Influence of Periodontitis in the Development of Nosocomial Pneumonia: A Case Control Study

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Background: Although a number of studies on the role of periodontitis in the development of nosocomial pneumonia (NP) have been published, the debate surrounding the existence and nature of this association continues. The present study investigates the influence of periodontitis in NP.

Methods: This case-control study involved 315 individuals: 85 cases (with NP) and 230 controls (without NP), at a general hospital in Feira de Santana, Bahia, Brazil. Sociodemographic characteristics, health conditions, and lifestyle habits were recorded. A full-mouth periodontal examination was performed and periodontal condition assessed. The diagnosis of NP was made in accordance with established medical criteria, after physical, microbiologic, and/or radiographic examination. Logistic regression was used to calculate the strength of the association between periodontitis and NP.

Results: Individuals with periodontitis were three times as likely to present with NP (unadjusted odds ratio [$OR_{unadjusted}$] = 3.06, 95% confidence interval [95% CI]: 1.82 to 5.15) as those without periodontal disease. After adjusting for age, time between hospitalization and data collection, last visit to dentist, smoking habit, and present occupation, the association measurement had a slight decrease ($OR_{adjusted}$ = 2.88, 95% CI: 1.59 to 5.19), but the results continued to be statistically significant.

Conclusion: These findings suggest that periodontal infection may influence the development of NP, highlighting that periodontitis is a factor positively associated with this respiratory tract infection. *J Periodontol 2014;85:e82-e90.*

KEY WORDS

Cross infection; epidemiology; periodontal diseases; periodontal medicine; periodontitis; respiratory tract infections.

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Nosocomial pneumonia (NP) has been recognized as an important public health problem, as it is a major cause of morbidity and mortality in hospitalized individuals.[1,2] NP develops within the hospital environment; i.e., it is not present when the patient is admitted.[1-5]

After dental biofilm bacteria in the oropharyngeal cavity were identified in the 1970s,[4] it was suggested that NP may be associated with the bacterial composition of dental biofilm, mainly in patients with periodontitis, and this colonization may be aggravated as a result of poor oral hygiene during hospitalization.[6-15]

In Brazil, there is no national data about the frequence of NP but pneumonia represents 51.6% of all causes of hospitalization from respiratory diseases in the public health system.[5] About 5% to 10% of participants admitted to hospitals in the United States develop a nosocomial infection.[16] NP also places a high financial burden on society, as it increases therapeutic demand and hospital stay duration.[16]

An interrelationship between periodontitis and NP is biologically plausible.[7,8] This respiratory infection can occur through the micro-aspiration of colonized oropharyngeal secretions, aspiration of gastro-esophageal content, and inhalation of infected aerosols.[7] Less frequently, it can occur by hematogenous

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dissemination from a distant site of infection, exogenous penetration, direct inoculation into the airway in participants intubated by the staff, and massive aspiration of gastric contents.[7] The translocation of bacteria from the gastrointestinal tract has also been considered as a mechanism of pulmonary infection.[7,8,12,13,17-22]

While the plausibility of the impact of periodontitis on NP has been investigated as stated above, the hypothesis regarding the influence of periodontitis in the development of NP is not completely confirmed. The existing studies are limited, insufficient, and contradictory with regard to confirming this hypothesis: some show no association,[23-25] others point to a significant association between periodontitis and NP.[6,14,15,21,22,26-31]

Given these controversial results and the possibility that biologic and environmental factors promote this association, and considering the impact of this NP on morbidity and mortality, the objective of this study is to evaluate the influence of periodontitis in development of NP, by estimating the magnitude of the association between the two conditions.

MATERIALS AND METHODS

Study Design

A case-control study was conducted in participants admitted to a general hospital in Feira de Santana, Bahia, Brazil, from May 2010 to August 2011. This study was approved by the Research Ethics Committee of Feira de Santana State University, Bahia, Brazil (protocol 079/2007). All participants signed an informed consent form agreeing to participate in the study.

Sample Size

To estimate the sample size calculation, for a study power of 90%, 95% confidence interval (95% CI), ratio of 1:3 between cases and controls was used with a variation range from 1.7 to 3.4 times the odds of an individual with periodontal disease developing NP.[26] The estimated minimum sample size was 298 individuals, 75 cases of NP and 223 controls.

