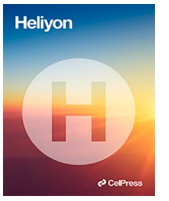
Heliyon 10 (2024) e23782

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Salivary and gingival crevicular fluid biomarkers of periodontal health and/or obesity among children and adolescents: A systematic review and meta-analysis

Qianyi Deng [a,b,c], Hai Ming Wong [a], Simin Peng [a,*]

[a] Paediatric Dentistry and Orthodontics, Faculty of Dentistry, The University of Hong Kong, Hong Kong SAR, China
[b] Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, Guangzhou, China
[c] Guangdong Provincial Key Laboratory of Stomatology, Guangzhou, China

ARTICLE INFO

Keywords:
Saliva
Gingival crevicular fluid
Obesity
Biomarker
Systematic review
Meta-analysis

ABSTRACT

Objectives: To investigate the association of salivary and gingival crevicular fluid (GCF) biomarkers with periodontal status and obesity in children and adolescents.
Data/sources: A literature search up to July 2023 was conducted through PubMed, Web of Science, Embase, ProQuest Medical Database, ProQuest SciTech Premium Collection, and the Cochrane Library. Observational studies comparing salivary and GCF biomarkers in children and adolescents with compromised periodontal status and/or obesity were included for data extraction. A meta-analysis was performed to estimate the overall standardised mean difference.
Study selection: Fifteen observational studies met the inclusion criteria and were included in this systematic review. Meta-analysis was only applicable in synthesising the dyadic relationship between GCF biomarkers and obesity. The results demonstrated that children and adolescents with obesity had significantly higher GCF levels of tumour necrosis factor-alpha (SMD:0.56; 95% CI:0.07, 1.04), adiponectin (SMD:0.33; 95% CI:0.06, 0.60), leptin (SMD:0.52; 95% CI:0.15, 0.90), and interleukin-1 beta (SMD:0.71; 95% CI:0.44, 0.99) than those with normal weight.
Conclusion: To date, no study has well addressed the triadic association between salivary or GCF biomarkers, periodontal status, and obesity among children and adolescents. Further in-depth, high-quality studies are required to investigate these associations.
Clinical significance: Periodontal disease and obesity are growing public health crises worldwide. Their relationship has been intensively studied. Investigating the salivary or GCF biomarkers alterations could help better understand the relationship between periodontal disease and obesity, which would assist in tailoring future oral health promotion programs.

1. Introduction

Periodontal disease, a chronic inflammation of the tooth-supporting tissues caused by the host's immune response to bacteria, is widespread worldwide. According to the recent World Health Organization (WHO) Global Oral Health Status Report, severe periodontal disease is a public health concern, with a significant estimated increase in prevalence by 24% from 1990 to 2019 [1].

* Corresponding author. Paediatric Dentistry and Orthodontics, Faculty of Dentistry, The University of Hong Kong, 34 Hospital Road, Sai Ying Pun, Hong Kong SAR, China.
E-mail address: pengsm@hku.hk (S. Peng).

https://doi.org/10.1016/j.heliyon.2023.e23782
Received 12 May 2023; Received in revised form 30 November 2023; Accepted 13 December 2023
Available online 18 December 2023

Periodontal health in childhood and adolescence lays the foundation for periodontal health in adulthood [2]. Gingivitis is the predominant form of periodontal disease in children and adolescents, and its prevention is regarded as the initial step in preventing future periodontitis in susceptible individuals [3,4].

With its increasing global prevalence, obesity in children and adolescents has been identified as a rising public health concern [5]. Adipose tissues secrete numerous inflammatory cytokines or hormones, such as tumour necrosis factor-alpha (TNF-α), resistin, adiponectin, leptin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and adipsin, leading to low-grade chronic systemic inflammation [6], which in turn, contributes to the initiation and progression of periodontal disease [7]. As obesity and periodontal disease are both inflammatory disorders and share similar inflammatory cytokines or hormones, their association has been studied for years.

Two recent systematic reviews that examined this association in adult studies reported a positive association between obesity and periodontal disease (including gingival inflammation [8] and periodontitis [9]). Similarly, a systematic review and meta-analysis that investigated the association in children and adolescents demonstrated that obesity was associated with several clinical parameters of periodontal disease, including the visible plaque index, bleeding on probing, subgingival calculus, and probing depth [10]. However, the underlying mechanisms are not fully understood.

Saliva is a gatekeeper of the oral cavity and is considered an essential immune defence component against oral infections [11]. Gingival crevicular fluid (GCF), an exudate from the circulation, contains the necessary molecular and cellular immune response components for defending against tissue invasions by subgingival bacteria [12]. Some pro-inflammatory biomarkers, such as vastatin and interleukin-1 beta (IL-1β) in the saliva and GCF, are elevated in patients with both obesity and periodontitis [13,14]. As the collection of both saliva and GCF is non-invasive, investigation of the components in saliva and/or GCF has become increasingly popular in risk prediction, diagnosis, and prognosis determination of some diseases, such as periodontitis [15,16]. Examining the salivary or GCF biomarker alterations allows a better understanding of the relationship between periodontal disease and obesity. One meta-analysis assessed the associations between salivary and GCF inflammatory biomarkers, periodontitis, and obesity in adults and demonstrated that GCF resistin levels were significantly higher in periodontally compromised adults with obesity than in those with normal weight [17]. To date, no systematic reviews or meta-analyses have evaluated these relationships specifically in children and adolescents. Investigating the salivary or GCF biomarkers alterations could provide valuable information for tailoring future oral health promotion programs for children and adolescents. Thus, this systematic review and meta-analysis aimed to investigate the association of salivary and GCF biomarkers, periodontal status, and obesity in children and adolescents.

2. Methods

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO/; registration number: CRD42022357594). This review was undertaken following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [18] guidelines and reported following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [19]. The research question was developed using the Population, Exposure, Comparison, Outcomes, and Study design (PECOS) framework (Table S1).

2.1. Search strategy

Six electronic databases, namely, PubMed, Web of Science, Embase, ProQuest Medical Database, ProQuest SciTech Premium Collection, and the Cochrane Library, were searched from inception to July 22nd, 2023. The controlled vocabulary thesauruses including Medical Subject Headings (MeSH), Embase subject headings (Emtree), and/or keywords on saliva, gingival crevicular fluid, obesity, and periodontal health were used. A librarian was consulted on the appropriateness and comprehensiveness of the search terms. Table S2 shows the complete search strategies for each database.

2.2. Study selection

Study selection was conducted by two independent reviewers (Q.D. and S.P.), with a third reviewer (H. M. W.) consulted in cases of any disagreement. Studies that met the following criteria were included: 1) Studies on children and adolescents (aged 2–18 years) free of any systemic diseases such as diabetes mellitus, hypertension, rheumatoid arthritis, and metabolic syndrome; 2) Original studies with an observational design (including cross-sectional, case-control, and cohort studies); 3) Studies that compared biomarkers in saliva or gingival crevicular fluid (GCF) among children and adolescents with compromised periodontal status (including periodontitis, gingivitis, and poor oral hygiene) and/or obesity; 4) Studies that assessed adiposity based on anthropometric measurements, such as body mass index (BMI), body fat percentage, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR); 5) Studies that assessed periodontal status based on clinical measurements, such as visible plaque index (VPI), bleeding on probing (BOP), gingival index (GI), probing pocket depth (PPD), and community periodontal index (CPI), were included. The exclusion criteria were as follows: (1) Not original articles, including narrative review articles, case reports, editorials, and meeting abstracts, or preprints that has not been peer reviewed. (2) Laboratory experimental studies using animal or cellular models. (3) Full texts were unavailable. (4) Articles were in a language other than English and could not be translated. (5) Studies that included subjects with smoking habits or undergoing orthodontic treatment. (6) Studies of highly selective populations without a control group. (7) Studies lacking in key information, such as sample size. The inter-reader agreement was assessed by κ statistics.

2.3. Data extraction

A data extraction sheet was developed to record the extracted data including the first author's surname, publication year, study design, participant demographics, sample size, methodology, and effect measures. A separate data extraction sheet was used for each independent reviewer (Q.D. and S.P.), which were subsequently combined, and then checked by H.M.W.

2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies [20] was adopted to assess the risk of bias in the included studies with a cross-sectional design or prospective cohort studies reporting data of interest only at baseline. It evaluates study quality under three domains (selection, comparability, and outcome), with a maximum of 10 stars. In contrast, the NOS for cohort studies, consisting of three domains (similar to the NOS adapted for cross-sectional studies) graded with a maximum of nine stars, was used to assess the included prospective cohort studies reporting data of interest after follow-up [21]. Studies with 1–3 stars were considered low quality, 4–6 stars of medium quality, and ≥7 stars of high quality [22]. The risk of bias was measured according to eight criteria related to the NOS domains, as specified by Strieder et al. [23]. Furthermore, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of the evidence [24].

