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## REVIEW ARTICLE

### Obesity and Periodontal Disease: A Narrative Review on Current Evidence and Putative Molecular Links

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#### Abstract:

#### Background:

Obesity represents one of the main health problems worldwide and is considered a risk factor for several diseases, including periodontitis, which is a microbially-associated inflammatory disease affecting the tooth-supporting structures.

#### Objective:

The aim of this review was to report the current direct and indirect evidence concerning the possible association between obesity and periodontitis and their putative molecular links.

#### Methods:

A literature search was conducted between January 1999 and September 2019, in PubMed/MEDLINE and Science Direct databases, using pertinent keyword combined by Boolean operators. Through a multi-step screening process (literature search; articles title and abstract evaluation and full-text reading), studies fitting inclusion/exclusion criteria were considered for the review.

#### Results:

35 studies were included in the present review (17 observational studies; 7 systematic reviews; 11 systematic reviews with meta-analysis), focusing on the direct and indirect evidence of the possible association between obesity and periodontitis and their potential etiopathogenic molecular links

#### Conclusion:

Although the majority of the studies reported a positive association between obesity and periodontitis, the heterogeneity of the classification criteria and of the clinical parameters employed in the studies for both obesity and periodontitis evaluation, complicated the comparison of the results, thus considered inconclusive. Although several putative molecular pathogenic links between obesity and periodontitis have been highlighted, further studies, with longer follow-ups and with homogeneous clinical criteria, are needed to better understand the putative relation between obesity and periodontal disease.

**Keywords:** Obesity, Periodontal disease, Overweight, Periodontitis, Adipokines, Cytokines.

#### Article History

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## 1. INTRODUCTION

Obesity represents one of the main health problems

worldwide, with a prevalence triplicated in the last 40 years [1, 2] and estimated between 2015 and 2016, of 13.9% for US

children (2-5 years old), 18.4% in school-aged children (6-11 years old), 20.6% in adolescents (12-19 years old), and 39.8% in adults [3].

Obesity is defined as an excessive body fat accumulation, due to the imbalance between the food eaten and the calories spent [4], and is evaluated through Waist Circumference (WC) [5] and Body Mass Index (BMI) [6] assessment.

Waist circumference measurement is applied for cardiovascular diseases risk prediction, indicating: a moderate risk, with values  $\geq 94$  cm in men and  $\geq 80$  cm in women; a severe risk, with values  $\geq 102$  cm in men and  $\geq 88$  cm in women; an extremely high risk, with values  $\geq 120$  cm in men and  $\geq 110$  cm for women [7].

BMI calculation, obtained by dividing a person's weight by height square ( $\text{Kg} / \text{m}^2$ ), identifies overweight with values between 25 and 29.9, while, values ranging from 30 to 34.9, from 35 to 39.9, and over 40, indicate a Slight or First Degree of obesity, a Moderate or Second degree of obesity, and a Severe or Third degree of obesity, respectively [6]. BMI, is the most common measure for obesity screening, even though it is not able to differentiate lipids distribution neither in somatic and visceral fat or in relation to age, sex and race [8].

Obesity is the result of many disorders arising from a number of different causes, including complex interactions among genetic, biochemical, neural and psychological factors, on one side, and environmental, social and economic factors, on the other side [9]. Moreover, obesity is considered itself a risk factor for several diseases, such as type 2 diabetes mellitus, cardiovascular disease, tumors and, potentially, for periodontal disease [1].

Periodontitis is an inflammatory microbially-associated disease, leading to the destruction of the tooth-supporting structures [10, 11]. It is likely associated with diabetes, cardiovascular disease, cancer, respiratory infections, metabolic syndrome and, according to recent evidence, to obesity too [12, 13].

Since the first report suggesting in a rat model the existence of a possible relation between obesity and periodontal disease in 1977 [14], only 21 years later, Saito *et al.* conducted the first human study on the Japanese population, revealing that obese subjects showed a probability of suffering from periodontitis 8.6 times greater than non-obese ones [15].

The present review aims to report current higher-level evidences relating obesity to periodontal disease and the putative molecular pathogenic links.

