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Literature Review

Analysis of leptin concentrations in oral fluids (saliva and crevicular gingival fluid) and blood in patients with chronic periodontal disease: systematic review of literature

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Abstract – Objective: The objective of this systematic analysis was to perform a qualitative and quantitative synthesis of the literature concerning salivary and serum leptin variations in patients with chronic periodontitis (CP) compared with healthy subjects. Saliva leptin concentration analysis could be a relevant and non-invasive biological test for the evaluation of periodontal disease in both medical and clinical trials, beyond the clinical and radiographic elements. **Material and Method:** Querying the PubMed and Web of Science databases identified articles that met our inclusion criteria. Quantitative analysis of the literature data was performed with the Review Manager 5.3 software. **Results:** The qualitative analysis included 14 articles and showed a decrease of salivary leptin (5 studies out of 5) and an increase of serum leptin (11 of 12 studies) in patients with CP compared to unaffected subjects of CP. Quantitative analysis was performed on 4 trials. For salivary leptin, we confirmed a decrease in its level in patients with CP with a standardized mean difference (SMD) of −2.27, 95% CI [−2.68, −1.86]. The difference was highly significant but we detected a very important heterogeneity in this dataset ($I^2 = 94\%$). For serum leptin, we also confirmed an increase in its rate in patients with CP with an SMD of 2.18, 95% CI [1.75, 2.61]. The difference was highly significant but the heterogeneity measured in this dataset was also too high ($I^2 = 95\%$). Conclusion: The current level of evidence was insufficient to assert an increase in serum leptin and a decrease in salivary leptin in CP patients compared to healthy controls due to a great heterogeneity of the values measured in the studies.

Introduction

Periodontal disease is a major oral health problem with a multifactorial origin that affects a large number of people around the world whose origin is multifactorial. In Europe, >50% of the population is affected, with prevalence increasing to 70–85% in the 60–65 age group [1].

In 1999, Armitage [2] established a nosological classification splitting periodontal disease into seven distinct forms. Currently, this has been simplified by the terms acute periodontitis (AP) and chronic periodontitis (CP) [3].

Aggressive periodontitis, AP, is a very destructive form of periodontal disease. APs include precocious, prepubertal, juvenile, rapid progressive, and refractory periodontitis. They can be localized or generalized and affect 10–15% of the adult population around the world [4]. The earlier age of onset, faster progression rates, destruction patterns, clinical signs of inflammation, and lower relative plaque and calculus abundance [3] distinguish AP from CP.

CP is the most common form of periodontitis. It can begin at any time of life but is most often detected in adulthood. Periodontitis is localized when <30% of sites are affected and generalized when >30% of sites are affected. Its severity is assessed according to the loss of the attachment: light, 1–2 mm; moderate, 3–4 mm; and severe, >5 mm.

Specific clinical indices are used in epidemiological studies and daily practice to determine the degree of impairment and monitor the progress of patients' periodontal status. The aim is to evaluate gingival inflammation [5], the presence of dental plaque [6] and tartar, the clinical level of periodontal attachment, the pocket depth in mm, and mobility and/or tooth displacement and to look for bleeding on probing [7].

The initiation and progression of periodontal disease have been reported as the result of complex interactions between

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specific subgingival bacteria and the host's immunoreactive response [8,9]. This host response to periodontal disease consists of immune cells and their products (particularly cytokines) and complex interactions [10].

Immunocytes activated by exogenous bacteria destroy the bacteria and release myriads of substances, called inflammatory cytokines, which exert an antibacterial effect and contribute to the destruction of the periodontal tissues [11].

Therefore, considerable attention has been paid in establishing an association between periodontitis and certain inflammatory cytokines, such as leptin, which could modulate the host's response to infectious agents and play a role in certain inflammatory conditions because of its direct effect on innate and adaptive immune cells [11], including periodontal ligament cells, which are major resident cells of the periodontium [12].

