Does Periodontal Infection Have an Effect on Severe Asthma in Adults?

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Background: The effect of periodontal infection on systemic diseases and conditions has been the subject of numerous studies worldwide. It is considered that periodontitis may influence the hyperinflammatory response in patients with severe asthma as a result of immuno-inflammatory changes. This study aims to evaluate the influence of periodontitis on severe asthma in adults.

Methods: A case-control study was carried out, comprising 220 adult individuals: 113 diagnosed with asthma (case group) and 107 without asthma diagnosis (control group). The diagnosis of periodontitis was established after a full clinical examination using probing depth, clinical attachment level, and bleeding on probing. The diagnosis of severe asthma was based on the criteria recommended by the Global Initiative of Asthma (2012). Descriptive analyses of the variables were performed, followed by bivariate analyses, using the χ^2 test. Association measurements (odds ratio [OR]), with and without adjustment for potential confounders, were obtained. A significance level of 5% was used.

Results: The $OR_{unadjusted}$ for the main association was 4.38 (95% confidence interval [CI] = 2.47 to 7.75). In the logistic regression model, after adjusting for age, education level, osteoporosis, smoking habit, and body mass index, the $OR_{adjusted}$ was 4.82 (95% CI = 2.66 to 8.76), which was statistically significant. Individuals with periodontal infection showed, approximately, five times more likelihood to have bronchial inflammation than those without such periodontal tissue infection.

Conclusion: The findings demonstrate the influence of periodontitis on severe asthma, given that the frequency of periodontitis is higher in individuals with severe asthma than in those without a diagnosis of bronchial inflammation. *J Periodontol 2014;85:e179-e187.*

KEY WORDS

Asthma; bronchial diseases; epidemiology; oral medicine; periodontal diseases; periodontitis.

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The impact of periodontal infection on systemic conditions and diseases has been widely investigated in the last decades, to the point that the impact of periodontitis on a systemic level has been associated with unfavorable gestational outcomes,[1] cardiovascular diseases,[2] and insulin resistance,[3] as well as respiratory tract diseases.[4] More recently, a small number of studies have investigated the impact of periodontal disease on asthma,[5,6] a bronchial inflammation with increasing prevalence worldwide. It is estimated that ≈300 million people are currently suffering from asthma and that ≈100 million more will be diagnosed with this disease by the year 2025.[7]

Asthma is a chronic inflammation of the airways characterized by bronchial hyperresponsiveness, reversible limitation of airflows, wheezing, coughing, and short episodes of breathlessness.[8] Several factors are related to its natural history, including environmental and genetic components.[9] The exacerbation of bronchial inflammation can be triggered by various factors, for example, exposure to environmental allergens and pollutants and the presence of chronic infections, such as periodontitis.[10]

The biologic plausibility linking periodontal infection and severe asthma seems to be related to immunologic components common to both diseases that affect epithelial integrity, in both

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periodontal and respiratory tissue. The tissue breakdown present in periodontitis results, for the most part, from the actions of the immune system and of the related effector mechanisms. Similarly, bronchial inflammation is the result of complex interactions among inflammatory cells, chemical mediators, and the structural cells of the airways.[11] Of these immunologic components, matrix metalloproteinases stand out. They are responsible for the breakdown of collagen and are found at elevated levels during the periodontal breakdown process. In the same way, these enzymes are also associated with bronchial remodeling in individuals with severe asthma.

The literature relating to the role of periodontitis in asthma is still incipient, with few studies on the topic,[5,6,12,13] with small sample sizes and no clear definition of the exposure factor, periodontal disease, or the outcome, bronchial inflammation. Confronted by this knowledge gap, the aim of this study is to evaluate the influence of periodontitis on severe asthma in adults.