## 2. METHODS

### 2.1. Search Methods

A literature search was independently conducted by two reviewers through PubMed / MEDLINE and Science Direct

pertinent keywords, combining databases, using the following them with the three Boolean operators AND, OR, NOT, for each search in the above-mentioned databases:

1. Periodontitis
2. Periodontal diseases
3. Gingivitis
4. Periodontal inflammation
5. 1 OR 2 OR 3 OR 4
6. Obesity
7. Overweight
8. 6 OR 7
9. CAL (acronym of Clinical Attachment Level) AND 8
10. PPD (acronym of Periodontal Probing Depth) AND 8
11. BoP (acronym of Bleeding on Posing) AND 8
12. 9 OR 10 OR 11
13. BMI (acronym of Body Mass Index) AND 5
14. Waist to Hip ratio AND 5
15. Periodontal treatment AND 8 OR 12 OR 13
16. Bariatric Surgery AND 5 OR 12
17. Weight Loss AND 5 OR 12
18. 15 OR 16 OR 17
19. CRP (acronym of c-Reactive Protein) AND 5 OR 8 OR 12 OR 18
20. Oxidative stress AND 5 OR 8 OR 12 OR 18
21. IL-1b AND 5 OR 8 OR 12 OR 18
22. TNF-a AND 5 OR 8 OR 12 OR 18
23. IL-6 AND 5 OR 8 OR 12 OR 18
24. IL-8 AND 5 OR 8 OR 12 OR 18
25. Inhibitor of the plasminogen activator AND 5 OR 8 OR 12 OR 18

### 2.2. Inclusion and Exclusion Criteria

Cross-sectional and longitudinal studies, systematic reviews and meta-analysis, in the English language, in press or published in scientific journals, between January 1999 and September 2019, were included in the present study.

Literature reviews, case reports and case series studies, together with conference papers and oral communications, edited books and book chapters, were excluded from the present study, together with cross-sectional and longitudinal studies, systematic reviews and meta-analysis not published in English language or published before January 1999.

## 3. RESULTS

### 3.1. Studies Screening Process

From literature research, 554 articles were identified; out of these, subsequently to articles title and abstract evaluation,

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119 were considered eligible for the present review; after the full-text evaluation, 35 articles, fitting the above-mentioned inclusion and exclusion criteria, were included in the present study, as shown in Fig. (1).

### 3.2. Studies Included in the Present Review

Among the 35 articles considered in the present study: 17 reported observational studies (6 cross-sectional, 13 case-control and 8 pro-/retro-spective studies, respectively); 7 were systematic reviews; 11 were systematic reviews with meta-analysis. Included studies type is reported in (Table 1).

### 3.3. Studies Features

Two systematic reviews with meta-analysis, together with 2 longitudinal and 1 cross-sectional studies, analyzed the direct evidence of the possible association between obesity and periodontitis; in addition, 3 systematic reviews and 1 systematic review with meta-analysis evaluated the possible influence on such a relationship of age and gender, and 2 systematic reviews and 1 systematic review with meta-analysis of the smoking habit.

The indirect evidence of the possible association between obesity and periodontal disease derived from 2 systematic reviews with meta-analysis, investigating the impact of bariatric surgery and weight loss on periodontal status, on the one side, and 2 systematic reviews and 1 systematic review with meta-analysis, reporting the effect of the periodontal treatment on body weight and obesity, on the other side.

Twenty-five observational studies (5 cross-sectional, 14 case-control and 6 pro-/retrospective studies, respectively), 3 systematic reviews and 7 systematic reviews with meta-analysis focused on the potential etiopathogenic and molecular links between obesity and periodontitis, evaluating also the role of: CRP, oxidative stress, IL-1b, TNF-a, IL-6, IL-8, and the inhibitor of plasminogen activator. Included studies features are shown in Table 1.

### 3.4. Summary of the Results

The direct evidence of the possible association between obesity and periodontal disease, also in relation to gender, and smoking habit, was not conclusive, except for Chaffee *et al.* who reported a stronger association between obesity and periodontitis in women when compared to men. Studies evaluating the effect of bariatric surgery on periodontal status, as well as the influence of overweight/obesity on periodontitis development, also reported contrasting results, weakening the indirect evidence of the possible relationship between obesity and periodontitis.

