Original Article

Increased risk of periodontitis occurrence in patients with rheumatoid arthritis and its association with the levels of IL-1β and TNF-α in gingival crevicular fluid

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Background: Periodontitis (PD) is a chronic inflammatory disease caused by infection of the periodontal supporting tissues. Clinical studies have reported that rheumatoid arthritis (RA) patients have a higher prevalence of PD. This study aimed to explore the correlation between RA and PD.

Methods: A total of 307 RA patients (RA group) and 324 healthy individuals (control group) who received physical examinations during the same period were recruited to this study. The incidence of PD in the two groups was analyzed, and the periodontal disease index (PDI) and bleeding on probing (BOP) were recorded. Then, 42 RA patients with PD and 56 control group patients with PD were selected for further analysis. Enzyme-linked immunosorbent assay (ELISA) was used to detect the levels of interleukin 1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the gingival crevicular fluid (GCF) of the two groups. For patients with both RA and PD, the level of serum C-reactive protein (CRP) and the duration of morning stiffness were also recorded.

Results: The prevalence of PD in the RA group (51.5%) was significantly higher than that in the control group (31.2%), and the prevalence of PD also increased notably with the increase of age and the duration of the disease in RA patients. The levels of TNF-α and IL-1β in the PDI and the GCF in the concurrent RA and PD group were significantly higher than those in the PD group ($P<0.05$). Partial correlation analysis showed that TNF-α in the GCF positively correlated with the BOP of patients with RA and PD. Multiple linear regression analysis showed that the level of TNF-α in the GCF and serum CRP were independent influencing factors of the level of IL-1β in the GCF (the r values were 1.074 and 3.851, respectively; $P<0.01$).

Conclusions: The presence of RA can increase risk of PD occurrence and is positively correlated with the levels of IL-1β and TNF-α in the GCF.

Keywords: Rheumatoid arthritis (RA); periodontitis (PD); interleukin 1β (IL-1β); tumor necrosis factor-α (TNF-α)

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Introduction

Periodontitis (PD) is a chronic inflammatory disease caused by infection of the periodontal supporting tissues (including alveolar bone, cementum, periodontal ligament, and gums) and seriously affects health and quality of life (1). As one of the most common and frequent oral chronic inflammatory diseases, PD is characterized by gingival recession or redness, loss of attachment, alveolar bone resorption, and periodontal pocket formation, all of which are also principal contributors to adult tooth loss (2). It is currently believed that the pathogenic mechanism of PD involves periodontal bacteria invading susceptible individuals and local bacteria with their products and inducing the aggregation and infiltration of the white blood cells, which produces a variety of cytokines and inflammatory mediators, thereby destroying the periodontal supporting tissues; therefore, PD is a complex etiological disease influenced by various factors, including environment and heredity (3).

Recent studies have found that PD is very closely related to certain systemic diseases, such as diabetes, cardiovascular diseases, digestive tract diseases, respiratory diseases, and others (4). Besides these, rheumatoid arthritis (RA) is another prominent systemic immune disease. According to statistics, the prevalence of RA in China is about 0.24–0.40%, the peak onset age of is 30–40 years old, and the male to female incidence ratio is 1:2–4 (5). RA mostly affects the joints and is among the leading diseases that causes labor loss and disability in China (6).

Studies have shown that patients with different degrees of PD, especially adults, have significantly increased levels of rheumatoid factor (RF) in their subgingival plaque, serum, and saliva, which positively correlates to the disease activity of RA (7). In addition, RA and PD are inflammatory diseases that can interact with each other through cytokines and inflammatory mediators, such as tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interleukin 6 (IL-6), and IL-1, such that RA and PD have even been classified as a single disease type by some researchers (8). The periodontal pathogenic bacteria and their products that are present in mouths of PD patients can stimulate the body's immune cells after entering the bloodstream, thus inducing the host's immune response (9). Correspondingly, the development of RA can also lead to an increase in the secretion of inflammatory mediators and cytokines, leading to the occurrence and development of local periodontal inflammation (10). It can be seen then that RA and periodontitis are closely related through the common pathological process of inflammation, acting as mutual risk factors to one another. Clinical studies have reported that RA patients have a higher prevalence of PD, which is also an important risk factor for RA (11).

