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Prevalence and Severity of Periodontitis in Indonesian Patients With Rheumatoid Arthritis

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Background: Patients with rheumatoid arthritis (RA) may have more prevalent and severe periodontitis than healthy controls. Periodontitis may increase the systemic inflammation in RA. The aim of this study is to assess periodontitis prevalence and severity and its potential association with systemic inflammation in Indonesian patients with RA.

Methods: A full-mouth periodontal examination including probing depth, gingival recession, plaque index, and bleeding on probing was performed in 75 Indonesians with RA and 75 age-, sex-, and smoking-matched Indonesian controls. A validated questionnaire was used to assess smoking, body mass index, education, and medical conditions. In addition, in all participants, the use of drugs was noted, and erythrocyte sedimentation rates and serum levels of high-sensitivity C-reactive protein (hsCRP), rheumatoid factor, and anti-citrullinated protein antibodies were measured. Differences in periodontitis prevalence and 12 measures of periodontitis severity between patients with RA and controls were analyzed using univariate analyses.

Results: No significant differences in periodontitis prevalence and 11 measures of periodontitis severity between patients with RA and controls were observed. Conversely, patients with RA had a significantly lower surface area of healthy pocket epithelium versus controls ($P = 0.008$), and a tendency toward higher hsCRP levels was observed in patients with RA with severe periodontitis compared with patients with RA with no mild or moderate periodontitis ($P = 0.063$). It has to be noted that all patients with RA were on anti-inflammatory drugs, whereas none of the controls used such drugs.

Conclusion: Prevalence and severity of periodontitis in Indonesian patients with RA is comparable to controls but with less healthy pocket epithelium than in controls and a tendency toward a higher inflammatory state in patients with RA and severe periodontitis. *J Periodontol 2013;84:1067-1074.*

KEY WORDS

Arthritis, rheumatoid; C-reactive protein; inflammation; periodontal pocket; periodontitis; prevalence.

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetric inflammation of mainly hand and wrist joints, which leads to permanent deformity and breakdown of these joints.[1] RA impairs quality of life and is associated with early mortality. The cause of RA is still unknown.

Studies in Australia, America, Europe, and Africa have shown that patients with RA have more prevalent and severe periodontitis than non-RA controls when controlling for important confounders, such as dental plaque, age, sex, and smoking.[2-9] However, studies in Sweden, Brazil, the United States, Turkey, and Japan did not find a higher prevalence and severity of periodontitis in patients with RA.[10-14] In other words, the prevalence and severity of periodontitis in patients with RA may be influenced by genetic, dietary, cultural, and other differences associated with differences in nationality and ethnicity. Although white, African-American, Latin-American, North African, and Japanese populations have been studied,[2-8,11] no study has yet been performed in a Southeast Asian population. Furthermore, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and rheumatoid agents in patients with RA may affect the proinflammatory and anti-inflammatory cytokine levels in patients with RA and thus confound the association between RA and periodontitis.[15,16]

In addition to differences in results attributable to variations in nationality and ethnicity, the association between RA and periodontitis may also differ because a variety of definitions for periodontitis prevalence and severity have been used. Although various studies have assessed the association between periodontitis and RA,[2-16] no study has yet investigated the effect of using several definitions for periodontitis prevalence and severity on the association between periodontitis and RA.

Recently, some pilot-intervention studies have pointed toward periodontitis as a risk factor for RA.[17-20] After treating periodontitis, a reduction in RA disease activity was shown, possibly related to a reduction in periodontitis-associated inflammatory burden. Periodontitis poses an inflammatory burden, as evidenced by increased levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients with RA with periodontitis.[2-5] Thus, periodontitis may increase systemic inflammation, which may in turn lead to increased RA severity.[21] Likewise *Helicobacter pylori* infections may contribute to increased RA severity by posing inflammatory burden, whereas eradication of this bacterium in patients with RA improves the clinical condition and laboratory markers of RA disease activity.[22]

Thus, the aims of this study are to compare periodontitis prevalence and periodontitis severity in Indonesian patients with RA with Indonesian age-, sex-, and smoking-matched controls, using a variety of definitions for periodontitis severity.[23] In addition, whether inflammatory burden differed between participants with or without periodontitis was analyzed, for both patients with RA and controls.

