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Cytokines profile in gingival crevicular fluid of subjects wearing fixed dental prostheses: a systematic review and meta-analysis

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Abstract

Background Fixed dental prostheses (FDP) can affect the production of inflammatory cytokines causing damage to periodontal tissues. A systematic review and meta-analysis was carried out with the following two objectives: (1) to determine the prevalence and function of the different inflammatory cytokines present in gingival crevicular fluid (GCF) of teeth with metal–ceramic (M/C) and all-ceramic (A-Cs) prostheses, and (2) to analyze and compare the levels of inflammatory cytokines in GCF of teeth with M/C and A-Cs prostheses.

Methods The protocol followed PRISMA and Cochrane guidelines and was registered in the OSF:10.17605/OSF.IO/RBHJU. A digital search was conducted in the databases PubMed/MEDLINE, Cochrane Library, Dentistry & Oral Sciences Source, Scopus, Web of Science, ScienceDirect, and Google Scholar, from July 15th, 2000 to March 1st, 2024. Study quality was assessed using the JBI tool for cross-sectional and longitudinal studies. A meta-analysis was performed using a random-effects model to evaluate the concentration of IL-1β in GCF of teeth with FDP of M/C and A-Cs.

Results The search strategy provided a total of 8,172 articles, of which 14 investigations met the inclusion criteria. The total number of patients studied was 468 of whom 53% were women and the rest (47%) were men. The ages of the patients ranged from 19 to 73 years, with a mean age ± standard deviation (SD) of 38,5 ± 12,8 years. A total of 843 fixed dental prostheses were studied, of which 407 (48,27%) were M/C prostheses and 410 (48,63%) were A-Cs prostheses. We found that the levels of IL-1β, IL-1α, PGE_2, NKA, CGRP, and CX3CL1 were increased in teeth with M/C prostheses compared to teeth with A-Cs prostheses. Meta-analysis revealed that there are no significant differences between IL-1β levels in GCF in teeth with M/C prostheses compared to teeth with A-Cs prostheses (SMD = 13.89 pg/ml (CI = −14.29–42.08), $p = > 0.05$).

Conclusions A trend toward increased levels of inflammatory cytokines was found in GCF of teeth with M/C prostheses compared to teeth with A-Cs prostheses.

Keywords Dental fixed prostheses, Metal–ceramic, Ceramic free-metal, Cytokines, Systematic review

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Background

When it is desired to rehabilitate or replace teeth lost due to an infectious process (caries/periodontal disease), dental trauma or partial edentulism, fixed dental prostheses (FDP) are considered as one of the first treatment options as it provides promising clinical results [1]. In fact, oral rehabilitation using these devices has been shown to improve oral health-related quality of life [2]. FDP can be fabricated from all-metal, metal/ceramic (M/C) or all-ceramic (A-Cs) [3]. In addition, constructions can be realized by conventional methods (CM) [4] or by computer-aided design/computer-aided manufacturing (CAD/CAM) [5]. A-Cs FDP offer better optical qualities (good esthetics) and higher translucency, also require more conservative preparations, are biocompatible with periodontal tissues, and biomechanically exhibit high fracture and flexural strength [6–8]. On the other hand, M/C FDP are usually more economical, are required in sites where there is little tooth structure and show high survival rates, however, it lacks esthetic properties, are heavier in structure, have high thermal and electrical conductivity, as well as have been associated with allergic reactions and increased polymicrobial dysbiosis, which results in increased levels of different inflammatory mediators causing damage to periodontal tissues [9–12].

Regarding these last two points; first, we know that FDP are considered substrates for biofilm formation [13]. In this sense, immediately after placing a FDP in the mouth, the surface of the material is covered by an acquired salivary pellicle, which is formed by selective adsorption of salivary biopolymers (glycoproteins, carbohydrates, lipids) constituting a series of receptors that facilitate adhesion and primary colonization by microorganisms, subsequently they aggregate, proliferate, and grow until form a mature film that adheres firmly on the surface of prosthetic restorations [14]. Finally, some microorganisms (bacteria) return to their planktonic state to colonize new surfaces [15]. The chemical composition of biomaterials and physical characteristics (rough and irregular surfaces and surface free energy) can influence bacterial colonization [16]. Biofilm formation on different types of dental ceramics and alloys depends on the bacterial genus and species [17]. A higher bacterial load has been demonstrated on teeth with FDP compared to natural teeth free of prosthetic restorations [18], in addition, on teeth with M/C prostheses and periodontitis at the phylum level, a higher prevalence of *Spirochaetes* and *Bacteroidetes* has been found, while at the genus level, a higher prevalence of *Treponema* and *Prevotella* [19]. At the species level, the most predominant bacteria are *Streptococcus gordonii*, *Veillonella parvula*, *Eubacterium nodatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*. While, in teeth with A-Cs prostheses and periodontitis increases the prevalence of the above mentioned bacterial species, with the exception of *S. gordonii*, *V. parvula*, and *T. denticola*, compared to their natural teeth and with the same periodontal condition [20]. These mostly Gram-negative periodontopathogenic bacteria produce a series of virulence factors such as lipopolysaccharides (LPS) that activate the host immune response [21]. Therefore, upon bacterial challenge, gingival sulcus cells (keratinocytes, neutrophils, dendritic cells, macrophages, B and T lymphocytes) release a variety of inflammatory mediators [22]. Hence, one way to study the dynamics of inflammation in prosthetic restorations using different types of biomaterials is through the evaluation of molecules in gingival crevicular fluid (GCF), since it is a biofluid in close contact with the prosthetic margins, easy to collect, noninvasive, and reflects the inflammatory state of the periodontium [23, 24]. Numerous studies have demonstrated differences in the levels of interleukin 1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), interleukin 8 (IL-8), interleukin 1 alpha (IL-1α), matrix metalloproteinase 2 (MMP-2), fractalkine (CX3CL1), interleukin 1 receptor antagonist (IL-1ra), prostaglandin E2 (PGE_2) interleukin 4 (IL-4), immunoglobulin G (IgG), active matrix metalloproteinase (aMMP-8), matrix metalloproteinase 8 (MMP-8), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 1 (TIMP-1), tissue inhibitor of metalloproteinase 2, (TIMP-2), substance P (SP), neurokinin A (NKA), y calcitonin-gene related peptide (CGRP) in GCF of teeth with M/C and A-Cs prostheses [20, 25–37]. Therefore, the clinical performance of both types of prosthetic restorations is determined by the periodontal condition, i.e., maintenance of periodontal health is the key to success for prosthetic treatment [38, 39]. Based on recent findings in the literature we hypothesized that if there is a greater bacterial dysbiosis in teeth restored with M/C prostheses, there will be a greater increase in the levels of the different inflammatory mediators compared to teeth with A-Cs prostheses.