Therefore, the control of PD is of great significance to the occurrence and development of RA, and it can reduce the occurrence risk of RA to a certain extent (12). However, most of the relevant studies have been retrospective and case-control in their design; furthermore, there are limited results from prospective research, only a small number of cases have been reported, and research on the relationship between the severity of PD and the disease activity of RA has not yet been conducted. Therefore, to provide a theoretical basis for studying the possible relationship between PD and RA, we used a cross-sectional method to analyze the periodontal health condition of the RA patients through a multi-index observational correlation analysis. We further performed a correlation analysis of the clinical indicators, laboratory indicators, and PD detection indicators of RA to clarify the internal correlation between RA and PD. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1782).

Methods

Participants

A total of 307 RA patients (RA group) who were admitted to and hospitalized in our hospital from June 2012 to June 2015 were recruited to this study. During the same period, 324 non-RA healthy volunteers (control group) who received physical examination in our hospital were recruited without screening. Based on whether or not the patient had PD, the participants were divided into patients with both RA and PD (RA + PD group) and patients with PD alone (PD group). All procedures performed in this study involving human participants were conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (No. [2021]02-354), and informed consent was taken from all the patients.

Screening criteria

Inclusion and exclusion criteria for RA patients

The inclusion criteria for RA patients were as follows: (I) presence of the clinical manifestations, laboratory

examinations, and X-ray examination results for RA according to the 1987classification criteria of the American Rheumatism Association; (II) no long-term use of anticoagulant drugs or adrenal cortex hormone treatment; (III) no use of antibiotic drugs, nonsteroidal anti-inflammatory drugs (NSAIDS), or immunosuppressants within 3 months; (IV) no neuropsychiatric disorders; and (V) no history of smoking and no periodontal treatment in the past 6 months.

The exclusion criteria for RA patients were as follows: (I) patients with other autoimmune diseases; (II) patients with tumors, diabetes or other metabolic disorders, or bacterial, viral, or fungal infections; and (III) patients with severe liver disease, hyperthyroidism, renal dysfunction, cardiac insufficiency, or hematopoietic diseases, or those who were pregnant or lactating.

Inclusion and exclusion criteria for PD

The inclusion criteria for PD patients were as follows: (I) aside from PD, no other inflammatory diseases, systemic diseases, or acute infectious diseases; (II) women who were not menstruating, taking contraceptives, or pregnant; (III) no use of antibiotics, NSAIDS, or immunosuppressants within 3 months; and (IV) no history of smoking and no periodontal treatment in the past 6 months.

The exclusion criteria for PD patients were as follows: (I) systemic diseases, such as diabetes, heart disease, hypertension, hyperthyroidism, RA, liver and kidney diseases, and hematopoietic system diseases; (II) malignant tumors, long-term intake of anticoagulant drugs, long-term intake of adrenal cortex hormone to treat neuropsychiatric disorders, and bacterial, viral, or fungal infections; and (III) bone metabolic diseases, including endocrine bone disease, osteoporosis, deformity osteitis, renal bone disease, and hereditary bone disease.

Collection of general information and recording of the morning stiffness time

The age and gender of the participants in each group were collected and recorded in detail. The morning stiffness time was defined as the time between waking in the morning and feeling the stiffness of the joints and relief or disappearance of that pain after movement or warmth.

Periodontal inspection

Periodontal conditions were divided into PD, gingivitis, and a healthy condition. The periodontal condition of all participants was checked. Periodontal disease index (PDI) and bleeding on probing (BOP) were used as the scoring criteria for periodontal disease (13). The normal periodontal condition was defined as a PDI score of 0 and a negative result for BOP; gingivitis was defined as a PDI score of 1–3 and a positive BOP result; periodontitis was defined as a PDI score of 4–6 and a positive BOP result. All clinical procedures were performed by the same dentist.

Gingival crevicular fluid examination

The first molars in the 4 quadrants of the participants with periodontal disease were selected (if missing, adjacent teeth were used instead). After soft scales and plaque were removed, the teeth were kept moist and dry. Then, a 2 mm × 8 mm Whatman grade 1 qualitative filter paper that was weighed by electronic scales was inserted into the buccal periodontal pocket or gingival sulcus of the tooth and then removed after 30 seconds. The paper was discarded if it was contaminated by blood, and the above steps were repeated. The filter paper was placed into a 1.5-mL centrifuge tube, and then 200 μL of 0.01 mmol/L phosphate-buffered saline (PBS) was added and centrifuged at 5,000 r/min for 5 minutes. After this, the filter paper strip was removed to collect the supernatant, which was the gingival crevicular fluid (GCF). According to the instructions of the IL-1β enzyme-linked immunosorbent assay (ELISA) kit (Shenzhen Jingmei Bioengineering Co., Ltd., Shenzhen, China) and TNF-α ELISA (United Biosource, Blue Bell, PA, USA), respectively the levels of IL-1β and TNF-α in the GCF were detected.

