subjects with chronic periodontitis.

Materials and methods

PICOD and research question

The PICOD algorithm was used:

1. P (Problem): Subjects with chronic periodontitis (Exposure group/EG).
2. I (Intervention): IL-18 levels in serum, plasma, saliva, gingival tissue and GCF.
3. C (Control): Systemically and periodontally healthy subjects (Control group/CG).
4. O (Outcomes): Differences in IL-18 levels in serum, plasma, saliva, gingival tissue and gingival crevicular fluid in EG compared to CG.
5. D (Design): Cross-sectional studies and clinical trials.

Thus, the following research question was posed: Is there an increase in IL-18 levels in serum, plasma, saliva, gingival tissue and GCF in EG compared to CG?

Elegibility criteria

All cross-sectional studies and clinical trials comparing serum, plasma, saliva, saliva, gingival tissue and GCF IL-18 levels in EG compared to CG were accessed. Determination of EG was based on the evaluation of clinical

parameters such as PD ≥ 3 mm and CAL ≥ 1 mm, whereas CG was based on the evaluation of systemically healthy subjects, without bone loss and with a PD > 2 mm and CAL < 1 mm. Only studies published in the English language and in peer-reviewed journals were considered. Studies in animal models or cell lines, systematic or narrative reviews, editorials, reviews, and letters to the editor were excluded.

Search strategy and study selection

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [38]. The protocol was registered in Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/BS9GM.

PubMed, ScienceDirect, Google Scholar, Web of Science and Dentistry & Oral Sciences Source databases were consulted from March 15th, 2005 to February 10th, 2023. The search strategy employed for PubMed was (((((“Interleukin-18“[Mesh]) OR “Serum“[Mesh]) OR “Plasma“[Mesh]) OR “Saliva“[Mesh]) OR “Gingival Crevicular Fluid” [Mesh]) AND “Periodontitis“[Mesh]. For the rest, the keywords used were “IL-18”, “Serum”, “Plasma”, “Saliva”, “Gingival tissue”, “Gingival crevicular fluid” and “Periodontitis”. A secondary hand search was also performed in the following Journals: *Periodontology 2000*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, *Journal of Periodontal and Implant Science* and *International Journal of Periodontics & Restorative Dentistry*.

The titles and abstracts of the literature search were then evaluated by two reviewers (M.A.A.S and J. S. B.R) according to previously established eligibility criteria. If the abstract matched the topic, the full text was accessed, while irrelevant articles were excluded. Any disagreement was consulted with a third expert reviewer (A.H) to resolve the debate.

Data items

Initially, data were extracted and tabulated in a Microsoft Office Excel version 16.72 (Microsoft Corporation, Redmond, USA) server sheet by two reviewers independently (M.A.A.S and S.R.S). The data extracted were as follows: First author’s name, year, country, study design, ethics committee approval, journal name, inclusion criteria, exclusion criteria, gender, age, number of EG and CG cases, total study population, periodontal criteria to define the exposure group, clinical parameters evaluated as PS, CAL, plaque index (PI), BOP and radiographic bone loss (RBL), the type of biological sample, type of marker, immunoassay technique used, the mean ± standard deviation (SD), the *p* value and the main results and conclusions.

Assessment of the risk of bias and quality of the recommendations

To assess the quality and risk of bias of the included cross-sectional studies and clinical trials, the Joanna Brigs Institute (JBI) tool [39] was used. Questions were scored as “Yes”, “No”, “Unclear”, or “Not applicable.” Studies were classified according to their quality, and were placed into three levels; high bias, when the study reached up to 49% of the scores. Moderate bias, when scores were 50–69% and low bias, when scores were > 70%.

Synthesis methods

STATA V.17 (Stata Corp, College Station, TX, USA) was used to perform the meta-analyses. The standardized mean difference (SMD) of IL-18 levels assessed in pg/mL between study groups (exposure vs. control) in different biological samples (serum, plasma, saliva, gingival tissue and GCF) was analyzed using a fixed and/or random effects model (depending on the heterogeneity found). Heterogeneity was estimated using the Chi^2 test and quantified with the I^2 statistic. Values up to 25% were categorized as low heterogeneity, values between 50% and 75% as medium heterogeneity and values above 75% as high heterogeneity. If moderate-high heterogeneity was detected, a random-effects model was used. A funnel plot together with Egger test was used to evaluate publication bias. A p value ≤ 0.05 was considered statistically significant.

Ethical approval

This study complies with ethical standards.

Results

Study selection

Initially 3,156 articles were found in the five databases, including PubMed (2,080 articles were found), ScienceDirect (178 articles were found), Google Scholar (823 articles were found), Web of Science (3 articles were found), Science and Dentistry & Oral Sciences Source (68 articles were found), and hand searching (4 articles were found). Duplicates were removed and, based on title and abstract, the remaining 2,152 studies were reviewed. After analyzing the full text of the remaining articles, 2,138 records were excluded as irrelevant. A total of 14 articles were assessed for eligibility, plus an additional 4 articles resulting from the hand search. Thus, a total of 18 articles were included for the qualitative analysis and 15 for the quantitative analysis of the present review. Details of the study selection are shown in Fig. 1.

Demographic and clinical features of the studies analyzed

Thirteen articles (72,22%) with a cross-sectional design [20–22, 24–26, 29, 31–33, 35–37] and 5 clinical trials (27,77%) [23, 27, 28, 30, 34] were reviewed in this study.