Conversely, Keller *et al.* and Suvan *et al.* hypothesized that overweight and obesity may affect periodontitis onset and worsening and several studies highlighted the bi-directional role of several inflammatory response markers (C-Reactive Protein, Nitric Oxide, Myeloperoxidase), pro-inflammatory cytokines and adipokines (Interleukin-1b; Tumour Necrosis Factor alpha; Interleukin-6; Interleukin-8; Plasminogen-1 activator inhibitor) in such a possible association.

## 4. DISCUSSION

### 4.1. Direct Evidence of the Possible Association between Obesity and Periodontal Disease

Kongstad *et al.* reported, in a cross-sectional study, that obese subjects had lower Clinical Attachment Level (CAL) values, measured in mm as the distance between the cemento-enamel junction and the periodontal pocket bottom [16], but an higher predisposition for bleeding, when compared to normal-weight subjects, neither if smokers or non-smokers [17].

Saxlin *et al.* concluded, in a longitudinal study, that BMI and WC values appeared to be associated with the number of teeth showing Probing Pocket Depth (PPD) values, measured in mm as the distance between the free gingival margin and the periodontal pocket bottom [16],  $\geq 4$  mm; such results could not be considered conclusive due to the study limits, such as randomness, restriction in enrolled patients age range (45-64 years old) and lack of anamnestic records (*e.g.* smoking habit; systemic conditions; *etc.*) [18].

Similarly, Chaffee *et al.* reported a slight positive association between obesity and periodontal disease, since both higher CAL values were registered in obese compared to normal-weight subjects and higher BMI values were observed in subjects affected by periodontal disease compared to subjects with healthy periodontal conditions [19]; the relation between overweight or obesity and tooth loss was not confirmed in the studies reviewed by the authors, in contrast with Nascimento *et al.* findings, who subsequently found a positive association between tooth loss and obesity in all meta-analyses included in their systematic review [20].

De Castilhos *et al.* observed, in a cohort study, an association between BMI and WC with PPD, CAL, Bleeding on Probing (BOP) and Plaque Index (PI) [21, 22].

#### 4.1.1. Age and Gender Influence

A positive association between obesity and periodontal disease in adults as well as in adolescent subjects was reported in a review by Khan [23].

Gender influence on the association between overweight or obesity and the development of periodontal disease is still controversial. Martinez-Herrera *et al.* [24] and Keller *et al.* [25] could not achieve conclusive results, while Chaffee *et al.* reported a stronger association between obesity and periodontal disease in women when compared to men [19].

#### 4.1.2. Smoking Habit Effect

Chaffee *et al.* in their systematic review reported a stronger association between obesity and periodontal disease in non-smokers subjects compared to the general adult population [19].

Conversely, AlJehani *et al.* in a review and Keller *et al.* in a systematic review stated that, in the putative relation between obesity and periodontal disease, smoking habit has not been widely investigated, and may be a possible confounder because of both the negative effect exerted on the periodontal health and the positive effect on the body weight [25, 26].