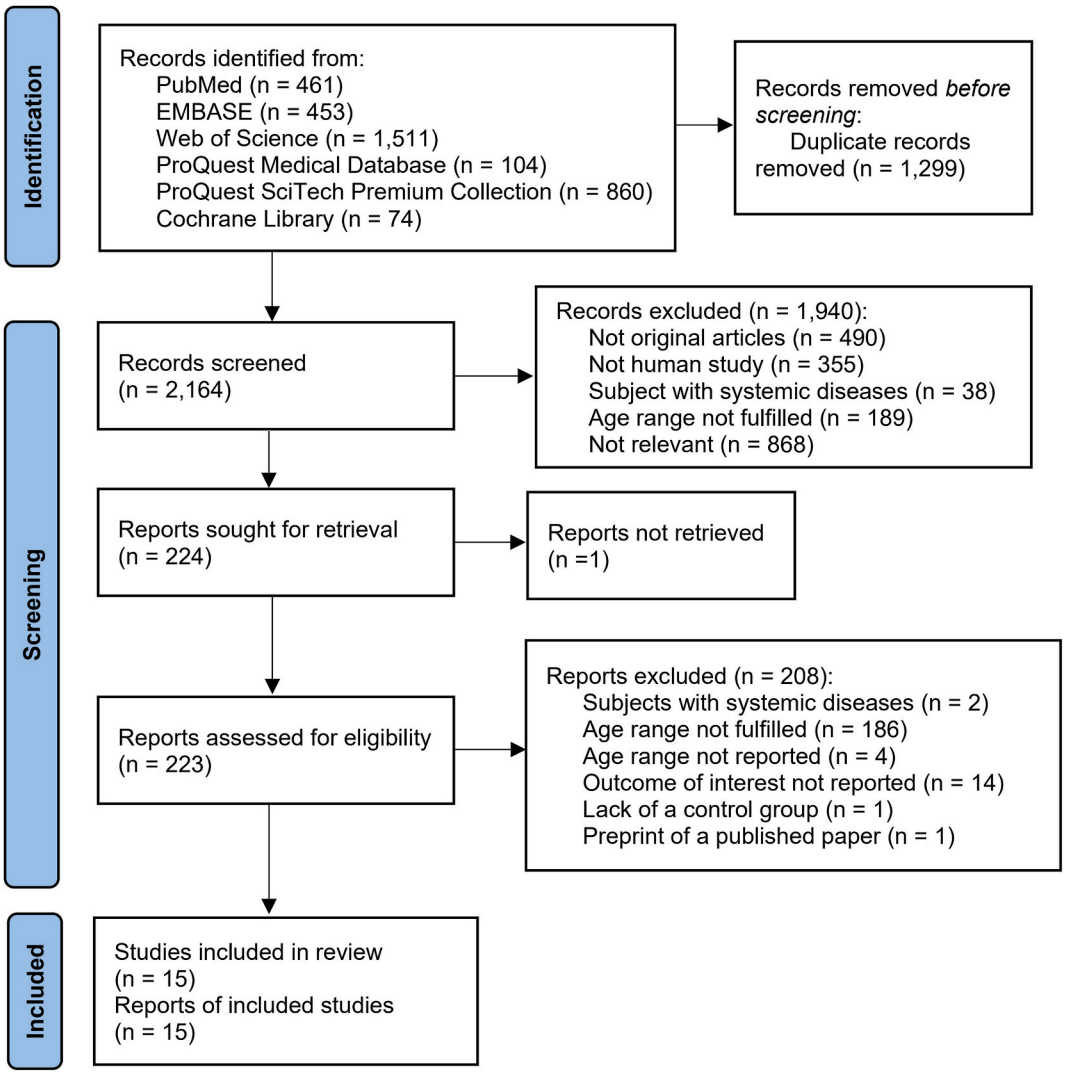


Fig. 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram of the study selection process.

Table 1
Characteristics of studies examining salivary or GCF biomarkers and their correlation with periodontal status and/or obesity.

Reference	Study country	Subjects (*n*, sex, age)	Sample type	Anthropometric standards	Periodontal status measurements	Obesity and periodontal status	Salivary or GCF profile studied with key findings	QA
Alghamdi 2022 [28]	Saudi Arabia	95 (9 OB, 6 OW, 23 NW, 57 underweight), sex distribution not mentioned, aged 5–14 y	saliva	BMI (kg/m^2): Underweight (<18), NW (18.5–24.9), OW (25–29.9), OB (≥30)	PI (Quigley–Hein), mSBI	The PI and mSBI scores were high among the normal and overweight BMI categories. The BMI score was positively correlated with PI, mSBI.	The salivary 1,5-AG levels were highest among the obese participants. The BMI score was positively correlated with salivary 1,5-AG levels. However, salivary 1,5-AG was not correlated with PI or mSBI.	6/10
Soares Bonato 2022 [40]	Brazil	60 (30 OB, 30 NW), 27 M/33 F, aged 13–18 y	GCF	BMI-for-age (5–19 years) (WHO, 2007)	PPD, BOP, presence of calculus	OB vs. NW: % sites with PPD 4–5 mm ↑, % BOP ↑, % teeth with calculus ∼	OB vs. NW: GCF IL-1β ↑, GCF leptin ∼, GCF TNF-α ∼	7/10
Araujo 2020 [33]	Brazil	248 (44 OB, 62 OW, 142 NW), 129 M/119 F, aged 14–17 y	UWS	BMI-for-age (5–19 years) (WHO, 2007)	Spontaneous gingival bleeding, gingival bleeding when brushing teeth, gingivitis (self-report and clinical), number of sextants with gingival bleeding	There was no difference in frequency of gingival bleeding (males: $p = 0.110$; females: $p = 0.702$), and in the frequency of gingivitis (males: $p = 0.078$; females: $p = 0.495$) between groups classified according to BMI.	% *P. gingivalis* in saliva did not vary according to group (OB, OW, NW) or sex.	8/10
Goodson 2020 [30]	USA	68 (15 OG, 7 OH, 19 NWG, 27 NWH), 43 M/25 F, aged 7–15 y	UWS	Criterial based on WC by the international diabetes foundation	Gingivitis: % red gingival sites (mesial, buccal, distal, and lingual of each tooth): ≥10.2% (the median value)	OB vs. NW: % of red gingival sites ↑OG vs. NWG% of red gingival sites ↑ OH vs. NWH:% of red gingival sites ∼	OG vs. NWG, OH: salivary hydroxyproline ↑	6/10
Zalewska 2020 [37]	Poland	80 (20 OB, 20 OW, 40 NW), 40 M/40 F, aged 11–18 y	UWS, SWS	BMI-for-age (5–19 years) (WHO, 2007)	GI	OB or OW vs. NW: GI ∼	OB vs. NW: peroxidase in SWS ↑, catalase in UWS and SWS ↑, uric acid in UWS and SWS ↑, peroxidase in UWS ∼; OW vs. NW: peroxidase in SWS ↑, catalase in SWS ↑, uric acid in SWS ↑, peroxidase in UWS ∼, catalase in UWS ∼	7/10
Perez 2019 [36]	Brazil	91 (41 OW/OB, 50 NW), 38 M/53 F, aged 6–12 y	UWS	BMI-for-age (5–19 years) (WHO, 2007)	OHI–S, GI	OW/OB vs. NW: OHI–S ∼, GI ∼	OW/OB vs. NW: salivary sIgA ↑	8/10
Doğusal 2018 [29]	Turkey	130 (33 OG, 32 OH, 32 NWG, 33 NWH), 78 M/52 F, aged 8–12 y	UWS, GCF	BMI-for-age (5–19 years) (WHO, 2007)	PPD, GI, and PI (Silness & Löe, 1964) gingivitis: GI ≥ 1, PPD ≤3 mm at all measured sites for 12 permanent teeth; periodontally healthy: GI < 1, PPD <3 mm for these teeth.	OB vs. NW: PPD ∼, GI ∼, PI ∼ OG, NWG vs. OH, NWH: GI ↑, PI ↑, PPD ∼	OB vs. NW: GCF volume ∼, salivary resistin ∼, GCF resistin ∼, salivary TNF-α ∼, GCF TNF-α ∼ OG, NWG vs. OH, NWH: GCF volume ↑, salivary resistin ↑, GCF resistin ↑, salivary TNF-α ∼, GCF TNF-α ∼ GCF resistin levels was positively correlated with PI, GI, and GCF TNF-α levels. ($r = 0.396$, 0.359, and 0.314, respectively). Salivary resistin and TNF-α levels were positively correlated ($r = 0.567$).	8/10
Janem 2017 [35]	USA	33 (14 OB, 19 NW), 19 M/14 F, aged 10–19 y	UWS	US BMI-for-age percentile growth chart (2–20 years) (CDC, 2000)	GI, PPD	OB vs. NW: GI ↑, average PPD ∼, deepest pocked PPD ∼, number of pockets ≥4 mm ∼	OB vs. NW: salivary CRP ∼, salivary IL-1β ∼, salivary nitric oxide ∼, salivary glucose ∼	6/10
Saloom 2017 [41]	Switzerland	55 (27 OB, 28 NW), 27 M/28 F, aged 12–18 y	GCF	OB: BMI-centile >98, NW: BMI-centile 2-91	PI (Silness & Löe, 1964), GI	OB vs. NW (baseline): PI ∼, GI ∼	OB vs. NW (baseline): GCF leptin ↑, GCF resistin ↑, GCF myeloperoxidase ↑, GCF RANKL ↑, GCF TIMP-1 ↑, GCF MMP-8 ↑,	9/10

(*continued on next page*)

Table 1 (*continued*)