MATERIALS AND METHODS

From July 2008 to February 2009, all consecutive patients with RA visiting the Internal Medicine Department of the Dr. Sardjito Hospital, Yogyakarta, Indonesia; the Clinic for Rheumatology of PKU Muhammadiyah Hospital, Yogyakarta, Indonesia; or a private rheumatology clinic in Surabaya, Indonesia, that matched the inclusion criteria were informed about the nature of the study and asked to participate. All patients with RA had been diagnosed by rheumatologists (NK and JS) according to revised American College of Rheumatology 1987 criteria[1] and were on a regular recall schedule for RA. During the same period, age-, sex-, and smoking-matched controls were recruited from the consecutive patients that visited the Prof. Soedomo Dental Hospital, Faculty of Dentistry Gadjah Mada University, Yogyakarta, Indonesia, for their routine dental checkup. Likewise, these controls were informed about the nature of the study and asked to participate. The inclusion criteria for patients with RA and controls were: 1) ≥18 years old and 2) ≥8 remaining teeth. The criterion of eight remaining teeth was chosen because there should at least be a minimum periodontitis-associated inflammatory burden, given that this inflammatory burden decreases with decreasing number of teeth (e.g., edentulous patients do not have any periodontitis-associated inflammatory burden). Exclusion criteria were: 1) presence of other systemic diseases or conditions (e.g., diabetes) that are known as risk factors for periodontitis and 2) a history of treatment for periodontal disease. With regard to controls, additional exclusion criteria were the use of medication or consuming drugs that are known to be risk factors for periodontitis.[15,16] Because no (pilot) data concerning differences between Indonesian patients with RA and controls were available, a formal power analysis was not performed. Each patient with RA was matched with one control. This study was approved by the Ethical Committee for Research of the Medical Faculty of Gadjah Mada University. Both oral and written informed consent were obtained from all patients and controls.

All participants completed a validated general health assessment questionnaire to assess the presence of other diseases and the use of medication. This questionnaire was composed of questions assessing symptoms related to systemic diseases, such as heart disease, pulmonary disease, endocrine

disorders, hematologic disease, gastrointestinal disorders, genitourinary disorders and neurologic disease, and the use of medications.[24] Information about age, sex, smoking (current and pack years), education level, and body mass index (BMI) was obtained by means of a questionnaire.

All participants underwent a full-mouth periodontal examination on six sites per tooth assessing probing depth (PD), gingival recession (GR), plaque index (PI), bleeding on probing (BOP), and clinical attachment loss (AL). All permanent fully erupted teeth were examined with a manual periodontal color-coded standard probe.** Measurements were made in millimeters and were rounded to the nearest whole millimeter. BOP was recorded as either present or absent within 30 seconds of probing. PI was defined as being present or absent at six points on each tooth.[2] The number of missing teeth was also recorded.

Periodontitis prevalence was established according to Page and Eke[23] case definitions. Periodontitis severity was operationalized using a variety of methods (number of sites with PD ≥4, ≥5, and ≥6 mm; number of sites with AL ≥3, ≥4, ≥5, and ≥6 mm; mean PD; mean AL; and percentage of sites with BOP anywhere in the dentition), which are all currently used to study the association between periodontitis and other diseases.[25-27] To facilitate calculation, a freely accessible spreadsheet†† was used online.[28] Furthermore, two recently introduced measures of periodontitis severity, the periodontal epithelial surface area (PESA) and the periodontal inflamed surface area (PISA),[29] were calculated, again using the same spreadsheet.[28] PESA reflects the surface area of all pocket epithelium in square millimeters, whereas PISA reflects the surface area of bleeding pocket epithelium in square millimeters. PESA and PISA were calculated using conventional AL, GR, and BOP measurements. PISA quantifies the surface area of inflamed periodontal tissue in square millimeters and is a measure of inflammatory burden posed by periodontitis.[26,29]

