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Periodontitis in rheumatoid arthritis: a case-control study in a brazilian sample

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Aim: To investigate the presence of periodontitis in RA patients comparing it with controls in a Brazilian sample. **Methods:** This is a case control study conducted in a public health rheumatologic center. One hundred and sixteen RA patients and 68 paired controls were compared for epidemiological data and presence of periodontal disease evaluated by number of remaining teeth, presence of bacterial plaque, bleeding on probing, probing depth and clinical level of gingival insertion. In addition, data on comorbidities was collected. **Results:** RA patients and controls have the same amount of teeth loss (P = 0.84). RA patients had more calculus (P = 0.02); dental plaques (P = 0.04); gingival recession (P = 0.02) and bleeding (P = 0.01). Although the number of individuals with periodontitis was higher in RA patients, the severity of periodontitis was similar in both groups (P = ns). Presence of diabetes and hypothyroidism also associated with periodontitis (P = 0.01 and 0.02 respectively). In a model of logistic regression built to assess the independence of association of RA and its comorbidities with periodontitis, only diabetes and RA remained independent. **Conclusion:** This case control study shows higher frequency of periodontitis in RA patients than controls.

Keywords: Arthritis, rheumatoid. Oral health. Periodontitis.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease of unknown etiology. It affects 0.5% to 1% of the population and it is a disease with important repercussions in the patient's daily life[1]. It causes articular pain, stiffness, fatigue, and the persistence of the inflammatory process in the joints may lead to structural articular damage and deformities with consequent disability[1,2]. Although there is an undoubtable role of autoimmunity and genetic factors predisposing RA appearance, the agents able to trigger the clinical disease are unknown until now[1,3].

Periodontitis is a very common situation that damage the tooth supporting tissues[4]; it affects nearly 10% of worldwide population leading to tooth loss if left untreated[4]. Periodontitis have been linked to the appearance of RA[5]. In both diseases, RA and periodontitis, hard and soft tissue destruction are seen with pro inflammatory cytokines such as IL (interleukin)-6, tumor necrosis factor (TNF)-alpha and IL-1 playing active role[6]. Several studies have detected increased periodontal disease in RA patients[5], and periodontitis is considered to influence the RA appearance and disease activity[6].

At least two hypothesis have tried to establish a link between these two diseases. The first states that RA autoimmune responses appear when proteins are modified by inflammatory process or enzymes from microorganism in periodontal tissues[7,8]. In RA, two main autoantibodies are seen: the rheumatoid factor (RF) and the antibodies against citrullinated proteins (ACPA). The latter is generated against proteins that suffer posttranslational alterations with citrullination. It has been observed that some agents from oral microbiota, namely *Porphyromonas gingivalis* - a microorganism found in subgingival plaques[7,8] expresses the enzyme peptidylarginine deiminase (PAD), a bacterial virulence factor unique to this microorganism that citrullinates epitopes[9]. This favors the appearance of ACPAs and may trigger the RA appearance. In the second - that follows a two-hit hypothesis- chronic inflammation of periodontal tissues occurs as the first hit, followed by a second arthritogenic hit that exacerbates the inflammatory response[10]. Studies in non-surgical treatment of periodontal disease have been shown to improve disease activity markers in RA[6] and treatment of RA with tocilizumab and anti-TNF alpha drugs have shown to ameliorate periodontal disease[11]. Another possibility that should be considered in this context is smoking. Smoking is connected to both, RA and periodontal disease[7]. It favors RA appearance by increasing autoantibody formation, oxidative stress, inflammation, and by causing epigenetic changes[12]. In periodontitis, tobacco exposure impairs the local immunological defenses and the vascular supply[13].

High prevalence of periodontitis in RA patients, from 51% to even 94%, at different levels of severity, was described in some epidemiological studies[7,14]. Nevertheless, this association is not uniformly supported. A systematic review by de Oliveira Ferreira et al.[15], concluded that most of the investigations supported the connection between periodontitis and RA, but that the studies were quite heterogeneous pointing to the need for further investigations. Furthermore, a metanalysis by Fuggler et al.[16]

that compared RA patients with healthy controls and to patients with osteoarthritis, showed a significant increase in the risk of periodontitis in RA patients when compared to controls but not when compared with osteoarthritis patients. Periodontal disease prevalence may vary according to studied population as it is linked to access to dental care (removal of the microbial biofilm)[17], smoking[7], and daily self-performed oral hygiene[15]. Also, the prevalence of the HLA-DRB1*04 allele that is responsible for increasing RA susceptibility and related with the presence of anti CCP antibodies varies across different ethnic groups[14,16]. This diversity may affect the outcome of studies. Few studies address this problem in the Brazilian population. Manzano et al.[17] compared 32 Brazilian RA patients with controls and found a higher prevalence of periodontitis and caries index in the RA sample. De Azevedo Branco et al.[18], analyzing oral health-related quality of life in 42 RA Brazilian patients, found that they have a higher number of decayed, missing, and filled teeth than controls with negative impact in their quality of life.