Reference	Study country	Subjects (*n*, sex, age)	Sample type	Anthropometric standards	Periodontal status measurements	Obesity and periodontal status	Salivary or GCF profile studied with key findings	QA
							GCF MMP-8/TIMP-1 ~, GCF MMP-9 ~, GCF MMP-9/TIMP-1 ↓, GCF adiponectin ~, GCF CRP ~	
Alqaderi 2016 [42]	Kuwait	5456, 2103 M/3353 F, aged 10 y	UWS (fasting)	WC	GI	Central obesity was not a significant predictor of gingivitis ($P > 0.05$)	Higher salivary glucose level was a significant predictor of gingivitis ($P < 0.05$)	8/9
Zhao 2016 [39]	China	53 (30 OB, 23 NW), sex distribution not reported, aged 6–14 y	GCF	BMI standards for Chinese school-age children	SBI, PI (Quigley–Hein), BOP %, PPD	OB vs. NW: SBI ~, PI ~, BOP% ~, PPD ~	OB vs. NW: GCF TNF-α ↑, GCF sICAM-1 ~	6/10
Fadel 2014 [34]	Sweden	55 (27 OB, 28 NW), 29 M/26 F, aged 13–18 y	UWS, SWS, and GCF	BMI according to IOTF criteria	marginal gingival bleeding, modified plaque control record, PPD, BOP	OB vs. NW: marginal gingival bleeding ↑, BOP ↑, plaque harbouring sites ~, PPD ~	OB vs. NW: salivary sIgA ↑, GCF volume ~, GCF IL-1β ~, GCF IL-6 ~, GCF IL-8 ~, GCF TNF-α ~, GCF leptin ~, GCF resistin ~, GCF PAI-1 ~, GCF adiponectin ~, GCF adipsin ~	9/10
Zeigler 2012 [38]	Sweden	87 (29 OB, 58 NW), 54 M/33 F, aged 14.5 ± 1.7 y	GCF	OB: ISO-BMI >30, NW: ISO-BMI <25	VPI, BOP, supragingival calculus, subgingival calculus, incipient alveolar bone loss	OB vs. NW: % subjects with VPI >25% ↑, % subjects with BOP >25% ~, presence of supragingival calculus ~, presence of subgingival calculus ~	OB vs. NW: GCF sum of bacterial cells ↑, *P. gingivalis* ↑, *Aggregatibacter actinomycetemcomitans* ↑, *Fusobacterium nucleatum* ↑, *Tannerella forsythia* ↑, *Prevotella intermedia* ↑, *Fusobacterium nucleatum* ↑	7/10
Modéer 2011 [32]	Sweden	104 (52 OB, 52 NW), 58 M/46 F, aged 10.9–17.9 y	GCF	OB: ISO-BMI >30, NW: ISO-BMI <25	VPI%, BOP%, PPD, supragingival calculus, subgingival calculus, incipient alveolar bone loss	OB vs. NW: % subjects with VPI >25% ↑, % subjects with BOP >25% ↑, % subjects with pocket depth >4 mm ↑, presence of supragingival calculus ~, presence of subgingival calculus ~, incipient alveolar bone loss ~ Multiple logistic regression analysis: BMI-SDS was significantly associated with the occurrence of pathological periodontal pockets (>4 mm) after adjusting for BOP (>25%) and BOP (>25%) (OR = 1.87; 95% CI: 1.08–3.26).	OB vs. NW: GCF IL-1β ↑, GCF IL-8 ↑, GCF volume ~, GCF adiponectin ~, GCF PAI-1 ~, GCF TNF-α ~ Bivariate logistic regression analysis with the occurrence of pathological periodontal pocket (>4 mm) as dependent variable: GCF volume, adiponectin, PAI-1, IL-1β, IL-8, TNF-α ~	8/10
Khosravi 2009 [31]	Canada	178 (40 OB, 31 OW, 107 NW), 102 M/76 F, aged 8–10 y	GCF	US BMI-for-age percentile growth chart (2–20 years) (CDC, 2000)	CPI: presence or absence of visible plaque, bleeding on probing, calculus	–	In boys, OW/OB vs. NW: GCF TNF-α ↑ (β = 37.1) In girls, OW/OB vs. NW: GCF TNF-α ~ In both boys and girls, high vs. low levels of dental plaque: GCF TNF-α level ~ In both boys and girls, high vs. low levels of gingival bleeding: GCF TNF-α level ~	9/10

Abbreviations: 1,5- AG, 1,5- anhydroglucitol; BMI, body mass index; BOP, bleeding on probing; CPI, community periodontal index; CRP, C-reactive protein; F, female; GCF, gingival crevicular fluid; GI, gingival index; IL, interleukin; IOTF, International Obesity Taskforce; M, male; MMP, matrix metalloproteinase; mSBI, modified sulcular bleeding index; NW, normal-weight group; NWG, group of participants with normal weight and gingivitis; NWH, group of participants with normal weight and healthy periodontium; OB, obese group; OG, group of participants with obesity and gingivitis; OH, group of participants with obesity and healthy periodontium; OHI–S, oral hygiene index-simplified; OW, overweight group; *P. gingivalis*, *Porphyromonas gingivalis*; PI, plaque index; PPD, probing pocket depth; RANKL, receptor activator of nuclear factor kappa-B ligand; SBI, sulcular bleeding index; sICAM-1, soluble intercellular adhesion molecule-1; SWS, stimulated whole saliva; TIMP-1, tissue inhibitor of metalloproteinase-1; TNF-α, tumour necrosis factor-alpha; UWS, unstimulated whole saliva; VPI, visible plaque index; WC, waist circumference.
↑ significantly higher; ↓ significantly lower; ~ no significant difference.

2.5. Data synthesis and statistical analysis

Standardised mean differences (SMDs) of the salivary and/or GCF biomarkers among different groups were pooled and synthesised using a random-effects model. In some studies, the sample means and standard deviations were not reported. Hence, these were estimated from the sample size, median, range, and/or interquartile range before data synthesis using the method proposed by Wan et al. [25]. Cochran's Q test and Higgins I^2 statistic were used for testing heterogeneity between studies. In addition, Galbraith's radial plot was employed to identify outliers as potential major sources of heterogeneity [26]. Sensitivity analyses were carried out to explore the influence of each study on the overall estimates by excluding each study individually [27]. Data analysis was performed using Review Manager software RevMan Version 5.4 (The Cochrane Collaboration, Copenhagen). A *P*-value of <0.05 was considered statistically significant. STATA 17.0 (StataCorp, College Station, TX) was used to generate the Galbraith's radial plots.

3. Results

3.1. Literature search

A total of 3463 records were identified, 2164 of which were screened by title and abstract after removing duplicates. Of these, 224 full-text reports were retrieved for eligibility assessment. Finally, 15 studies were included in this systematic review (Fig. 1). The inter-reader κ agreement was 0.87 ± 0.07 (mean $\pm$ standard error).

3.2. Study characteristics

The review included 12 cross-sectional studies [28–39] and three prospective cohort studies [40–42]. The included studies were conducted in 10 countries: Brazil [33,36,40], Sweden [32,34,38], the United States [30,35], Canada [31], China [39], Kuwait [42], Poland [37], Saudi Arabia [28], Switzerland [41], and Turkey [29]. Except for two studies that did not provide information on the sex of the participants [28,39], all remaining studies included children and adolescents of both sexes. Two studies assessed both saliva and GCF biomarkers [29,34], seven studies detected biomarkers only in saliva [28,30,33,35–37,42], and six studies evaluated biomarkers only in GCF [31,32,38–41]. Among the three prospective cohort studies, two studies reported data of interest only at baseline [40,41].

Five studies focused on the relationship between obesity, periodontal status, and salivary or GCF biomarkers [28–32]. Most of the remaining studies focused on the dyadic relationships between salivary or GCF biomarkers and obesity [33–41,43], except for one study which focused on salivary biomarkers and gingivitis [42]. Table 1 summarises the characteristics of the included studies, and Table 2 provides an overview of the salivary and GCF biomarkers studied.

3.3. Quality assessment

As only baseline data were extracted from two of the included cohort studies [40,41], NOS adapted for cross-sectional studies was used for the quality assessment of these two studies to make the results comparable. According to the NOS, the included studies obtained 6 to 9 stars (Tables S3 and S4). More than two-thirds of the included studies ($n = 11$) were categorised as high quality [29, 31–34,36–38,40–42]. Four studies were categorised as medium quality [28,30,35,39]. Inter-reader κ agreement was 0.82 ± 0.12. A summary of the risk-of-bias assessment is presented in Fig. S1. The GRADE assessment demonstrated that the quality of the body of evidence for each outcome was rated as "very low" (Table S5).

3.4. Qualitative and quantitative analyses

Among the five studies [28–32] that focused on the association between obesity, periodontal status, and salivary or GCF biomarkers, only two studies categorised participants into four subgroups based on their periodontal and adiposity status, namely, subjects with obesity (OB) and gingivitis (G) (OB + G group); subjects with obesity and healthy periodontium (H) (OB + H group); subjects with normal weight (NW) and gingivitis (NW + G group); subjects with normal weight and healthy periodontium (NW + H group) [29,30]. However, these two studies used different biomarkers with different statistical analyses to address the triadic relationship of obesity, periodontal status, and salivary or GCF biomarkers. Two other studies only categorised participants according to adiposity status and investigated the dyadic relationship between salivary or GCF biomarkers and periodontal status using correlation coefficients or binary logistic regression [28,32]. Another study investigated the dyadic relationship by separately comparing the GCF biomarker levels in participants with high or low levels of dental plaque or gingival bleeding [31]. Thus, a quantitative synthesis of the findings from these studies was not applicable.

In addition to the five studies that focused on all three aspects, one more study [42] evaluated the dyadic relationships between salivary or GCF biomarkers and periodontal status. Of these six studies, three studies compared the levels of salivary or GCF biomarkers in different groups of participants with different periodontal status using the *t*-test or Kruskal–Wallis test [29–31], while the other three studies employed the Spearman rank correlation coefficient [28], bivariate logistic regression [32], or multilevel linear regression [42] to address the dyadic relationship between salivary or GCF biomarkers and periodontal status. Hence, quantitative synthesis of the changes in saliva and/or biomarkers between different periodontal status was not feasible.

Almost all the included studies ($n = 14$) classified participants into different groups according to their adiposity status. Of these, most studies classified the participants into obese/overweight and normal-weight groups using the BMI. Two other studies used WC to

define central obesity [30,42]. In contrast, WHR or WHtR was not employed by any of the included studies. Considering the variations among the included studies, a meta-analysis was only applicable to the dyadic relationship between GCF biomarkers and obesity.

3.4.1. Adipokines and other inflammatory markers

3.4.1.1. Tumour necrosis factor-alpha (TNF-α). The level of TNF-α in the GCF was measured in six studies [29,31,32,34,39,40], while among these, only one study [29] also evaluated salivary TNF-α level.

Among these six studies, only one focused on the triadic relationship by classifying participants into four groups according to their adiposity and periodontal status. This study reported no significant difference in salivary or GCF TNF-α levels among the four groups [29]. Two studies examined the dyadic association between periodontal status and the GCF TNF-α level but did not report statistically significant results [31,32]. One study demonstrated that the GCF TNF-α level was not significantly associated with the presence of pathological periodontal pockets (PPD >4 mm) via bivariate logistic regression [32]; the other study reported no significant difference in the GCF TNF-α level between children with high and low levels of dental plaque or between those with high and low levels of gingival bleeding [31].