Finally, a blood sample via vena puncture was taken from all participants (patients with RA and controls) to determine CRP, ESR, rheumatoid factor (RF), and anti-citrullinated protein antibody (ACPA). High-sensitivity CRP (hsCRP) was determined by chemiluminescent enzyme immunoassay.‡‡ ESR was determined by the Westergren method, RF was determined by latex agglutination methods, and ACPA was determined by an enzyme-linked immunosorbent assay.§§

Data are presented as mean and standard deviation in case of normal distribution, medians and interquartile range (IQR) in case of non-normal distribution, and percentages for categorical data. Because patients with RA and controls were matched (age, sex, and smoking), differences between patients with RA and controls were analyzed using paired-sample *t* test or, in case of a non-normal distribution, Wilcoxon signed-rank test and McNemar test. Differences between periodontal status groups within patients with RA and controls were analyzed using Kruskal-Wallis (for medians) and χ^2 (for percentages) tests, with linear-by-linear association. In case of lack of expected cell count, the exact method was used. Statistics were calculated using statistical software.‖‖

RESULTS

Prevalence and Severity of Periodontitis in Patients With RA and Controls

In total, 75 patients with RA (median disease duration of 4 years; IQR = 2.0; 6.0 range; 1 to 15 years) and 75 age-, sex-, and smoking-matched controls were included. All consecutive patients with RA and controls that fulfilled the inclusion criteria during the recruiting period agreed to participate in this study. The characteristics of patients with RA and controls, including level of education, origin, BMI, and medication use, are summarized in Table 1. Level of education and origin were comparable between patients with RA and controls. Mean age, BMI, and number of teeth of patients with RA were significantly lower than controls, whereas PI was significantly higher. None of the controls used medication other than birth control pills or antihypertensives. Prevalence and severity of periodontitis were comparable between patients with RA and control individuals, but the surface of healthy pocket epithelium (PESA) was significantly smaller in patients with RA.

Serum Laboratory Markers in Patients With RA and Controls According to Periodontal Status

Patients with RA and severe periodontitis had a significantly lower PI and tended to be older than patients with RA and no, mild, or moderate periodontitis. There was a tendency toward higher hsCRP levels in patients with RA and severe periodontitis. Low education level was more common among patients with RA and severe periodontitis (Table 2; only the percentage of patients with a low education level was added to this table, as about half or more of the participating patients had a low level as opposed to medium or high). None of the abovementioned differences or tendencies was found in controls (Table 3).

DISCUSSION

The prevalence of moderate-to-severe periodontitis in patients with RA in the current study is fairly high

** Dentsply International, London, UK.
†† Excel 2003 for Windows, Microsoft, Redmond, WA.
‡‡ Immulite 2000, Diagnostic Products, Los Angeles, CA.
§§ ELISA, Euroimmun Medizinische Labordiagnostika, Lübeck, Germany.
‖‖ PASW v.18.0, IBM SPSS, Armonk, NY.

Table 1.