The plasma levels of leptin increase in cases of acute inflammation and acute severe diseases such as sepsis. High plasma concentrations of leptin have been suggested as a risk factor for cardiovascular disease. The resolution of inflammation depends on the balance between pro- and anti-inflammatory cytokines [10].

These markers present in gingival crevicular fluid, saliva, and plasma have the potential to provide insight into the pathological process of periodontitis well beyond conventional clinical and radiographic findings. In addition, saliva is a noninvasively accessible biological fluid containing a set of locally produced biomolecules. Saliva has become a potential diagnostic fluid in the evaluation of oral and systemic diseases, particularly periodontal diseases [13,14].

There are two meta-analyses [15,16] evaluating the relationship between serum leptin concentrations and periodontal disease, but these do not rule out other adipokines, including adiponectin.

The aim of our study was to perform a qualitative and quantitative synthesis of the literature concerning the presence of leptin (salivary and serum) in patients with CP.

Materials and methods

Research strategy

Research studies were conducted using the PubMed and Web of science bibliographic databases.

Two computer queries were made using the following terms:

- First request: [*leptin and periodontal disease*] [MeSH]
- Second query: [*leptin and periodontal disease]* [MeSH major topic]

We then manually revised all bibliographic reference lists from previously selected studies to identify clinical trials evaluating leptin difference in patients with and without periodontitis.

The research concerned literature published before March 2019.

Selection of studies and eligibility of criteria

Inclusion criteria

Type of study

Randomized trials, published in English or French before March 2019, were included. A clinical trial has been considered randomized if the author declares it as such or in the text the word "random, randomly, randomized, or randomization" appear [17].

Type of intervention

Studies evaluating salivary and/or serum leptin variations in CP and healthy subjects.

Judgment criteria

The diagnostic criteria for CP were established for each patient on the basis of the following clinical results: gingival index, probing depth ≥4 mm in 3–4 sites in >4 teeth in each quadrant, loss of clinical attachment >1 mm, and radiological evidence of bone loss without specifying the nature of the X-ray.

Exclusion criteria

The following cases have been excluded:

- Therapeutic trials where the salivary and/or serum leptin dosage was not assessed in both healthy and patients with CP.
- Studies conducted in animals or in humans *in vitro*.
- Studies where chronic periodontal disease is associated with a general pathology when it is mentioned.
- Factors that have been excluded are as follows:
  - Smoking
  - Alcoholism
  - Body mass index (BMI) >30
  - Pregnant and lactating women
  - Any antimicrobial, anti-inflammatory, or immunosuppressive treatment in the last 6 months known to affect periodontal status
  - Periodontal treatment in the last 12 months
  - All patients who did not provide their consent.

Nonrandomized cohort studies, nonrandomized trials, and studies not written in English or French were also excluded.

Data collection

The studies identified during the electronic research stages were listed in the chronological order of publication in a summary table indicating the principal author's name, publication year, journal review, study type, and exclusion criteria.

This information will be presented in the form of tables describing the selected studies.

After this census phase, a flow diagram that graphically represents the study selection process was created.

Extraction of data

The studies eligible for the analysis are presented in a summary table specifying the following:
- The principal author, the journal, and the publication year
- The description of the judgment criteria affected subjects/healthy subjects
- Quantitative evaluation of the judgment criterion in each group
  - Number of subjects in recruitment and distribution of case/control subjects
  - The characteristics of the population studied in each group
    - Age
    - Sex ratio
    - BMI
    - The type of leptin studied (serum and/or salivary)

To obtain the relevant missing information from included studies for the meta-analysis, we attempted to contact the corresponding authors twice by e-mail without receiving a response from them.

Risk of bias in the evaluation

Case selection was done by two trained and qualified reviewers who considered a case adequate when a patient was representative for the defined type of periodontitis.

Selection of controls was appropriate when sampled from the same population as cases. The cases and controls were compared by sex, age, BMI, and group size.