The overall objective of the present systematic review was to qualitatively assess cytokine function and prevalence and also to quantitatively compare these levels between M/C and A-Cs prostheses through a meta-analysis.

Materials and methods

Protocol, register and permission

We structured the study protocol following the preferred reference guidelines for systematic reviews and meta-analyses (PRISMA) [40] and Cochrane [41]. Subsequently, we applied for enrollment in the Open Science

Framework (OSF): https://doi.org/https://doi.org/10.17605/OSF.IO/RBHJU.

PECOS focus question

The PECOS items were taken into account to formulate the following research question: What is the prevalence and function of the different inflammatory cytokines that have been studied in GCF of teeth restored with fixed dental prostheses? The following sub-question was also posed: Are there differences in the levels of inflammatory cytokines in GCF of teeth with M/C and A-Cs prostheses?

1. (P): Systemically healthy subjects who underwent GCF sample collection.
2. (E): Teeth with A-Cs prostheses.
3. (C): Teeth with M/C prostheses.
4. (O): Differences in the levels of inflammatory cytokines in GCF of teeth restored with M/C and A-Cs prostheses.
5. (S): Original clinical studies: cross-sectional and longitudinal.

Eligibility criteria

The articles were selected based on the following inclusion and exclusion criteria. For this systematic review and meta-analysis we included those original clinical studies, with a cross-sectional or longitudinal design, published after the year 2000, written in the English language and analyzing the levels of inflammatory cytokines in GCF using the ELISA technique in subjects wearing prosthetic restorations (veneers, partial/full coverage single crowns or bridges of three or more units) of metal–ceramic (including any type of alloy) and metal-free ceramic prostheses, including biomaterials such as zirconia, lithium disilicate, and porcelain. Periodontal condition was evaluated according to clinical parameters such as probing depth, clinical attachment level, bleeding on probing, plaque index, and presence or absence of radiographic bone loss. In this sense, the teeth restored with fixed dental prostheses were classified as healthy, with gingivitis or periodontitis. In addition, the compatibility of the prosthetic devices with periodontal tissues was evaluated. In this case, when comparing the different biomaterials, were compatible if there was a decrease in the levels of proinflammatory cytokines, indicating a reduction in the inflammatory process and therefore less tissue damage.

Studies that will analyze inflammatory cytokine levels in teeth supporting a removable partial denture and in other biofluids such as saliva, mouth rinses, serum, and plasma were excluded. Also, subjects with any systemic condition, smokers, pregnant women, and those individuals under treatment with antibiotics or immunomodulators were excluded. Studies in animal models and cell lines, as well as book chapters, posters, systematic reviews, meta-analyses, narrative, comprehensive or scoping reviews were also excluded.

Information sources and search strategy

A digital search was conducted in the databases PubMed/MEDLINE, Cochrane Library, Dentistry & Oral Sciences Source, Scopus, Web of Science, ScienceDirect, and Google Scholar, from July 15th, 2000 to March 1st, 2024, in order to search for relevant titles with respect to the PECOS question formulated. The search strategy employed for PubMed/MEDLINE was (("Dental Prosthesis"[Mesh]) AND "Cytokines"[Mesh]) AND "Gingival Crevicular Fluid"[Mesh]. For the rest, the following keywords "fixed dental prostheses", "gingival crevicular fluid", and "cytokines" were used. To enrich and check for relevant supplementary studies that met the requirements, a hand search was performed in the following Journals: *Journal of Prosthodontics-Implant Esthetic and Reconstructive*, *Journal of Advanced Prosthodontics*, *International Journal of Prosthodontics*, *Journal of Oral Implantology*, *Oral Health & Preventive Dentistry*, *Journal of Oral Science*, *Journal of Periodontal and Implant Science*, *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Journal of Periodontal Research*, and *Dental Materials Journal*.

Screening, data collection, and assessment quality

After searching the pre-established electronic databases, the titles and abstracts were examined by a single investigator (M.A.A.S), then duplicate titles were eliminated and the titles and abstracts of the remaining studies were evaluated taking into account the eligibility criteria. The full texts of the selected titles were then reviewed and the articles that met the inclusion criteria were collected. The principal investigator (A.H) reviewed and discussed the selected studies with the first author and those in dispute were resolved by discussion in consultation with a third external reviewer. Thus, once a consensus was reached, all relevant information from the selected articles was extracted and tabulated in a self-designed table by the first author. The information obtained from the articles was as follows: first author's name and year of publication, country, approval by the ethics committee of the corresponding institution, gender, age (mean and standard deviation or range), number of M/C and A-Cs prosthetic restorations, total number of prosthetic restorations, periodontal condition, compatibility, type of sample, inflammatory marker and immunoassay

technique, as well as the mean value and standard deviation of the inflammatory cytokine evaluated in pg/mL. The graph was designed in GraphPad Prism 8 software.

The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess the quality and risk of bias of cross-sectional and longitudinal [42] studies. Questions were rated as "Yes", "No", "Unclear", or "Not applicable". The studies were ranked according to their quality, and were placed in three levels; high bias, when the study reached up to 49% of the scores. Moderate bias, when the scores were 50 to 69% and low bias, when the scores were > 70%.

Statistical analysis

A quantitative synthesis (meta-analysis) was performed that calculated and analyzed the standardized mean difference (SMD) of inflammatory cytokine levels, assessed in pg/mL, between the study groups (M/C vs A-Cs prostheses) using a random-effects model. Heterogeneity was estimated using the Q statistic 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. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed with STATA version 17 software (Stata Corp, College Station, TX, USA).

Results

Study selection

Initially 8,171 articles were found in the seven databases, including PubMed/MEDLINE (1,071 articles were found), Cochrane Library (6 articles were found), Dentistry & Oral Sciences Source (2,201 articles were found), Scopus (3 articles were found), Web of Science (2 articles were found), ScienceDirect (168 articles were found), Google Scholar (4,720 articles were found), and hand searching (1 article was found in Dental Materials Journal). Duplicates (42) were removed and, based on title and abstract, the remaining 8,129 studies were reviewed. After analyzing the full text of the remaining articles, 8,114 records were excluded as irrelevant. A total of 16 articles were evaluated for eligibility (including 1 item from manual search), of which 2 studies were excluded because cytokine expression was evaluated in subjects wearing removable partial dentures as well as those teeth that were in contact with a fixed prostheses. Therefore, a total of 14 articles were included for the qualitative analysis and from these, 5 articles were selected for the quantitative analysis of the present review. Details of the study selection are shown in Fig. 1.