Criteria for Sample Selection

In the case group, participants who developed respiratory tract infection (NP) after admission to hospital were included, regardless of the cause of hospitalization, with the exception of pulmonary diseases (patients not included), diagnosed by the medical staff of the hospital. The control group participants (non-NP) were selected randomly from the same hospital, in the same period. The main inclusion criterion to the control group was no presence of NP. Exclusion criteria were the same for both groups.

Exclusion criteria were: 1) aged <18 years; 2) <6 teeth in the mouth; 3) admission to hospital with a diagnosis of community-acquired pneumonia; 4) general condition not allowing a periodontal examination; 5) *delirious tremens*; or 6) presence of intense angular cheiliti; 7) patients residing in nursing homes or home care treatment patients who received intravenous antibiotics or chemotherapy within the last 30 days of the current infection; 8) patients with renal transplantation; and 9) patients admitted to emergency for ≥2 days in the last 90 days.

The sample included 315 individuals (232 males and 83 females, aged 18 to 84 years; mean age: 42.06 years ±19.69): 85 cases (NP) and 230 controls (non-NP). The case group had a mean age of 47.39 ± 19.01 years and a median of 44 years (range: 18 to 84 years). The control group had a mean age of 40.10 ± 15.66 years and a median of 37 years (range: 18 to 80 years).

Data-Gathering Procedures

General data were obtained through interviews of patients or their guardians through a structured questionnaire.

The oral health status was assessed in their hospital bed by a single dentist (TFLO), previously trained by an experienced periodontist (ISGF), using a manual periodontal probe# at six sites per tooth. Probing depth (PD) was defined as the distance from the gingival margin to the greatest penetration of the probe. Clinical attachment level (CAL) was the sum of the values of PD measurements with recession. Bleeding on probing (BOP) was defined as bleeding present within 10 seconds of removing the probe. Visible plaque was evaluated at four sites, using the probe only to confirm the presence of plaque on the tooth surface.

The reproducibility assessment was made by periodontal repeated measurements using an experienced periodontist (ISGF) as a reference in ≈10% of the sample. The κ interexaminer (± 1 mm), for PD and recession measurements, was respectively 0.79 and 0.85. In intra-examiner agreement, the κ index (± 1 mm) was 0.82 and 0.84 for these measurements, respectively.

Diagnosis of Periodontitis

Individuals diagnosed with periodontitis had ≥4 teeth with ≥1 site with PD ≥4 mm, CAL ≥3 mm, and BOP.[32]

Diagnosis of NP

The diagnosis of nosocomial respiratory tract infection was obtained from the volunteers' medical records. NP was identified according to the following: 1) underlying fluid density or dullness on percussion, crackles or clinical examination of the chest, and one

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of the following: a) appearance of purulent sputum or change in existing features of the sputum at hospital admission; b) microorganism isolated from blood cultures; c) microorganism isolated in bronchoalveolar lavage or lung biopsy; or d) histologic evidence of pneumonia; or 2) chest x-ray showing a new or progressive infiltration, consolidation, cavitation, or pleural effusion, together with any of the signs mentioned above.[3,12]

Statistical Analyses

Descriptive analyses were conducted of the main independent variable (periodontitis) and all covariables considered in the study, for example: age, sex, race, conjugal situation, education level, family income, place of residence, hypertension, diabetes, allergy to drugs, cardiopathy, liver disease, bone disease, blood abnormality, time between hospitalization and data collection, type of ventilation, tracheostomy, smoking habit, alcohol consumption, physical activity, frequency of tooth brushing per day, use of dental floss, periodic visit to dentist, professional advice about oral care, loss of permanent, teeth, and self-reported cause of tooth loss. Simple frequencies and central trend measurements were obtained, and statistical differences were evaluated using the χ^2 test for categorical variables and the *t* test for continuous variables, with a significance level of $P \leq 0.05$. The evaluation of the association between periodontitis and NP was estimated by odds ratio (OR) and 95% CIs, using the Mantel–Haenszel test to make statistical inferences. Stratified analysis and logistic regression analysis were also conducted.