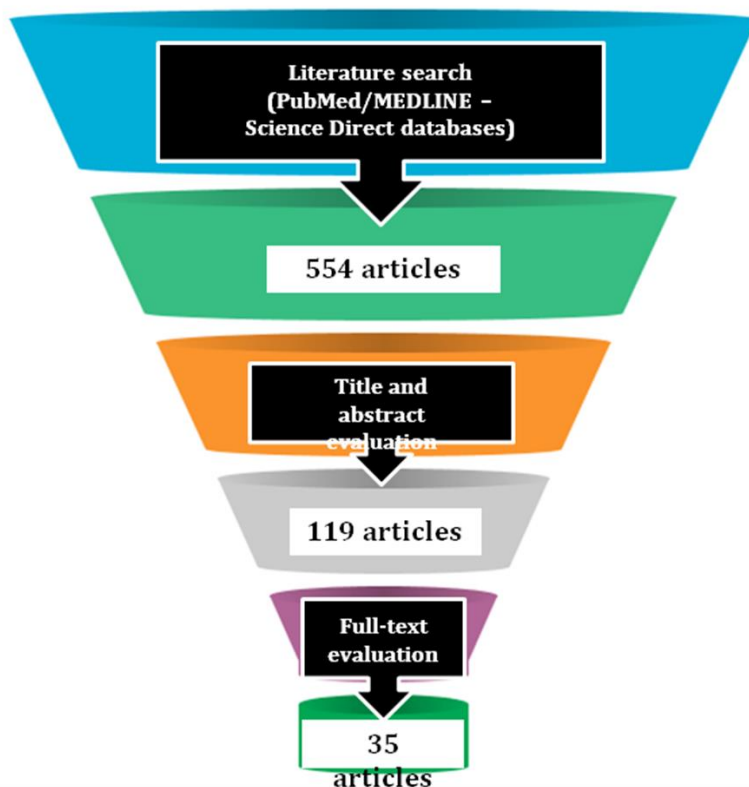


Fig. (1). Multi-step articles screening process.

Table 1. Included studies: authors, year of publication, full title, type and topic(s) of the article.

Authors	Year	Title	Type of the Article	Topic(s)
Kongstad <i>et al.</i>	2009	The relationship between body mass index and periodontitis in the Copenhagen city hearth study	Cross-sectional	Direct evidences of the possible association between obesity and periodontitis
Saxlin <i>et al.</i>	2010	Overweight and obesity weakly predict the development of periodontal infection	Longitudinal	Direct evidences of the possible association between obesity and periodontitis
Chaffee <i>et al.</i>	2010	Association between chronic periodontal disease and obesity: A systematic review and meta-analysis	Systematic review + meta-analysis	Direct evidences of the possible association between obesity and periodontitis + Age and Gender influence ( <i>etc.</i> )
Nascimento <i>et al.</i>	2016	Is there a relationship between obesity and tooth loss and edentulism? A systematic review and meta-analysis	Systematic review + meta-analysis	Direct evidences of the possible association between obesity and periodontitis
De Castilhos <i>et al.</i>	2012	Association between obesity and periodontal disease in young adults: A population-based birth cohort	Longitudinal	Direct evidences of the possible association between obesity and periodontitis
Khan <i>et al.</i>	2018	Is overweight/obesity a risk factor for periodontitis in young adults and adolescents?: A systematic review	Systematic review	Age and Gender influence on the possible association between obesity and periodontitis
Martinez-Herrera <i>et al.</i>	2017	Association between obesity and periodontal disease. A systematic review of epidemiological studies and controlled clinical trials	Systematic review	Age and Gender influence on the possible association between obesity and periodontitis
Keller <i>et al.</i>	2015	Association between periodontal disease and overweight and obesity: A systematic review	Systematic review	Age and Gender ( <i>etc.</i> ) + Smoking habit influence on the possible association between obesity and periodontitis + Overweight/obesity effect on periodontitis onset and worsening