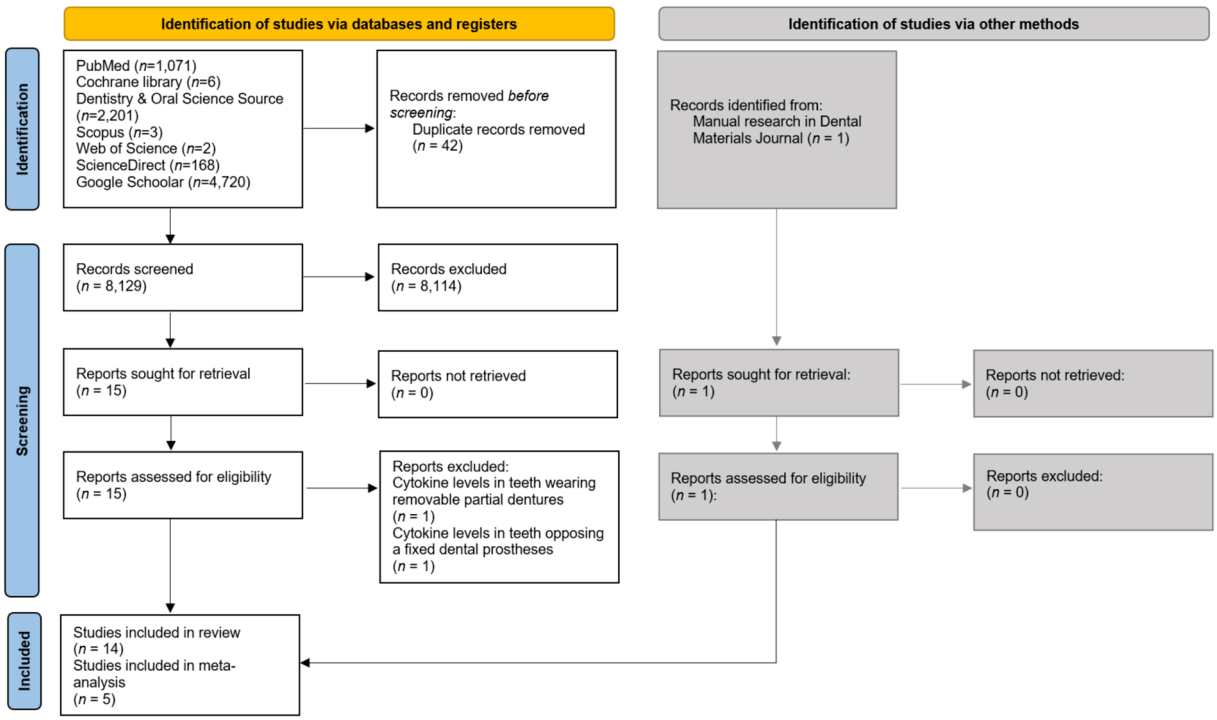


Fig. 1 PRISMA 2020 flow diagram for study selection

Table 1 Sociodemographic and clinical characteristics of the included studies

Study (year)	Country	Study type	Ethical	Gender F^e/M^a	Age (M/R)	*n*		*n* Total	PC / CY = Y	Biological sample/ technique	Immune markers	Assay/system	IL-1β value in M/C M (SD)	IL-1β value in Cs M(SD)
						M/C	A-Cs							
Alarcón-Sánchez et al., 2024[20]	Mexico	CS	Yes	26/14	55.9	20	20	40	17-G 23-P 20-Y	GCF / PSs	IL-1β, TNF-α, CX3CL1	ELISA (R&D)	17(1.80) pg/mL	16(2.66) pg/mL
Alrahlah et al., 2022[25]	Saudi Arabia	PS	Yes	16/11	23.5–40.6	–	288	288	288-H	GCF / PSs	TNF-*α*, IL-6	Luminex 100 IS	-	-
Abo-Elmagd et al., 2021[26]	Egypt	PS	Yes	NR	NR	–	24	24	24-H	GCF /PSs	IL-1β	ELISA (PicoKine)	-	6293(3.2) pg/mL
Saravanakumar et al., 2019[27]	India	PS	Yes	10/10	30 20–40	10	10	20	20-H 10-Y	GCF / PSs	IL-1β	ELISA (NR)	141.98(27.7) pg/mL	79.8(13.6) pg/mL
Ariaans et al., 2016[28]	Germany	CS	Yes	6/5	49.2	–	11	11	11-H	GCF / PSs	IL-1β, IL-1ra, aMMP-8	ELISA (R&D)	-	57.7(61.1) pg/mL
Sakallioğlu et al., 2015[29]	Turkey	CS	Yes	0/14	35–45	14	14	14 Same surface	14-H 14-Y	GCF / PSs	IL-1β, IL-1α, PGE_2, SP, NKA, CGRP	ELISA (Cayman Chemical Company)	0.93 pg/mL	0.81 pg/mL
Chang et al., 2014[30]	USA	CS	Yes	7/5	26–73	12		12	NR	GCF / PSs	IL-1α, IL-8, IL-6, IL-4	ELISA (R&D)	-	-
Yu et al., 2013[31]	China	PS	Yes	30/30	27.9	60	–	60	60-H	GCF / PSs	IL-6, IL-8	ELISA (Hysen Hun)	-	-
Kushlinskii et al., 2012[32]	Russia	CS	Yes	65/40	NR	58	47	105	39-P 66-H 47-Y	GCF / NR	IL-1β, IL-2, IL-6, TNF-*α*, MMP-2,8,9, TIMP-1, 2	ELISA (R&D) (Bender MS) (Biosource)	401(425) pg/mL	312(208.4) pg/mL
Passariello et al., 2012[33]	Italy	CS	Yes	39/35	29–47	102	–	102	34-H 31-G 37-P	GCF / PSs	IL-1β, IL-6, TNF-*α*	ELISA (R&D)	NR	-
Moretti et al., 2011[34]	Brazil	PS	Yes	NR	NR	10	–	10	10-G	GCF / PSs	IL-1β MMP-2	ELISA (R&D)	101.6 pg/mL	-
Erdemir et al., 2010[35]	Turkey	PS	Yes	10/13	43.5 30–60	23	–	23	23-P	GCF / PSs	IL-6, IL-8	ELISA (Biosource)	-	-
Weishaupt et al., 2007[36]	Germany	PS	Yes	27/25	NR	104	–	104	104-H	GCF / PSs	IgG	ELISA (NR)	-	-
Özen et al., 2000[37]	Turkey	CS	Yes	12/18	24.5 19–30	20	10	30	30-H 10-Y	GCF / PSs	IL-1β	ELISA (R&D)	99.3(41.7) pg/mL	93.6(45) pg/mL