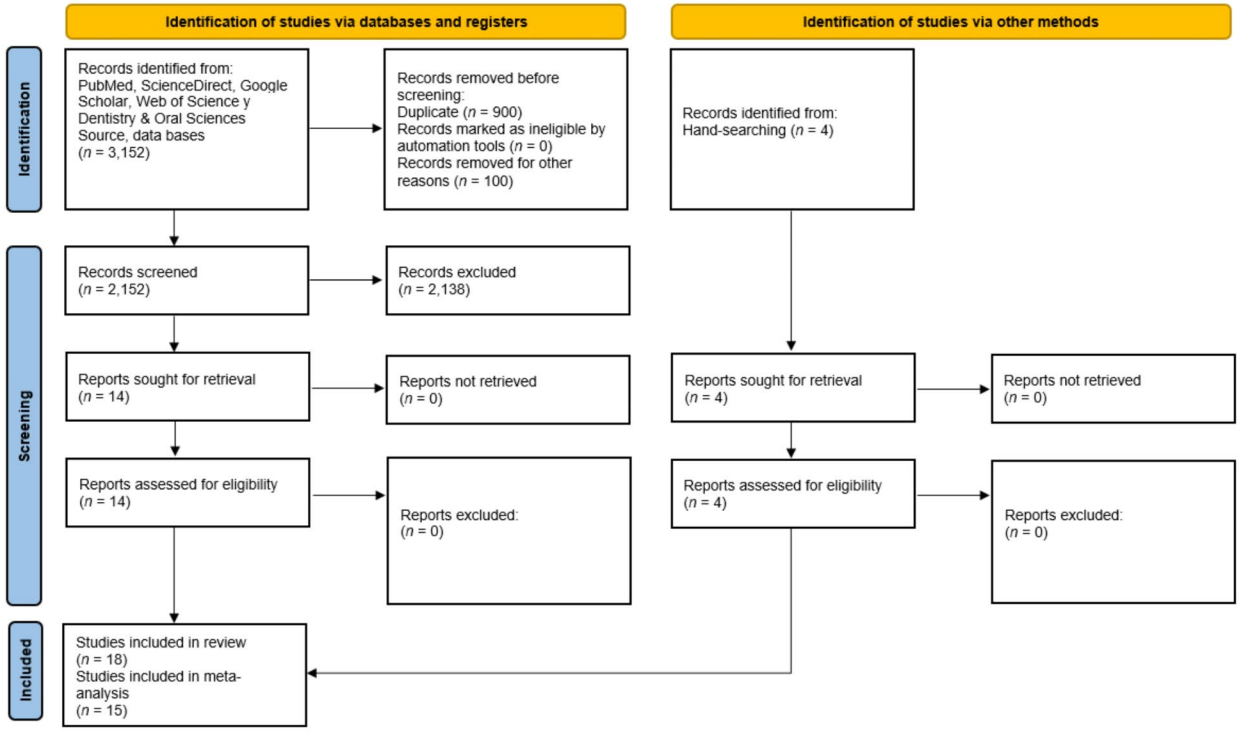

Fig. 1 PRISMA 2020 flow diagram for study selection

The total number of subjects studied in the included investigations was 1,275 of which 682 represented the EG and 593 represented the CG. The ages of the individuals ranged from 25 to 65 years, with a mean age±SD of 41.52±6.84 years. The 37.33% were male, 47.21% were female and in the remainder (15.45%) sex was not reported [27, 28, 30, 35]. Most of the articles were published after 2009 (15:83.33%) [20–34]. The oldest study was from 2005 [37], and the most recent from 2023 [20]. All studies (100%) were approved by the ethics committee of their respective institutions [20–37]. The most frequent exclusion criteria in all the studies analyzed was the presence of systemic diseases (100%) that could be affecting the periodontal condition [20–37]. The 18 articles were published in 11 different countries. Five (27.77%) studies were conducted in India [21, 27–29, 34], three (16.6%) studies in Brazil [25, 30, 35], two (11.11%) studies in Iran [23, 24] and Turkey [31, 33], and other studies (5.55%) in Bosnia [20], Romania [22], China [26], Mexico [32], Australia [36] and USA [37]. In addition, the journals of publication are shown (Table 1).

The most frequently evaluated clinical parameters were PD (88.88%) [20, 24, 26–35, 37] and CAL (77.77%) [20–24, 26–28, 30–35]. Regarding the analysis of the different biological samples for the determination of IL-18 levels, ten (55.55%) studies evaluated GCF samples [21–23, 27, 28, 30, 33–36], six (33.33%) studies serum samples [20, 25, 26, 28, 32, 36], four (22.22%) studies saliva samples [24, 26, 29, 31], two (11.11%) studies plasma samples [29, 31] and gingival tissue [32, 37]. In addition, only one (5.55%) study used Bead-based Flow Cytometric Assay [20], whereas, the rest (94.44%) used ELISA technique [21–37] (Table 2).

Meta-analysis of IL-18 in serum samples

Six studies [20, 25, 26, 28, 32, 36] compared serum IL-18 levels between EG (n=309) and CG (n=217). The results of the meta-analysis indicated a SMD=62.73(25.43-100.03, p=0.001*) demonstrating a significant increase of this cytokine in serum samples from EG compared to CG. Based on the chi-square test, there was no evidence of heterogeneity between studies (I^2=41.3%, p=0.182), noting that, study heterogeneity was low (Fig. 2, panel A).

Meta-analysis of IL-18 in plasma samples

Two studies [29, 31] compared plasma IL-18 levels between EG (n=62) and CG (n=41). The meta-analysis results indicated a SMD=236.67(-36.69-510.02), p=0.090) demonstrating a non-significant increase of this cytokine in plasma samples from EG compared to