(Table 1) *contd....*

Authors	Year	Title	Type of the Article	Topic(s)
Fontanille <i>et al.</i>	2018	Bariatric surgery and periodontal status: A systematic review with meta-analysis	Systematic review + meta-analysis	Indirect evidences of the possible association between obesity and periodontitis
De Souza <i>et al.</i>	2018	Relationship between bariatric surgery and periodontal status: A systematic review and meta-analysis	Systematic review + meta-analysis	Indirect evidences of the possible association between obesity and periodontitis
Papageorgiou <i>et al.</i>	2015	Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis	Systematic review + meta-analysis	Indirect evidences of the possible association between obesity and periodontitis
Suvan <i>et al.</i>	2000	Periodontal complications with obesity	Systematic review	Indirect evidences of the possible association between obesity and periodontitis + Overweight/obesity effect on periodontitis onset and worsening
Gerber <i>et al.</i>	2016	Influence of obesity on the outcome of non-surgical periodontal therapy - A systematic review	Systematic review	Indirect evidences of the possible association between obesity and periodontitis
Moura-Grec <i>et al.</i>	2014	Obesity and periodontitis: systematic review and meta-analysis	Systematic review + meta-analysis	Overweight/obesity effect on periodontitis onset and worsening
Suvan <i>et al.</i>	2011	Association between overweight/obesity and periodontitis in adults. A systematic review	Systematic review	Overweight/obesity effect on periodontitis onset and worsening
Furugen <i>et al.</i>	2008	The relationship between periodontal condition and serum levels of resistin and adiponectin in elderly Japanese	Cross-sectional	Potential etiopathogenic and molecular links between obesity and periodontitis + Inhibitor of the plasminogen activator + Adiponectin + Leptin
Genco <i>et al.</i>	2005	A proposed model linking inflammation to obesity, diabetes and periodontal infections	Cross-sectional	Potential etiopathogenic and molecular links between obesity and periodontitis
Vivekannada <i>et al.</i>	2019	Impact of Weight Reduction on Adiponectin and TNF- $\alpha$ Levels in the Gingival Crevicular Fluids of Obese Patients with and without Periodontal Disease	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis
Dos Santos <i>et al.</i>	2019	Clinical periodontal conditions in individuals after bariatric surgery: A systematic review and meta-analysis	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis
Nascimento <i>et al.</i>	2015	Is weight gain associated with the incidence of periodontitis? A systematic review and meta-analysis	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis
Wilkins <i>et al.</i>	2017	Influence of Obesity on Periodontitis Progression Is Conditional on Interleukin-1 Inflammatory Genetic Variation	Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis + IL-1
Kopp <i>et al.</i>	2003	Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients	Cross-sectional + Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis + CRP
Visser <i>et al.</i>	1999	Elevated C-reactive protein levels in overweight and obese adults	Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis + CRP
Cairo <i>et al.</i>	2008	Severe periodontitis in young adults is associated with sub-clinical atherosclerosis	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis
Higashi <i>et al.</i>	2008	Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis
Paraskevas <i>et al.</i>	2008	A systematic review and meta-analyses on C-reactive protein in relation to periodontitis	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis
Nam <i>et al.</i>	2018	Salivary biomarkers of inflammation and oxidative stress in healthy adults	Cross-sectional	Potential etiopathogenic and molecular links between obesity and periodontitis + CRP

(Table 1) contd....

Authors	Year	Title	Type of the Article	Topic(s)
Dezayee <i>et al.</i>	2016	Saliva C-reactive protein as a biomarker of metabolic syndrome in diabetic patients	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + CRP
Keaney <i>et al.</i>	2003	Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study	Cross-sectional	Potential etiopathogenic and molecular links between obesity and periodontitis
Virgolici <i>et al.</i>	2005	A comparative oxidative stress study – obesity with and without diabetes mellitus	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis
Uzun <i>et al.</i>	2004	Changes in leptin, plasminogen activator factor and oxidative stress in morbidly obese patients following open and laparoscopic Swedish adjustable gastric banding	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Oxidative stress
Cherian <i>et al.</i>	2019	Malondialdehyde as a Marker of Oxidative Stress in Periodontitis Patients	Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis + Oxidative stress
Saita <i>et al.</i>	2016	Novel antioxidative nanotherapeutics in a rat periodontitis model: Reactive oxygen species scavenging by redox injectable gel suppresses alveolar bone resorption	Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis + Oxidative stress
Takane <i>et al.</i>	2002	New biomarker evidence of oxidative DNA damage in whole saliva from clinically healthy and periodontally diseased individuals	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Oxidative stress
da Silva <i>et al.</i>	2017	Genetic Factors and the Risk of Periodontitis Development: Findings from a Systematic Review Composed of 13 Studies of Meta-Analysis with 71,531 Participants	Systematic review	Potential etiopathogenic and molecular links between obesity and periodontitis + IL-1
Stadler <i>et al.</i>	2016	Gingival crevicular fluid levels of cytokines/chemokines in chronic periodontitis: A meta-analysis	Systematic review	Potential etiopathogenic and molecular links between obesity and periodontitis + IL-1 + IL-8
Joshi <i>et al.</i>	2014	Association between obesity-related adipokines and colorectal cancer: A case-control study and meta-analysis	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + TNF-a and IL-6 + Adiponectin + Resistin
Joshi <i>et al.</i>	2014	Obesity related adipokines and colorectal cancer: A review and meta-analysis	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis + TNF-a and IL-6 + Resistin
Zimmermann <i>et al.</i>	2013	Local and circulating levels of adipocytokines in obese and normal weight individuals with chronic periodontitis	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + TNF-a and IL-6
Akram <i>et al.</i>	2017	Cytokine Profile in Chronic Periodontitis Patients with and without Obesity: A Systematic Review and Meta-Analysis	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis + IL-8
Akram <i>et al.</i>	2016	Resistin as potential biomarker for chronic periodontitis: A systematic review and meta-analysis.	Systematic review + meta-analysis	Potential etiopathogenic and molecular links between obesity and periodontitis + IL-8 + Resistin