CRP detection

The venous blood of participants in the RA + PD group and PD group was collected and centrifuged at a temperature of 4 ℃ at 2,000 r/min for 5 minutes to remove cells and cell debris; the resulting supernatant, which was the serum, was collected in a 1.5-mL centrifuge tube. The immunoturbidimetric method was adopted, and a Beckman AU680 automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA) was used to detect the level of CRP.

Statistical analysis

All data were statistically analyzed by SPSS 26.0 statistical software (IBM Corporation, Armonk, NY, USA). The

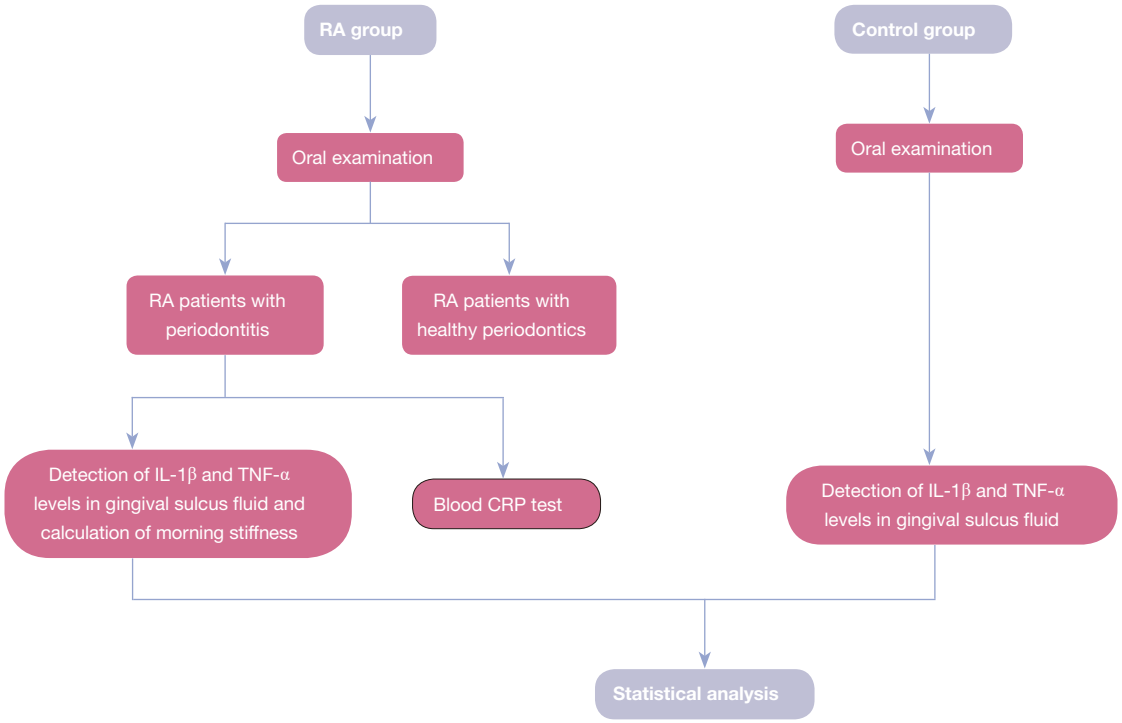

Figure 1 Flow chart of the research. RA, rheumatoid arthritis; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein.

Table 1 General information of RA and control group participants

Variables	RA group (n=307)	Control group (n=324)	P value	t/χ^2
Age (years)	40.36±10.13	41.93±11.52	0.069	t=−1.820
Gender (male/female)	128/179	151/173	0.214	χ^2=1.541

RA, rheumatoid arthritis.

independent samples t test was used, and a P value <0.05 indicated statistical significance. Correlation analysis and multiple linear regression analysis of the GCF inflammatory factors and clinical indicators in the RA + PD group were performed. In the multiple linear regression analysis, 1 variable was selected as the dependent variable, and the other multiple independent variables were selected in stepwise fashion (entry, 0.05; removal, 0.10).