Herein, we aimed to study the presence of periodontitis in a sample of Brazilian patients with RA comparing with the general population.

Methods

Ethical issues

This study was approved by the local committee of ethics in research under protocol 2952814 in October, 2018 and all participants signed consent.

Sampling and study design

It was a cross sectional study with a convenience sample that included patients diagnosed with RA from a single tertiary center that cares for patients from the Public Health System in Southern Brazil that agreed to participate in the study and come for regular consultation during the period of 2018 October to 2019 November. As controls, family members who accompanied the patient at the consultation, paired for age and sex, were invited to participate. The choice for family members in the control group was based in the supposition that they should have the same socio-economic status as the patients.

Inclusion criteria

To be included, RA patient should have disease onset after 16 years and fulfill at least six points in the classification criteria from American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) for this disease[19]. Patients and controls should be older than 18 years.

Exclusion criteria

RA patients and controls should not have any other chronic inflammatory disease or have had used antibiotics for the last three months. Pregnant patients, with HIV (immunodeficiency virus) infection, with alcohol or drug addiction were also excluded.

Data collection

Epidemiological data

Data on sex, age, smoking, years of formal study and comorbidities were obtained through char review or upon direct questioning.

Oral exam

Clinical periodontal data were collected by an experienced dentist. In the periodontal analysis, the following items were included: number of teeth present; presence of bacterial plaque; presence of bleeding to the probing; probing depth and clinical level of gingival insertion. Bleeding on probing, probing depth and clinical level of insertion were measured at six sites, around each tooth, by means of a Williams millimeter probe (Hu-Friedy, Chicago, Illinois, United States).

The classification of periodontal disease was defined as follows[20]:

a) Severe periodontitis: presence of 2 proximal sites, with clinical insertion level of 6 mm (not in the same tooth) and at least 1 proximal site, with probing depth of 5 mm;

b) Moderate periodontitis: presence of 2 proximal locci, with a clinical insertion level of 4 mm, or 2 proximal sites, with probing depth of 5 mm (not in the same tooth);

c) Mild periodontitis: presence of 2 proximal sites, with a clinical insertion level of 3 mm, and 2 proximal sites, with probing depth of 4 mm (not in the same tooth) or one site with a probing depth of 5 mm.

Participants who did not meet these criteria were considered not to have periodontitis.

Statistical analysis

Data was collected in frequency and contingency tables. Nominal data was expressed in percentages and compared by Fisher and chi-squared tests. Data distribution on numerical data was studied by Shapiro wilks test and expressed in median and interquartile range (IQR). Comparison of numerical data was done by Mann Whitney test and the significance adopted was 5%. A logistic regression using the presence of periodontitis (yes/no) as depend variable and RA and its comorbidities as independent variables was done to study the independency of associations. The study was performed using the software MedCalc Statistical Software version 20.007 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Results

One hundred and sixteen RA patients and 68 controls were included.

The epidemiological and pairing data of this sample is on Table 1. This tables shows that the sample had mainly middle-aged women reflecting the RA epidemiology. In this RA sample 56.2% received prednisone (median dose 5.0 mg/day; IQR 5.0-10.0 mg/day); 41.6% used methotrexate, 40.9% leflunomide; 18.7% anti-TNF drugs, 14.5% anti IL-6; 10.8% tofacitinib; 9.0% antimalarials; 2.0% rituximab and 2.0% abatacept. The disease duration ranged from 1 to 42 years (median 10 years; IQR=6-16 years). In this sample, 63.4% had a positive rheumatoid factor.

Table 1. Epidemiological, comorbidities and pairing data in 116 rheumatoid arthritis patients and 68 controls.

	Rheumatoid arthritis n = 116	Controls n = 68	P-value
Median age (IQR) (years)	55.0 (46.0-61.0)	53.5 (46.2-61.0)	0.53
Female sex (n)	81.0%	85.2%	0.46
Smokers (n)	18.1%	26.4%	0.57
Median years of formal education	8 (8-12)	12 (8-16)	0.15
Comorbidities			
Diabetes mellitus (n)	10.3%	10.2%	0.99
Hypothyroidism (n)	15.5%	11.7%	0.52
Dyslipidemia (n)	6.8%	8.8%	0.77
Arterial hypertension (n)	22.4%	29.4%	0.29

IQR = interquartile range.

Comparing the number of dental prothesis, number of teeth loss, presence of lithiasis, presence of dental plaque, gingival bleeding and gingival retraction, the results of Table 2 were found showing that the RA patients' performance was worse than controls.