(Table 1) *contd....*

Authors	Year	Title	Type of the Article	Topic(s)
Yamaguchi <i>et al.</i>	2007	Adiponectin inhibits osteoclast formation stimulated by lipopolysaccharide from <i>Actinobacillus actinomycetemcomitans</i>	Cross-sectional	Potential etiopathogenic and molecular links between obesity and periodontitis + Adiponectin
Karthikeyan <i>et al.</i>	2007	Leptin levels in gingival crevicular fluid in periodontal health and disease	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Leptin
Karthikeyan <i>et al.</i>	2007	Gingival crevicular fluid and serum leptin: their relationship to periodontal health and disease	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Leptin
Gonullu <i>et al.</i>	2010	Association between adiponectin, resistin, insulin resistance, and colorectal tumors	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Resistin
Suresh <i>et al.</i>	2018	Effect of nonsurgical periodontal therapy on plasma-reactive oxygen metabolite and gingival crevicular fluid resistin and serum resistin levels in obese and normal weight individuals with chronic periodontitis	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Resistin
Salman <i>et al.</i>	2019	Study of changes of obesity-related inflammatory cytokines after laparoscopic sleeve gastrectomy	Longitudinal	Potential etiopathogenic and molecular links between obesity and periodontitis
Patel <i>et al.</i>	2014	Gingival crevicular fluid and serum levels of resistin in obese and non-obese subjects with and without periodontitis and association with single nucleotide polymorphism at -420	Case-control	Potential etiopathogenic and molecular links between obesity and periodontitis + Resistin

Similar results were later reported by Reibel *et al.* (2003) and Bergstrom *et al.* (2004), showing that smokers had a higher prevalence of periodontal disease and worse PPD values and furcation defects compared to non-smokers [3, 27].

Martinez-Herrera *et al.* [24] in a recent review, concluded that smoking habit predisposes to periodontal disease and that smoking habit and obesity are independent risk factors for periodontal disease.

#### 4.2. Indirect Evidence of the Possible Association between Obesity and Periodontal Disease

The indirect evidence of the possible association between obesity and periodontal disease derived totally from 4 systematic reviews with meta-analysis and 1 systematic review with meta-analysis, is discussed below.

##### 4.2.1. Impact of Bariatric Surgery and Weight Loss on Periodontal Health Conditions

Fontanille *et al.* reported in their systematic review and meta-analysis a periodontal health status worsening 6 months after bariatric surgery, therefore recommending periodontal screening procedures even before bariatric surgery to avoid a postoperative worsening [28].

Conversely, de Souza *et al.* [29] concluded that bariatric surgery may improve the periodontal health status, and mainly the plaque index, in obese patients probably promoting behavioral changes, metabolic control of glycemic level, and reducing inflammatory mediators.

##### 4.2.2. Impact of Periodontal Treatment on Obesity

In the systematic review results of Papageorgiou *et al.*, after the periodontal treatment, no statistically significant

differences were found between obese and normal-weight in relation to most of the periodontal parameters [30]

Suvan *et al.* reported in a systematic review inconsistent evidence of different clinical responses to non-surgical periodontal therapy in obese subjects compared to nonobese ones [30, 31].

Conversely, Gerber *et al.* concluded in their systematic review that obesity may be associated with poorer periodontal health and might also decrease the therapeutic response to non-surgical periodontal treatment [32].

#### 4.3. Potential Etiopathogenic and Molecular Links between Obesity and Periodontitis

A strong relation between obesity and periodontal disease was reported by a systematic review, stating that obese subjects were significantly more prone to develop periodontal disease compared to non obese ones [33].