MATERIALS AND METHODS

Study Groups and Design

From March to November 2012, a case-control study was carried out, in which the case group consisted of adults (20 males and 92 females, age ≥18 years) with severe asthma assisted by the Program for Control of Asthma in Bahia (ProAR), Salvador, Bahia, Brazil. For each participant found for the case group, another was selected for the control group (15 males and 92 females). The present investigation was not a paired study and the discrepancy between final number of males studied in the groups was also due to missing information regarding to data collection of some controls. Individuals without a diagnosis of respiratory diseases were invited to participate in the control group, consisting of residents of the same neighborhood and seeking services available at the same health center as the case group. The participation was voluntary, participants were informed of how the investigation would be conducted, and a consent form was signed. This study was approved by the Research Ethics Committee of the Climério de Oliveira Maternity Hospital, part of the Federal University of Bahia (CONEP No. 15782).

Sample Size and Calculation

To calculate the sample size, periodontitis frequency of 30.34% among individuals without a diagnosis of asthma (control group) and periodontitis frequency of 55.17% among those with severe asthma (partially controlled, case group) were used, based on information obtained from a pilot study in individuals treated by ProAR (unpublished data), since no previous studies using robust criteria for diagnosis of periodontal disease were identified. Also, a 95% confidence interval (CI) and a study power of 80% were applied. Thus, respecting the 1:1 ratio, the estimated minimum number of individuals in the case and control groups was approximately 68 participants.

Data Collection Procedures

The individuals who made up the case and control groups had their airway condition classified in accordance with the evaluation of a pneumologist. All participants were interviewed through a questionnaire that considered socioeconomic data, biologic factors, health status, lifestyle habits, and dental care.

After the interview, all participants underwent a complete oral examination, performed by a single examiner (KS-M, periodontist) previously trained by an experienced periodontist (IG-F), and the correlation of the measurements was calculated using intra- and interexaminer κ index in 10% of the sample.[14,15] The intra- and interexaminer κ index (±1 mm) for probing depth (PD) were 0.81 and 0.84, and for recession measurements, 0.80 and 0.83.

In the oral examination, number of teeth, number of decayed teeth, and number of satisfactory restorations were assessed. Then, a complete periodontal examination was performed, in six sites per tooth: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual, excluding the third molars, to evaluate the following clinical parameters: recession index, PD, clinical attachment level (CAL), bleeding on probing (BOP), and visible plaque index (PI).[16,17]

Diagnosis of Periodontitis

Individuals who had ≥4 teeth with ≥1 sites with PD ≥4 mm, CAL ≥3 mm, and BOP at the same site were diagnosed as having periodontitis.[18]

Diagnosis of Severe Asthma

The diagnosis of severe asthma followed the criteria established by the Global Initiative for Asthma,[8] in which individuals who showed one or two of the following criteria were considered to have severe asthma:1) ≥3 daytime symptoms, such as shortness of breath, wheezing, coughing, or chest tightness; 2) any activity limitation; 3) any nocturnal symptoms or awakenings; 4) need for use of rescue medication ≥3 times a week; and 4) lung function <80%, measured by spirometry tests to evaluate the peak expiratory flow and forced expiratory volume in 1 second. All individuals with a diagnosis of bronchial inflammation showed partially controlled severe asthma after the evaluation of a pneumologist from ProAR.

Statistical Analyses

Initially, descriptive analyses were conducted of the main independent variable (periodontitis) and the covariables considered in this study.

Table 1.

Sociodemographic Characteristics Between Case (individuals with diagnosis of severe asthma, n = 113) and Control (individuals without severe asthma, n = 107) Groups

Characteristic	Controls		Cases		*P*
	n	%	n	%	
Age (years)					
18 to 39	46	43.0	30	26.5	0.10
>39	61	57.0	83	73.5	
Sex					
Males	15	14.0	21	18.6	0.36
Females	92	86.0	92	81.4	
Race/skin color					
White	23	21.5	22	19.5	0.71
Black/Hispanic	84	78.5	91	80.5	
Education level (years of study)					
≤4 years	16	15.0	26	23.0	0.13
>4 years	91	85.0	87	77.0	
Household density (number of people)					
≤3	58	54.2	71	62.8	0.19
>3	49	45.8	42	37.2	
Marital status					
With partner	53	49.5	58	51.3	0.79
Without partner	54	50.5	55	48.7	
Place of residence					
Salvador	98	91.6	94	83.2	0.06
Other	9	8.4	19	16.8	
Family income					
≤1 minimum wage	47	43.9	50	44.2	0.96
>1 minimum wage	60	56.1	63	55.8	
Habitation					
Homeowner	83	77.6	82	72.6	0.39
Does not own home	24	22.4	31	27.4	