CS cross-sectional study, *PS* prospective study; F^e female, M^a male, *M* mean, *R* range, *NR* not reported, *GCF* gingival crevicular fluid, *PSs* paper strips, *ELISA* enzyme linked immunoabsorbent assay, *IL-1β* interleukin- 1 beta, *M/C* metal–ceramic, *A-Cs* all-ceramic, *PC* periodontal condition, *H* healthy, *G* gingivitis, *P* periodontitis, *CY* compatibility, *Y* yes, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *IL-8* interleukin 8, *IL-1α* interleukin 1 alpha, *MMP-2* matrix metalloproteinase 2, *CX3CL1* fractalkine, *IL-1ra* interleukin 1 receptor antagonist, PGE_2 prostaglandin E2, *IL-4* interleukin 4, *IgG* immunoglobulin G, *aMMP-8* active matrix metalloproteinase, *MMP-8* matrix metalloproteinase 8, *MMP-9* matrix metalloproteinase 9, *TIMP-1* tissue inhibitor of metalloproteinase 1, *TIMP-2* tissue inhibitor of metalloproteinase 2, *SP* substance P, *NKA* neurokinin A, *CGRP* calcitonin-gene related peptide

Sociodemographic and clinical aspects of studies

In this study, 14 investigations were reviewed, of which 7 (50%) were cross-sectional studies [20, 28–30, 32, 33, 37] and 7 (50%) were longitudinal studies [25–27, 31, 34–36]. The total number of patients studied in the included investigations was 468, of whom 53% were women and the rest (47%) were men. The ages of the patients ranged from 19 to 73 years, with a mean age ± standard deviation (SD) of 38.5 ± 12.8 years. Most of the articles were published after 2012 (10:71.42%) [20, 25–33]. The oldest study was published in 2000 [37], whereas, the most recent was from 2024 [20]. The included articles were published in 11 different countries [20, 25–37]. Three (21.42%) studies were conducted in Turkey [29, 35, 37], two (14.28%) studies were conducted in Germany [28, 36], and other studies (7.14%) were conducted in Mexico [20], Saudi Arabia [25], Egypt [26], India [27], USA [30], China [31], Russia [32], Italy [33], and Brazil [34] (Table 1).

Immunological aspects of studies

A total of 843 fixed dental prostheses were studied, of which 407 (48.27%) were M/C prostheses and 410 (48.63%) were A-Cs prostheses [20, 25–37]. One study evaluated the levels of IL-1β, IL-1α, PGE_2, SP, NKA, CGRP in GCF of 14 prosthetic constructs on two different surfaces, one metal and the other metal-free ceramic [29], whereas, another study did not specify the type of prosthetic biomaterial used [30]. Of the teeth restored with prostheses, 651 (77%) had no periodontal disease (healthy), 58 (7%) had gingivitis, 122 (15%) had periodontitis, the rest (1%) did not specify periodontal status. The compatibility of FDP was analyzed based on clinical parameters and proinflammatory cytokine expression. In this regard, A-Cs prostheses were more biocompatible with periodontal tissues compared to M/C prostheses [20, 27, 29, 32, 37]. Thirteen (92.85%) studies collected GCF samples with absorbent paper strips [20, 25–31, 33–37] and only one study (7.14%) did not report the type of collection [32]. Likewise, for the determination of protein levels in GCF, the most frequently used immunoassay technique was the ELISA technique (92.85%) [20, 26–37], whereas, only one study (7.14%) used the Luminex technique [25]. Furthermore, among the 14 included studies, the R&D Systems ELISA kit, was the most commonly used (50%) [20, 28, 30, 32–34, 37], followed by the BioSource kit (14.28%) [32, 35] (Table 1).

Regarding the prevalence of inflammatory cytokines, enzymes and neuropeptides analyzed in GCF of teeth restored with fixed dental prostheses (M/C vs A-Cs), it was found that, most of the studies (64, 28%) analyzed IL-1β [20, 26–29, 32–34, 37], followed by IL-6 (43%) [25, 30–33, 35], TNF-α (29%) [20, 32, 33], IL-8 (21.4%) [31, 35], IL-1α (14.3%) [29], and MMP-2 (14.3%) [32] (Fig. 2). Finally, we found that the levels of IL-1β, IL-1α, PGE_2, NKA, CGRP, and CX3CL1 were increased in teeth with M/C prostheses compared to teeth with A-Cs prostheses [20, 27, 29, 32, 37]. It was also observed that IL-6, TNF-α, and MMP-8 levels were increased in M/C prosthetic teeth compared to contralateral natural teeth [31–33]. On the other hand, SP levels were found to be increased in A-Cs prosthetic teeth compared to M/C prosthetic teeth [29], whereas, aMMP-8 and TNF-α levels were increased compared to their natural contralateral teeth free of prosthetic restorations [20, 28] (Table 2).

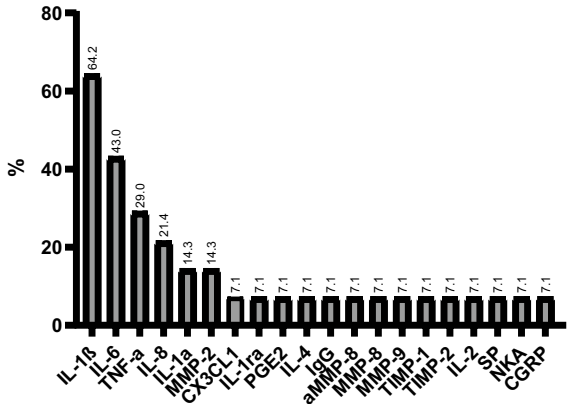


Fig. 2 Prevalence of the different inflammatory cytokines that have been studied in fixed dental prostheses. IL-1β: interleukin 1 beta; IL-6, interleukin 6; TNF-α: tumor necrosis factor alpha; IL-8; interleukin 8; IL-1α: Interleukin 1 alpha; MMP-2: matrix metalloproteinase 2; CX3CL1: fractalkine; IL-1ra: interleukin 1 receptor antagonist; PGE_2: prostaglandin E2; IL-4: interleukin 4; IgG: immunoglobulin G; aMMP-8: active matrix metalloproteinase; MMP-8: matrix metalloproteinase 8; MMP-9: matrix metalloproteinase 9; matrix metalloproteinase 9; TIMP-1: tissue inhibitor of metalloproteinase 1; TIMP-2: tissue inhibitor of metalloproteinase 2; SP: substance P; NKA: neurokinin A; CGRP: calcitonin-gene related peptide

Quality assessment

The JBI checklist was used to assess the quality of cross-sectional and longitudinal studies. According to the established criteria, 8 (57.14%) studies showed moderate risk of bias [25–27, 31, 32, 34–36] and 6 (42.85%) showed low risk of bias [20, 28–30, 33, 37] (Tables 3 and 4).