In one study, the salivary TNF-α level between children with obesity and those with normal weight was similar [29]. Conversely, in two studies, the GCF TNF-α level was significantly elevated in children and adolescents with obesity compared to those with normal weight [31,39], while the other four studies reported no significant difference between the two groups [29,32,34,40]. Interestingly, a significant difference in GCF TNF-α level was found in boys but not in girls in one study [31]. The result of the meta-analysis demonstrated that the GCF TNF-α level was significantly higher in the obese group than in the normal-weight group (SMD:0.56; 95% CI:0.07, 1.04; $I^2 = 86\%$, $n = 6$ studies) (Fig. 2A).

3.4.1.2. Resistin. The GCF resistin level was reported in three studies [29,34,41]. One study also evaluated the salivary resistin level [29]. One study assessed salivary and GCF resistin levels in four groups of children with different levels of adiposity and periodontal health. Among children who were obese, GCF and salivary resistin levels were significantly higher in those with gingivitis than in those

Table 2
Summary of included studies.

Biomarkers	Associations with adiposity status (OB vs. NW)	Associations with periodontal status
Adipokines and other inflammatory markers		
TNF-α	In saliva: (~) [29] In GCF: (↑) [31,39], (~) [29,32,34,40]	In saliva: (~) (OG, OH, NWG, and NWH) [29] In GCF: (~) (OG, OH, NWG, and NWH) [29]; no association with the presence of pathological periodontal pockets [32], levels of dental plaque or gingival bleeding [31]
Resistin	In saliva: (~) [29] In GCF: (↑) [41], (~) [29,34]	In saliva: (↑) (OG vs. OH, and NWG vs. NWH) [29] In GCF: (↑) (OG vs. OH, and NWG vs. NWH) [29]
Adiponectin	In GCF: (↑) [41], (~) [32,34]	In GCF: no significant association with the presence of pathological periodontal pockets [32]
Leptin	In GCF: (↑) [41], (~) [34,40]	Not reported
IL-1β	In saliva: (~) [35] In GCF: (↑) [32,40], (~) [34]	In GCF: no significant association with the presence of pathological periodontal pockets [32]
IL-6	In GCF: (~) [34]	Not reported
IL-8	In GCF: (↑) [32], (~) [34]	In GCF: no significant association with the presence of pathological periodontal pockets [32]
PAI-1	In GCF: (~) [32,34]	In GCF: no significant association with the presence of pathological periodontal pockets [32]
Adipsin	In GCF: (~) [34]	Not reported
CRP	In saliva: (~) [35] In GCF: (~) [41]	Not reported
Periodontal disease markers and periodontal pathogens		
Hydroxyproline	In saliva: (↑) (OG vs. NWG) [30]	In saliva: (↑) (OG vs. OH) [30]
MMP-8	In GCF: (↑) [41]	Not reported
RANKL	In GCF: (↑) [41]	Not reported
sICAM-1	In GCF: (~) [39]	Not reported
P. gingivalis	In saliva: (~) [33] In GCF: (↑) [38]	Not reported
Glucose and glycaemic control		
Glucose	In saliva: (~) [35]	In saliva: a significant positive predictor of gingivitis [42]
1,5-AG	In saliva: (↑) [28]	In saliva: no correlation with PI or mSBI [28]
Antimicrobial defence system		
sIgA	In saliva: (↑) [34,36]	Not reported
Peroxidases	In stimulated whole saliva: (↑) [37] In GCF (myeloperoxidase): (↑) [41]	Not reported

Abbreviations: 1,5-AG,1,5-Anhydroglucitol; CRP, C-reactive protein; GCF, gingival crevicular fluid; IL-1β, interleukin-1 beta; IL-8, interleukin-8; mSBI, modified sulcular bleeding index; NR, not reported; NW, normal-weight group; NWG, group of participants with normal weight and gingivitis; NWH, group of participants with normal weight and healthy periodontium; OB, obese group; OG, group of participants with obesity and gingivitis; OH, group of participants with obesity and healthy periodontium; PAI-1, Plasminogen activator inhibitor-1; *P. gingivalis*, *Porphyromonas gingivalis*; PI, plaque index; sICAM-1, soluble intercellular cell adhesion molecule-1; TNF-α, tumour necrosis factor-alpha.
(↑) significantly higher; (↓) significantly lower; (~) no significant difference.

with healthy periodontium (OB + G group vs. OB + H group). A similar result was observed among normal-weight children (NW + G group vs. NW + H group) [29].

The salivary resistin level was not significantly different between children with obesity and those with normal weight [29]. All three studies evaluated the association between obesity and the GCF resistin level. Of these, one reported a significantly higher GCF resistin level in adolescents with obesity than in normal-weight controls [41], while the other two studies found no significant difference between the two groups [29,34]. Quantitative synthesis demonstrated no significant difference in the GCF resistin level between children and adolescents with obesity and those with normal weight (SMD:0.48; 95% CI: −0.27, 1.23; $I^2 = 86\%$, $n = 3$ studies) (Fig. 2B).

3.4.1.3. Adiponectin. Three studies detected the GCF adiponectin level in adolescents [32,34,41]. In contrast, the salivary adiponectin level was not investigated in any of the studies. Only one study analysed the associations between periodontal status, adiposity status, and the GCF adiponectin level. The bivariate logistic regression results demonstrated that the GCF adiponectin level was not significantly associated with the presence of pathological periodontal pockets (PPD >4 mm), and that the GCF adiponectin level was similar between adolescents with obesity and those with normal weight [32].

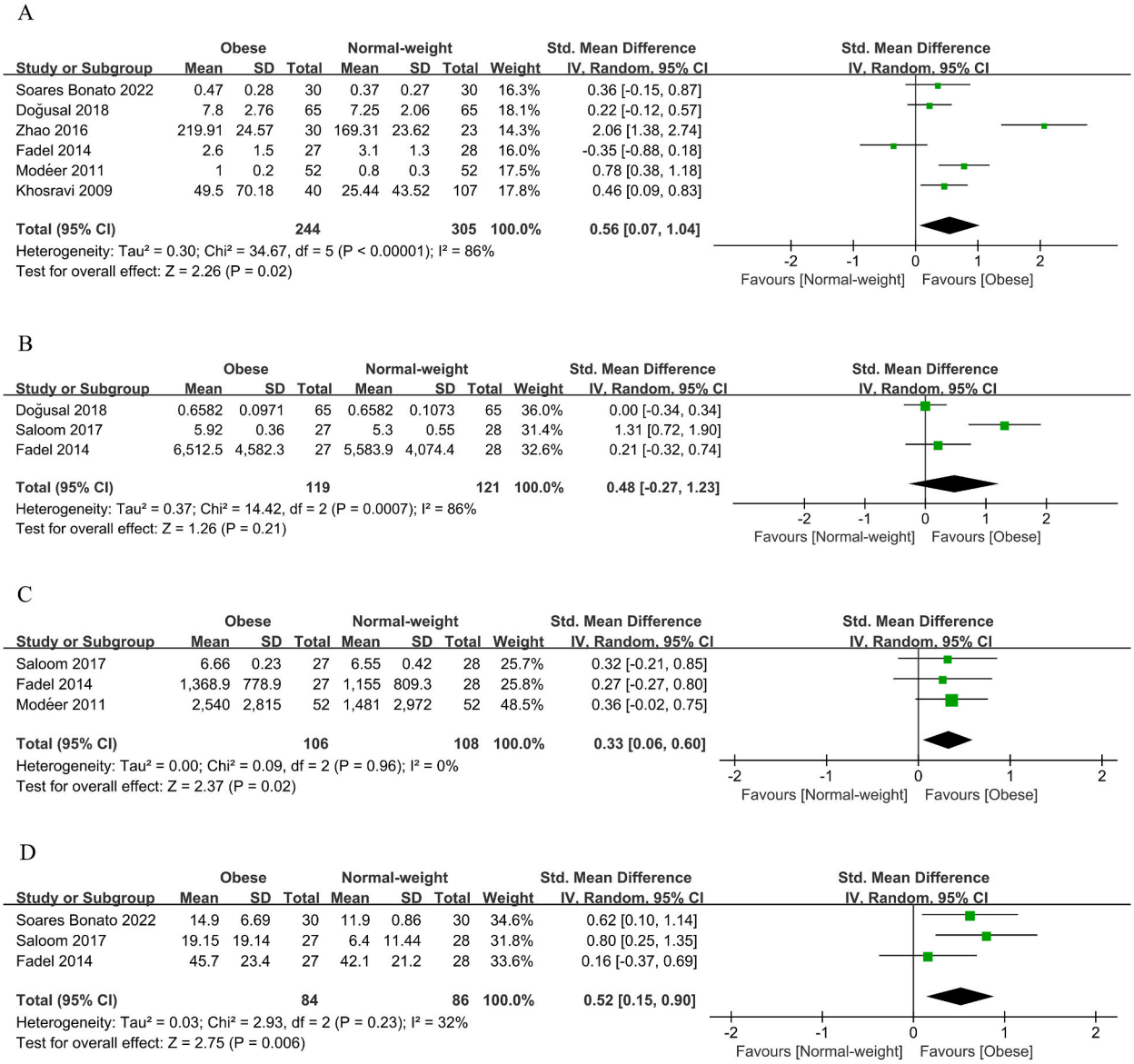


Fig. 2. Differences in the gingival crevicular fluid level of tumour necrosis factor-α (A), resistin (B), adiponectin (C), and leptin (D) between children and adolescents with normal weight and obesity. Standardised mean differences and the 95% confidence intervals were indicated by the diamonds in the forest plots.

The dyadic relationship between obesity and the GCF adiponectin level was reported in all three studies. One study showed that the adiponectin level in the GCF was significantly higher in adolescents with obesity than in those of normal weight [41]. The other two studies reported no significant differences between the two groups, although the mean GCF adiponectin level exhibited a similar trend [32,34]. The meta-analysis demonstrated that the GCF adiponectin level was significantly higher in adolescents with obesity than in normal-weight controls (SMD:0.33; 95% CI:0.06, 0.60; $I^2 = 0\%$, $n = 3$ studies) (Fig. 2C).