Moreover, Keller *et al.* in their systematic review, including many longitudinal studies, some of them with a 20 years follow-up, suggested that overweight, obesity, weight gain, and increased WC may be considered as risk factors for periodontal disease development and for periodontal parameters worsening [25].

Suvan *et al.* in a systematic review reported a positive relation between obesity and periodontitis [31], confirmed in a very recent review, showing that obese subjects were more prone to periodontal disease onset compared to normal-weight subjects, regardless of age and gender [34]

The potential mechanism underlying the putative mutual relationship between obesity and periodontitis may be related to low-grade inflammation.

The periodontal disease itself determines an increase in the circulating levels of pro-inflammatory cytokines, that contribute to the worsening of chronic systemic disorders [35], on one side, and the higher levels of cytokines secreted by the adipose tissue in overweight and obese subjects may affect local and systemic inflammation caused by periodontal disease, on the other side.

This bi-directional mechanism may be responsible for the increased levels of the inflammatory response markers, such as C-Reactive Protein (CRP), Nitric Oxide (No) and Myeloperoxidase (MPO), as well as of the pro-inflammatory cytokines secreted by the adipose tissue, such as Interleukin-1b (IL-1b); Tumour Necrosis Factor alpha (TNF-a); Interleukin-6 (IL-6); Interleukin-8 (IL-8); and Plasminogen-1 activator inhibitor [33, 36]. In addition, adipose tissue secretes also hormone-like proteins, called adipokines, such as Leptin, Adiponectin and Resistin; It is noteworthy that some of these play an important role in periodontal disease too [36 - 40].

#### 4.3.1. C-Reactive Protein

C-Reactive Protein is considered one of the main inflammatory markers [41].

Its serum concentration resulted higher in obese people compared to normal weight ones [31, 42]. Kopp *et al.*, similarly to Visser *et al.*, reported that increased serum levels of C-Reactive Protein were associated with serum IL-6 ones, released by the adipose tissue in larger amounts in obese compared to non obese subjects [43, 44].

In addition, serum CRP levels have been found higher in subjects suffering from periodontitis compared to periodontally healthy ones [45, 46]; these levels decreased after the periodontal therapy [47]. CRP was also detected in the saliva as well as in the gingival crevicular fluid of subjects affected by the periodontal disease [48, 49].

#### 4.3.2. Oxidative Stress

It has been proposed that obesity may affect chronic disorders through both the inflammatory state and the alteration of the oxidative state [50, 51].

Virgolici *et al.* observed that the plasmatic parameters of oxidative stress were altered in obese subjects compared to normal-weight ones [52]. Moreover, weight loss has been related to decreased oxidants formation [53].

Reactive oxygen species can be produced also in periodontitis [54], as proposed by Krol *et al.*, who assessed that the oxidative stress can lead to the formation of lesions in periodontal tissue [55]. Lipid peroxidation is one of the main events associated with inflammation in periodontal tissue [56].

#### 4.3.3. IL-1b

IL-1 is a pro-inflammatory cytokine active in immune response against microbial agents. IL-1 induces chemokines and prostaglandins secretion, together with metalloproteinases production, enhancing, in turn, tissue destruction [57].

IL-1b role in periodontal disease pathogenesis is well-established and its genetic variation is considered as a risk

factor for PD [41, 58]. Indeed, it has been hypothesized that only in obese subjects with IL1b polymorphism, the systemic inflammation related to obesity may affect PD progression, alternatively, it has been proposed that subjects genetically predisposed to IL-1b over-expression may be more susceptible to visceral adiposity formation and to PD development and severity [41].

#### 4.3.4. TNF-a and IL-6

TNF-a and IL-6, proinflammatory cytokines released by adipose tissue and immune cells, are detected in higher serum concentrations in obese compared to nonobese subjects, with a tendency to decrease with weight loss [59, 60].

Higher serum TNFa concentration has been reported in obese periodontally healthy subjects compared to obese subjects affected by PD, suggesting the existence of a relation between TNFa and obesity independently of the periodontal status, while increased serum IL6 levels resulted in subjects affected simultaneously by obesity and PD, indicating a synergistic role of these pathologic conditions in serum IL6 levels [61].