Results

General information

The research flow chart is shown in *Figure 1*. The diagnosis of all RA participants was performed by the same rheumatologist, and all periodontal examinations were completed by the same periodontist. There was no significant difference in age or gender between the RA group and the control group (P>0.05), and the data were thus considered comparable (*Table 1*).

Periodontal status of RA participants

In the RA group, there were 158 (51.5%) cases of PD, 89 (29.0%) cases of gingivitis, and 60 (19.5%) cases of good periodontal health. In the control group, there were 101 (31.2%) cases of PD, 147 (45.4%) cases of gingivitis, and 76 (23.4%) cases of good periodontal health. The incidence of PD in the RA group was significantly higher than that in the control group (P<0.05; *Table 2*).

Table 2 Comparison of periodontal status between the RA and control groups

Group	n	Periodontitis (%)	Gingivitis (%)	Periodontally healthy (%)	χ^2	P value
RA group	307	158 (51.5)	89 (29.0)	60 (19.5)	28.243	0.000
Control group	324	101 (31.2)	147 (45.4)	76 (23.4)		

RA, rheumatoid arthritis.

Table 3 Comparison of age and periodontal status of RA participants

Age (years old)	Cases	Periodontitis (%)	Gingivitis (%)	Periodontally healthy (%)	χ^2	P value
–30	15	4 (26.7)	2 (13.3)	9 (60.0)	34.650	<0.001
30–39	58	25 (43.1)	23 (39.7)	10 (17.2)		
40–49	86	28 (32.6)	47 (54.7)	11 (12.8)		
50–59	65	18 (27.7)	34 (52.3)	13 (20.0)		
60–69	42	7 (16.7)	28 (66.7)	7 (16.7)		
70–	41	7 (17.1)	28 (68.3)	6 (14.6)		

RA, rheumatoid arthritis.

Table 4 Relationship between disease course and periodontal status of RA patients

Disease course (years)	Cases	Periodontitis (%)	Gingivitis (%)	Periodontal healthy (%)	χ^2	P value
–1	12	3 (25.0)	3 (25.0)	6 (50.0)	27.185	<0.001
1–4	55	20 (36.4)	19 (34.5)	16 (29.1)		
4–7	109	25 (22.9)	61 (56.0)	23 (21.1)		
7–	131	41 (31.3)	79 (60.3)	11 (8.4)		

RA, rheumatoid arthritis.

We further analyzed the relationship between RA in patients of different ages and different courses of disease and PD. The participants were divided into 6 groups: less than 30, 30–39, 40–49, 50–59, 60–69, and over 70 years old. The prevalence rate of PD was the highest in the 60–70 years old group (66.7%) and the >70 years old group (68.3%); meanwhile, the <30 years old group had the lowest prevalence, with only 2 cases, accounting for 13.3% of the group (*Table 3*). Participants were also divided into the following four groups according to disease duration, which was counted from the diagnosis of RA: less than 1, 1–4, 4–7, and more than 7 years. The RA group with the most PD cases was the >7 years group with 79 cases (60.3%); meanwhile, the less-than-1-year group had the least number of PD cases, with just 3 (25%; *Table 4*). These results confirmed that the older the RA patients were, the longer the course of the disease, and the more likely they were to suffer from PD.

Comparison of periodontal indexes and levels of inflammatory factors of concurrent RA and PD patients and simple PD patients

There were 42 cases of concurrent RA and PD, and 56 cases of simple PD. The periodontal index and inflammatory factor levels were compared between the two groups. The results (*Figure 2A-2C*) revealed that, compared with those in the PD group, the levels of PDI, IL-1β, and TNF-α were distinctly higher in the RA + PD group, but there was no obvious difference in BOP.

The relationship between morning stiffness and various clinical indicators and inflammatory factors in RA patients with PD

According to the time of morning stiffness, participants in the RA + PD group were divided into subgroups of <30,