Characteristics of and Differences Between Patients With RA and Controls

Characteristic	Patients With RA (n = 75)	Controls (n = 75)	Mean Difference (SD)	*P*
Females, n (%)	60 (80)	60 (80)		
Smokers, n (%)	5 (7)	5 (7)		
Age (years), mean (SD)	46.5 (11.3)	46.9 (11.2)	0.4 (1.3)	0.015*
Education (low), n (%)	45 (60)	43 (57)		0.868†
Java origin (yes), n (%)	63 (84)	65 (87)		0.815†
BMI (kg/m^2), mean (SD)	22.5 (3.7)	24.1(3.6)	1.6 (5.0)	0.005*
PI (%), median (IQR)	97 (94; 99)	95 (90; 98)		0.023‡
Number of teeth, median (IQR)	26 (22; 29)	28 (25; 29)		0.034‡
Periodontitis severity, median (IQR)				
PESA (mm^2)	825.0 (676.1; 944.3)	892.1 (786.4; 1,040.1)		0.008‡
PISA (mm^2)	98.7 (43.2; 179.4)	98.6 (35.3; 221.6)		0.669‡
Number of sites				
AL ≥3, median (IQR)	22 (9; 44)	32 (14; 54)		0.099‡
AL ≥4, median (IQR)	5 (1; 18)	4 (1; 17)		0.998‡
AL ≥5, median (IQR)	0 (1; 6)	0 (0; 4)		0.666‡
AL ≥6, median (IQR)	0 (0; 2)	0 (0; 1)		0.890‡
PD ≥4, median (IQR)	1 (0; 5)	2 (0; 6)		0.638‡
PD ≥5, median (IQR)	0 (0; 1)	0 (0; 1)		0.734‡
PD ≥6, median (IQR)	0 (0; 0)	0 (0; 0)		0.963‡
BOP, median (IQR)	11 (6; 21)	10 (4; 25)		0.951‡
PD (mm), mean (SD)	1.7 (0.4)	1.8 (0.4)	0.1 (0.6)	0.205‡
AL (mm), mean (SD)	2.0 (0.8)	2.1 (0.8)	0.0 (1.1)	0.930‡
Periodontitis prevalence,§ n (%)				0.547‡
No/mild	22 (29)	23 (31)		
Moderate	37 (49)	40 (53)		
Severe	16 (21)	12 (16)		
Biomarkers, median (IQR)				
ACPA IgG (RU/mL)	1.2 (0.0; 46.2)	0.0 (0.0; 0.0)		<0.001‡
ESR (mm/hour)	36 (18; 53)	22 (13; 35)		0.001‡
hsCRP (mg/L)	4.8 (1.7; 17.1)	1.1 (0.6; 2.9)		<0.001‡
Medication, n (%)				
Corticosteroid (prednisolone)	60 (80)	0 (0)		
NSAIDs	55 (73)	0 (0)		
Methotrexate	52 (69)	0 (0)		
Chloroquine	36 (48)	0 (0)		
Leflunomide	7 (9)	0 (0)		
Sulfasalazine	6 (8)	0 (0)		
Antihypertensives	5 (7)	6 (8)		
Birth control pills	0	1 (1)		

IgG = immunoglobulin G; RU = relative units.
Data were analyzed pairwise.
* Paired *t* test.
† McNemar test.
‡ Wilcoxon signed-rank test.
§ Criteria of Page and Eke.[23]

(71%) but similar to those reported in other studies.[2,8] However, the prevalence of moderate-to-severe periodontitis in controls was also high (69%) and not significantly different. Likewise, some other studies reported no significant differences in periodontitis prevalence between patients with RA and controls,[10-14] which also might be (partially) attributable to the potent anti-inflammatory medications used by the patients with RA.[15,16] The vast majority of studies did find a higher prevalence of periodontitis in patients with RA compared with controls.[2,6-8] It has to be noted that the patients in these studies, like

Table 2.
Biomarkers and Characteristics of Patients With RA According to Periodontal Status

Characteristic	No or Mild Periodontitis (n = 22)	Moderate Periodontitis (n = 37)	Severe Periodontitis (n = 16)	*P*
Age (years), median (IQR)	44.0 (34.0; 54.0)	49.0 (38.5; 54.0)	50.5 (42.5; 55.8)	0.255*
BMI (kg/m^2), median (IQR)	21.8 (19.6; 26.3)	22.2 (19.8; 25.2)	22.6 (20.2; 24.6)	0.981*
PI (%), median (IQR)	98.0 (96.0; 99.0)	97.0 (95.0; 98.0)	92.5 (91.0; 97.5)	0.010*
ACPA IgG (RU/mL), median (IQR)	1.3 (0.0; 46.1)	0.0 (0.0; 31.6)	1.6 (0.0; 78.4)	0.612*
ESR (mm/hour), median (IQR)	29.0 (17.0; 38.0)	36.0 (18.0; 60.0)	41.5 (24.0;69.5)	0.257*
hsCRP (mg/L), median (IQR)	4.1 (2.6; 5.4)	3.3 (0.8; 24.9)	15.4 (6.3; 21.8)	0.063*
Years RA, median (IQR)	5.0 (2.0; 10.0)	4.0 (2.0; 6.0)	3.0 (1.5; 5.0)	0.301*
Females, n (%)	19 (86)	31 (84)	10 (63)	0.105†
SES (low), n (%)	9 (41)	25 (68)	11 (69)	0.064†
Smokers, n (%)	0 (0)	3 (8)	2 (13)	0.192†
RF (yes), n (%)	8 (36)	6 (16)	6 (38)	0.883†