The presence of effect-modifying and confounding covariables were investigated. For variables in which the presence of effect modification was empirically identified, the role of confounding variables was evaluated by means of the backward strategy. Both a theoretical and an empirical basis were considered in selecting potential confounding variables, and it was assumed that these would produce a change of at least 10% in the association measurement. The Hosmer–Lemeshow statistic was applied to verify the diagnosis of the goodness-of-fit regression model used. The results were analyzed using software.**

RESULTS

The patients' general characteristics, according to the presence or absence of NP, are shown in Table 1. The two groups were relatively homogeneous, although some differences were to be expected. Statistically significant differences were observed with regard to age ($P = 0.01$), education level ($P = 0.05$), present occupation ($P = 0.02$), hypertension ($P = 0.00$), and kidney disease ($P = 0.05$).

The case group had higher frequencies of participants aged >42 years (58.82% versus 42.61%); more participants with education levels ≤4 years of study (55.4% versus 43.5%); higher unemployment (40% versus 26.2%); and more hypertension (41.2% versus 23.9%) and kidney disease (8.2% versus 3.3%).

Some features related to NP were statistically significantly different: time between hospitalization and data collection ($P = 0.00$), type of ventilation ($P = 0.00$), and tracheostomy ($P = 0.00$). The case group had more participants with >5 days of hospitalization (92.9% versus 48.7%),invasive ventilation (44.7% versus 0%), and tracheostomy (48.2% versus 0%).

Regarding behavioral factors relating to oral health (Table 2), both groups were homogeneous, except for clinical diagnosis of periodontitis with statistically significant difference. The frequency of periodontitis in the control group was 38.7% and 65.9 % in the case group ($P = 0.00$).

Worse periodontal clinical parameters were observed in the case group (Table 3), with statistically significant mean differences for number of sites with CAL 1 to 2 mm ($P = 0.00$) and number of sites with PD ≥4 mm ($P = 0.00$).

In the unadjusted association analysis, among the case group, the chance of having NP was three times higher than controls ($OR_{unadjusted} = 3.06$, 95% CI: 1.82 to 5.15; $P = 0.00$), and this difference was statistically significant. In the stratified analysis, no interaction effects were detected; however, last visit to dentist, type of ventilation, and time between hospitalization and data collection were identified as potential confounders.

The logistic regression analysis confirmed that there was no presence of effect-modifying covariables and that last visit to dentist and time between hospitalization and data collection were confirmed as confounders in relation to the covariables. Age, smoking habit, and present occupation remained the final model on the basis of theoretical considerations. Adjustment for these variables produced a slight decrease in the magnitude of the association (Table 4), but reaffirmed that periodontitis had an independent effect on NP ($OR_{adjusted} = 2.88$, 95% CI: 1.59 to 5.19; $P = 0.00$).

The Hosmer–Lemeshow statistic was applied to verify the diagnosis of the goodness-of-fit regression model used; there was a *P* value of 0.96, and the null hypothesis was not rejected, indicating the goodness-of-fit for the regression model.

DISCUSSION

The findings show the influence of periodontal infection on NP and that among individuals with

** Stata, v.9.0, Stata Corp., College Station, TX.

Table 1.

General Characteristics of the Study Population (N = 315)

Characteristic	Cases (n = 85; n [%])	Controls (n = 230; n [%])	*P*
Age (years)			
18 to 42	35 (41.18)	132 (57.39)	
>42	50 (58.82)	98 (42.61)	0.01
Sex			
Females	22 (25.9)	61 (26.5)	
Males	63 (74.1)	169 (73.5)	0.91
Race (self-reported)			
White	09 (10.7)	22 (9.6)	
Black	75 (89.3)	207 (90.4)	0.77
Conjugal situation			
Married/stable union	46 (54.1)	126 (54.8)	
Single/divorced/separated/widowed	39 (45.9)	104 (45.2)	0.92
Education level (years of study)			
>4	37 (44.6)	130 (56.5)	
≤4	47 (55.4)	100 (43.5)	0.05
Present occupation			
Employed	51 (60.0)	169 (73.8)	
Unemployed	34 (40.0)	60 (26.2)	0.02
Family income (minimum monthly salaries)*			
>01	49 (57.6)	138 (60.0)	
≤01	36 (42.4)	92 (40.0)	0.71
Place of residence			
Feira de Santana	56 (65.9)	140 (61.1)	
Other cities	29 (34.1)	89 (38.9)	0.44
Hypertension			
No	50 (58.8)	175 (76.1)	
Yes	35 (41.2)	55 (23.9)	0.00
Diabetes			
No	69 (81.2)	200 (87.0)	
Yes	16 (18.8)	30 (13.0)	0.20
Allergy to drugs			
No	84 (98.8)	223 (96.7)	
Yes	1 (1.2)	07 (3.3)	0.35
Cardiopathy			
No	79 (92.9)	210 (91.3)	
Yes	06 (7.1)	20 (8.7)	0.64
Kidney disease			
No	78 (91.8)	223 (96.7)	
Yes	07 (8.2)	07 (3.3)	0.05
Liver disease			
No	85 (100.0)	226 (98.2)	
Yes	0	04 (1.8)	0.22