Both reviewers included studies for which patients had a normal BMI, according to the 2002 World Health Organization table, and obesity influencing leptin levels present in serum.

Definition of the group

We divided case–control comparisons into three categories: patients with AP, subjects with CP, and healthy control subjects.

The healthy group consisted of people who showed no clinical sign of gingival inflammation or bone loss and who had good oral hygiene.

According to the articles, the dosage of leptin was present in saliva, gingival crevicular fluid, or in the blood.

Quantitative analysis

Quantitative data on serum and salivary leptin and the total number of patients with CP and control subjects were extracted to calculate, for each study, the standardized mean difference (SMD) and the 95% confidence interval (95% CI). All data were presented in the form of a data summary table. Statistical calculations were performed with the help of Review Manager 5.3.

SMD is used as a summary statistic in the meta-analysis when all studies evaluate the same result but measure it in various ways. In these circumstances, it is necessary to standardize the results of the studies on a uniform scale before they can be combined. SMD expresses the magnitude of the effect of the intervention in each study relative to the variability observed in this study.

$$\mathrm{SMD} = \frac{\text{difference in average result between groups}}{\text{the standard deviation of results between participants}}$$

Therefore, studies in which the mean difference between groups is of the same proportion as the standard deviation between the participants will have the same SMD, regardless of the actual scales used to perform the measurements.

Necessarily, the studies selected for a systematic review will not be identical and all the forms of variability within these studies will be grouped under the term of heterogeneity. The observed differences in the population recruited, the nature of the intervention performed, or the judgment criteria constitute the clinical variability. The methodological variability concerns the risk of bias and the design of each study. The variability in the measurement of the effect in the different studies results from the addition of clinical and methodological variability and can be quantified by measuring the statistical heterogeneity.

The Chi-square test proposed by Review Manager assesses whether the observed difference between studies is due to chance alone. A high Chi-square or low *P* value indicates heterogeneity in estimating the effect of an intervention.

The interpretation of these figures should be cautious, as it is highly dependent on the number of studies selected and the size of the samples from each of them, and small and few studies expose to under-screening for heterogeneity.

This means that even though a statistically significant result may indicate a problem of heterogeneity, a nonsignificant result should not be taken as evidence of the absence of heterogeneity. Thus, a *P*-value of 0.10 is sometimes used instead of the conventional 0.05 level to determine statistical significance.

Methods have been developed to quantify the inconsistency between studies that focus on assessing heterogeneity rather than assessing its impact on the meta-analysis.

$$I^2 = \left(\frac{Q - \mathrm{df}}{Q}\right) \times 100\%$$

Q = result of Chi-squared test and df = number of degrees of freedom of Chi-squared test; I^2 is the percentage of variability in the measure of effect attributable to heterogeneity rather than sampling fluctuations.

The value of I^2, according to the Cochrane Handbook for Systematic Review, will be interpreted as follows:
- 0–40%: insignificant heterogeneity
- 30–60%: moderately significant heterogeneity
- 50–90%: heterogeneity to be considered
- 75–100%: very significant heterogeneity