3.4.1.4. Leptin. The GCF leptin level was assessed in three studies [34,40,41]. However, the salivary leptin level was not evaluated by any studies. Moreover, none of these studies addressed the association between periodontal status and leptin. However, a dyadic relationship between the GCF leptin level and obesity was observed in all three studies. One study found that adolescents with obesity had significantly higher GCF leptin levels than their normal-weight counterparts [41]. However, two other studies reported no significant differences between the two groups [34,40]. The meta-analysis demonstrated that the GCF leptin level was significantly elevated in adolescents with obesity compared to those with normal weight (SMD:0.52; 95% CI:0.15, 0.90; $I^2 = 32\%$, $n = 3$ studies) (Fig. 2D).

3.4.1.5. Interleukin-1 beta (IL-1β). The GCF IL-1β level was assessed in three studies [32,34,40], and the salivary IL-1β level was measured in one study [35]. Of these, only one study analysed the associations between periodontal status, adiposity status and IL-1β levels. Results of the bivariate logistic regression showed that the GCF IL-1β level was not significantly associated with the presence of pathological periodontal pockets (PPD >4 mm), but the level was significantly elevated in adolescents with obesity compared to their normal-weight controls [32].

Two studies, including the study by Modéer et al. found that the GCF IL-1β level was significantly higher in adolescents with obesity than in those with normal weight [32,40], but no significant difference was found between the two groups in Fadel et al.'s study [34]. Quantitative analysis showed that the GCF IL-1β level was significantly elevated in adolescents with obesity compared to those with normal weight (SMD:0.71; 95% CI:0.44, 0.99; $I^2 = 0\%$, $n = 3$ studies) (Fig. 3A). Furthermore, no significant difference in the salivary IL-1β level was found between the two groups, although the mean salivary IL-1β level in adolescents with obesity was higher than that in their normal-weight controls [35].

3.4.1.6. Interleukin-6 (IL-6). The GCF IL-6 level was evaluated in adolescents with obesity and normal weight in one study; however, no significant differences were found [34].

3.4.1.7. Interleukin-8 (IL-8). The GCF IL-8 level was reported in two studies [32,34], while the salivary IL-8 level was not investigated by any studies. One study evaluated the relationship between periodontal status, adiposity status, and the IL-8 level in GCF. Although the GCF IL-8 level was significantly elevated in adolescents with obesity compared with normal-weight controls, no significant association was found between the GCF IL-8 level and the presence of pathological periodontal pockets in adolescents (PPD >4 mm) [32].

Both studies compared the GCF IL-8 level in adolescents with different adiposity levels. One study showed a significantly higher GCF IL-8 level in adolescents with obesity than in their normal-weight counterparts [32], while the other study reported a similar trend, but the difference was not statistically significant [34]. The quantitative synthesis showed no significant difference in the GCF IL-8 level between adolescents with obesity and those with normal weight (SMD:0.74; 95% CI: −0.44, 1.92; $I^2 = 92\%$, $n = 2$ studies) (Fig. 3B).

3.4.1.8. Plasminogen activator inhibitor-1 (PAI-1). The associations between periodontal status, adiposity status, and the GCF PAI-1 level were analysed in one study. The results reported that the GCF PAI-1 level was not significantly associated with the presence of pathological periodontal pockets (PPD >4 mm). Moreover, the GCF PAI-1 level was found to be similar between adolescents with obesity and those with normal weight [32].

Two studies compared the GCF PAI-1 level in adolescents with different adiposity status [32,34]. The results demonstrated that the GCF PAI-1 level between adolescents with obesity and those with normal weight was similar (SMD:0.01; 95% CI: −0.31, 0.32; $I^2 = 0\%$, $n = 2$ studies) (Fig. 3C).

3.4.1.9. Adipsin. Adipsin was detected in the GCF in one study. The results showed that adolescents with obesity had a higher mean adipsin level in the GCF than those with normal weight, but the difference was not statistically significant. Additionally, the association between the GCF adipsin level and periodontal status was not evaluated [34].

3.4.1.10. C-reactive protein (CRP). None of the included studies evaluated the association between CRP level and periodontal status. Two studies compared the salivary [35] and GCF [41] CRP levels in adolescents with different adiposity status, but no significant difference was found.

3.4.2. Periodontal disease markers and periodontal pathogens

Some potential periodontal disease markers, such as hydroxyproline (a biomarker for collagen destruction), matrix metallopeptidase-8 (MMP-8) (collagen cleaving enzyme), receptor activator of nuclear factor kappa-B ligand (RANKL) (cytokine in bone cell regulation), and soluble intercellular adhesion molecule-1 (sICAM-1) were detected. One study compared the total

hydroxyproline ion count in the saliva of children and adolescents among four groups (OB + G, OB + H, NW + G, and NW + H) and found that children and adolescents with both obesity and gingivitis had significantly higher salivary hydroxyproline levels than those with obesity or gingivitis alone [30]. Moreover, higher levels of MMP-8 and RANKL in the GCF have been found in adolescents with obesity than in those with normal weight [41]. In contrast, the GCF sICAM-1 level was not significantly different between children and adolescents with obesity and those of normal weight [39].

The levels of periodontal pathogens were assessed in the saliva [33] and the GCF [38]. Zeigler et al. found that adolescents with obesity had higher counts of periodontal pathogens, including *Porphyromonas gingivalis (P. gingivalis)*, *Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum*, *Tannerella forsythia*, *Prevotella intermedia* in their GCF than that of the normal-weight controls [38]. Conversely, the salivary levels of *P. gingivalis* were not statistically different among adolescents with different adiposity in another study [33].

3.4.3. Glucose and a marker for glycaemic control

One longitudinal study of 6316 Kuwaiti children evaluated the association between the salivary glucose level and gingivitis. The results demonstrated that a high salivary glucose level (>1.13 mg/dL) was a significant predictor of gingivitis [42]. Another study of 33 participants investigated the association between salivary glucose and obesity and reported that the salivary glucose level was similar between adolescents with obesity and those of normal weight [35].

Another study focused on the level of 1,5-anhydroglucitol (1,5-AG), an emerging marker for glycaemic control, and found that the salivary level of 1,5-AG was significantly increased in children and adolescents with obesity. However, an increase in 1,5-AG was not significantly correlated with periodontal health status, in terms of oral hygiene status (as indicated by the plaque index) and gingival inflammation (as indicated by the modified sulcular bleeding index) [28].

3.4.4. Biomarkers of the antimicrobial defence system

Several studies have also focused on biomarkers of the antibacterial defence system in the oral cavity. Specifically, secretory immunoglobulin A (sIgA) and peroxidases (including myeloperoxidase) have been evaluated in children and adolescents with overweight or obesity. In two studies, the salivary sIgA level was significantly higher in children and adolescents who were overweight or obese than those with normal weight [34,36]. Moreover, peroxidase in stimulated whole saliva [37] and myeloperoxidase in the GCF [41] were significantly elevated in adolescents with obesity compared with their normal-weight controls.

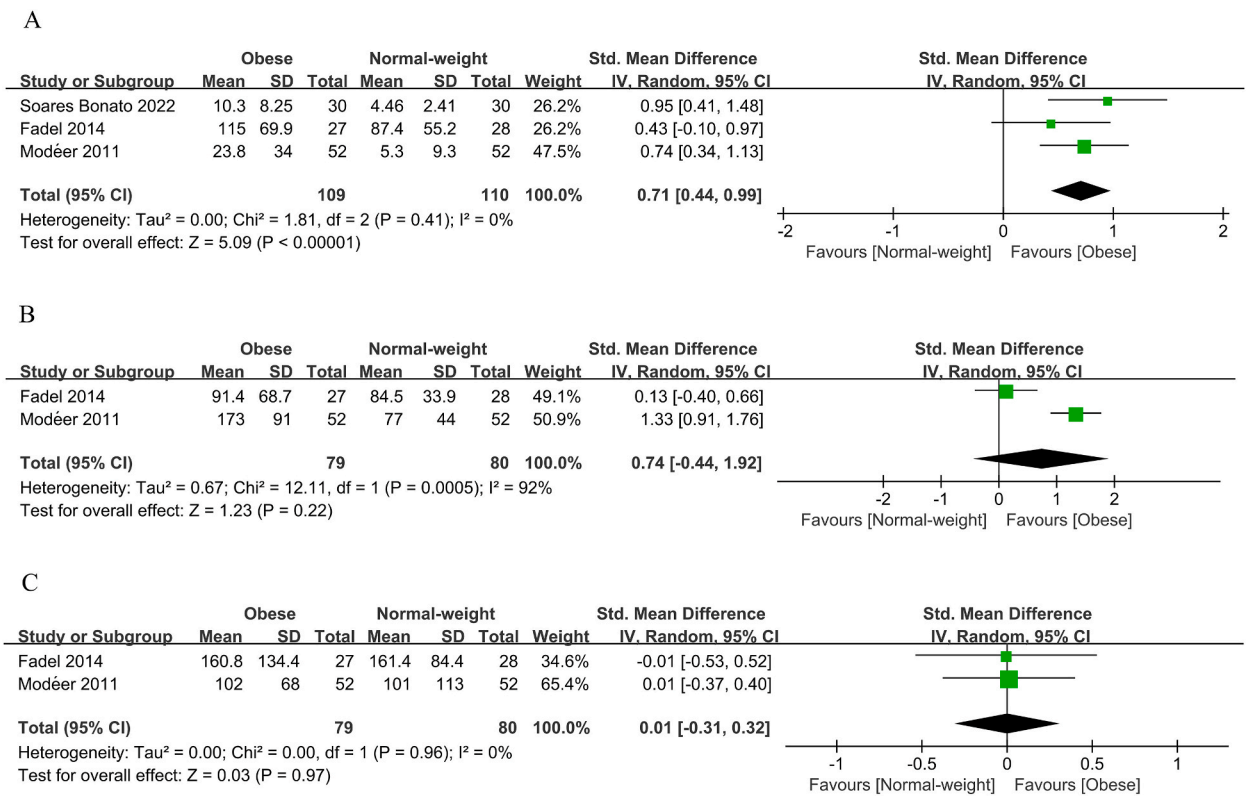


Fig. 3. Differences in the gingival crevicular fluid levels of interleukin-1β (A), interleukin-8 (B), and plasminogen activator inhibitor-1 (C) between children and adolescents with normal weight and obesity. Standardised mean differences and the 95% confidence intervals were indicated by the diamonds in the forest plots.