On the other hand, higher TNFa concentrations were reported in gingival crevicular fluids of overweight and obese subjects compared to normal-weight ones, collected from sites affected by both gingivitis and PD and may partially derive from the adipose tissue. This finding may indicate a putative negative effect exerted by obesity on PD, with crevicular TNFa elevation and subsequent connective tissue and bone destruction [61].

#### 4.3.5. IL-8

IL-8 is associated with the inflammation of the initial periodontal lesion and with chronic periodontitis [58]; however, no significant difference in IL-8 levels was found between obese and normal-weight subjects suffering from periodontal disease [62, 63].

#### 4.3.6. Inhibitor of the Plasminogen Activator

Inhibitor of the plasminogen activator secretion, involved in autocrine and paracrine signaling, promotes other chronic diseases, such as diabetes, cardiovascular disease and periodontal disease onset and/or worsening [36].

Inhibitor of the plasminogen activator serum levels and leptin levels have been reported to be reduced in the bloodstream from obese subjects [64].

#### 4.3.7. Adiponectin

Adiponectin, produced by the adipose tissue, is a 30-kDa polypeptide, increasing insulin sensitivity and decreasing circulating fatty acids [36].

Adiponectin exerts both an anti-inflammatory effect, mainly antagonizing TNF-a, and an anti-cancer effect, inhibiting cell growth and angiogenesis, together with pro-inflammatory cytokines secretion [59].

It has been found to inhibit osteoclast formation induced by periodontopathic bacteria Lipopolysaccharides [65] and



subsequent alveolar bone loss; in this perspective, adiponectin may be considered as a protective factor for PD [36].

The observation that adiponectin serum levels are reduced in type 2 diabetes, as well as in obesity, may explain the reduced protective effect even towards PD [36].

#### 4.3.8. Leptin

Leptin is a 16-kDa non-glycosylated peptide, produced by adipose tissue. Its serum levels correspond to adipose tissue total amount, resulting in increased levels in obese subjects. It is also produced by pre-adipocytes, under the paracrine stimulation of the surrounding macrophage-derived cytokines, especially IL-1, IL-6, TNF- $\alpha$ , and of the bacterial Lipopolysaccharides [36].

Leptin receptors are expressed on adipocytes and also on vascular endothelial cells and T lymphocytes, suggesting a possible role in immune response, possibly reducing regulatory T CD4<sup>+</sup> lymphocytes. In compliance with this hypothesis, leptin may favour periodontal tissue inflammation interfering with T cells activity [36].

Higher levels of serum Leptin have, indeed, been detected in periodontopathic patients. Conversely, gingival crevicular leptin concentrations resulted lower in periodontopathic sites compared to healthy ones probably due to leptin local consumption in the inflamed sites [66, 67].

#### 4.3.9. Resistin

Resistin is an adipokine and it is secreted from adipose tissue and monocytes/macrophages [68], involved in the inflammatory process, affecting the secretion of IL-6, TNF- $\alpha$  and Adiponectin [59, 60, 69].

Resistin serum level has been found to increase in several chronic inflammatory conditions, such as obesity, diabetes and rheumatoid arthritis [70].

Similarly, resistin was found consistently elevated in subjects suffering from periodontal disease [63], as confirmed by Patel *et al.*, who reported the association between periodontal inflammation and higher resistin levels [71].

## CONCLUSION

Although the majority of the studies reported a positive association between obesity and periodontitis, the heterogeneity of the classification criteria and of the clinical parameters employed in the studies, for both obesity and periodontitis evaluation, complicated the comparison of the results, thus considered inconclusive. The use of the Classification of Periodontal and Peri-Implant Diseases and Conditions proposed in the 2017 World Workshop [10 - 12] in the future studies might make studies results uniform and thus simpler to compare one another.

Most of the studies reported that the potential pathogenic mechanism underlying the relationship between obesity and periodontitis may rely on the shared and potentially inter-related low-grade inflammation, involving several cytokines, adipokines and oxidative stress. Anyway, although several putative molecular pathogenic links between obesity and

periodontitis have been highlighted, further studies, with longer follow-ups are needed to better understand the putative relation between obesity and periodontal disease, in order to possibly pave the way for novel biomarkers for obesity and periodontitis and for innovative preventative strategies and special recommendation for both obese and periodontal subjects.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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