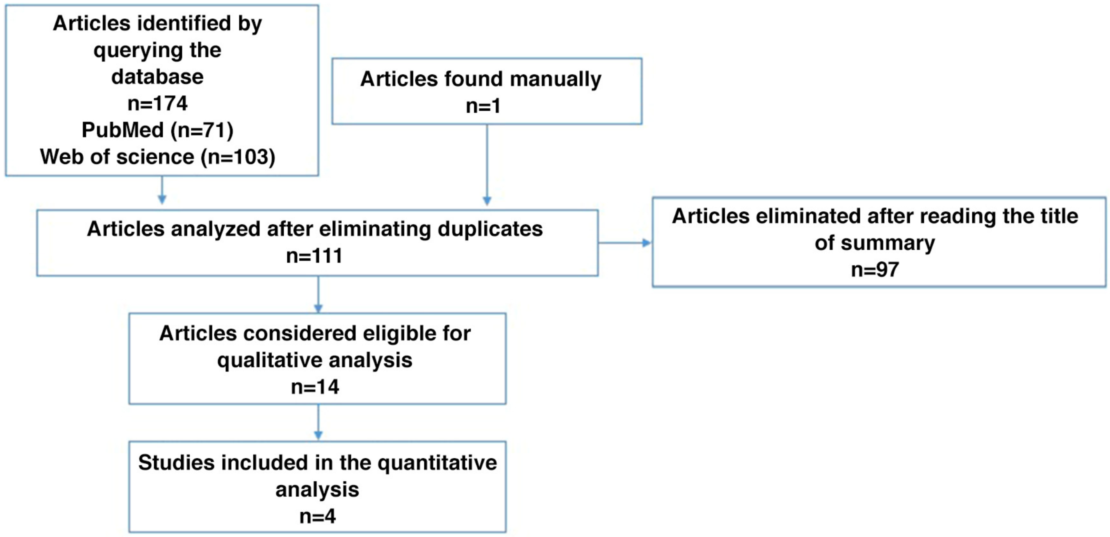

Fig. 1. Flowchart of the study selection process.

Results

Figure 1 describes the number of publications identified during the research strategy and details the process for selecting clinical trials. The manual revision of the bibliographic reference lists made it possible to select one additional publication that could be included in the analysis. The study characteristics are presented in Table I.

All the results of the qualitative analysis of the 14 studies were grouped together as a table (Tab. II). It groups together studies of leptin in its various forms in patients with CP with a BMI of $\leq$30 compared with healthy controls. All of these studies were not included in the quantitative analysis because they combined factors that we decided to exclude from our study.

Only four randomized trials were selected for quantitative analysis. They compared leptin dosages between the CP group and the control group. We decided not to include the Khorsand study [11] as the data collected on CP were too different from the other included studies and the definition criteria of the CP were not clearly specified in this publication.

Description of selected studies for quantitative analysis

The four studies selected for quantitative analysis recruited a population of 186 patients from throughout India. The age of the patients included varies between 30 and 60 yr. All these studies analyzed the salivary and serum leptin dosage, except for the Karthikeyan study [18], which only studies the salivary leptin dosage.

In the two Purwar studies [20,21] and the Karthikeyan study [18], CP was defined for each patient by plaque index, gingival index, pocket depth, and clinical level of periodontal attachment that were scored on six sites (mesiovestibular, vestibular, distovestibular, mesiolingual, lingual, and distolingual) in each tooth, excluding the third molar, and the presence of bleeding during probing was evaluated using a sterile periodontal probe. All clinical parameters were recorded by one independent person.

The diagnosis of CP was established on the basis of clinical findings of gingival inflammation, clinical loss of periodontal attachment of >5 mm for Purwar [20,21] and only >1 mm for Karthikeyan [19], pocket depth of ≥4 mm in 3–4 sites in >4 teeth in each quadrant, and radiographic evidence of bone loss.

On examination, >30% of the sites examined were positive for the above criteria, and the patients were classified under generalized CP.

For Karthikeyan [18], CP was based on the clinical signs of gingival inflammation with loss of attachment, radiographic evidence of bone loss, and gingival index, as well as Ramfjord's Periodontal Disease Index.

The salivary samples for obtaining leptin concentrations in both media were performed according to two separate procedures specific to each of the two authors [18–21].

Purwar [20,21] took nonstimulated whole salivary samples (approximately 2 ml) that were collected using a modified drainage method. Patients were asked to expectorate in disposable polypropylene tubes every 30 s over a period of 5 min. The desired volume (about 2 ml) of saliva was pipetted into an Eppendorf tube. Participants who were unable to expectorate the required saliva volume were excluded. The saliva samples were centrifuged at 4000× rpm for 10 min to remove cell debris, and 0.5 ml of the supernatant was stored in 1.5 ml aliquots at −80 °C until the analysis was performed.

