Study of *Porphyromonas gingivalis* in periodontal diseases: A systematic review and meta-analysis

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Abstract

**Background:** The mouth cavity hosts various types of anaerobic bacteria including *Porphyromonas gingivalis*, which causes periodontal inflammatory diseases. *P. gingivalis* is a gram-negative oral anaerobe and is considered as a main etiological factor in periodontal diseases. Several studies have reported a relationship between *P. gingivalis* in individuals with periodontal diseases and a critical role of this bacterium in the pathogenesis of periodontal diseases. The present study aimed at estimating this probability using a meta-analysis.

**Methods:** We searched several databases including PubMed, Scopus, Google Scholar, and Web of Science to identify case-control studies addressing the relationship between *P. gingivalis* with periodontal diseases. A total of 49 reports published from different countries from 1993 to 2014 were included in this study. I² (heterogeneity index) statistics were calculated to examine heterogeneity. Data were analyzed using STATA Version 11.

**Results:** After a detailed analysis of the selected articles, 49 case-control studies with 5924 individuals fulfilled the inclusion criteria for the meta-analysis. The healthy controls included 2600 healthy individuals with a Mean±SD age of 36.56±7.45 years. The periodontal diseases group included 3356 patients with a mean age of 43.62±8.35 years. There was a statistically significant difference between *P. gingivalis* in periodontal patients and healthy controls; 9.24 (95% CI: 5.78 to 14.77; P = 0.000). In the other word, there was a significant relationship between the presence of *P. gingivalis* and periodontal diseases.

**Conclusion:** Analyzing the results of the present study, we found a strong association between the presence of *P. gingivalis* and periodontal diseases. This result suggests that another research is needed to further assess this subject.

**Keywords:** *Porphyromonas gingivalis*, Periodontal Diseases, Chronic Periodontitis, Aggressive Periodontitis, Gingivitis

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Introduction

Periodontal diseases are complicated oral diseases, which are specified by bacterial-induced inflammatory destruction of tooth-supporting tissues (1). Periodontal diseases can be described as one of the predominant polymicrobial infections of humans, which can advance and lead to gum retrogression, soft tissue harm, weakness of the bone, eventual osteoporosis and tooth loss (severe periodontitis). Periodontal disease have many risk factors including smoking and diabetes, moreover, several bacteria have been connected to the intensity and progress of periodontitis (2, 3). The oral cavity is a source of different microorganisms that cause a class of infections and inflammation inside the cavity (4). So far, more than 700 bacterial taxa have been identified in samples taken from oral cavities (2). Evidence for periodontal etiology relies on the performance of several criteria described by Socransky (5).

Of the bacteria believed to be pathogenic in periodontal disease, *P. gingivalis* has been extensively studied due to its unique ability to evade the immune response (6). *P. gingivalis* is a gram-negative oral anaerobe and considered as a main etiological factor in periodontal diseases by produc-

↑What is “already known” in this topic:

More than 700 bacteria are found in samples taken from the oral cavity. In several studies, qualitative information of the *p. gingivalis* has been done in oral diseases.

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What this article adds:

A variety of qualitative studies have been done on Gengivals, but there are just a few conducted quantitative studies on it which their results are poor and inconsistent as well. So a Meta Analysis method is used in this study to integrate the results of the all previous quantitative investigations into a unique and statistically valid conclusion.
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ing a number of virulence factors and extracellular proteases such as lipopolysaccharide, fimbria, gingipain etc., resulting in destruction of periodontal tissues (7–11). The various surface components of P. gingivalis enable the bacterium to interact with the external medium and simplify its growth, nutrient gain, colonization, and formation of a biofilm that protects it against the host’s defense (12, 13). In addition to being painful, persistent dental disease is linked to diabetes, heart disease, high blood pressure, and MS in later years of life; therefore, extensive studies have been conducted to control the bacteria causing dental diseases (14).

The pathogenicity of P. gingivalis has been investigated in a variety of experimental animal models such as rat, mouse, rabbit, drosophila, and cell models, showing complicated mechanisms of P. gingivalis -host interplay in the expansion of periodontal diseases (15-19).

Although many studies aimed to specify the microbiotic dependents of specific disease types and the extent of periodontal destruction, there is yet no quantitative data on the levels of P. gingivalis in periodontal diseases. To authenticate the studies, performing a meta-analysis seemed necessary. Thus, this study aimed at evaluating the prevalence of P. gingivalis in patients with periodontal diseases.