In the second stage, bivariate analysis was performed using the χ^2 test with a significance level of 5% to estimate the effect of covariables between the case and control groups. To estimate the influence of periodontitis on severe asthma, association measurements were obtained, using a logistic regression model, and taking into consideration modifiers and confounding factors. Two software packages[#**] were used.

RESULTS

The final sample consisted of 220 participants, 107 individuals without a diagnosis of asthma (control group) and 113 individuals with severe asthma (case group), from both sexes, with a mean age of 43.6 ± 14.4 years and 46.8 ± 11.2 years, median of 45 years and 48 years, and range of 18 to 78 years and 18 to 72 years, respectively.

Characterization of study participants is shown in Tables 1 to 4 in accordance with the presence or not of severe asthma, case and control groups, respectively. In general, it can be observed that the comparison groups are very homogeneous in relation to sociodemographic characteristics (Table 1), as well as lifestyle and oral health (Table 2), and general health conditions (Table 3). As expected, a frequency of 87.6% of individuals with the habit of mouth breathing in the group with severe asthma was observed compared with 54.2% in the control group, and this difference was statistically significant. The other characteristics did not differ between the comparison groups.

Stata Data Analysis and Statistical Software, StataCorp LP, College Station, TX.
** SPSS Software v.21.0, IBM, Armonk, NY.

Table 2.

Characteristics Related to Life Habits and Oral Health Between Case (n = 113) and Control (n = 107) Groups

Characteristic	Controls		Cases		*P*
	n	%	n	%	
Smoking habit					
Yes	3	2.8	4	3.5	0.76
No	104	97.2	109	96.5	
Former smoker					
Yes	19	17.8	28	24.8	0.41
No	85	79.4	81	71.7	
Physical activity					
Yes	34	31.8	43	38.1	0.33
No	73	68.2	70	61.9	
Dentist consultation					
Yes	46	43.0	44	38.9	0.54
No	61	57.0	69	61.1	
Last dentist consultation					
Never or ≥1 year	71	66.4	84	74.3	0.19
<1 year	36	33.6	29	25.7	
Oral health guidance					
Yes	83	77.6	82	72.6	0.39
No	24	22.4	31	27.4	
Mouth-breathing habit					
Yes	58	54.2	99	87.6	<0.001
No	49	45.8	14	12.4	
Brushing frequency					
<3 times/day	45	42.1	54	47.8	0.39
≥3 times/day	62	57.9	59	52.2	
Flossing (at least once a day)					
Yes	52	48.6	51	45.1	0.61
No	55	51.4	62	54.9	
Use of oral mouthwash (at least once a day)					
Yes	44	41.1	56	49.6	0.21
No	63	58.9	57	50.4	
Dental brush change					
<4 months	61	57.0	75	66.4	0.15
≥4 months	46	43.0	38	33.6	

The case group presented a higher proportion of individuals with the following covariables: race/skin color black/Hispanic, education level ≤4 years of study, family income ≤1 minimum wage, not homeowners (Table 1), smoking habit, former smokers (Table 2), hypertension, diabetes, osteoporosis, body mass index (BMI) ≥25 (Table 3), those who had never consulted or who had not visited the dentist for at least 1 year, those who did not have guidance on oral hygiene, those with frequency of brushing <3 times a day, and those who do not floss (Table 2).

The characteristics related to oral conditions between cases and controls are presented in Table 4. The worst conditions were observed in the group with severe asthma characterized by a higher mean and median of missing teeth; decayed, missing, and filled teeth (DMFT) index; PI; and BOP. These differences were statistically significant.