Meta-analysis: comparison of IL-1β levels in GCF of teeth with M/C and A-Cs prostheses

Five studies [20, 27, 29, 32, 37] compared IL-1β levels in GCF of teeth with M/C ($n=122$) and A-Cs ($n=101$) prostheses. The results of the meta-analysis indicated a (SMD = 13.89 pg/ml (CI = -14.29—42.08), $p = > 0.05$), demonstrating that IL-1β levels in GCF of teeth with M/C prostheses were higher compared to teeth with

Table 2 Influence of metal–ceramic and metal-free ceramic prostheses on the levels of different inflammatory mediators, tissue destruction enzymes and neuropeptides in GCF

Molecules	Biological function	Comments about effects of M/C and A-Cs prostheses
IL-1β	-Differentitation of Th17 cells -RANKL upregulated -Secretion of proinflammatory cytokines -Promotion of myeloid cells[54]	↑ Teeth with M/C prostheses compared to teeth with A-Cs prostheses [20, 27, 29, 32, 37] ↓ Levels 2 weeks after placement of the final zirconia prostheses [26] Levels were similar in teeth with zirconia prostheses compared to natural teeth [28] ↑ Cases of gingivitis and periodontitis [33] ↓ After NSPT [34]
IL-6	-Differentitation of Th17 and Tfh cells -RANKL upregulated -Secretion of proinflammatory cytokines[52]	Baseline IL-6 levels were similar at 24 weeks after restoration placement [25] Not detected [30] ↑ Teeth with M/C prostheses and periodontitis compared to their natural teeth with the same periodontal condition [31, 32] ↑ 6 months after placement of the restoration [33] ↓ After NSPT [35]
TNF-α	-Differentitation of Th17 cells -RANKL upregulated -Suppression of osteoblastic activity -Secretion of proinflammatory cytokines[55]	↑ Teeth with monolithic zirconia prostheses and gingivitis compared to their natural teeth with the same periodontal condition [20] ↑ Levels at week 4, 12 and 24 compared to baseline [25] ↑ Teeth with M/C prostheses and periodontitis compared to their natural teeth with the same periodontal condition [32, 33]
IL-8	-Chemoattractant -Secretion of proinflammatory cytokines[56]	↑ Equigingival margins compared to supragingival margins [30] ↓ After NSPT [31, 35]
IL-1α	-RANKL upregulated -Secretion of proinflammatory cytokines[57]	↑ Teeth with M/C prostheses compared to teeth with A-Cs prostheses [29] ↑ Equigingival margins compared to supragingival margins [30]
MMP-2	-Angiogenesis, neovascularization, promoting and inhibiting inflammation[58]	↑ Natural teeth with periodontitis compared to M/C prostheses with the same periodontal condition [32] Not detected [34]
CX3CL1	-Chemoattractant -Cell adhesion -RANKL upregulated -Secretion of proinflammatory[59]	↑ Teeth with M/C prostheses and periodontitis compared to teeth with monolithic zirconia prostheses and natural teeth with the same periodontal condition [20]
IL-1ra	-Inhibits the IL-1 signaling pathway by binding to IL-1R[57]	↓ Teeth with zirconia prostheses compared to natural teeth [28]
PGE_2	-Pyrexia, pain sensation and inflammation[60]	↑ Teeth with M/C prostheses compared to teeth with Cs prostheses [29]
IL-4	-Differentitation of Th2 cells -Production of protective antibodies and reduces levels of proinflammatory cytokines[61]	Not detected [30]
IgG	-Opsonization -Complement activation[62]	↓ Levels at 12 months compared to baseline [36]
aMMP-8	-Tissue degradation[58]	↑ Teeth with zirconia prostheses compared to natural teeth [28]
MMP-8	-Tissue turnover, antiinflammatory activiy, wound healing[58]	↑ Teeth with M/C prostheses and periodontitis compared to their natural teeth with the same periodontal condition [32]
MMP-9	-Wound healing, embryo implantation, neovascularization, immune cells functtion, tissue remodeling[58]	↑ Natural teeth with periodontitis compared to M/C prostheses with the same periodontal condition [32]
TIMP-1	-MMPs inhibition, interaction with surface proteins, apoptosis[63]	↑ Natural teeth with periodontitis compared to M/C prostheses with the same periodontal condition [32]
TIMP-2	-MMPs inhibition, modulate transduction signals, apoptosis[63]	↑ Natural teeth with periodontitis compared to M/C prostheses with the same periodontal condition [32]
IL-2	-Increases the growth and activity of T and B cells[64]	↑ Natural teeth with periodontitis compared to M/C prostheses with the same periodontal condition [32]
SP	-Neurogenic inflammation [65]	↑ Teeth with Cs prostheses compared to teeth with M/C prostheses [29]
NKA	-Neurogenic inflammation[65]	Levels were similar in teeth with M/C prostheses compared to teeth with Cs prostheses [29]
CGRP	-Neurogenic inflammation[65]	Levels were similar in teeth with M/C prostheses compared to teeth with Cs prostheses [29]

IL-1β interleukin 1 beta, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *IL-8* interleukin 8, *IL-1α* interleukin 1 alpha, *MMP-2* matrix metalloproteinase 2, *CX3CL1* fractalkine, *IL-1ra* interleukin 1 receptor antagonist, PGE_2 prostaglandin E2, *IL-4* interleukin 4, *IgG* immunoglobulin G, *aMMP-8* active matrix metalloproteinase, *MMP-8* matrix metalloproteinase 8, *MMP-9* matrix metalloproteinase 9, *TIMP-1* tissue inhibitor of metalloproteinase 1, *TIMP-2* tissue inhibitor of metalloproteinase 2, *SP* substance P, *NKA* neurokinin A, *CGRP* calcitonin-gene related peptide

Table 3 Quality assessment according to the JBI for clinical cross-sectional studies

Questions→ Author's (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Quality-score
Alarcón-Sánchez et al., 2024[20]	Y	Y	Y	Y	Y	N	Y	Y	78
Ariaans et al., 2016[28]	Y	Y	Y	Y	U	U	Y	Y	75
Sakallioğlu et al., 2015[29]	Y	Y	Y	Y	U	U	Y	Y	75
Chang et al., 2014[30]	Y	Y	Y	Y	U	U	Y	Y	75
Kushlinskii et al., 2012[32]	U	Y	Y	Y	U	U	Y	Y	63
Passariello et al., 2012[33]	Y	Y	Y	Y	U	U	Y	Y	75
Özen et al., 2000[37]	Y	Y	Y	Y	Y	U	Y	Y	78

(1) Were the criteria for inclusion in the sample clearly defined?