Table 1 Clinical and demographic features of included studies

Study/Year	Country	Design	Ethics	Journal	Inclusion criteria	Exclusion criteria	Sex F[e]/M[a]	Age (M/R)	*n* (CG/EG)	*n* (Total)
Cicmil *et al.*, 2023[20]	Bosnia	CS	Yes	J. Clin. Med.	Subjects with CP	Systemic diseases, pregnancy, antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	47/31	35.92	39/39	78
Nair *et al.*, 2022[21]	India	CS	Yes	Medicina	Subjects with CP	Systemic diseases, pregnancy, non smokers antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	60/30	30.66	30/30	90
Surlin *et al.*, 2021[22]	Romania	CS	Yes	Mediators Inflamm.	Subjects with CP	Systemic diseases, pregnancy, non smokers and antibiotics / inflammatory drugs	16/14	52.99	15/15	30
Shahbeik *et al.*, 2021[23]	Iran	CT	Yes	Iran J Allergy Asthma Immunol.	Subjects with CP	Systemic diseases, non smokers and antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	9/9	46.5	0/18	18
Vahabi *et al.*, 2019[24]	Iran	CS	Yes	Dent Res J.	Subjects with CP	Systemic diseases, non smokers and antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	19/21	37.82	20/20	40
Tsuneto *et al.*, 2019[25]	Brazil	CS	Yes	Mediators Inflamm.	Subjects with CP	Systemic diseases and periodontal treatment in the previous 6 months	212/169	46.9	189/192	381
Wang *et al.*, 2019[26]	China	CS	Yes	Mol Med Rep.	Subjects with CP	Systemic diseases, pregnancy and antibiotics / inflammatory drugs	28/32	44.45	30/30	60
Mahajani *et al.*, 2017[27]	India	CT	Yes	J Contemp Dent Pract.	Subjects with CP	Systemic diseases, non smokers, antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	NR	25–45	45/45	90
Nair *et al.*, 2016[28]	India	CT	Yes	J Indian Soc Periodontol.	Subjects with CP	Systemic diseases, non smokers, antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	NR	31.6	40/20	60
Banu *et al.*, 2014[29]	India	CS	Yes	J Periodontol.	Subjects with CP	Systemic diseases, pregnancy, non smokers and antibiotics / inflammatory drugs	37/23	40–65	20/40	60
Campos *et al.*, 2012[30]	Brazil	CT	Yes	Braz Dent J.	Subjects with CP	Systemic diseases	NR	43.6	9/15	14
Ozçaka *et al.*, 2011[31]	Turkey	CS	Yes	J Periodontal Res.	Subjects with CP	Systemic diseases, antibiotics and periodontal treatment in the previous 6 months	16/27	45.75	21/22	43
Sánchez-Hernández *et al.*, 2011[32]	Mexico	CS	Yes	Oral Dis.	Subjects with CP	Systemic diseases, non smokers, pregnancy, antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	19/8	43	9/18	27
Türkoğlu *et al.*, 2009[33]	Turkey	CS	Yes	J Periodontol.	Subjects with CP	Systemic diseases, pregnancy, non smokers antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	39/20	34–64	39/20	59
Pradeep *et al.*, 2009[34]	India	CT	Yes	J Oral Sci.	Subjects with CP	Systemic diseases, non smokers antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	20/20	23–49	20/20	40
Figueredo *et al.*, 2008[35]	Brazil	CS	Yes	Oral Microbiol Immunol.	Subjects with CP	Systemic diseases/ infections	NR	44.45	15/18	33
Orozco *et al.*, 2006[36]	Australia	CS	Yes	Oral Microbiol Immunol.	Subjects with CP	Systemic diseases, pregnancy, non smokers antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	10/10	46.2	10/10	20
Johnson *et al.*, 2005[37]	USA	CS	Yes	J Periodontol.	Subjects with CP	Systemic diseases, pregnancy, non smokers antibiotics / inflammatory drugs and periodontal treatment in the previous 6 months	70/62	31.55	42/90	132

Abbreviations: F[e] Female; M[a] Male; M Mean; R Range; CG Control group; EG Exposure group; CP Chronic periodontitis; CS Cross-sectional; CT Clinical trials

CG. Based on the chi-square test, there was no evidence of heterogeneity between studies (I^2=0.0%, p=0.994), noting that, study heterogeneity was low (Fig. 2, panel B).

Meta-analysis of IL-18 in saliva samples

Four studies [24, 26, 29, 31] compared saliva IL-18 levels between EG (n=112) and CG (n=91). The meta-analysis results indicated a SMD=243.63(8.68-478.59), p=0.042) demonstrating a significant increase of this cytokine in saliva samples from EG compared to CG. Based on the chi-square test, there was evidence of heterogeneity among the studies (I^2=89.6%, p=0.000*), noting that, the heterogeneity of the studies was high, therefore a random effects model was used to pool the primary results (Table 3). The funnel plot shown the asymmetry and possibility of publication bias. However, Egger's test (t=2.50, p=0.129) showed no evidence of bias (Fig. 2, panel C and Fig. 3).

Meta-analysis of IL-18 in gingival tissue samples

Two studies [32, 37] compared IL-18 levels in gingival tissue between EG (n=108) and CG (n=51). The results of the meta-analysis indicated a SMD=206.82(-172.37-586.00), p=0.285) demonstrating a non-significant increase of this cytokine in gingival tissue samples from EG compared to CG. Based on the chi-square test, there was evidence of heterogeneity among the studies (I^2=99.1%, p=0.000), noting that, study heterogeneity was high, therefore a random effects model was used to pool the primary results (Fig. 2, panel D).

Meta-analysis of IL-18 in GCF samples

Eight studies [21–23, 27, 28, 30, 33–36] compared IL-18 levels in GCF between EG (n=173) and CG (n=184). The results of the meta-analysis indicated a SMD=150.26(56.86-243.66), p=0.02*) demonstrating a significant increase of this cytokine in GCF samples from the EG compared to the CG. Based on the chi-square test, there was evidence of heterogeneity among the studies (I^2=98.1%, p=0.000), noting that, the heterogeneity of the studies was high, therefore a random effects model was used to pool the primary results (Table 3). The funnel plot shown the asymmetry and possibility of publication bias. However, Egger's test (t=2.30, p=0.06) showed no evidence of bias (Fig. 2, panel E and Fig. 3).

Quality assessment and risk of bias

The JBI checklist was used to assess the quality of cross-sectional studies and clinical trials. According to the established criteria, 11 (61.11%) studies had a low risk of bias [20, 21, 24, 26, 29, 31–33, 35–37], 6 (33.33%) studies a moderate risk of bias [23, 25, 27, 28, 30, 34] and only 1 (5.55%) a high risk of bias [22] (Figs. 4 and 5).

Discussion

This study investigated IL-18 levels in serum, plasma, saliva, gingival tissue and GCF samples of subjects with chronic periodontitis compared to periodontally healthy subjects. A total of 18 articles published in 11 different countries were analyzed. Overall, the most important findings of the present meta-analysis showed a significant increase in IL-18 levels in serum, saliva and GCF of EG compared to CG. On the other hand, of the two studies that evaluated IL-18 levels in plasma, one of them showed inverse results (>0.05) [31], while, in gingival tissue, another study showed no significant differences (>0.05) [32], therefore, for these biological samples the results were inconclusive.