Table 3.

Characteristics Related to General Health Conditions Between Case (n = 113) and Control (n = 107) Groups

Characteristic	Controls		Cases		*P*
	n	%	n	%	
Hypertension					
Yes	31	29.0	40	35.4	0.31
No	76	71.0	73	64.6	
Diabetes					
Yes	9	8.4	11	9.7	0.73
No	98	91.6	102	90.2	
Osteoporosis					
Yes	4	3.7	8	7.1	0.27
No	103	96.3	105	92.9	
Renal disease					
Yes	2	1.9	2	1.8	0.96
No	105	98.1	111	98.2	
Hypercholesterolemia					
Yes	16	15.0	16	14.2	0.87
No	91	85.0	97	85.8	
Cardiovascular disease					
Yes	5	4.7	5	4.4	0.93
No	102	95.3	108	95.6	
BMI (kg/m^2)					
<25	36	34.6	30	26.5	0.19
≥25	68	65.4	83	73.5	

Table 5 shows the distribution of periodontitis between the case and control groups, as well as analysis of the association between periodontitis and severe asthma. The frequency of periodontal infection in individuals with severe asthma was 61.9% compared with those without asthma (27.1%), and this difference is statistically significant. The unadjusted association measurement revealed that among individuals with periodontitis, the likelihood of having severe asthma was ≈4 times greater than among those without periodontal infection (unadjusted odds ratio [$OR_{unadjusted}$] = 4.38, 95% CI = 2.47 to 7.75). In stratified analysis, neither modifier nor confounding covariables were identified, subsequently confirmed by logistic regression analysis. However, the covariables age, education level, osteoporosis, smoking habit, and BMI were retained in the final analysis model, so as to obtain the adjusted association measurement, because the influence of these covariables on the association in study is well known. An increase in the magnitude of the association was observed, revealing that among those participants with periodontitis the likelihood of having severe asthma was ≈5 times higher than among those without periodontal infection and reaffirming that periodontitis has an effect on severe asthma ($OR_{adjusted}$ = 4.82, 95% CI = 2.66 to 8.76).

When the covariable habit of mouth breathing was considered for an exploratory subgroup analysis (Table 6), it was observed that among those individuals without such a habit the association showed a slight decrease. However, it remained statistically

Table 4.

Other Characteristics Related to Oral Condition Between Case (n = 113) and Control (n = 107) Groups

Characteristic	Control			Cases			*P*
	Mean	Median	Min/max	Mean	Median	Min/max	
Decayed teeth	1.85	1	0/14	2.56	2	0/15	0.15
Missing teeth	9.00	8	0/28	11.65	10	0/27	0.02
Filled teeth	3.53	3	0/21	3.46	2	0/18	0.87
DMFT index	14.66	16	0/30	18.13	19	0/31	0.001
PI (%)	31.64	22.3	2.2/100	54.14	56.2	5.1/100	<0.001
BOP (%)	14.69	7.7	0/100	28.43	24.4	0/100	<0.001

DMFT = decayed, missing, and filled teeth.

Table 5.

Association Measurements, Unadjusted and Adjusted, OR and CI, Between Periodontitis and Severe Asthma (N = 220)

	Controls		Cases					
Diagnosis of periodontitis	n	%	n	%	$OR_{unadjusted}$	95% CI	$OR_{adjusted}$*	95% CI
Yes	29	27.1	70	61.9	4.38	2.47 to 7.75	4.82	2.66 to 8.76
No	78	72.9	43	38.1				

* Adjusted for age, education level, osteoporosis, smoking habit, and BMI.

Table 6.