Table 1. (continued)

General Characteristics of the Study Population (N = 315)

Characteristic	Cases (n = 85; n [%])	Controls (n = 230; n [%])	*P*
Bone disease			
No	84 (98.8)	229 (99.6)	
Yes	01 (1.2)	01 (0.4)	0.46
Blood abnormality			
No	83 (97.6)	227 (98.7)	
Yes	02 (2.4)	03 (1.3)	0.51
Time between hospitalization and data collection (days)			
≤5	06 (7.1)	118 (51.3)	
>5	79 (92.9)	112 (48.7)	0.00
Type of ventilation†			
Non-invasive	47 (55.3)	229 (100.0)	
Invasive	38 (44.7)	0	0.00
Tracheostomy†			
No	44 (51.8)	229 (100.0)	
Yes	41 (48.2)	0	0.00
Smoking habit			
No (non-smoker/former smoker)	60 (70.6)	181 (78.7)	
Yes (current smoker)	25 (29.4)	49 (21.3)	0.13
Alcohol consumption			
No (non-consumer/former consumer)	46 (54.1)	123 (53.5)	
Yes (current consumer)	39 (45.9)	107 (46.5)	0.92
Physical activity			
No	74 (87.0)	186 (80.9)	
Yes	11 (13.0)	44 (19.1)	0.20

* Value of the minimum monthly salary: R$545.00 (US$ 298.13), at the time of data gathering.
† One lost observation.

periodontitis the chance of having NP is higher than in those without periodontitis, even after adjustment for potential confounders, with statistical significance. Although there was a decrease in the measurement with adjustment, the association is strong. Individuals with periodontitis were approximately three times as likely to have NP as those not clinically diagnosed with periodontitis.

This topic is still controversial in the literature. Some studies corroborate these positive findings,[15,20-22,26,28] while others do not support the hypothesis that the presence of periodontitis is positively associated with NP.[23-25]

This interrelationship between periodontitis and NP is biologically plausible, because bacterial proliferation in patients with periodontitis may promote colonization of the oropharynx, thereby perpetuating infection through inflammatory and immunologic mediators. In turn, this may contribute toward greater adhesion of microorganisms in the pulmonary parenchyma, thus making this the primary locus for establishing NP. However, it needs to be borne in mind that these biologic mechanisms are not yet fully understood.

Other determinants play an important role in this association, mediating the above biologic mechanism: socioeconomic factors such as family income and education level, difficulty in accessing health care services, other diseases that have an influence on the individual's immune response, mechanical ventilation, tracheostomy, advanced age (>70 years), and harmful habits such as smoking, alcoholism, and deficient oral hygiene.[7,8,12,13,17-22,33,34]

Thus, this study seeks to advance the important issues presented in the Materials and Methods section to ensure that the biologic factors were not solely responsible for the findings. This was achieved by collecting and analyzing data that addressed covariables that also mediate the relationship being studied, so as to avoid any spurious association.

It should also be noted, that this is a case-control, retrospective, observational study design. Because it is more sensitive to bias, this design does not

Table 2.