3.5. Heterogeneity analysis and sensitivity analysis

Subgroup analysis by the level of risk of bias was performed for GCF TNF-α. After excluding one study with a high risk of bias in the comparability domain [39], the I^2 of GCF TNF-α reduced from 86% to 66%; however, the heterogeneity was still significant, and the overall effect became non-significant with a borderline *P*-value of 0.05 (SMD:0.32; 95% CI: −0.01, 0.64; $I^2 = 66\%$, $n = 5$) (Fig. S2). Additionally, the Galbraith's radial plot for GCF TNF-α also spotted the same study [39] as the outlier which may be the major source of heterogeneity. Nevertheless, due to the small number of studies included for each biomarker, we did not perform further subgroup analysis to explore possible sources of heterogeneity.

Sensitivity analyses were performed and the results were displayed in Tables S6–S10. No notable changes on the pooled effect on GCF IL-1β and resistin were observed when applying sensitivity analysis.

4. Discussion

The current systematic review and meta-analysis summarised the state-of-the-art evidence on the relationships among salivary or GCF biomarkers, obesity, and periodontal status in children and adolescents. Only two included studies categorised the participants into four groups according to their adiposity and periodontal status. Most studies have provided information on the dyadic relationship between salivary or GCF biomarkers and obesity; thus, the applicability of meta-analysis was only in assessing this dyadic relationship.

One of the two studies that focused on the triadic relationship evaluated the salivary hydroxyproline level of children and adolescents [30]. Hydroxyproline is a major component of collagen and is considered a biomarker of collagen breakdown [44]. The hydroxyproline level is generally elevated in periodontal diseases [45,46]. Goodson [30] found that the salivary hydroxyproline level and the extent of gingival redness were significantly higher in children and adolescents with obesity and gingivitis than in those with obesity or gingivitis alone. These findings indicate disease reciprocity, meaning the comorbidity of obesity and gingivitis results in more severe gingival inflammation and collagen breakdown. However, the sample size of this study was relatively small, especially in the obese but without gingivitis group ($n = 7$). The overall quality of this study was not high as assessed by NOS. In the future, further studies with a larger sample size and higher quality are required to verify the current evidence.

Another study focusing on the triadic relationship demonstrated that the salivary and GCF resistin levels were significantly elevated in the presence of gingival inflammation in children and adolescents with either obesity or normal weight [29]. However, obesity was not significantly associated with gingival inflammation severity or the salivary or GCF levels of resistin. To date, no comprehensive study has well addressed the triadic association between salivary or GCF biomarkers, obesity, and periodontal status among children and adolescents.

In the present meta-analysis, GCF levels of TNF-α, leptin, adiponectin, and IL-1β were significantly higher in children and adolescents with obesity than those with normal weight, with no significant difference in GCF levels of resistin, IL-8, and PAI-1 between the two groups. The levels of GCF TNF-α and IL-1β were consistent with the findings of a previous meta-analysis of chronic periodontitis patients with and without obesity [47]. According to sensitivity analyses, the significant increase in GCF level of IL-1β in adolescents with obesity in our meta-analysis appeared to be robust and without significant heterogeneity. However, the results in GCF TNF-α, leptin, and adiponectin were less robust. In addition, the exclusion of the study conducted by Zhao et al. [39] (the only study with a high risk of bias in the comparability domain) from the meta-analysis of GCF TNF-α resulted in partially reduced heterogeneity and a non-significant effect size. We speculate that this study was part of the sources of inter-study heterogeneity. However, unexplained heterogeneity still existed in the meta-analysis of GCF TNF-α, so the results should be interpreted with caution. In addition, high heterogeneity in the meta-analyses of GCF resistin and IL-8 was observed, which could not be explained due to a small number of included studies. Even so, we still present the synthesised results to provide a general impression of the current evidence because data in this age group are scarce. Nevertheless, these results should be interpreted more cautiously.

The localised elevation of pro-inflammatory biomarkers such as TNF-α and IL-1β [48,49] in the GCF has been hypothesised to be associated with increased inflammation in the periodontal tissues [50,51]. Previous systematic reviews have shown that GCF TNF-α and IL-1β levels were significantly increased in patients with periodontal disease compared to periodontally healthy controls and were considered potential markers for periodontal diseases [52,53]. However, almost all studies were conducted on adults. The evidence among children and adolescents remains limited, and a consensus has not been reached yet. Although our meta-analysis demonstrated that children and adolescents with obesity had significantly higher GCF TNF-α and IL-1β levels, one study with a four-group design reported similar levels of GCF TNF-α in participants with obesity and those with normal weight [29], and no study has compared GCF IL-1β level in children and adolescents with different adiposity and periodontal status. In the future, further investigations in different populations to determine whether individuals with obesity and a compromised periodontal status would have higher GCF TNF-α and IL-1β levels compared to the controls with only one condition are warranted.

Leptin is a hormone encoded by the obese (*OB*) gene, primarily functioning as an appetite suppressant. It exerts proinflammatory effects by modulating the secretion of cytokines, such as TNF-α, IL-1, and IL-6 [54,55]. However, the GCF leptin level is inversely associated with periodontal inflammation in adults [54,56–58]. One study compared the GCF leptin level in four groups of adults with different adiposity and periodontal status, namely, subjects with obesity (OB) and chronic periodontitis (CP) (OB + CP group); subjects with obesity and healthy periodontium (H) (OB + H group); subjects with normal weight (NW) and chronic periodontitis (NW + CP group); subjects with normal weight and healthy periodontium (NW + H group). The results demonstrated that the mean GCF leptin level was highest in the OB + H group, followed by the NW + H group, then the OB + CP group, with the NW + CP group showing the lowest mean levels [54]. Kanoriya et al. hypothesised that a decreased leptin level in the GCF could be caused by increased leptin-leptin receptor complex formation in the gingiva when leptin receptor expression is upregulated during inflammation [54]. Although the GCF

leptin level was significantly increased in children and adolescents with obesity in the current meta-analysis, studies investigating the relationship between periodontal status and the GCF leptin level in this age group are lacking. Further studies are needed to elucidate the role of leptin in the relationship between obesity and periodontal status.

Adiponectin has been identified as an anti-inflammatory adipokine that downregulates some inflammatory cytokines, such as TNF-α and IL-6 [48,59]. Moreover, its level in the circulation is lower in individuals with obesity than in the lean controls [60,61]. In one study, the GCF adiponectin level was found to be significantly lower in adults with obesity than in those without obesity one month after an orthodontic stainless steel archwire placement [62]. It was also found that the GCF adiponectin level was significantly lower in adult patients with periodontitis and obesity than in normal-weight controls with healthy periodontium; however, the level elevated at the 3-month follow-up after non-surgical periodontal therapy [63]. Conflicting results were found in another study, which reported that the GCF adiponectin level was significantly higher in women with obesity and periodontitis than lean controls with healthy periodontium [64]. In this systematic review and meta-analysis, the GCF adiponectin level was significantly increased in adolescents with obesity. However, the current evidence regarding the relationship between the GCF adiponectin level and periodontal status among children and adolescents remains insufficient. We assumed that the elevated GCF adiponectin level in adolescents with obesity might be the outcome of a feedback response of the human body to reduce the inflammation caused by obesity or compromised periodontal health, which follows a different pattern from that in adults.

Although several studies have evaluated the triadic association between obesity, periodontitis, and salivary or GCF biomarkers in adults [17], evidence among children and adolescents is scarce. Periodontal disease in children and adolescents exhibits a different pattern than those in adults because periodontal attachment loss and alveolar bone resorption are relatively uncommon [65]. As the duration of obesity and periodontal disease may be longer in adults than in children and adolescents, the severity of inflammation may also differ, leading to discrepancies in the findings. Targeting certain biomarkers in non-invasive samples, including saliva and GCF, that can predict the future risk of periodontitis in children and adolescents with obesity will help customise oral health promotion programs in those at-risk populations. Nevertheless, the studies published to date have only provided insights into the cross-sectional associations. More longitudinal studies are necessary in the future.

The strengths of this systematic review and meta-analysis were firstly, we followed the recommendation and guidelines suggested by PRISMA [19] and the MOOSE guidelines [18]. Secondly, six databases were used to comprehensively identify available studies on the topic. Thirdly, we tried to estimate the sample mean and standard deviation from studies only reporting the sample size, median, range, and/or interquartile range, to make the meta-analysis more comprehensive. The findings did provide substantial state-of-the-art evidence on the topic.

However, our study also has several limitations. First, the biomarkers reported in the included studies varied, resulting in a limited number of studies being included in the meta-analysis, thus compromising the publication bias assessment and the exploration of heterogeneity by subgroup analyses or meta-regression. Although the heterogeneities were observed in meta-analyses, the results provided up-to-date first-hand evidence on such topic in this age group (2–18 years). Second, most studies employed a cross-sectional design. Therefore, a cause-effect relationship could not be confirmed. Further longitudinal studies in cohorts are warranted. Finally, a large proportion of studies only focused on the dyadic association between obesity and salivary or GCF biomarkers. As assessed by GRADE, the quality of evidence for the dyadic association was rated as "very low". More high-quality studies with comparable findings are needed to evaluate the triadic association of periodontal status, obesity, and oral biomarkers.