Association Measurements, Unadjusted and Adjusted, OR and CI, Between Periodontitis and Severe Asthma Stratified by Mouth-Breathing Habit (N = 220)

Mouth-breathing habit	$OR_{unadjusted}$	95% CI	$OR_{adjusted}$*	95% CI
No	4.98	1.41 to 17.64	4.61	1.21 to 17.53
Yes	4.21	2.08 to 8.52	5.21	2.40 to 11.29

* Adjusted for age, education level, osteoporosis, smoking habit, and BMI.

significant ($OR_{unadjusted}$ = 4.61, 95% CI = 1.21 to 17.53). For those with the habit of mouth breathing, the magnitude of the association increased, while also remaining statistically significant ($OR_{adjusted}$ = 5.21, 95% CI = 2.40 to 11.29).

DISCUSSION

The main findings of this study show that periodontitis influenced severe asthma, since individuals with periodontal infection showed ≈5 times more likelihood of having bronchial inflammation than those without such periodontal tissue infection. These findings were confirmed even after adjustment for possible confounding covariables, such as age, education level, osteoporosis, smoking habit, and BMI.

Investigation on the theme is still incipient, with only four studies having been conducted concerning the association of periodontal disease, gingivitis, and periodontitis with asthma, and the findings of this study concur with most of the previous studies.[5,6,19] However, they go against Friedrich et al.,[20] who found no association. The limited number of studies related to the topic makes the comparability of findings more difficult due to the use of different methods, while at the same time highlighting the importance of the findings obtained by the present investigation as they will contribute to the further understanding of the theme.

The scientific evidence that supports the biologic plausibility of the influence of periodontitis on severe asthma is related to the action of matrix metalloproteinases (MMPs), a group of enzymes responsible for the degradation of the extracellular matrix and basement membranes.[21-23] The presence of elevated levels of MMPs in individuals with asthma diagnosis, due to periodontal infection via hematogenous route, could contribute to increasing the ability to cleave structural proteins in the respiratory tissue, culminating in bronchial remodeling, exacerbation of symptoms, and increase in disease morbidity.

Although some studies exist on the subject, and the majority report a positive association between periodontitis and asthma,[5,6,19] confirming the findings of this study, it is important to show the improvements and limits obtained by each study, comparing the methodologic strategies used.

The sample size calculation for this study estimated a minimum number of 68 individuals for each comparison group: cases of severe asthma and controls with no diagnosis of bronchial inflammation. The final total sample consisted of 220 individuals divided into 113 cases and 107 controls. From the four studies analyzed, two were conducted with only 40 individuals in the entire sample, and the results showed a positive association.[6,19] In the other two, 100 and 2,837 individuals in the total sample, respectively, the results were discordant: the first found a positive association,[10] whereas the second did not observe an association.[20] It is worth noting that to conduct an association study, such as the present

one, it is mandatory that the diagnostic criteria of both the exposure and outcome factors are robust, with sufficient specificity so that there is a reduced likelihood of individuals with false-positive diagnosis among those diagnosed with the disease in question.

With regard to periodontitis, the exposure factor, the criterion used in the studies mentioned above, is not robust enough to ensure a clinical diagnosis of periodontal disease in an association study.[5,6,19,20] In the present study, a full periodontal examination and a combination of four clinical parameters (PD, gingival recession, BOP, and CAL) were used.[19] Chosen for the characteristics of periodontitis, which is a disease that comes in bursts of activity and in generalized or localized forms, the above criteria for classifying periodontal disease has been used in other epidemiologic studies that have sought to elucidate the association between periodontitis and other systemic diseases and conditions.[24-28]

The same methodologic care was taken regarding the diagnosis of severe asthma. The present study uses the parameters of clinical control of asthma that are based on the extent to which the manifestations of bronchial inflammation can be suppressed, either spontaneously or through treatment.[8] All participants who took part in this study were diagnosed with severe asthma, partially controlled, in accordance with the clinical control of bronchial inflammation. Such criteria have been previously used in Ponte et al.'s study that assessed this respiratory condition.[29]

Another important aspect to be evaluated is the mean age of the sample group. Stensson et al.'s studies[6,19] were performed using a young age group, ranging from 12 to 16 and 18 to 24, respectively. While Yaghobee et al.'s study had an average age of 39.6,[5] Friedrich et al. assessed individuals from 20 to 59 years old.[20] Such an age difference can make the diagnosis of a periodontal condition compatible with chronic periodontitis difficult, because it usually occurs in older age groups (>30). In the present study, the age of the participants in the control group ranges from 18 to 78 years, and in the severe asthma group, the range is 18 to 72 years.