The presence of a polymicrobial dysbiotic film in direct and constant contact with periodontal tissues initiates the host immune response, which is constituted by an innate immune response, which provides the initial defense against periodontopathogens and its different components are; the gingival barrier, antimicrobial peptides produced by oral keratinocytes and other cells of the gingival sulcus, phagocytic cells such as macrophages (MΦ) and neutrophils, dendritic cells (DC), natural killer (NK) cells and other innate lymphoid cells [40]. B and T cells, on the other hand, regulate the adaptive immune response [41]. Both responses are closely related to each other, and among other mechanisms, lead to the production and release of inflammatory molecules such as TNF-α IL-1β, IL-6 and IL-18 which up-regulate the expression of matrix metalloproteases (MMPs) such as aMMP-8, MMP-9, MMP-13 which contribute in the degradation of the extracellular matrix of the gingival tissue and on the other hand, these proinflammatory cytokines increase the expression of RANKL, which binds with its receptor (RANK) and activates intracellular signaling pathways that initiate the process of osteoclastogenesis, leading to alveolar bone loss [42].

Proinflammatory cytokines reach oral biofluids (GCF and saliva) and can be detected through different techniques such as enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, in situ hybridization, polymerase chain reaction (PCR), among others [43]. Therefore, there is increasing evidence in the literature indicating associations between these inflammatory mediators (TNF-α IL-1β, IL-6, IL-8, IL-23/IL-17, IL-18) and periodontitis. In this sense, most authors concluded that these molecules could be considered as potential biomarkers to diagnose, prognosticate and monitor periodontal diseases [19, 44–46].

In relation to IL-18, its role has been demonstrated in some inflammatory diseases such as Crohn's disease, celiac disease, type 2 diabetes mellitus, obesity, rheumatoid arthritis, systemic lupus erythematosus, and graft-versus-host disease [13]. For example, patients with

Table 2 Immunological features of included studies

Study/Year	Periodontal criteria of EG	Clinical parameters	Biological sample	Marker type	Immunoassay	Marker value EG pg/mL	Marker value CG pg/mL	*P*-value	Main results
Cicmil *et al*., 2023[20]	PD > 3mm, CAL > 1mm	PI, GI, BOP, PD, CAL	Serum	IL-18	Bead-based Flow Cytometric	NR	NR	< 0.05	↑ IL-18 levels in group with EG compared to CG
Nair *et al*., 2022[21]	PD ≥ 5mm, CAL ≥ 3mm, RBL	PI, GI, PD, CAL	GCF	IL-18	ELISA	144.61(20.83)*	20.105(1.83)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Surlin *et al*., 2021[22]	NR	PI, GI, PD, CAL	GCF	IL-18	ELISA	200(30)*	75(70)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Shahbeik *et al*., 2021[23]	PD ≥ 5mm, CAL ≥ 3mm	PD, CAL	GCF	IL-18	ELISA	141(60)	-	> 0.05	↓ IL-18 levels after periodontal treatment
Vahabi *et al*., 2019[24]	PD ≥ 5mm, CAL ≥ 4mm, PI > 40%, BOP 80%	BOP, PD, CAL	Saliva	IL-18	ELISA	143.10(155.30)*	78.33(101.96)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Tsuneto *et al*., 2019[25]	PD ≥ 5mm, CAL ≥ 3mm, BOP 25%	NR	Serum	IL-18	ELISA	164.8(66.4)*	82.3(43.3)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Wang *et al*., 2019[26]	PD ≥ 3mm	PI, GI, PD, CAL	Serum Saliva	IL-18	ELISA	NR 22.45(3.65)*	NR 15.81(2.18)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Mahajani *et al*., 2017[27]	PD ≥ 4mm, CAL ≥ 3mm, RBL	PI, GI, PD, CAL	GCF	IL-18	ELISA	5.30(0.57)*	3.56(0.65)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Nair *et al*., 2016[28]	PD ≥ 5mm, CAL ≥ 3mm, RBL	PI, GI, PD, CAL	Serum GCF	IL-18	ELISA	55.12(19.77)* 144.61(25.85)*	19.61(5.61) 20.10(1.83)	< 0.05 < 0.05	↑ IL-18 levels in group with EG compared to CG
Banu *et al*., 2014[29]	PD ≥ 5mm, CAL ≥ 4mm, BOP 80%	PI, PD	Plasma Saliva	IL-18	ELISA	236.06(37.60)* 616.19(135.50)*	162.20(15.40) 119.64(8.73)	< 0.001 < 0.001	↑ IL-18 levels in group with EG compared to CG
Campos *et al*., 2012[30]	PD ≥ 5mm	PI, GI, PD, CAL	GCF	IL-18	ELISA	15.3(8.4)	15.0(8.3)	> 0.05	No difference between IL-18 levels in both groups
Ozçaka *et al*., 2011[31]	PD ≥ 5mm, CAL ≥ 4mm, RBL	PI, BOP, PD, CAL	Plasma Saliva	IL-18	ELISA	238.39(106.42) 275.05(289.46)*	273.18(198.32) 143.71(103.68)	> 0.05 < 0.05	↑ IL-18 levels in group with EG compared to CG
Sánchez-Hernández *et al*., 2011[32]	PD ≥ 6mm, CAL ≥ 5mm	PI, BOP, PD, CAL	Serum Gingival tissue	IL-18	ELISA	427.3(56.9)* 14.5(2.7)	278.2(41.6) 14.6(5.6)	< 0.05 > 0.05	↑ IL-18 levels in group with EG compared to CG
Türkoğlu *et al*., 2009[33]	PD ≥ 6mm, CAL ≥ 5mm, BOP 50%	PI, BOP, PD, CAL	GCF	IL-18	ELISA	NR	NR	< 0.05	↑ IL-18 levels in group with CG compared to EG
Pradeep *et al*., 2009[34]	PD > 4mm, CAL ≥ 3mm, RBL	PD, CAL	GCF	IL-18	ELISA	450.54(276.83)*	26.69(12.76)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Figueredo *et al*., 2008[35]	PD ≥ 5mm	BOP, PD, CAL	GCF	IL-18	ELISA	27.43(21.86)	23.37(25.18)	< 0.001	↑ IL-18 levels in group with EG compared to CG
Orozco *et al*., 2006[36]	PD ≥ 5mm, RBL	NR	Serum GCF	IL-18	ELISA	NR 710(198)*	NR 294(79.40)	< 0.05	↑ IL-18 levels in group with EG compared to CG
Johnson *et al*., 2005[37]	PD ≥ 3mm	PD	Gingival tissue	IL-18	ELISA	401.44(43.21)*	33.25(4.15)	< 0.05	↑ IL-18 levels in group with EG compared to CG