Methods
Search Strategies
A database was built for the prevalence of P. gingivalis periodontal diseases from 1993 to 2014 using PubMed, Web of Science, Google scholar Medline, Embase, the Cochrane Library, and Scopus databases. The search was restricted to original articles published in English that presented the prevalence or incidence of P. gingivalis among patients with periodontal diseases. The following keywords were used from medical subject headings, titles, or abstracts were used with the help of Boolean operators (and, or): P. gingivalis, chronic periodontitis, aggressive periodontitis, and gingivitis. We also searched bibliographies of the retrieved articles for additional references. The titles from the search results were examined closely and determined to be suitable for potential inclusion into the study. In addition, the references from the selected articles were examined as a further search tool. Relevant trials noted in the reference lists of each selected article were also evaluated for inclusion. All papers whose keywords were present in their titles or abstracts were used in the initial list and other unrelated articles were eliminated.

Inclusion and Exclusion Criteria
All original articles presenting case-control studies on the prevalence of P. gingivalis in periodontal diseases were considered. The selection of articles for review was completed based on 3 stages: titles, abstracts, and full texts. When necessary, authors were contacted for additional information. Studies were excluded if they presented insufficient data, if they were not epidemiologic studies, and if they focused on the prevalence of P. gingivalis in diseases other than periodontal diseases. Review articles, congress abstracts, studies reported in languages other than English or Persian, meta-analyses or systematic reviews, and duplicate publication of the same study were also excluded. The STROBE (strengthening the reporting of observational studies in epidemiology) statement was used for quality control of the studies. We assessed the quality of studies according to variables related to the study objectives, characteristics of the study population, clearly explained inclusion/exclusion criteria, data collection method, as well as the validity, explicit findings, and appropriate data analysis methods of the studies.

Data Extraction
For all studies, the following data were extracted: first author, year of publication, location, sample size, sample age, P. gingivalis screening method, and sample specimens, percentage of P. gingivalis in patients and healthy individuals. Abstracts and full articles were reviewed independently by 2 of the authors, and if results were discordant, papers were reviewed jointly until the differences were resolved.

Data Synthesis and Analysis
Studies were combined based on the sample size, mean and standard deviation. The difference between the average variance of the normal distribution was calculated using the formula of 2 integrated variance. To assess the heterogeneity of the studies, Cochran test and the I² (heterogeneity index) were used. Due to the significant heterogeneity in the studies, random effects model was used. The findings are described in forest plots (the point estimations and their 95% CI). To examine publication bias, Begg plot and regressions method were used. P value less than 5% was considered as a significant heterogeneity test. Sensitivity analyses were prespecified. Statistical analyses were performed using STATA version 11.

Results
Our initial search strategy yielded 172 potential articles for inclusion; in a secondary screening, 48 of them were excluded based on title and abstract evaluation, and 124 were retained for detailed full text evaluation. We excluded another 75 articles (9 review articles, 18 articles with other diseases, 13 for lack of enough information, 23 articles with percentage of P. gingivalis only in patients group, and 12 duplicates). After a detailed analysis of the selected articles, 49 case-control studies with 5924 individuals (3356 patients and 2600 healthy individuals) fulfilled the inclusion criteria for the meta-analysis (Fig. 1). The characteristics of the 49 trials and the quality scores included in the meta-analysis are summarized in Table 1.

The healthy controls comprised 2600 healthy individuals, with the age range of 14 to 67 years and a mean age of 36.56±7.45 years. The periodontal diseases group included 3356 patients with periodontal diseases, ranging from 14 to 59 years, and with a mean age of 43.62±8.35 years.

In the present study, a statistically significant difference was found between P. gingivalis in periodontal patients and healthy controls; 9.24 (95% CI: 5.78 to 14.77; p<0.001) (Fig. 2). In the other word, on analyzing the results of the present study, a strong association was found between the
presence of \textit{P. gingivalis} and periodontal diseases (Fig. 2).

According to publication bias figure, the effect of bias in these studies was not significant. In fact, most studies were located inside the Funnel Plot, and thus the results of most relevant studies, considering the title, were included into the analysis (p = 0.005) (Fig. 3).