ACPA = anti-citrullinated protein antibody; IgG = immunoglobulin G; RU = relative unit; SES = socioeconomic status.
* Differences in medians were tested using Kruskal-Wallis test.
† Differences in percentages were tested using χ^2 analyses, linear-by-linear association. Exact method was used in case of lack of expected cell count.

in the present study, were taking anti-inflammatory drugs. Furthermore, an association between periodontitis and RA also has been shown in animal studies.[30,31] Both human and animal studies point toward an association between periodontitis and RA that might be attributable to sharing similar inflammatory markers, namely, increased cytokines, matrix metalloproteinases (MMPs), and CRPs.[32,33] This association is also in line with results from animal studies, showing that induction of arthritis in rats resulted in an increased periodontal breakdown and that expression of an endogenous inhibitor of host-derived MMPs, namely, tissue inhibitor of MMPs (TIMPs), reduces the severity of periodontitis. Also in human studies, such a possible beneficial effect of TIMPs is shown.[34,35] For example, O'Dell et al.[34] showed that systemic administration of a TIMP (sub-antimicrobial-dose doxycycline), Food and Drug Administration–approved for periodontitis, reduced the severity of RA in these patients. Administration of this TIMP to patients with severe cardiovascular disease was found to significantly reduce CRP, interleukin-6 (IL-6), and MMP-9 in peripheral blood.[35]

Given the abovementioned, the findings of the present study might well be explained by the use of potent anti-inflammatory medication in patients with RA. RA and chronic and aggressive periodontitis are chronic inflammatory disorders characterized by deregulation of the host inflammatory response. Increased secretion of proinflammatory mediators results in soft and hard tissue breakdown of the synovium and periodontium, respectively. Both diseases share risk factors and have pathologic pathways in common, resulting in loss of function and disability as a final clinical outcome.[36] As such, drugs used for RA have also been reported to reduce periodontitis severity.[11,15,16] Approximately 80% of the patients with RA in the present study are on corticosteroids (Table 1). Corticosteroids have anti-inflammatory activities by inhibiting proinflammatory proteins, such as cyclooxygenase 2, IL-1, IL-2, and IL-6, tumor necrosis factor alpha, and adhesion molecules.[37] Approximately three quarters of patients with RA in the present study used NSAIDs, which have anti-inflammatory activity inhibiting cyclooxygenase, an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and thromboxanes. NSAIDs also have been shown to reduce

Table 3.
Biomarkers and Characteristics of Controls According to Periodontal Status

Characteristic	No or Mild Periodontitis (n = 23)	Moderate Periodontitis (n = 40)	Severe Periodontitis (n = 12)	*P*
Age (years), median (IQR)	48.0 (39.0; 54.0)	44.5 (38.5; 54.0)	50.0 (44.5; 56.0)	0.429*
BMI (kg/m^2), median (IQR)	23.2 (20.6; 25.3)	23.7 (22.2; 27.0)	24.6 (20.3; 30.7)	0.448*
PI (%), median (IQR)	97.0 (95.0; 99.0)	94.0 (90.0; 98.0)	93.0 (80.0; 96.5)	0.127*
ACPA IgG (RU/mL), median (IQR)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.959*
ESR (mm/hour), median (IQR)	20.0 (12.0; 26.0)	25.5 (13.0; 35.5)	21.0 (16.0; 36.0)	0.640*
hsCRP (mg/L), median (IQR)	0.9 (0.6; 1.3)	1.2 (0.5; 3.8)	2.4 (0.6; 3.7)	0.273*
Females, n (%)	18 (78)	31 (78)	11 (92)	0.522†
Smokers, n (%)	1 (4)	3 (8)	1 (8)	0.734†
SES (low), n (%)	17 (74)	20 (50)	6 (50)	0.103†
RF (yes), n (%)	2 (9)	0 (0)	0 (0)	0.115†