In [18,19] the CP group, Karthikeyan collected the site with the highest gingival index, pocket depth, and clinical level of periodontal attachment (range, 1–4 mm) for gingival crevicular fluid sampling. The site chosen for sampling was isolated with a cotton roll, and the supragingival plaque was removed with a curette, without touching the marginal gingiva. Crystalline

Table I. Risk of bias; *N* = number of studies considered adequate for the corresponding element.

Study characteristics	Studies *N*	Bias risk evaluation	Studies *N*
Year of publication		**Selection**	
≤2010	2	Definition of case	14
2011–2015	11	Selection of case	14
≥2016	1	Definition of controls	14
		Selection of controls	14
Study design		**Comparability**	
Case control	14	*As a function of age*[*]	
		<18 years old	1
		25–40 years old	3
Type of periodontitis		Over 40 years old	10
Chronic periodontitis	12		
Unspecified periodontitis	2	*As a function of sex*	
		Equality respected	2
Leptin studied		Differences between male and female	11
Salivary	5	Not mentioned	1
Serum	12		
		Size of group	
		<60	6
		>60	8
		As a function of other factors (BMI)	14
		≤30	
		Measurement criteria	
		Measurement description	14
		Measurement validation	14

[*] Only one study provided the average age (Karthikeyan 2007 [18]).

Table II. Biological publications comparing leptin dosage in patients with periodontitis compared to healthy controls. ↑ : significantly high concentrations, ↓ : significantly decreased concentrations, N : number.

	Studies No. =	Chronic periodontitis
Leptin		
Salivary ↓	5	Karthikeyan 2007 [18] Karthikeyan 2007 [19] Purwar 2015 [20] Purwar 2015 [21] Khorsand 2016 [11]
Serum ↑	12	Karthikeyan 2007 [19] Gangadhar 2011 [22] Ay 2012 [23] Zimmermann 2013 [24] Gundala 2014 [25] Thanakun 2014 [26] Purwar 2015 [21] Purwar 2015 [20] Mendoza-Azpur 2015 [27] Zeigler 2015 [28] Leira 2017 [29]
↓		Sete MR 2015 [30]

gingival fluid specimens were obtained before probing the site by placing micro capillary pipettes. At each test site, a standard volume of 1 ml was collected using micropipette calibration. Any trial site that did not express any volume of gingival crevicular fluid and/or a micropipette that was contaminated with blood and saliva was excluded from the study. The gingival crevicular fluid collected was immediately transferred to a plastic vial and stored at −70 °C until the time of testing.

The serum samples were taken, identically for the two authors Karthikeyan and Purwar [18–21] by peripheral venipuncture. After 1 h, the serum was separated from the blood by centrifugation. Each tube was designated by a tracking number and stored at −80 °C until further analysis could be performed.

The two authors [18–21] performed the same technical procedure for leptin analysis using highly sensitive enzyme-linked immunosorbent assay (ELISA) kits to detect leptin levels in saliva and serum. Each plate was checked prior to use to ensure that the standard curve measured leptin standards (0–1000 µg/ml) within the indicated range of the dosage. The absorption of the colored reaction of the substrate was read on the ELISA reader using 405 nm as the primary wavelength. Each patient was used as the unit of analysis. Total leptin was

Table III. Studies included in the quantitative analysis M/F: Male/Female.