(2) Were the study subjects and the setting described in detail?

(3) Was the exposure measured in a valid and reliable way?

(4) Were objective, standard criteria used for measurement of the condition?

(5) Was confounding factors identified?

(6) Were strategies to ideal with confounding factors stated?

(7) Were the outcomes measured in a valid and reliable way?

(8) Was appropriate statistical analysis used?

Question (Q), *N/A* not applicable, *Y* yes, *U* unclear

Table 4 Quality assessment according to the JBI for clinical longitudinal studies

Questions→ Author's (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Quality-Score
Alrahlah et al., 2022[25]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Abo-Elmagd et al., 2021[26]	N	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Saravanakumar et al., 2019[27]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Yu et al., 2013[31]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Moretti et al., 2011[34]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Erdemir et al., 2010[35]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62
Weishaupt et al., 2007[36]	U	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y	U	62

(1) Was true randomization used for assignment of participants to treatment groups?

(2) Was allocation to treatment groups concealed?

(3) Were treatment groups similar at the baseline?

(4) Were participants blind to treatment assignment?

(5) Were those delivering treatment blind to treatment assignment?

(6) Were outcomes assessors blind to treatment assignment?

(7) Were treatment groups treated identically other than the intervention of interest?

(8) Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?

(9) Were participants analyzed in the groups to which they were randomized?

(10) Were outcomes measured in the same way for the treatment groups?

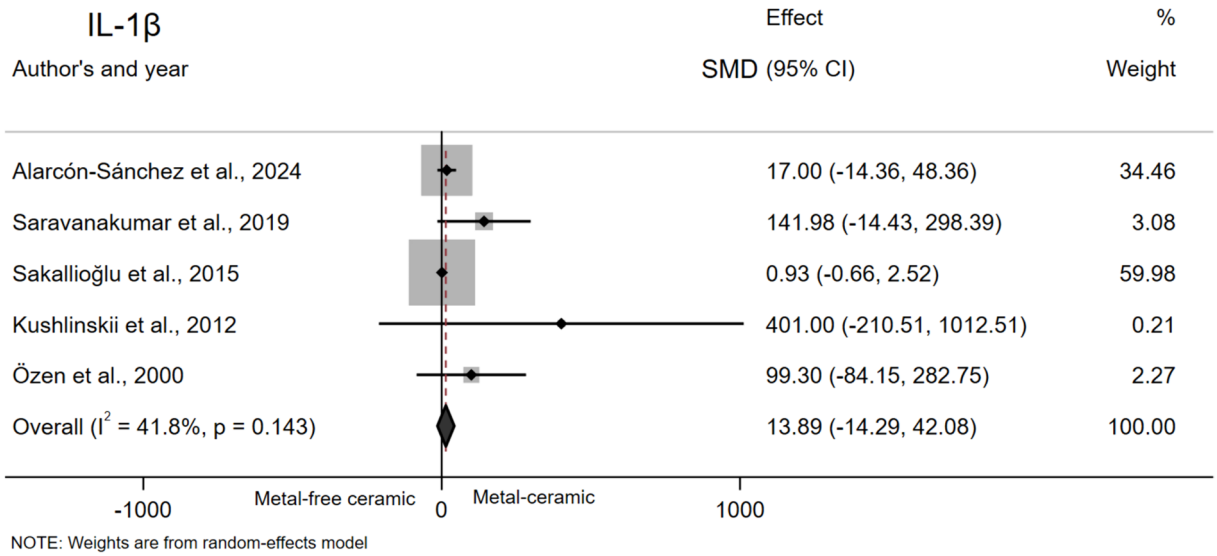
(11) Were outcomes measured in a reliable way?

(12) Was appropriate statistical analysis used?

(13) Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Question (Q), *N/A* not applicable, *Y* yes, *U* unclear

A-Cs prostheses, but without statistical significance. Based on the Chi-square test, there was no evidence of heterogeneity among the studies ($I^2 = 41.8\%$, $p = 0.143$), noting that, the heterogeneity of the studies was low. However, the funnel plot showed asymmetry and publication bias (Egger's t-test = 7.59 $^*p = 0.005$) (Fig. 3, panel A and B).



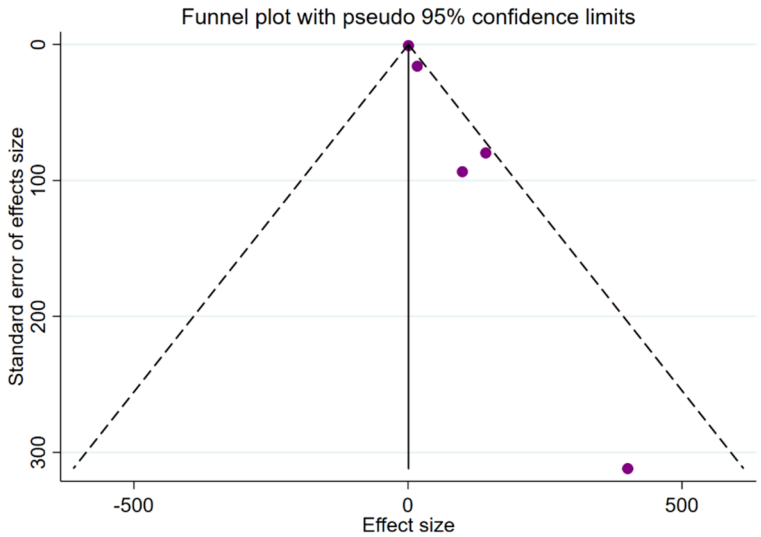


Fig. 3 Forest plot comparing the IL-1β levels of A metal-free ceramic group vs metal–ceramic group. B Funnel plot check the publication bias

Discussion

We performed a comprehensive review of the literature to know and study the different molecules (inflammatory cytokines, enzymes, and neuropeptides) present in GCF of teeth rehabilitated with M/C and A-Cs prostheses. Of the 14 studies included, half were cross-sectional studies and half were longitudinal studies. In addition, the studies were conducted in 11 different countries around the world. The most important findings, despite the great heterogeneity found, were: a similar study population (*n*) in both types of restorations (M/C vs A-Cs), and that in most of the studies IL-1β, IL-6, and TNF-α were analyzed, which are representative cytokines of the inflammatory and destructive process that occurs in periodontal disease. Therefore, it reflects the state of health and/or diseases of the tissues that support the teeth with DFP. Quantitative analysis was only possible with IL-1β, since there was not enough information available to compare the levels of other cytokines. However, although the results of the meta-analysis were not significant, the qualitative analysis revealed a trend toward increased levels of inflammatory mediators in GCF of teeth that had been restored with M/C prostheses compared with those that had been restored with A-Cs prostheses.