Table 2. Comparison of teeth loss and gingival status in RA patients and controls

	RA n = 116	Controls n = 68	P-value	OR; 95% CI
Median number of teeth loss/person (IQR)	11 (3-22)	9 (3-23)	0.84	-
Calculus (n)	48/116-41.3%	17/68 (25%)	0.02	OR = 2.1; CI = 1.1-4.2
Plaques (n)	48/116-41.3%	18/68 (26.4%)	0.04	OR = 1.9; CI = 1.1-3.8
Gingival recession (n)	27/116-23.2%	7/68 (10.2%)	0.02	OR = 2.6; CI = 1.1-6.9
Bleeding (n)	33/116-28.4%	9/68 (13.2%)	0.01	OR = 2.6; CI = 1.1-6.0

RA = rheumatoid arthritis; OR = odds ratio; CI = confidence interval; IQR = interquartile range.

Excluding edentulous individuals, the study of the presence of periodontitis in RA patients and controls revealed the results on Table 3. This table shows that RA patients have more periodontitis but no differences could be found in the periodontitis severity between the studied groups.

Table 3. Comparison of periodontitis between rheumatoid arthritis (RA) patients and controls

	RA n = 107	Controls n = 58	P
Without periodontitis	47-43.9%	39-67.2%	0.005
With periodontitis			
Mild	28-26.1%	10-17.2%	0.98
Moderate	15-14.0%	4-6.8%	0.20
Severe	17-15.8%	5-8.6%	0.18

The study of periodontitis association with comorbidities such as hypertension, diabetes, hypothyroidism, dyslipidemia and with smoking is on Table 4. This table shows that in the whole sample and in the RA sample, there was association of periodontitis with diabetes and hypothyroidism but not with hypertension and dyslipidemia. Only a trend towards association with smoking and periodontitis was found when the whole sample was studied.

Table 4. Study of comorbidities associations in periodontitis rheumatoid arthritis (RA) patients (data available in 163 patients)

	Whole sample (RA patients and controls)			RA patients		
	With the variable	Without the variable	P	With the variable	Without the variable	P
Diabetes mellitus						
No	4/19-21.0%	80/144-55.5%		1/12-8.3%	46/95-48.4%	
Mild	5/19-26.3%	33/144-22.9%	0.01	3/12-25%	12/95-12.6%	0.01
Moderate	4/19-21.0%	15/144-10.4%		3/12-25%	25/95-26.3%	
Severe	6/19-31.5%	16/144-11.1%		5/12-41.6%	12/95-12.6%	
Systemic arterial hypertension						
No	23/46-50.0%	61/117-52.1%		10/26-38.4%	37/81-45.6%	
Mild	10/46-21.7%	28/117-23.9%	0.83	6/26-23.0%	22/81-27.1%	0.37
Moderate	5/46-10.8%	14/117-11.9%		3 /26-11.5%	12/81-14.8%	
Severe	8/46-17.3%	14/117-11.9%		7/26-26.9%	10/81-12.3%	
Hypothyroidism						
No	11/26-42.3%	73/137-53.2%		5/18-27.7%	42/89-47.1%	
Mild	12/26-46.1%	26/137-18.9%	0.01	11/18-61.1%	17/89-19.1%	0.02
Moderate	0	19/137-13.8%		0	15/89-16.8%	
Severe	3/26-11.5%	19/137-13.8%		2/18-11.1%	15/89-16.8%	
Dyslipidemia						
No	8/14-57.1%	76/149-51.0%		4/8-50.0%	43/99-43.3%	
Mild	3/14-21.4%	35/149-23.4%	0.88	2/8-26.2%	26/99-26.2%	0.98
Moderate	2/14-14.1%	17/149-11.4%		1/8-14.1%	14 /99-14.1%	
Severe	1/14-7.1%	21/149-14.0%		1/8-16.1%	16/99-16.1%	
Smokers (current)						
No	17/31-54.3%	67/132-50.7%		7-58.3%	40-38.8%	
Mild	4/31-12.9%	34/132-25.7%	0.07	3-25.0%	25-24.2%	0.26
Moderate	2/31-6.4%	17/132-12.8%		1-8.3%	14-13.5%	
Severe	8/31-25.8%	14/132-10.6%		1-8.3%	12-11.6%	

A model of logistic regression was done using periodontitis present or not (as a binary value) as dependent variable and RA, smoking, diabetes, and hypothyroidism as inde-

pendent variables, only RA (P = 0.01; odds ratio, OR = 2.45; 95%; confidence interval, CI = 1.1-5.2) and diabetes (P = 0.006; OR = 5.2; 95%; CI = 1.5-17.1) remained independently associated with periodontitis.