Behavioral Characteristics Relating to Oral Health of the Study Population (N = 315)

Characteristic	Cases (n = 85; n [%])	Controls (n = 230; n [%])	*P*
Periodontitis			
No	29 (34.1)	141 (61.3)	
Yes	56 (65.9)	89 (38.7)	0.00
Frequency of toothbrushing per day*			
None or once	16 (19.0)	37 (16.1)	
Twice or more	68 (81.0)	193 (83.9)	0.54
Use of dental floss*			
No	59 (70.2)	174 (75.7)	
Yes	25 (29.8)	56 (24.3)	0.33
Periodic visits to dentist†			
No	67 (84.8)	196 (85.2)	
Yes	12 (15.2)	34 (14.8)	0.93
Last visit to dentist†			
≤1 year	19 (24.1)	67 (29.1)	
>1 year	60 (75.9)	163 (70.9)	0.39
Professional advice about oral care‡			
No	39 (50.6)	127 (55.2)	
Yes	38 (49.4)	103 (44.8)	0.49
Loss of permanent teeth			
No	10 (11.8)	30 (13.0)	
Yes	75 (88.2)	200 (87.0)	0.76
Self-reported cause of tooth loss§			
Caries and/or periodontitis	75 (98.7)	198 (98.0)	
Trauma/orthodontic indication	01 (1.3)	04 (2.0)	0.71

* One lost observation.
† Six lost observations.
‡ Eight lost observations.
§ Nine lost observations.

investigate if periodontitis is a causal factor of NP; to do so would require a different study, such as a clinical trial.[17,18] Furthermore, it should be kept in mind that the development of such a study would be difficult, due to the critical condition of individual patients. The oral examination, which was performed by a single examiner in beds at the intensive care unit or hospital ward, as well as the necessary examinations for respiratory evaluation, were performed in non-ideal conditions, both for the patients and the health professionals. Thus, in this study scenario, there was no way of using masking techniques so that the oral examiner would be unaware of whether the individuals belonged to the case or control groups.

However, the minimum sample size was achieved, allowing a suitable study power (95% probability was achieved; $P \leq 0.05$). This can be confirmed by the small CI obtained in the association measurements, both crude and adjusted, which demonstrates the accuracy of the results. In view of other determinants that mediate the relationship between periodontitis and NP, in the multivariate analysis, the logistic regression model was adjusted for those covariables that were identified both empirically and in previous studies[15-26] as confounding.

As expected, some factors related to respiratory infection were different between the case and control groups, and were confirmed as confounding covariables in the empirical analysis. These included time between hospitalization and data collection and time since last visit to a dentist. These covariables were included in the adjusted logistic regression model, together with those known to be important in the association study, such as age, present occupation, and smoking habit.

To avoid the possibility of overadjustment in the final model, it was decided not to include education level as a proxy variable of present occupation,

Table 3.

Distribution of Periodontal Condition Variables of the Study Population (N = 315)

Clinical parameter	Cases, n = 85	Controls, n = 230	*P*
BOP (%)			
Mean ± SD	30.59 ± 15.52	20.78 ± 15.31	0.50
Median	28.26	17.26	
Range	2.00 to 75.00	0.59 to 84.12	
Plaque index (%)			
Mean ± SD	30.84 ± 23.91	28.50 ± 19.98	0.26
Median	25.00	25.00	
Range	0 to 100	0 to 100	
PD (mm)			
Mean ± SD	3.11 ± 0.56	2.83 ± 0.51	0.14
Median	3.09	2.84	
Range	1.00 to 4.88	0.65 to 5.75	
CAL (mm)			
Mean ± SD	3.84 ± 1.28	3.37 ± 1.22	0.23
Median	3.4	3.00	
Range	1.17 to 8.25	1.51 to 10.40	
Number of teeth (n)			
Mean ± SD	16.07 ± 7.26	19.37 ± 6.75	0.36
Median	16.00	21.00	
Range	6.00 to 28.00	6.00 to 28.00	
Number of sites with CAL 1 to 2 mm (n)			
Mean ± SD	0.45 ± 1.44	1.26 ± 3.40	0.00
Median	0	0	
Range	0 to 9.00	0 to 22.00	
Number of sites with CAL 3 to 4 mm (n)			
Mean ± SD	11.96 ± 8.92	14.37 ± 8.12	0.15
Median	3.00	14.00	
Range	0 to 16.00	0 to 28.00	
Number of sites with CAL ≥5 mm (n)			
Mean ± SD	3.99 ± 3.77	3.73 ± 4.08	0.77
Median	3.00	3.00	
Range	0 to 16.00	0 to 22.00	
Number of sites with PD ≥4 mm (n)			
Mean ± SD	8.04 ± 5.81	4.30 ± 4.37	0.00
Median	6.00	3.00	
Range	0 to 25.00	0 to 20.00	

Table 4.