Discussion

It is widely accepted that the etiology of periodontal diseases is polymicrobial in nature. Worsening or improvement of periodontal situation goes along by a change in the bacterial composition of subgingival plaque (20). It has, therefore, been suggested that microbial testing be used to diagnose and optimize periodontal therapy and assess its outcome. However, this strategy may be confusing as the beginning and the progress of periodontal diseases are impressed by interaction of myriad genetic, environmental, host, and microbial factors (20-23). Furthermore, molecular studies reveal an unexpectedly high diversity of microorganisms and progression of disease remains to be investigated. Nevertheless, current microbiological testing

Table 1. Study characteristics

<table>
<thead>
<tr>
<th>First author (Reference)</th>
<th>Country (year)</th>
<th>Case Control</th>
<th>Mean age</th>
<th>Sex</th>
<th>Type of disease</th>
<th>Sample specimens</th>
<th>Methods of bacterial measurement</th>
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<td>M. Rafiei, et al.</td>
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Mostly involves the classic doubtful oral pathogens (20). The aim of this study was to evaluate the association between the presence of *P. gingivalis* and periodontal diseases. *P. gingivalis* has been known to be a risk factor for periodontal diseases although its exact roles in the initiation and progression of the oral diseases remain unclear (15, 24). In the present study, a significantly strong positive correlation was found between the presence of *P. gingivalis* and periodontal diseases. Published data suggests that the flora associated to chronic periodontal diseases is dominated by...

Fig. 1. The flow diagram of studies identified the systematic review and meta-analysis

Fig. 2. Meta-analysis of the association of *P. gingivalis* with periodontal diseases. Square represents effect estimate of individual studies with their 95% confidence intervals with size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author’s names, based on a random effects model.
the presence of Gram-negative anaerobic bacteria, and especially *P. gingivalis* (25). Slots and Ting described a synergistic association of *P. gingivalis* in presentations with evolutive lesions (26). Van Winkelhoff et al. concluded that *P. gingivalis* was the marker of a destructive lesion (27). Authors of previous studies reported similar results. The authors of various studies on *P. gingivalis* have reported that these pathogens are able to pollute soft tissues and flee the surgical debridement of periodontal lesions (28, 29).

Many epidemiological studies report a positive association between the presence of *P. gingivalis* and periodontal diseases (7, 25, 30-36), whereas in some studies, no association was found between the presence of *P. gingivalis* and periodontal diseases (20, 37-41). This has also been shown by Kumar et al. (42). The fact that all types of bacteria studied could be detected, even in healthy controls, might indicate that the presence of periodontal pathogens does not necessarily lead to periodontal diseases (1). However, these species show just a small percentage of whole bacteria, and the open-ended approach of their study may not be geared to indicate an association of this species with the disease (20). In another study, Kumar et al. demonstrated a significant association of *P. gingivalis* with chronic periodontitis using PCR amplification of 16S rRNA genes (43).

Some studies have reported a strong association between the presence of *P. gingivalis* and periodontitis, but did not find any association between the presence of *P. gingivalis* and gingivitis (1, 12, 44, 45). Although a number of putative bacteria are considered to be associated with chronic periodontitis, it has become clear that other factors are involved in the etiology of several types of periodontitis. In the other word, *P. gingivalis* is one of the risk factors responsible for periodontitis. *P. gingivalis* is one of the bacteria that form the classic ‘red complex’ described by Socransky et al. (46). It is the bacteria most frequently found in patients with periodontal disease (12). Wara-aswapati et al. (47) found that the mean age of patients was higher than that of the healthy participants. *P. gingivalis* has been reported to be related to adult periodontitis (48, 49). In a study by Liu et al (15), they analyzed the correlation of patients’ age and occurrence of *P. gingivalis* and found that the age of *P. gingivalis* positive and negative was statistically different, implying that the prevalence of *P. gingivalis* may increase as the patients’ age increase.

The association of certain putative pathogens with periodontal diseases shown in many studies may be explained in part by deeper pockets in these patients. In the present study, the association between probing severely and the occurrence of periodontal disease has not studied because most previous studies conducted on the association of particular bacteria with periodontitis did not test the influence of probing depth. Some studies found that the search depth had a much greater impact on the species than did the diagnosis. In study of Riep et al. (20), the prevalence of *P. gingivalis* was highly associated (p< 0.001) with pocket depth. Ali et al. (50) studied the existence of *P. gingivalis* in very deep pockets (> 6 mm) and deep pockets (4–5 mm) of 36 Romanian patients presenting with chronic periodontitis. *P. gingivalis* was recognized in 75.8% of the patients and 63.6% of the sampled sites.

Listgarten and Loomer (51) also questioned whether microbial identification should be considered as a strategy in managing this disease. They found no strong evidence supporting the benefit of microbial testing, partly due to a lack of standardization among diagnostic methods.

In summary, on analyzing the results of the present study, a strong association was found between the presence of *P. gingivalis* and periodontal diseases. Furthermore, the results of the present study indicated that *P. gingivalis* is one of the risk factors responsible for periodontitis. This result suggests that further research is needed to investigate their pathogenicity.

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**Conflict of Interests**

The authors declare that they have no competing interests.

**References**


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