Abbreviations: PI Plaque index; GI gingival index; BOP Bleeding on probing; PD Probing deep; CAL Clinical attachment loss; GCF Gingival crevicular fluid; CG Control group; EG Exposure group; IL-18 Interleukin 18

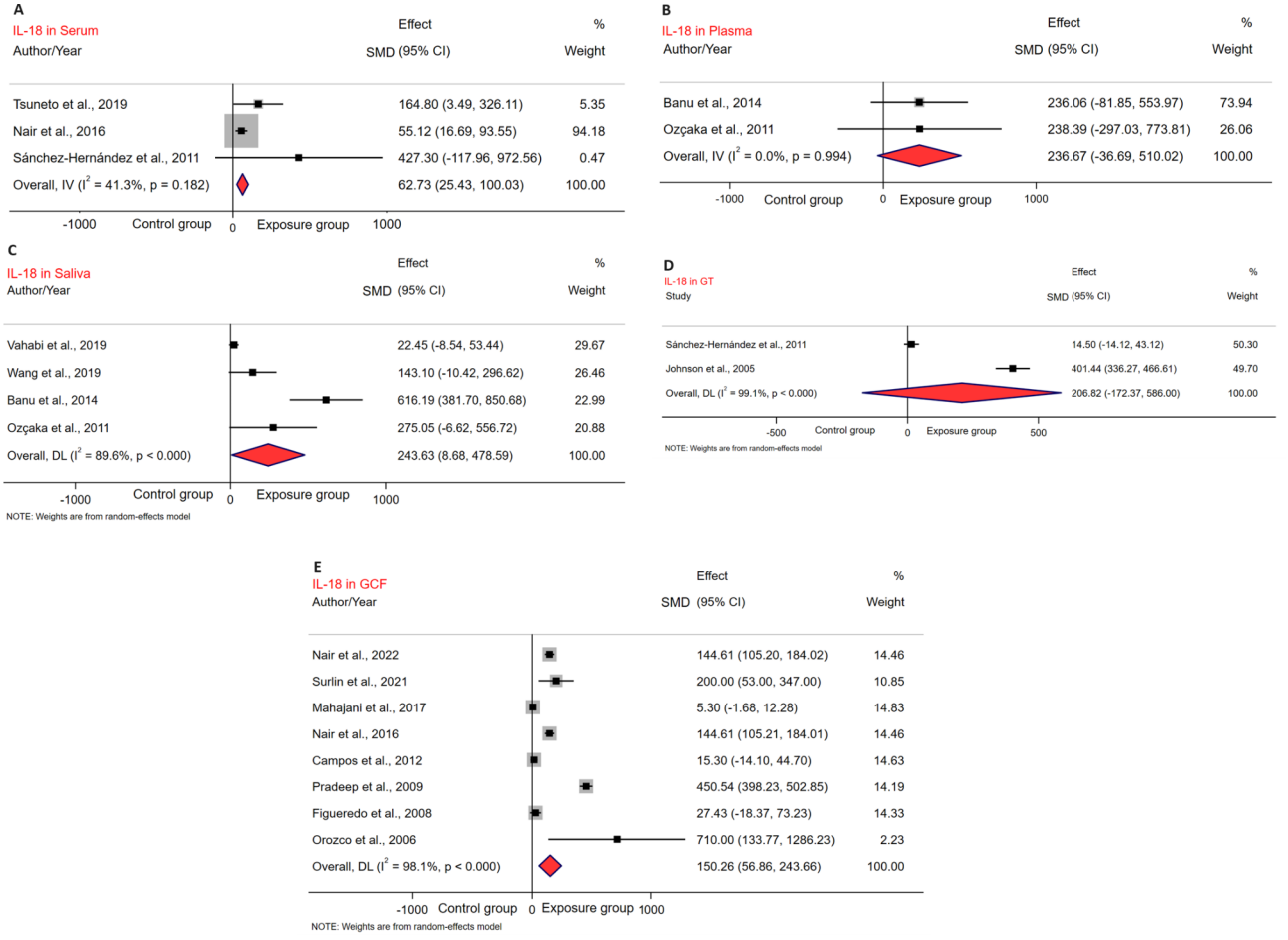

Fig. 2 Forest plot comparing the IL-18 levels in (**A**) Serum, (**B**) Plasma, (**C**) Saliva, (**D**) Gingival tissue, (**E**) Gingival crevicular fluid of Control group vs. Exposure group. E) Funnel plot to check the publication bias

Table 3 Summary of meta-analysis results and subgroups analysis

Groups	No of studies	Test of comparison				Heterogeneity		
		SMD (95% CI)	*P* value	Model	Z	Chi square	*P* value	I square (%)
IL-18 (Serum) EG vs CG	3	62.73(25.43–100.03)	**0.001**	Fixed	3.29	3.41	0.182	41.3
IL-18 (Plasma) EG vs CG	2	236.67(-36.69–510.02)	0.090	Fixed	1.697	0.00	0.994	0.00
IL-18 (Saliva) EG vs CG	4	243.63(8.68–478.59)	**0.042**	Random	2.032	28.83	**0.000**	89.6
IL-18 (GT) EG vs CG	2	206.82(-172.37–586.00)	0.285	Random	1.069	113.54	**0.000**	99.1
IL-18 (GCF) EG vs CG	8	150.26(56.86–243.66)	**0.02**	Random	3.153	365.8	**0.000**	98.1