Articles	Study type	Serum/ salivary leptin	Age		Sex: M/F	BMI		Group size	
			Case	Controls		Case	Controls	Case	Controls
Purwar Acta Odontologia Scandinavica 2015	case–control	Serum/saliva	35	60	24/20	20.45 ± 1.23	20.82 ± 1.67	22	22
Purwar Journal of Periodontology 2015	case–control	Serum/saliva	49.3	49.9	49/35	20.62	20.69	44	40
Karthikeyan Journal of Clinical Periodontology 2006	case–control	Serum/saliva	30–39		21/21	Normal BMI < 30		14	14
Karthikeyan Journal of Periodontal Research 2007	case–control	Salivary	37.2		20/15	Normal BMI < 30		15	15

determined in picograms (μg), and calculation of the concentration in each sample was performed by dividing the amount of leptin by the sample volume (μg/ml).

The characteristics of the included studies are detailed in Table III.

Analysis of the risk of bias in studies

Power bias

Among the four studies, three studies [19–21] obtained a result with $p < 0.05$, and one study with $p < 0.003$ corresponded to a highly significant study.

Sampling bias

From the available cohort descriptions, the four studies recruited cases and controls from the same population. For the four studies, it was explicitly stated that the witnesses did not have a personal history of periodontitis in the 12 months preceding recruitment. In addition, all studies are comparable by age, sex, and BMI (Tab. I).

Most studies on periodontitis applied adequate diagnostic criteria; the criteria for CP and Armitage periodontitis classification were applied by all four studies.

Sampling and measurement methods were adequate and described in all studies. With regard to the serum and saliva collection procedure, all studies applied the same protocol.

The main technique for analyzing leptin concentration was done using the ELISA test in all studies.

Heterogeneity bias

The main bias of our study is represented by the heterogeneity of the samples that were prepared differently (in total saliva or gingival crevicular fluid). As a result, we chose to analyze SMD rather than relative risk to correct this bias. We also ensured certain homogeneity in the four selected final studies with regard to the populations studied, the main endpoint, and the absence of systemic diseases associated with CP.

Quantitative analysis

We conducted two series of comparative analyses:

- Analysis 1: salivary leptin dosage in CP vs. control
- Analysis 2: serum leptin dosage in CP vs. control.

The results of each analysis (SMD, 95% CI) are presented using Review Manager 5.3.

1. Regarding the comparison of salivary leptin, we measured an SMD of −2.27, 95% CI [−2.68, −1.86]. The difference is highly significant, but we detected significant heterogeneity in this dataset ($I^2 = 94\%$) (Fig. 2).
2. For the results of the serum leptin comparison, we measured an SMD of 2.18, 95% CI [1.75, 2.61]. The difference was highly significant. The heterogeneity measured in this dataset was also too large ($I^2 = 95\%$) (Fig. 3).

Discussion

For several years, the literature on the influence of leptin on systemic and periodontal diseases has been steadily increasing and becoming controversial. Data from the first meta-analysis suggest that serum leptin levels are significantly higher and salivary leptin levels are lower in patients with CP than in healthy subjects. The results of our analysis show similar trends.

Study or Subgroup	Chronic periodontis Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Karthikeyan et al. 2006	1,071.89	160.95	15	2,292.69	187.29	15	4.2%	-6.80 [-8.78, -4.82]
Karthikeyan et al. 2007	1,312	215	14	2,658	339	14	7.4%	-4.60 [-6.10, -3.11]
Purwar el al. 2014	6,200.61	2,322.11	44	8,799.6	901.7	40	71.5%	-1.44 [-1.92, -0.95]
Purwar et al. 2015	4,710.1	1,133.21	22	8,721.1	1,019.58	22	16.8%	-3.65 [-4.65, -2.66]
Total (95% CI)			**95**			**91**	**100.0%**	**-2.27 [-2.68, -1.86]**

Heterogeneity: $Chi^2 = 48.36$, df = 3 (P < 0.00001); $I^2 = 94\%$
Test for overall effect: Z = 10.92 (P < 0.00001)

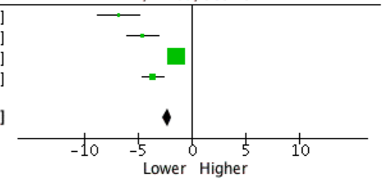

Fig. 2. Forest plot of salivary leptin concentrations in patients with chronic periodontitis versus controls. The squares represent the effect sizes of the individual studies (the size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the total size of the effect (the horizontal width indicates the 95% CI).