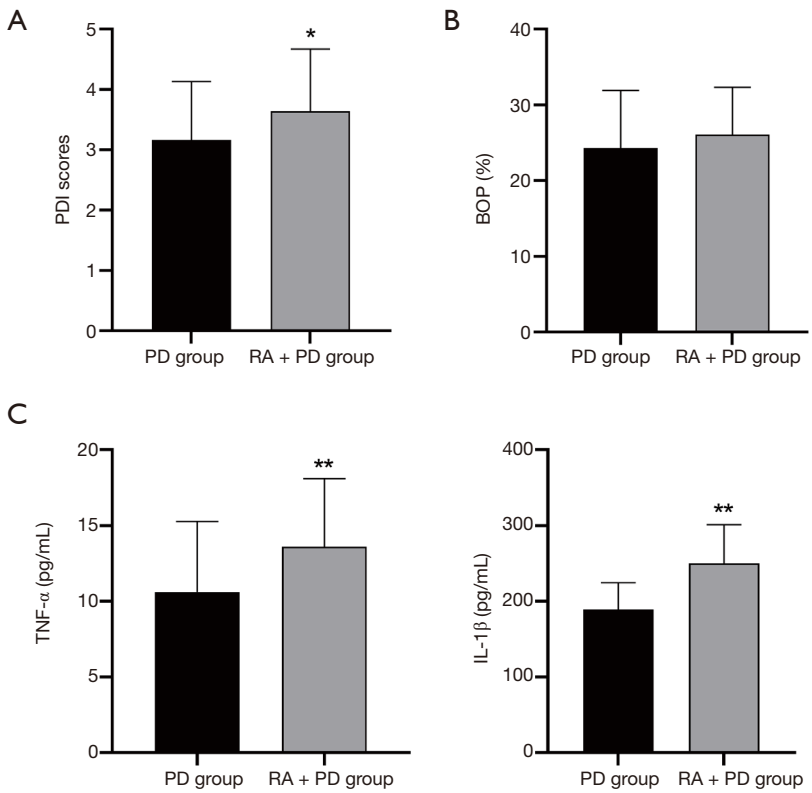

Figure 2 Comparison of periodontal indexes and levels of inflammatory factors of RA + PD participants and simple PD participants. (A) Comparison of PDI between the 2 groups; (B) BOP of the 2 groups; (C) IL-1β and TNF-α levels in the GCF of the 2 groups. *, P<0.05; **, P<0.01. RA, rheumatoid arthritis; PDI, periodontal disease index; BOP, bleeding on probing; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; GCF, gingival crevicular fluid.

30–60, and >60 minutes. The levels of PDI, IL-1β, and TNF-α were statistically different among the three subgroups (P<0.05). The longer the morning stiffness lasted, the higher the concentration level of PDI accompanied by PD, IL-1β, and TNF-α in the GCF. The difference between BOP and morning stiffness time was not statistically significant (*Table 5*).

Correlation between GCF inflammatory factors and clinical indicators in patients with RA + PD

Correlations between the indicators were further analyzed. The analysis results showed that BOP positively correlated with TNF-α and that IL-1β positively correlated with both TNF-α and CRP in the RA + PD group (*Table 6*).

Multiple linear regression analysis of GCF inflammatory factors and clinical indicators in patients with RA + PD

The results of multiple linear regression analysis (*Table 7*) showed that the level of IL-1β in the GCF of the RA + PD group was notably affected by the level of blood CRP and the level of TNF-α in the GCF. With the increasing levels of the blood CRP and TNF-α, the level of IL-1β also increased.

Discussion

The incidence of PD in the RA group was significantly higher than that of the healthy control group and close to the incidence of PD in RA patients reported internationally (14) but higher than that reported in the

Table 5 The relationship between morning stiffness time and various clinical indicators and GCF cytokines

Morning stiffness time (min)	n	PDI	BOP (%)	IL-1β (pg/mL)	TNF-α (pg/mL)
0–29	15	3.14±0.82[#]	25.30±7.01	240.07±49.05	11.63±3.59
30–59	17	3.80±1.13	25.22±5.60	234.82±42.93	13.60±5.29
>60	10	4.21±0.58	28.68±6.15	290.80±49.48[#]	16.53±2.65*
F	–	4.406	1.135	5.044	4.059
P value	–	0.019	0.332	0.011	0.025

[#], compared with the other 2 groups, P<0.05; *, P<0.05 compared with the 0–29 minute group. PDI, periodontal disease index; BOP, bleeding on probing; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; GCF, gingival crevicular fluid.