5. Conclusion

This review evaluated the state-of-the-art evidence of the associations between salivary and GCF biomarkers, periodontal status, and obesity in children and adolescents. Results from the meta-analysis indicated that children and adolescents with obesity had significantly higher GCF TNF-α, leptin, adiponectin, and IL-1β levels than those with normal weight. Studies have not yet addressed the triadic association of salivary or GCF biomarkers, periodontal status, and obesity among children and adolescents. Furthermore, the quality of the available evidence is low. Therefore, high-quality studies are required to investigate these associations thoroughly in the future.

Funding

The work described in this paper was fully supported by a grant from the Seed Fund for Basic Research (Project No. 201903159002) of the University of Hong Kong, Hong Kong Special Administrative Region, China.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article, its supplementary materials, and referenced in article.

CRediT authorship contribution statement

Qianyi Deng: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hai Ming Wong:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis, Data curation. **Simin Peng:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation,

Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Ms. Samantha Kar Yan Li for her valuable statistical assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23782.

References

[1] Global Oral Health Status Report: towards Universal Health Coverage for Oral Health by 2030, World Health Organization, Geneva, 2022. Licence: CC BY-NC-SA 3.0 IGO, https://www.who.int/publications/i/item/9789240070844.
[2] W.M. Jenkins, P.N. Papapanou, Epidemiology of periodontal disease in children and adolescents, Periodontol. 26 (2001) (2000) 16–32, https://doi.org/10.1034/j.1600-0757.2001.2260102.x.
[3] M. Rebelo, A. Corrêa de Queiroz, Gingival Indices: State of Art, NTECH Open Access Publisher, 2011.
[4] E. Marchetti, T. Pizzolante, L.M. Americo, S. Bizzarro, V. Quinzi, S. Mummolo, Periodontology Part 4: periodontal disease in children and adolescents, Eur. J. Paediatr. Dent. 23 (4) (2022) 332–335, https://doi.org/10.23804/ejpd.2022.23.04.14.
[5] M.F. Tsoi, H.L. Li, Q. Feng, C.L. Cheung, T.T. Cheung, B.M.Y. Cheung, Prevalence of childhood obesity in the United States in 1999-2018: a 20-year analysis, Obes. Facts 15 (4) (2022) 560–569, https://doi.org/10.1159/000524261.
[6] K. Nimptsch, S. Konigorski, T. Pischon, Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine, Metabolism 92 (2019) 61–70, https://doi.org/10.1016/j.metabol.2018.12.006.
[7] S. Jepsen, J. Suvan, J. Deschner, The association of periodontal diseases with metabolic syndrome and obesity, Periodontol. 2000 83 (1) (2020) 125–153, https://doi.org/10.1111/prd.12326.
[8] F.G. da Silva, N.M. Pola, M. Casarin, C.F.E. Silva, F.W.M.G. Muniz, Association between clinical measures of gingival inflammation and obesity in adults: systematic review and meta-analyses, Clin. Oral Invest. 25 (7) (2021) 4281–4298, https://doi.org/10.1007/s00784-021-03961-1.
[9] C.M. Kim, S. Lee, W. Hwang, E. Son, T.W. Kim, K. Kim, Y.H. Kim, Obesity and periodontitis: a systematic review and updated meta-analysis, Front. Endocrinol. 13 (2022), 999455, https://doi.org/10.3389/fendo.2022.999455.
[10] L.W. Li, H.M. Wong, L. Sun, Y.F. Wen, C.P. McGrath, Anthropometric measurements and periodontal diseases in children and adolescents: a systematic review and meta-analysis, Adv. Nutr. 6 (6) (2015) 828–841, https://doi.org/10.3945/an.115.010017.
[11] P.D. Marsh, T. Do, D. Beighton, D.A. Devine, Influence of saliva on the oral microbiota, Periodontol. 2000 70 (1) (2016) 80–92, https://doi.org/10.1111/prd.12098.
[12] J.J. Taylor, P.M. Preshaw, Gingival crevicular fluid and saliva, Periodontol. 2000 70 (1) (2016) 7–10, https://doi.org/10.1111/prd.12118.
[13] E.S. Kemer Doğan, N. Duran, Is periodontal inflamed surface area associated with serum and salivary levels of IL-1β, visfatin, and omentin-1 in overweight/obese patients? Clin. Oral Invest. 26 (8) (2022) 5351–5358, https://doi.org/10.1007/s00784-022-04502-0.
[14] D. Çetiner, A. Uraz, S. Öztoprak, G. Akça, The role of visfatin levels in gingival crevicular fluid as a potential biomarker in the relationship between obesity and periodontal disease, J. Appl. Oral Sci. 27 (2019), e20180365, https://doi.org/10.1590/1678-7757-2018-0365.
[15] K.M. Jaedicke, P.M. Preshaw, J.J. Taylor, Salivary cytokines as biomarkers of periodontal diseases, Periodontol. 2000 70 (1) (2016) 164–183, https://doi.org/10.1111/prd.12117.
[16] S.P. Barros, R. Williams, S. Offenbacher, T. Morelli, Gingival crevicular fluid as a source of biomarkers for periodontitis, Periodontol. 2000 70 (1) (2016) 53–64, https://doi.org/10.1111/prd.12107.
[17] R.S. Brum, P.M. Duarte, G.L. Canto, C. Flores-Mir, C.A.M. Benfatti, A.L. Porporatti, G.S. Zimmermann, Biomarkers in biological fluids in adults with periodontitis and/or obesity: a meta-analysis, J. Indian Soc. Periodontol. 24 (3) (2020) 191–215, https://doi.org/10.4103/jisp.jisp_512_19.
[18] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, D. Moher, B.J. Becker, T.A. Sipe, S.B. Thacker, Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group, JAMA 283 (15) (2000) 2008–2012, https://doi.org/10.1001/jama.283.15.2008.
[19] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71, https://doi.org/10.1136/bmj.n71.
[20] P.A. Modesti, G. Reboldi, F.P. Cappuccio, C. Agyemang, G. Remuzzi, S. Rapi, E. Perruolo, G. Parati, ESH working group on CV risk in low resource settings, panethnic differences in blood pressure in Europe: a systematic review and meta-analysis, PLoS One 11 (1) (2016), e0147601, https://doi.org/10.1371/journal.pone.0147601.
[21] G. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis, 2014. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed 1 January 2023).
[22] P.Y. Wu, K.M. Chen, W.C. Tsai, The Mediterranean dietary pattern and inflammation in older adults: a systematic review and meta-analysis, Adv. Nutr. 12 (2) (2021) 363–373, https://doi.org/10.1093/advances/nmaa116.
[23] A.P. Strieder, T.M. Oliveira, D. Rios, A.F.P. Cruvinel, T. Cruvinel, Is there a relationship of negative oral health beliefs with dental fear and anxiety regarding diverse dental patient groups? A systematic review and meta-analysis, Clin. Oral Invest. 23 (9) (2019) 3613–3621, https://doi.org/10.1007/s00784-018-2786-2.
[24] G.H. Guyatt, A.D. Oxman, G.E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello, H.J. Schünemann, GRADE Working Group, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 336 (7650) (2008) 924–926, https://doi.org/10.1136/bmj.39489.470347.AD.
[25] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135, https://doi.org/10.1186/1471-2288-14-135.

[26] R.F. Galbraith, A note on graphical presentation of estimated odds ratios from several clinical trials, Stat. Med. 7 (8) (1988) 889–894, https://doi.org/10.1002/sim.4780070807.

[27] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch (Eds.), Cochrane Handbook for Systematic Reviews of Interventions, second ed., John Wiley & Sons, Chichester (UK), 2019.

[28] S.A. Alghamdi, A. Aljohar, B. Almulhim, A. Alassaf, S.S. Bhardwaj, J.T. Thomas, A. Almalki, A.O. Aljuaid, S.K. Mallineni, Correlation between BMI and oral health status (DMFT, PI, mSBI, and salivary 1,5-AG) among the pediatric population in Saudi Arabia: a clinico-biochemical study, Children 9 (7) (2022) 1017, https://doi.org/10.3390/children9071017.

[29] G. Doğusal, B. Afacan, E. Bozkurt, I. Sönmez, Gingival crevicular fluid and salivary resistin and tumor necrosis factor-alpha levels in obese children with gingivitis, J. Periodontol. 89 (8) (2018) 973–982, https://doi.org/10.1002/JPER.17-0613.

[30] J.M. Goodson, Disease reciprocity between gingivitis and obesity, J. Periodontol. 91 (Suppl 1) (2020) S26–S34, https://doi.org/10.1002/JPER.20-0046.

[31] R. Khosravi, S.D. Tran, M. Lambert, J. O'Loughlin, K. Kâ, J.S. Feine, C. Caron, A. Tremblay, B. Nicolau, Adiposity and gingival crevicular fluid tumour necrosis factor-alpha levels in children, J. Clin. Periodontol. 36 (4) (2009) 301–307, https://doi.org/10.1111/j.1600-051X.2009.01374.x.

[32] T. Modéer, C. Blomberg, B. Wondimu, T.Y. Lindberg, C. Marcus, Association between obesity and periodontal risk indicators in adolescents, Int. J. Pediatr. Obes. 6 (2–2) (2011) e264–e270, https://doi.org/10.3109/17477166.2010.495779.

[33] D.S. Araujo, M.I. Klein, K.G.O. Scudine, L. de Sales Leite, T.M. Parisotto, C.M. Ferreira, F.L.A. Fonseca, M.M. Perez, P.M. Castelo, Salivary microbiological and gingival health status evaluation of adolescents with overweight and obesity: a cluster analysis, Front. Pediatr. 8 (2020) 429, https://doi.org/10.3389/fped.2020.00429.

[34] H.T. Fadel, A. Pliaki, E. Gronowitz, S. Mårild, P. Ramberg, G. Dahlèn, T. Yucel-Lindberg, L. Heijl, D. Birkhed, Clinical and biological indicators of dental caries and periodontal disease in adolescents with or without obesity, Clin. Oral Invest. 18 (2) (2014) 359–368, https://doi.org/10.1007/s00784-013-0972-9.