Abbreviations: SMD Standardized mean difference; CI Confidence interval; EG Exposure group; CG Control group; GT Gingival tissue; IL-18 Interleukin 18. A *p* value ≤ 0.05 was considered statistically significant

inflammatory bowel disease and periodontitis have been associated with higher serum levels of IL-8 and IL-18 compared to subjects without coexistence of both diseases [47]. Also, in patients with celiac disease, whose main complication is xerostomia, leading to dental caries and periodontal disease, the mean levels of IL-6, IL-18 and IL-21 in serum and saliva were higher compared to that of their control group [48]. On the other hand, it has been shown that in subjects with type 2 diabetes mellitus and periodontitis the serum and salivary levels of IL-17 and IL-18 were not different compared to systemically and periodontally healthy subjects. However, a statistically significant association was found between serum IL-18 levels and glycosylated hemoglobin (HbA1c), therefore, IL-18 levels reflected the patient's glycemic status and not the periodontal status [49]. Likewise, it has been shown that obesity could hinder the improvement of periodontal clinical and immunological parameters after non-surgical therapy in patients with diabetes mellitus and periodontitis [50].

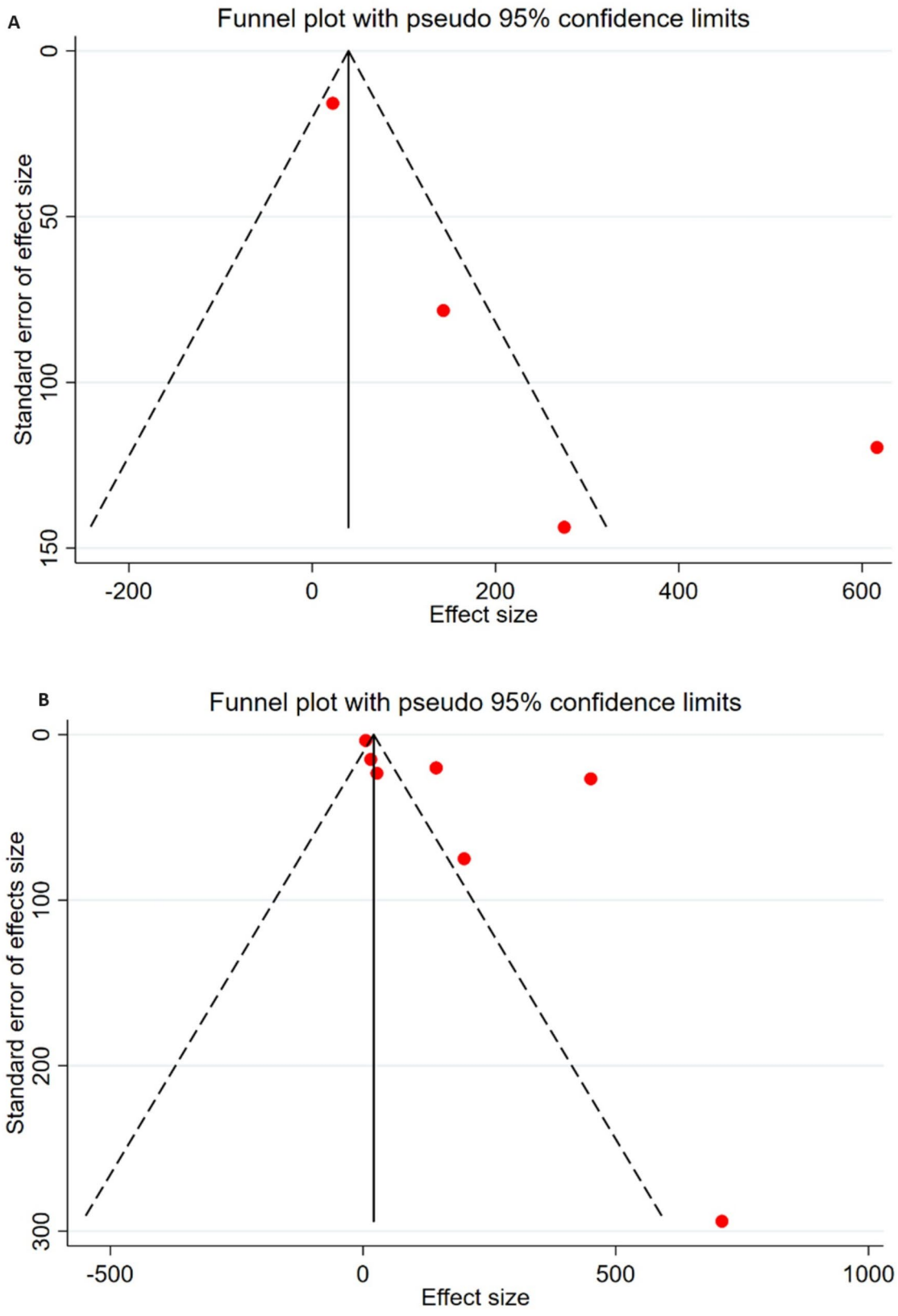

Fig. 3 Funnel plot to check the publication bias **A**) IL-18 in Saliva and **B**) Gingival crevicular fluid