Discussion

In this study, the oral health of both RA patients and controls can be considered very poor reflecting the low social economic status of individuals using public health system in Brazil. The controls were obtained from patients' companions, so the social conditions would be similar, and the samples were paired for age, sex, educational level, and comorbidities such as diabetes - that could have had some influence in the results, allowing a good comparison. Even though, the present findings show that the oral health of RA patients is worse than controls. Calculus, gingival recession, dental plaques, gingival bleeding, and the number of individuals with periodontitis were more common in RA than controls, in agreement with the studies of de Azevedo Branco et al.[18]. Calculus presence result from hardened dental plaque. The development and accumulation of plaque at the gum line due to inappropriate brushing and flossing of teeth favors the gingival bleeding that is a strong predictor of periodontitis[21]. Periodontitis is characterized by the development of pathogenic periodontal pocket, tissue destruction and bone resorption leading to pain and teeth loss and it is linked to important changes in microbial community and subgingival microbial composition with enrichment in the presence of some bacterial genera such as *Porphyromonadeceae*[22].

As mentioned earlier, oral microbiota, i.e. *Porphyromonas gengivalis*, may be important in the origin of citrullinated antigens that lead to the appearance of ACPAs[9]. Moreover, studies in blood donors have shown that ACPAs are detected in human's serum several years before arthritis onset suggesting that RA may start at mucosal sites such as gut or oral cavity[23]. These findings highlight the need of education in oral hygiene to avoid not only the consequences in oral health status but also to try to avoid or, at least, to postpone RA appearance.

More recently another periodontal bacteria, the *Aggregatibacter actinomycetemcomitans* has connected periodontitis to RA because of its ability to induce citrullinated autoantigens[24]. Antibodies against *Aggregatibacter actinomycetemcomitans* were found to be highly detectable in human RA patients[24].

In animal models, oral inoculation of *Porphyromonas gingivalis* was found to exacerbate arthritis through the increased production of IL-17[25]. Therefore, periodontitis may also be important in the patients with already stablished rheumatic disease. Corroborating this idea, a study by Al-Katma et al.[26] with 29 RA patients showed that periodontitis treatment may reduce the rheumatic disease activity. A systematic review by Kaur et al.[27] displayed that periodontal treatment was associated with reductions in erythrocyte sedimentation rate and a trend towards a reduction in TNF-α titers and DAS (Disease activity scores) but no influence was seen in the presence of rheumatoid factor, ACPA levels and interleukin (IL)-6. On the other side, Pinho et al.[28] could not demonstrate that the improvement in the periodontal status helped controlling the inflammatory activity in RA. Therefore, more studies are needed to better understand this relationship.

RA is associated with several comorbidities that may interplay in the periodontitis prevalence such as diabetes mellitus, hypothyroidism, etc.[29]. Even if these associated diseases explain at least partially the high prevalence of periodontitis in RA, this aspect does not diminish the burden of the problem over the patients. Currently associations of periodontitis with hypothyroidism and diabetes in whole sample and in the RA sample have been found. It is important to note that hypothyroidism is more commonly found in patients with rheumatic diseases than in general population, as Hashimoto thyroiditis is also an autoimmune disease[30]. This may explain why this variable was not independently associated with periodontitis in the present work.

Smoking is another factor associated with periodontitis and RA; it is linked to protein citrullination and with appearance of ACPA antibodies[31]. A trend towards association of periodontitis with smoking was found in the whole sample but not in the RA individuals. It is possible that the small sample size precluded this observation (statistical error type II). Besides, in this work, smoking was not quantified, neither the previous use of tobacco was taken into consideration and this is one of its limitations.

RA treatment may influence periodontitis; it has been described that the use of anti-IL-6 is associated with improvement in the gingival index, bleeding on probing, probing depth, and clinical attachment level[25]. Improvement in periodontal health with anti-TNF therapy and Jak inhibitors such as tofacitinib are also observed[32,33]. This may be due to the pro-inflammatory cytokine profile common to the two diseases.

This study is limited by its cross-sectional design and by not evaluating the RA disease activity, ACPA status and smoking load. Its main strength is to show that oral health in Brazilian RA patients is affected mainly in those with diabetes and hypothyroidism. These findings highlight that these patients do need a better education on oral health and care for the already stablished periodontal disease.

Conclusions

In conclusion, this case control study shows that oral health in Brazilian RA patients is poorer than controls with high prevalence of calculus, gingival recession, dental plaques, gingival bleeding, and periodontitis. Associations with diabetes mellitus and hypothyroidism impact the appearance of periodontitis. These findings highlight the importance of the attention to oral health that should be part of the provided care to RA patients.

Conflict of interests

All authors declare that there is no conflict of interest.

Acknowledgments

None.

Data availability

Datasets related to this article will be available upon request to the corresponding author.

Authors' contributions

All the authors conceived and carried out the study; TS and RN organized and analyzed data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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