[35] W.F. Janem, F.A. Scannapieco, A. Sabharwal, M. Tsompana, H.A. Berman, E.M. Haase, J.C. Miecznikowski, L.D. Mastrandrea, Salivary inflammatory markers and microbiome in normoglycemic lean and obese children compared to obese children with type 2 diabetes, PLoS One 12 (3) (2017), e0172647, https://doi.org/10.1371/journal.pone.0172647.

[36] M.M. Perez, J.S. Pessoa, A.L. Ciamponi, M.B. Diniz, M. Santos, H.H.O. Alves, R. Gorjao, R.O. Guare, Correlation of salivary immunoglobulin A with Body Mass Index and fat percentage in overweight/obese children, J. Appl. Oral Sci. 27 (2018), e20180088, https://doi.org/10.1590/1678-7757-2018-0088.

[37] A. Zalewska, A. Kossakowska, K. Taranta-Janusz, S. Zięba, K. Fejfer, M. Salamonowicz, P. Kostecka-Sochoń, A. Wasilewska, M. Maciejczyk, Dysfunction of salivary glands, disturbances in salivary antioxidants and increased oxidative damage in saliva of overweight and obese adolescents, J. Clin. Med. 9 (2) (2020) 548, https://doi.org/10.3390/jcm9020548.

[38] C.C. Zeigler, G.R. Persson, B. Wondimu, C. Marcus, T. Sobko, T. Modéer, Microbiota in the oral subgingival biofilm is associated with obesity in adolescence, Obesity 20 (1) (2012) 157–164, https://doi.org/10.1038/oby.2011.305.

[39] B. Zhao, C. Jin, L. Li, Y. Wang, Increased expression of TNF-α occurs before the development of periodontitis among obese Chinese children: a potential marker for prediction and prevention of periodontitis, Oral Health Prev. Dent. 14 (1) (2016) 71–75, https://doi.org/10.3290/j.ohpd.a35006.

[40] R.C. Soares Bonato, M.A. Abel Mapengo, L.J. de Azevedo-Silva, G. Janson, S.H. de Carvalho Sales-Peres, Tooth movement, orofacial pain, and leptin, interleukin-1β, and tumor necrosis factor-α levels in obese adolescents, Angle Orthod. 92 (1) (2022) 95–100, https://doi.org/10.2319/011321-44.1.

[41] H.F. Saloom, S.N. Papageorgiou, G.H. Carpenter, M.T. Cobourne, Impact of obesity on orthodontic tooth movement in adolescents: a prospective clinical cohort study, J. Dent. Res. 96 (5) (2017) 547–554, https://doi.org/10.1177/0022034516688448.

[42] H. Alqaderi, M. Tavares, M. Hartman, J.M. Goodson, Effect of sleep and salivary glucose on gingivitis in children, J. Dent. Res. 95 (12) (2016) 1387–1393, https://doi.org/10.1177/0022034516661509.

[43] G. Gunjalli, K.N. Kumar, S.K. Jain, S.K. Reddy, G.R. Shavi, S.L. Ajagannanavar, Total salivary anti-oxidant levels, dental development and oral health status in childhood obesity, J. Int. Oral Health 6 (4) (2014) 63–67.

[44] A.K. Srivastava, P. Khare, H.K. Nagar, N. Raghuwanshi, R. Srivastava, Hydroxyproline: a potential biochemical marker and its role in the pathogenesis of different diseases, Curr. Protein Pept. Sci. 17 (6) (2016) 596–602, https://doi.org/10.2174/1389203717666151201192247.

[45] F.A. Akalin, D. Sengün, K. Eratalay, N. Renda, G. Cağlayan, Hydroxyproline and total protein levels in gingiva and gingival crevicular fluid in patients with juvenile, rapidly progressive, and adult periodontitis, J. Periodontol. 64 (5) (1993) 323–329, https://doi.org/10.1902/jop.1993.64.5.323.

[46] S. Geiger, E. Harper, Human gingival collagenase in periodontal disease: the release of collagenase and the breakdown of endogenous collagen in gingival explants, J. Dent. Res. 59 (1) (1980) 11–16, https://doi.org/10.1177/00220345800590010101.

[47] Z. Akram, T. Abduljabbar, M.I. Abu Hassan, F. Javed, F. Vohra, Cytokine profile in chronic periodontitis patients with and without obesity: a systematic review and meta-analysis, Dis. Markers 2016 (2016), 4801418, https://doi.org/10.1155/2016/4801418.

[48] N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, Nat. Rev. Immunol. 11 (2) (2011) 85–97, https://doi.org/10.1038/nri2921.

[49] N. Kaneko, M. Kurata, T. Yamamoto, S. Morikawa, J. Masumoto, The role of interleukin-1 in general pathology, Inflamm. Regen. 39 (2019) 12, https://doi.org/10.1186/s41232-019-0101-5.

[50] G. Hajishengallis, T. Chavakis, Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities, Nat. Rev. Immunol. 21 (7) (2021) 426–440, https://doi.org/10.1038/s41577-020-00488-6.

[51] T.S. Miranda, N.d.F. Figueiredo, L.C. Figueiredo, H.D.P.d. Silva, F.R.G. Rocha, P.M. Duarte, Cytokine profiles of healthy and diseased sites in individuals with periodontitis, Arch. Oral Biol. 120 (2020), 104957, https://doi.org/10.1016/j.archoralbio.2020.104957.

[52] D.F. Madureira, I. Lucas De Abreu Lima, G.C. Costa, E.M.B. Lages, C.C. Martins, T. Aparecida Da Silva, Tumor necrosis factor-alpha in gingival crevicular fluid as a diagnostic marker for periodontal diseases: a systematic review, J. Evid. Base Dent. Pract. 18 (4) (2018) 315–331, https://doi.org/10.1016/j.jebdp.2018.04.001.

[53] A.F. Stadler, P.D.M. Angst, R.M. Arce, S.C. Gomes, R.V. Oppermann, C. Susin, Gingival crevicular fluid levels of cytokines/chemokines in chronic periodontitis: a meta-analysis, J. Clin. Periodontol. 43 (9) (2016) 727–745, https://doi.org/10.1111/jcpe.12557.

[54] D. Kanoriya, A.R. Pradeep, A. Mallika, S. Singhal, V. Garg, Correlation of crevicular fluid and serum levels of retinol-binding protein 4 and leptin in chronic periodontitis and obesity, Clin. Oral Invest. 21 (7) (2017) 2319–2325, https://doi.org/10.1007/s00784-016-2025-7.

[55] S. Loffreda, S.Q. Yang, H.Z. Lin, C.L. Karp, M.L. Brengman, D.J. Wang, A.S. Klein, G.B. Bulkley, C. Bao, P.W. Noble, M.D. Lane, A.M. Diehl, Leptin regulates proinflammatory immune responses, Faseb. J. 12 (1) (1998) 57–65.

[56] B.V. Karthikeyan, A.R. Pradeep, Gingival crevicular fluid and serum leptin: their relationship to periodontal health and disease, J. Clin. Periodontol. 34 (6) (2007) 467–472, https://doi.org/10.1111/j.1600-051X.2007.01078.x.

[57] A. Khorsand, M. Bayani, S. Yaghobee, S. Torabi, M.J. Kharrazifard, F. Mohammadnejhad, Evaluation of salivary leptin levels in healthy subjects and patients with advanced periodontitis, J. Dent. 13 (1) (2016) 1–9.

[58] S. Selvarajan, R. Perumalsamy, P. Emmadi, R. Thiagarajan, A. Namasivayam, Association between gingival crevicular fluid leptin levels and periodontal status - a biochemical study on Indian patients, J. Clin. Diagn. Res. 9 (5) (2015) ZC48–ZC53. https://doi.org/10.7860/JCDR/2015/12335.5941.

[59] J.E. Suvan, N. Finer, F. D'Aiuto, Periodontal complications with obesity, Periodontol. 2000 78 (1) (2018) 98–128, https://doi.org/10.1111/prd.12239.

[60] P. Panagopoulou, A. Galli-Tsinopoulou, A. Fleva, E. Pavlitou-Tsiontsi, N. Vavatsi-Christaki, S. Nousia-Arvanitakis, Adiponectin and insulin resistance in childhood obesity, J. Pediatr. Gastroenterol. Nutr. 47 (3) (2008) 356–362, https://doi.org/10.1097/MPG.0b013e31817fcb67.

[61] Y. Hao, J. Xiao, P. Fu, L. Yan, X. Zhao, X. Wu, M. Zhou, X. Zhang, B. Xu, X. Li, Z. Liu, C. Yang, X. Wang, L. Long, X. Jiang, J. Liao, B. Zhang, J. Li, Increases in BMI contribute to worsening inflammatory biomarkers related to breast cancer risk in women: a longitudinal study, Breast Cancer Res. Treat. 202 (2023) 117–127, https://doi.org/10.1007/s10549-023-07023-w.

[62] A. Alqerban, S.N. Asiri, F. Alharbi, A. Almalki, N. Alqhtani, A. Alenazi, A. Robaian, A. Samran, Effect of ten different biomarkers in the gingival crevicular fluid of obese and non-obese undergoing fixed orthodontic treatment, Eur. Rev. Med. Pharmacol. Sci. 27 (5) (2023) 1722–1728, https://doi.org/10.26355/eurrev_202303_31532.

[63] E. Duzagac, E. Cifcibasi, M.G. Erdem, V. Karabey, K. Kasali, S. Badur, S. Cintan, Is obesity associated with healing after non-surgical periodontal therapy? A local vs. systemic evaluation, J. Periodontal. Res. 51 (5) (2016) 604–612, https://doi.org/10.1111/jre.12340.
[64] B. Alkan, E. Guzeldemir-Akcakanat, Evaluation of adipokine levels in obese women with periodontitis: a cohort study, Am. J. Dent. 34 (5) (2021) 267–272.
[65] J.V. Califano, Research, science and therapy committee American academy of periodontology, position paper: periodontal diseases of children and adolescents, J. Periodontol. 74 (11) (2003) 1696–1704, https://doi.org/10.1902/jop.2003.74.11.1696.