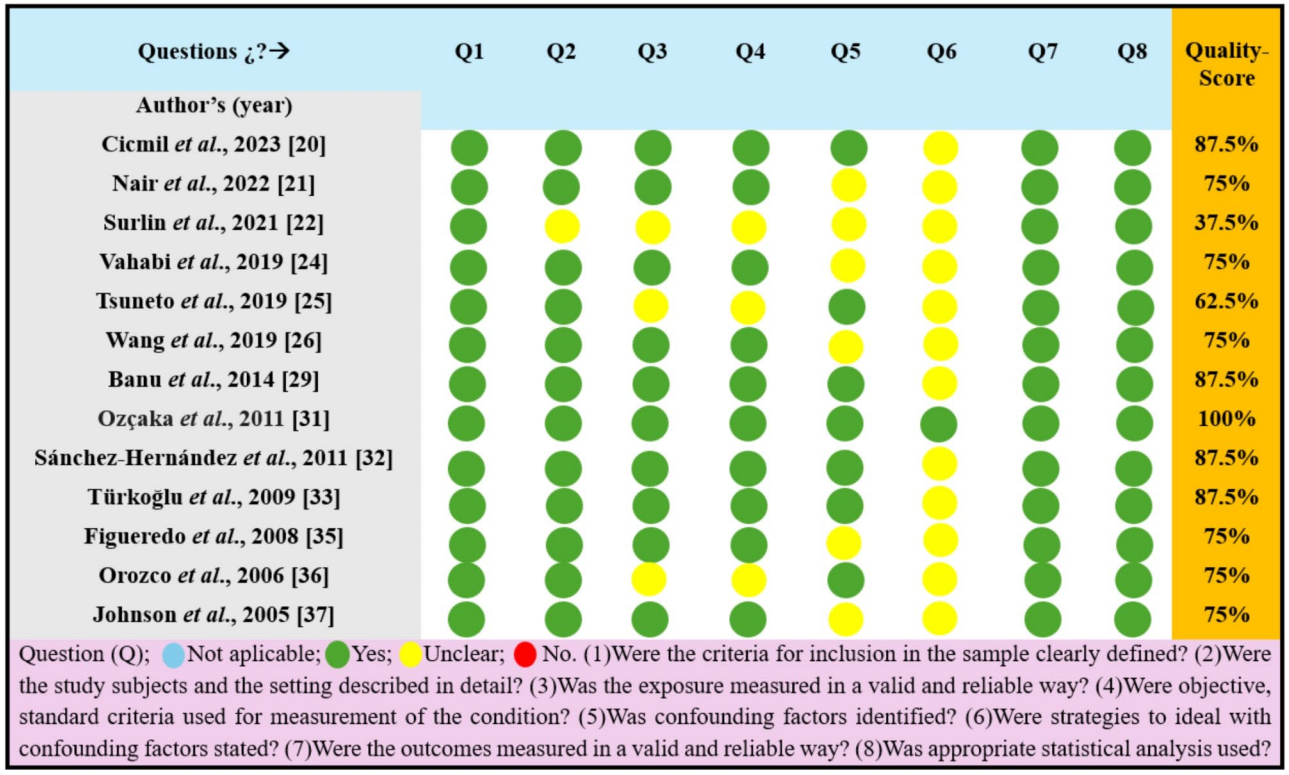

Fig. 4 Quality assessment according to the JBI for clinical cross-sectional studies

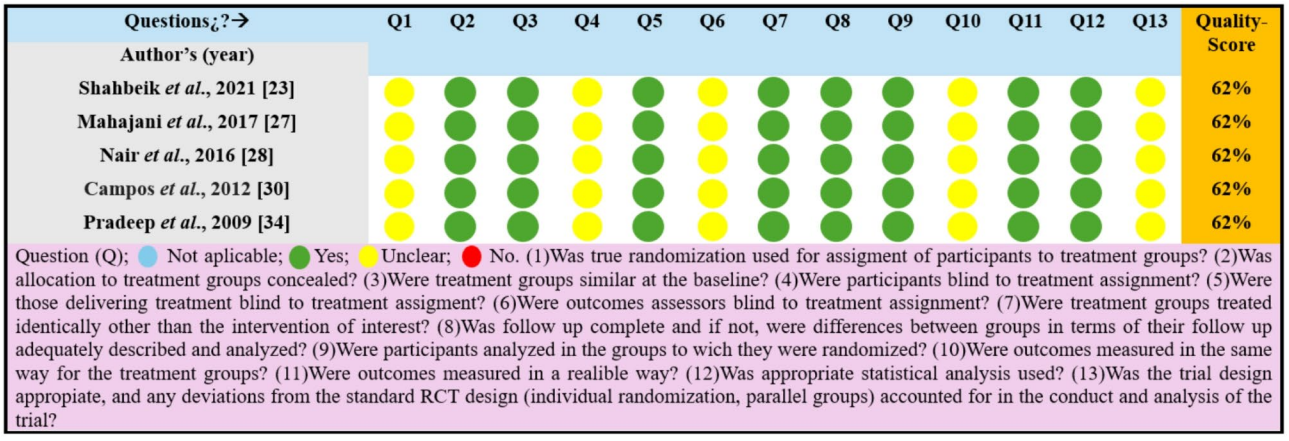

Fig. 5 Quality assessment according to the JBI for clinical trials

On the other hand, several studies have explored the role of IL-18 in periodontal diseases. In summary, it has been shown that IL-18 is mainly released from DC and acts synergistically with IL-12 on NK cells to trigger the production of IFN-γ from Th1 cells and IL-17 from Th17 cells, as well as exacerbating the inflammatory process by up-regulating other cytokines such as TNF-α, IL-1β and CX3CL1 that induce MMP-9 production and recruitment of osteoclast precursor cells, leading to further inflammation and destruction of periodontal tissues [20–37].

The activity and function of cytokines at the systemic level is evaluated by measuring their concentrations in serum and plasma, because the components of these biofluids reflect the inflammatory condition of the host in periodontal disease, therefore, it is plausible to evaluate IL-18 levels in these biological samples to investigate the pathogenesis of periodontitis [20, 25, 26, 28, 32, 36]. In this meta-analysis, it was shown that the serum IL-18 level in subjects with chronic periodontitis was significantly higher than that in healthy subjects, this finding is in agreement with the results of previous studies.