Study or Subgroup	Chronic periodontis Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Karthikeyan et al. 2007	12,082	1,815	14	8,783	1,748	14	22.9%	1.80 [0.90, 2.70]
Purwar el al. 2014	11,600	705.01	44	7,616.62	1,169.83	40	31.1%	4.13 [3.36, 4.90]
Purwar et al. 2015	10,749	2,062.24	22	8,085	2,859.68	22	46.0%	1.05 [0.42, 1.68]
Total (95% CI)			**80**			**76**	**100.0%**	**2.18 [1.75, 2.61]**

Heterogeneity: $Chi^2 = 37.63$, df = 2 (P < 0.00001); $I^2 = 95\%$
Test for overall effect: Z = 9.95 (P < 0.00001)

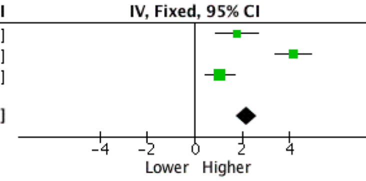

Fig. 3. Forest plot of serum leptin concentrations in patients with chronic periodontitis versus controls. The squares represent the effect sizes of the individual studies (the size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the total size of the effect (the horizontal width indicates the 95% CI).

We performed an electronic and manual literature review ensuring an exhaustive character of our selection. Our selection criteria were different from those of Zhu [15] and Jain [16] as we included only randomized case-control trials for CP, both salivary and serum leptin dosages. Our study selection criteria ensured certain homogeneity in the study populations (in terms of age, sex distribution, group size, and BMI), the primary endpoint, and the lack of systemic diseases associated with CP.

We chose to exclude patients whose BMI was >30 because an increase in BMI results in an increase in serum leptin; it is the obese (ob) gene that appears to be involved in this mechanism, with a greater amount of ob mRNA found in adipocytes of obese subjects than in those of subjects with normal weight.

The populations studied are also homogeneous in the definition of CP, serum data collection, and independent operators.

In agreement with Zhu [15] ($I^2 = 91.6\%$), we also measured an excessive heterogeneity during the serum leptin comparison of subjects with CP versus healthy subjects.

The significant heterogeneity modifies the interpretation of our results and presents one of the weak points of our study.

However, strict adherence to the inclusion and exclusion criteria limited the sample size of the study. Further longitudinal interventional studies with larger samples are needed to potentiate the role of salivary and serum leptin as a reliable biomarker in patients with periodontitis. It might be interesting to compare AP and CP in later studies as well.

Only Zhu's meta-analysis of [15] serum leptin can be compared to our study because Jain's [16] meta-analysis does not present precise data on leptin dosages and does not exclude systemic diseases from the study. Zhu *et al.* [15] obtained similar results in our study, favoring an increase in serum leptin levels in patients with periodontitis compared with those in controls in the population with a BMI of <30.

The role of leptin as a potential biomarker of periodontitis is suggested in different meta-analyses and [15,16] deserves to be emphasized. In fact, monitoring the adipokine profile may allow clinicians to predict risk factors of periodontitis. Future research should be focused on distinguishing what comes first and what is the cause and effect; recognizing bilateral relationships between periodontitis and systemic diseases will encourage endocrinologists and odontologists to collaborate closely in the future for treatment of patients with diabetes, obesity, atherosclerosis, and periodontal disease.

Conclusion

We can conclude that the current level of evidence is insufficient to assert that there is definitely an increase in serum leptin and a decrease in salivary leptin in patients with CP compared with healthy control subjects.

Further research could evaluate the influence of leptin levels on the response to periodontal disease treatment in a large patient population in randomized trials with rigorous methodology.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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