FDP will always trend to accumulate more dento-bacterial plaque (DBP) than normal, favoring polymicrobial dysbiosis compared to natural teeth, however, in recent years, the possibility of constructing devices that decrease or inhibit these effects has been extensively investigated [16]. Therefore, at least two aspects should be considered to improve this situation. On the one hand, preparation of supragingival margins will almost always offer better oral hygiene compared with juxta- and subgingival margins, which will benefit the patient's periodontal condition [43]. The other aspect is the marginal and internal fit, defined as the space between the prosthetic margins and the tooth preparation finish line. In healthy conditions, it is accepted that this space should be < 120 µm. However, when there is a greater marginal discrepancy (> 120 µm), this favors greater bacterial retention, increased GCF volume, generation of microleakage, hypersensitivity, recurrent dental caries, endodontic infection, and periodontal pathology, which severely affects the patient's oral health [44]. It has been clinically demonstrated that FDP A-Cs built by using CAD/CAM systems show better marginal and internal adaptation compared to M/C prostheses fabricated by this same system and also by CM, which decreases bacterial accumulation and thus the inflammatory process, contributing to the maintenance and restoration of periodontal condition and oral hygiene [45, 46]. Also, the microbial composition of the GCF and subgingival plaque in this type of restoration has been characterized by microbiological cultures, and using molecular biology techniques such as the Checkerboard technique for DNA–DNA hybridization and 16S rRNA gene sequencing. Thus, a higher prevalence of periodontopathogenic species has been found in M/C FDP constructed by CM compared to A-Cs FDP constructed by CAD/CAM technology. In addition, microbiological counts and in general, the composition of periodontal microbiota has been restored faster in teeth restored with A-Cs and CAD/CAM FDP compared to M/C FDP, suggesting a higher biocompatibility [18–20, 33]. These findings give us a clearer idea about the immunoinflammatory processes that might be occurring in periodontal tissues. Bacterial products (LPS) activate host cell pattern recognition receptors and initiate the inflammatory process. Therefore, we believe that M/C FDP increase the levels of different inflammatory mediators compared to A-Cs FDP, which would cause greater tissue damage. In fact, most of the studies published in the current literature show this trend [20, 25–37].

In this systematic review, we found that most of the studies analyzed the levels of IL-1β, IL-6, and TNF-α in GCF of teeth restored with FDP. These cytokines play an important role in the immunopathogenesis of periodontal disease [47]. Upon polymicrobial challenge, sulcus and gingival tissue cells fight pathogens by different mechanisms such as phagocytosis, release of extracellular traps, complement activation, chemotaxis of other leukocytes, and production of proinflammatory cytokines (IL-1, IL-6, and TNF-α) [48]. These cytokines serve different functions such as promotion of myeloid cells, differentiation of Th17 and Tfh cells, suppression of osteoblastic activity and induction of osteoclastic activity by upregulation of nuclear factor kappa B ligand (RANKL), leading to the process of bone resorption [49]. In fact, IL-1β, IL6, and TNF-α are currently considered as potential inflammatory biomarkers in the development and progression of gingivitis, periodontitis, and peri-implantitis [50–52]. In relation to FDP, a certain tendency has been demonstrated in relation to increased levels of these proinflammatory cytokines in teeth with M/C prostheses compared to A-Cs prostheses [20, 27, 29, 32, 37]. This is in agreement with another study, which found an increase in the levels of different proinflammatory cytokines and bone metabolism mediator proteins in peri-implant crevicular fluid adjacent to titanium and zirconia transmucosal abutments [53]. Therefore, they could be good indicators of the inflammatory and destructive process occurring around the tissues supporting a FDP.

Limitations and future

Analyzing the weaknesses and strengths of each of the studies included in the present review, the following clinical aspects should be taken into account to improve the methodological design of future studies and to be able to issue more concise conclusions. Therefore, it is recommended that:

1. Enlarge the sample size (*n*) uniformly: this will allow greater statistical power to be obtained in all tests performed.
2. Asymmetry funnel plot and publication bias: it is possible that the moderate heterogeneity is due to variations in subject populations among the selected studies and confounding factors. A meta-regression analysis could probably better explain this event, although it was not performed due to limited data availability.
3. Periodontal status: the levels of the parameters detected in the GCF vary according to periodontal health; gingivitis and/or periodontitis, and their severity. Researchers could improve their study designs and make comparisons according to the periodontal condition of the rehabilitated teeth.
4. Compare multiple prosthetic biomaterials: this will allow to obtain a clearer idea if the presence of any

type of alloy could be clinically causing a greater deterioration of periodontal tissues compared to metal-free ceramics (monolithic zirconia, lithium disilicate, feldspar-based porcelain). However, according to the available scientific evidence, the latter materials are preferred because they are more biocompatible.

5. Choose a manufacturing system: FDP should be built through both methods (CAD/CAM-CM). This will allow to evaluate the marginal and internal fit of the prosthetic devices. However, according to available studies, FDP fabricated by CAD/CAM technology are recommended.
6. Choose a type of tooth finish: this will allow comparison of the different prosthetic margins (supra, juxta, and subgingival). However, evidence suggests that supragingival margins are ideal for oral hygiene maintenance.
7. Choose a type of dental luting cement (DLC): ideally, one type of DLC should be used for each of the prosthetic restorations. However, to control any risk of bias in the research results, it is recommended to use one DLC suitable for both types of restorations.
8. Describe clinical periodontal parameters: this will allow a clinical evaluation of the periodontal condition before, during and after the prosthetic treatment.
9. Determine the type of inflammatory mediator and immunoassay technique: future studies should compare the levels of other molecules involved in the pathogenesis of periodontal disease, such as the IL-23/IL-17 axis and the OPG/RANK/RANKL axis, etc. In addition, the ELISA technique is still the method most commonly used by researchers for the evaluation of these molecules in GCF.