Association Measurements Between NP and Periodontitis (N = 315)

Model	OR	95% CI	*P*
Unadjusted	3.06	(1.82 to 5.15)	0.00
Adjusted*	2.88	(1.59 to 5.19)	0.00

* Adjusted for age, time between hospitalization and data collection, last visit to dentist, smoking habit, and present occupation.

because they are collinear, representing the socioeconomic condition, as well as tracheostomy and type of ventilation, because these covariables are directly related to the etiology of the NP.

Although this methodologic precaution to reduce bias in the association measurement is fundamental to a survey of this nature, such bias can still be observed in the current literature that investigates the theme: periodontitis and NP. The data in Sharma and Shamsuddin's study,[15] for example, did not undergo treatment for confounders, which may cause

bias, impacting the final association measurement. Those authors found a strong association between periodontal disease and respiratory infection, stratifying only for income.[15] The chance of developing respiratory infections was more than 4 times greater in individuals with attachment loss >3 mm, which may have been reduced if appropriate covariable adjustments had been made. In the present study, after adjustment for the multiple factors mentioned above, the association is still strong: individuals with periodontitis were, approximately, three times as likely to develop pneumonia, but the measurement presented is more realistic, as it tried to adjust the influence of these variables in the model being studied.

Among the factors studied, ventilator-associated pneumonia, which starts 48 hours after intubation, is the most common nosocomial infection and has been associated with increased morbidity, length of stay, increased costs in health care, and higher mortality rates. In mechanically ventilated participants the occurrence of pneumonia is 9% to 40%.[3,4,31,35,36]

With regard to age, elderly participants have alterations in mucosal defense barriers, making them more susceptible to oropharyngeal colonization by pathogens such as *Staphylococcus aureus* and aerobic Gram-negative bacilli (e.g. *Klebsiella pneumoniae* and *Escherichia coli*). On the other hand, with advancing age there is greater susceptibility to the onset and further progression of periodontitis.

As for smoking habit and socioeconomic status, these determinants are equally related to the predisposition to respiratory infections as to periodontal disease.

Finally, it has also been noted that within 48 hours of admission, the composition of the oropharyngeal microbiota of participants in critical condition undergoes a change to predominantly Gram-negative microorganisms, constituting a more virulent microbe, including potential pathogens for NP.[17,18,37] Given the importance of recognizing the oral pathogen and its relationship to respiratory infection, a microbiologic study is under development, but it is not the objective of this investigation.

CONCLUSIONS

In accordance with the limitations of this research, these findings together with other observational studies, which found a positive association between periodontitis and NP, increase the body of evidence supporting the hypothesis of the influence of periodontal infection in the development of NP.[15,20,22,26]

On the other hand, it is important to highlight that, although the findings suggest that periodontal infection, with all its pathogenic microorganisms, contributes to NP, classic factors such as those that favor the colonization of the aerodigestive tract, and their aspiration, together with those factors which favor bacterial inoculation in the lungs as well as those factors that decrease host immunity, are all recognized important determinants in the development of this multicausal disease.[7,8,12,17-22,33,34]

From the clinical point of view, the most important risk factors for colonization of the lungs by pathogenic bacteria are: age, especially >65 years; malnutrition; long period of hospitalization; hypotension; the use of antibiotics; acidosis; alcoholism; heart failure; smoking habit; use of drugs that increase gastric pH; diabetes; trauma; uremia; liver failure; and extensive burns.[7,8,12,17-22,33,34] The results of the current study would also suggest that periodontitis could be added to this list.

Finally, in an attempt to advance the knowledge of this hypothesis, intervention studies could be carried out focusing on periodontal treatment and biologic markers in individuals admitted to hospital settings, in an attempt to observe if there is reduced risk of NP by the control of periodontal disease.

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