Table 6 Partial correlation analysis of periodontal indexes and inflammatory factors in RA + PD patients

	Course of disease	PDI	BOP	TNF-α	IL-1β
PDI					
r	0.063	1			
P value	0.701				
BOP					
r	–0.201	0.217	1		
P value	0.214	0.179			
TNF-α					
r	0.06	0.048	0.345	1	
P value	0.715	0.767	0.029		
IL-1β					
r	–0.019	0.196	0.155	0.490	1
P value	0.905	0.226	0.341	0.001	
CRP					
r	–0.054	0.252	0.131	0.203	0.743
P value	0.741	0.116	0.420	0.209	0.000

RA, rheumatoid arthritis; PD, periodontitis; PDI, periodontal disease index; BOP, bleeding on probing; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; GCF, gingival crevicular fluid; CRP, C-reactive protein.

oral health epidemiological survey in China over the years (15). In addition, with the increase of age, the incidence of PD + RA gradually increased. Among RA patients over 60 years old, the incidence of PD was significantly increased. Moreover, the longer the course of RA was, the higher the incidence of PD, indicating that the presence of RA increases the occurrence risk of PD. This may due to the onset of PD in some older patients: before the onset of RA, the inflammation of the periodontal tissue caused by the invasion of pathogenic bacteria to the blood stimulates the body's inflammatory response and activates the immune cells, which leads to the onset of RA (16,17). Pischon *et al.*'s study (18) included 57 RA patients and 52 healthy people in a comprehensive oral examination. The results revealed that the prevalence of periodontal disease in RA patients was nearly 8 times that of the healthy controls. Overall, these findings suggest that there is a close correlation between RA and PD.

Due to the results from research in recent years, the relationship between PD and RA has attracted considerable

Table 7 Multiple linear regression analysis of periodontal indexes and inflammatory factors in RA + PD patients

Model	Coefficients[a]			*t*	Sig.
	Unstandardized coefficients		Standardized coefficients		
	β	Std. error	Beta		
(Constant)	162.057	13.476		12.026	0.000
CRP	1.074	0.135	0.691	7.963	0.000
TNF-α	3.851	0.984	0.340	3.913	0.001

[a], dependent variable: IL-1β. RA, rheumatoid arthritis; PD, periodontitis; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein.

attention from both Chinese and international academics. Cantley *et al.* found that mice with both periodontal disease and arthritis have more severe arthritis and an earlier onset (19), and Rowińska *et al.* reported similar results (20). We know that IL-1 and TNF-α are immunomodulatory cytokines with proinflammatory effects that play important roles in the formation of PD and RA. They induce inflammatory cells to invade the infected site, which causes bone destruction via the production of inflammatory factors and activation of cytokines, contributing to the resorption of alveolar bone and the destruction of collagen fibers in PD (21,22). CRP, a glycoprotein synthesized by the liver, is regulated and induced by a variety of cytokines, including IL-1, IL-6, and TNF-α, among others (23,24). CRP levels rise with the occurrence of certain diseases, such as acute inflammation, malignant tumors, tissue damage, or chronic inflammations like RA, and can contribute to the promotion of phagocytosis. In this study, the PDI of the RA + PD group was distinctly higher than that of the simple PD group, which may be related to the increase of inflammatory factors in the GCF of the RA + PD group. A further correlation analysis showed that TNF-α in the GCF was positively correlated with BOP and the results of multiple linear regression analysis indicated that the level of TNF-α in the GCF and serum CRP were independent factors influencing the level of IL-1β in the GCF. In addition, morning stiffness time, which is an important indicator for judging the condition of the disease (25,26), was closely related to the degree of RA. In this study, the severity of the periodontal tissue inflammation was determined by the participants' PDI and BOP. The results showed that RA participants in the group with a morning stiffness time >60 minutes had a higher PDI of PD as well as higher concentration levels of IL-1β and TNF-α in the GCF, which is consistent with the findings of previous studies (27). Thus, the severity and occurrence risk of the clinical symptoms of RA are closely related to their periodontal conditions.

Conclusions

The incidence of PD in RA patients was higher than that of healthy controls, and with the increase of age and the longer course of the disease, the prevalence PD also increased significantly. There is a correlation between the periodontal status of RA patients and their disease activity indicators: the levels of TNF-α and IL-1β in the GCF of the RA + PD patients were significantly higher than those in the simple PD group and were correlated with the clinical indicators of RA. However, due to time and resource constraints, this study failed to examine the full array of clinical indicators for PD; moreover, the samples were collected from a single hospital. Further research should be performed to better clarify the relationship between PD and RA as well as the activity between these two diseases.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1782

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of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (No.[2021]02-354), and informed consent was provided by all participants.

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