Cicmil et al., 2023 demonstrated an increase in biochemical (C-reactive protein, fibrinogen, triglycerides, total cholesterol and LDL-cholesterol), hematological (fibrinogen, systolic, diastolic blood pressure, right and left intima media thickness), and IL-8 and IL-18 levels in subjects with periodontitis compared to healthy subjects. In addition, the authors found a positive correlation between the levels of these cytokines with gingival index (GI), BOP, PD and CAL. Thus, these results suggest that dyslipidemia and an altered periodontal condition could be risk factors for the development of other serious systemic disease such as subclinical atherosclerosis [20]. Likewise, studies by Zhang et al., 2021, Tsuneto et al., 2019, Wang et al., 2019 and Sánchez-Hernández et al., 2012 showed a significant increase in IL-18 levels in subjects with periodontitis compared to periodontally healthy subjects. These findings suggest that this cytokine is involved in chronic inflammation and tissue destructive process, in subjects with periodontitis. Therefore, the authors conclude that serum IL-18 concentrations could be used as biomarkers to predict disease development [25, 26, 32, 50]. On the other hand, Nair et al., 2016 demonstrated in their study that serum IL-18 levels are directly proportional to the increase in the level of inflammation in periodontal tissues, while a decrease in the level of inflammation after non-surgical periodontal therapy leads to a reduction in the levels of this cytokine [28]. Only one study [36] reported very low levels of IL-18 in serum samples.

On the other hand, this meta-analysis showed that there were no significant differences in IL-18 levels between subjects with chronic periodontitis and healthy controls, as analyzed in plasma and gingival tissue. Banu et al., 2014 demonstrated increased levels of TLR-4 and IL-18 in plasma samples from subjects with periodontitis compared to healthy subjects. These results inform on the systemic immune response against periodontopathogenic bacteria. In addition, high levels of TLR-4 could play an important role in the production of other proinflammatory cytokines, wich would produce greater tissue damage [29]. However, Ozçaka et al., 2011 found no statistically significant difference between plasma levels of this cytokine in both EG compared to CG [31]. Sánchez-Hernández et al., 2011 [32] found no difference between the levels of this cytokine in gingival tissue samples, while, Johnson et al., 2005 [37] found increased levels of IL-18 in gingival tissue samples from the EG compared to the CG.

Saliva can be collected easily, noninvasively and painlessly. It consists of a wide variety of biological components such as proteins, carbohydrates, lipids, DNA, RNA, microorganisms and metabolites that could be considered as potential markers for the diagnosis of different oral and systemic diseases [51]. In this meta-analysis, it was shown that the salivary IL-18 level in subjects with chronic periodontitis was significantly higher than that in healthy subjects, this finding is in agreement with the results of previous studies. Vahabi et al., 2019, Wang et al., 2019, Banu et al., 2014 and Ozçaka et al., 2011 found increased levels of IL-18 in saliva of subjects with chronic periodontitis compared to healthy individuals. In addition, Wang et al., 2019 demonstrated a positive correlation between the levels of this cytokine with PI, GI, PD and CAL [26].

Finally, the qualitative analysis revealed that, of the five biological samples previously analyzed, GCF was the most reported [21–23, 27, 28, 30, 33–36]. In pathological conditions, GCF corresponds to an inflammatory exudate made up of a complex mixture of substances derived from serum, leukocytes, proteins, structural cells of the periodontium and oral bacteria [52]. The results of the meta-analysis demonstrated that IL-18 levels in GCF of subjects with chronic periodontitis were significantly higher than that of healthy subjects, this finding is in agreement with the results of previous studies. Nair et al., 2022, Surlin et al., 2021, Shahbeik et al., 2021, Mahajani et al., 2017, Nair et al., 2016, Campos et al., 2012, Türkoğlu et al., 2009, Pradeep et al., 2009, Figueredo et al., 2008 and Orozco et al., 2006 [21–23, 27, 28, 30, 33–36] demonstrated that IL-18 levels in GCF were increased in EG compared to CG. A positive correlation between IL-18 levels with periodontal clinical parameters (PI, GI, PD, CAL) was also demonstrated. The increase of IL-18 in GCF could be due to the damage produced by *P. gingivalis* and other periodontopathogenic species in the gingival sulcus cells. In addition, it is important to mention that high levels of locally secreted IL-18 (saliva and GCF) could increase circulating IL-18, indicating that periodontal inflammation could up-regulate serum levels of this cytokine in subjects with chronic periodontitis [20, 25, 26, 28, 32, 36]. The authors concluded that IL-18 levels present in GCF have the potential to be considered as biomarkers of periodontal inflammation and destruction. Importantly, variations in GCF flow and different collection methods during sampling may contribute to data heterogeneity, with absorbent paper strips being the most common method [19].

Limitations

The present systematic review and meta-analysis has provided valuable information on the association between IL-18 levels and periodontitis, however, it had some limitations:

- Lack of sufficient included studies. Mostly studies with a cross-sectional design were analyzed. Only one clinical trial was not added to the meta-analysis

due to lack of data. Mostly studies with a cross-sectional design were analyzed.
- The sample size could be larger, which could increase statistical power and make inferences in the general population.
- The heterogeneity of the data based on age, gender, inflammatory body conditions, presence of prosthetic restorations, polymicrobial dysbiosis, lipid, hormonal and hematological profile, sampling method and type of technique used for subsequent analysis, could affect this heterogeneity, so the results should be interpreted with caution.
- Follow-up studies with a larger sample size are suggested, which would allow stratification of the study population based on the new classification of periodontal and peri-implant diseases with more precise criteria and a complete consideration of the influential variables for statistical analysis.

Conclusions

IL-18 plays an important role in the immunopathogenesis of periodontitis. IL-18 levels in serum, saliva and GCF could have the potential to be used as complementary diagnostic tools to the clinical and radiographic parameters considered today as the gold standard in "periodontal diagnosis". Therefore, future studies in this regard are recommended to ensure their specificity and sensitivity as biomarkers.

Abbreviations

IFN-γ	Interferon gamma
IL-1β	Interleukin- 1 beta
TNF-α	Tumor necrosis factor- alpha
IL-6	Interleukin- 6
IL-8	Interleukin- 8
IL-17	Interleukin- 17
IL-18	Interleukin- 18
IL-23	Interleukin- 23
CX3CL1	C-X3-C motif ligand 1
TLR-4	Toll like receptor 4
aMMP-8	Active matrix metalloproteinase 8
MMP-9	Matrix metalloproteinase 9
MMP-13	Matrix metalloproteinase 13

Supplementary Information

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Supplementary Material 1

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Author contributions

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

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Data availability

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

Declarations

Ethical approval

Not applicable.

Informed consent

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Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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