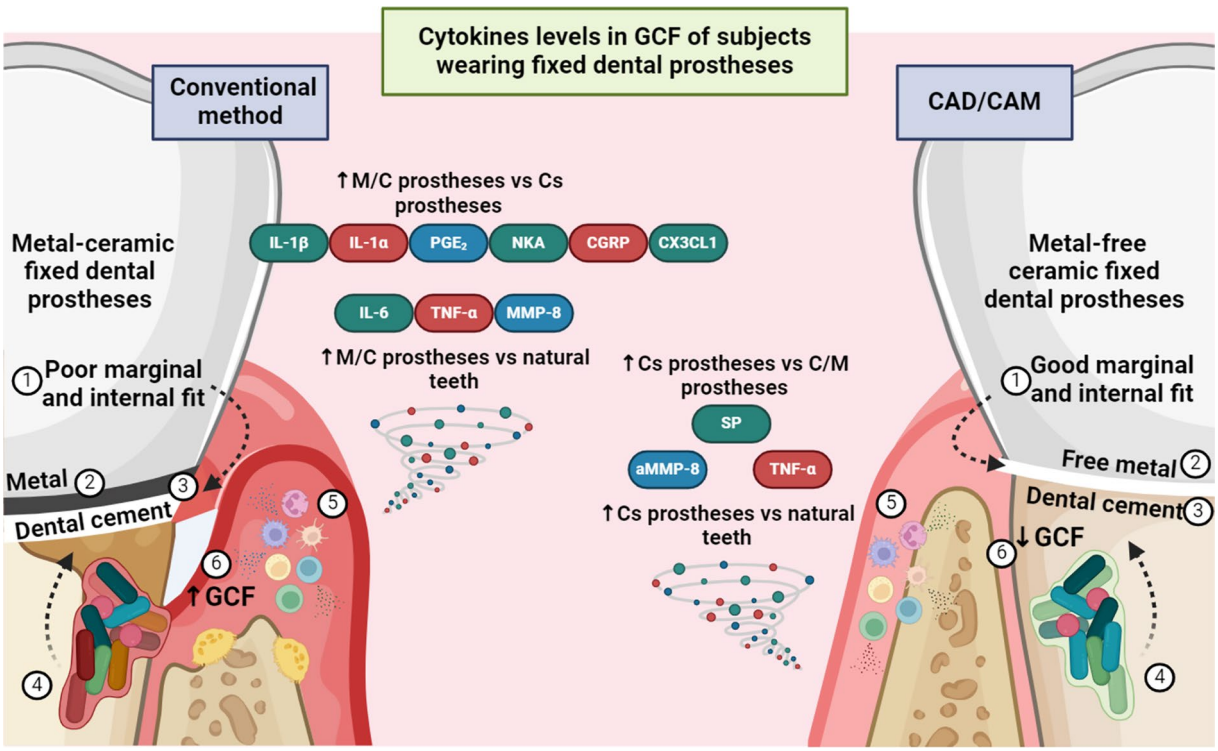


Fig. 4 Influence of metal–ceramic vs metal-free ceramic fixed dental prostheses with periodontal status. (1) Ceramic prostheses fabricated by CAD/CAM technology offer a better marginal and internal fit compared to metal–ceramic prostheses fabricated by conventional method. (2) Prosthetic biomaterials can affect biofilm formation by their chemical composition and physical characteristics. (3) Poor cementation technique also leads to the formation of biofilms that adhere between the margin of the prosthetic restoration and the tooth surface. (4) Metal-free ceramic prostheses show better results in qualitative and quantitative composition of microflora in the gingival sulcus compared to metal–ceramic prostheses, where a higher prevalence of recognized periodontopathogenic species has been observed. (5) Ceramic prostheses present a decrease in the levels of inflammatory markers compared with metal–ceramic prostheses, causing less damage to the periodontium. (6) Metal–ceramic prostheses increase gingival crevicular fluid levels compared to metal-free ceramic prostheses *CAD/CAM* computer-aided design/computer-aided manufacturing, *GCF* gingival crevicular fluid, *M/C* metal–ceramic prostheses, *A-Cs* ceramic prostheses, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *TNF*-α tumor necrosis factor alpha, *IL-1α* interleukin 1 alpha, *CX3CL1* fractalkine, PGE_2 prostaglandin E2, *aMMP-8* active matrix metalloproteinase, *MMP-8* matrix metalloproteinase 8, *SP* substance P, *NKA* neurokinin A, *CGRP* calcitonin-gene related peptide. Created with www.biorender.com (Accessed on 28 June 2023)

10. Plan follow-up studies evaluating changes in the levels of different inflammatory mediators and periodontal condition before and after prosthetic treatment.

Conclusions

Based on the analysis of the 14 studies included in the present review, we can conclude the following:

- In general, teeth with FDP will always accumulate more DBP compared to natural teeth. This will lead to increased levels of different inflammatory mediators and thus more damage to the periodontium.
- The most prevalent cytokine in GCF of teeth restored with FDP was IL-1β followed by IL-6 and TNF-α.
- The most common immunoassay method for the determination of inflammatory mediator levels was ELISA.
- A trend toward increased levels of IL-1β, IL-1α, PGE_2, NKA, CGRP, and CX3CL1 was found in GCF of M/C denture teeth compared to A-Cs denture teeth.
- On the other hand, a trend toward increased SP levels was found in teeth with A-Cs prostheses compared to teeth with M/C prostheses (Fig. 4).

Abbreviations

IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-1β	Interleukin-1 beta
IL-8	Interleukin-8
IL-1β	Interleukin-1 beta
MMP-2	Matrix metalloprotease 2
CX3CL1	C-X3-C motif ligand 1
IL-1ra	Interleukin 1 receptor antagonist
IL-1β	Interleukin-1 beta
IL-4	Interleukin-4
IgG	Immunoglobulin G
aMMP-8	Active matrix metalloprotease 8
MMP-8	Matrix metalloprotease 8
MMP-9	Matrix metalloprotease 9
TIMP-1	Tissue inhibitor of metalloproteinase-1
TIMP-2	Tissue inhibitor of metalloproteinase-1
IL-2	Interleukin-2
SP	Substance P
NKA	Neurokinin A
GCRP	Calcitonin-gene related peptide

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None

Author contributions

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

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Informed consent

Not applicable.

Competing interests

The authors declare no competing interests.

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