It is worth noting that the investigations cited in the above paragraph corroborate some oral health characteristics noted in the participants of this study. The worst oral conditions were confirmed in cases of severe asthma when compared with controls, with statistically significant mean differences in the index of DMFT, PI, and BOP. These findings were confirmed by other studies.[5,6,19] Stensson et al. also found that in the asthma group, salivary flow is less than in the control group and plaque pH is higher, which may be responsible for higher caries frequency found in studies with individuals with asthma.[6,19]

Additionally, the magnitude of the association between periodontitis and severe asthma in this study increased as the necessary adjustments were made for the possible confounding covariables age, education level, osteoporosis, smoking habit, and BMI, known for their influence on the association. For example, as the population ages, chronic diseases such as asthma now represent a significant and growing demand on health services, with an increase in the prevalence of chronic respiratory diseases among the adult population being observed.[30] Similarly, periodontal disease occurs more frequently in individuals with advanced age.[31]

Another example is the habit of smoking. Among individuals with asthma, smoking habit may interfere negatively in its control and may intensify its severity. Studies comparing individuals with asthma, categorized as smokers or non-smokers, showed that the first group had a larger number of symptoms, used more rescue medications, and had a poorer quality of life.[32,33] In relation to periodontitis, the habit of smoking is a recognized classic risk factor for the progression of periodontal tissue breakdown.[34]

Regarding education level, a covariable related to socioeconomic conditions, there is a consensus that both periodontitis and asthma are more prevalent the worse the education level is.[35] With respect to osteoporosis, it is known that treatment with corticosteroids, very commonly used for the control of asthma, can cause osteoporosis.[36] With regard to obesity, the inflammatory profile of individuals with BMI greater than the reference value is higher, and therefore increases the chances of inflammatory activation in those diagnosed with asthma.[37] Likewise, osteoporosis and obesity are factors associated with periodontitis.[38]

In this study, the prevalence of the covariable habit of mouth breathing, either transient or intermittent, is higher in the group of individuals with asthma diagnosis. Airflow obstruction caused by asthma triggers the need for inspiration of a greater volume of air, leading the individual to use the oral route as an alternative way of breathing. In an attempt to elucidate the role of the habit of mouth breathing, subgroup analysis was performed. An increased magnitude of association can be observed in the group of individuals with the habit, whereas for those without such habit, there was a slight decrease in the extent, although it remained statistically significant.

It is worthwhile emphasizing that the present study is the first that associates periodontitis with partially controlled severe asthma, in accordance with the clinical control of asthma. As such, only cases of this asthma category were included in the sample and, consequently, it may have reduced the magnitude of

the association. The participation of individuals with uncontrolled severe asthma could have increased the final association measurement even more.

Despite the positive results of the influence of periodontitis on severe asthma in this study, some limitations should be considered. Information regarding the presence of other systemic diseases was self-reported. However, the participants were provided with a health service for asthma control, and all the medication and tests related to the disease were obtained in this service, free of charge, giving greater homogeneity to the research participants. Another important factor that could not be analyzed was the diagnosis of depression among participants because there was not a proper instrument for assessment at the beginning of data collection. It is known that the use of antidepressants has an influence in controlling asthma.[39]

Finally, although the results reported in this study have provided more evidence for the influence of periodontitis on severe asthma, future prospective studies and randomized controlled trials should be conducted to better test the hypothesis of this important association, thereby increasing knowledge in this area and also further clarifying the biologic mechanism linking the two diseases.

CONCLUSION

The findings suggest the influence of periodontitis on partially controlled severe asthma, given that the occurrence of periodontitis was higher in individuals with severe asthma than those without the diagnosis of this bronchial inflammation.

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