ACPA = anti-citrullinated protein antibody; IgG = immunoglobulin G; RU = relative unit; SES = socioeconomic status.
* Differences in medians were tested using Kruskal-Wallis test.
† Differences in percentages were tested using χ^2 analyses, linear-by-linear association. Exact method was used in case of lack of expected cell count.

alveolar bone loss in periodontitis.[38] A high number of patients with RA (Table 1) also used disease-modifying antirheumatoid drugs, such as methotrexate, sulfasalazine, chloroquine, and leflunomide. These drugs are taken to reduce the inflammatory component in RA. Methotrexate in combination with prednisolone decreases blood levels of IL-1β and IL-6 and inhibits the intensity of free radical–mediated processes in RA,[39] which also may decrease periodontal inflammation.

Although the PISA was comparable between patients with RA and controls (Table 1), PESA was significantly lower in patients with RA, pointing toward more severe periodontitis in patients with RA. Furthermore, the fact that there is not a significant difference between prevalence of periodontitis between patients with RA and controls also might be attributable to the remarkably high periodontitis prevalence in the Indonesian controls of this study. This is not surprising because the prevalence of periodontitis in the Indonesian general population may, depending on the definition used, be as high as 80%.[40]

BMI may also have obscured an association between periodontitis and RA. Ideally, controls should also have been matched for BMI because fat tissue may cause a chronic, low-grade systemic inflammatory response that influences the level of CRP.[41] However, the randomly selected controls had, on average, a higher BMI. The higher BMI of controls compared with patients with RA has been reported previously in a study that failed to show BMI as a significant predictor of periodontitis in patients with RA.[8] In another study[42] BMI was statistically associated with missing teeth, PD, and PI but again not with AL, gingival index, or periodontitis.

Noteworthy is the fact that there was a tendency toward higher hsCRP levels in patients with RA and moderate-to-severe periodontitis compared with those with no/mild periodontitis (Table 2). Other studies also found higher levels of hsCRP in patients with RA and periodontitis.[2,7] No significant difference in hsCRP was observed between controls with periodontitis and controls without periodontitis (Table 3). Two main explanations can be given for these findings. First, periodontitis may aggravate RA because periodontitis is accompanied by higher CRP levels.[43-47] The elevation of inflammatory cytokines (such as IL-1 and IL-6) that are locally induced by periodontitis[48] is thought to induce systemic inflammation by increasing serum CRP levels and thus to contribute to an increased systemic inflammation in RA.[49] Second, RA may aggravate periodontitis. Because more severe RA

is also accompanied by higher CRP levels,[49,50] higher CRP levels may be a reflection of active RA, which may contribute to an increased inflammatory state in periodontitis. Interestingly, CRP level reduces in patients with RA after periodontal therapy,[20] lending support to the hypothesis that periodontitis may contribute to an increased systemic inflammation in RA.

Another explanation of higher CRP levels in patients with RA and moderate-to-severe periodontitis compared with patients with RA and no/mild periodontitis may be confounding by impaired maintenance of oral hygiene, smoking, and low education level. Regarding oral hygiene, RA affects the wrist joint and the small joints of the hand. The joint afflictions may impair motor function of the hand and as a result may impair proper oral hygiene maintenance, resulting in periodontitis.[51] However, patients with RA and moderate-to-severe periodontitis had lower mean PI than patients with RA and no/mild periodontitis (Table 2). Therefore, impaired maintenance of oral hygiene in patients with RA has probably not confounded the association between periodontitis and higher hsCRP levels.

CONCLUSIONS

Prevalence and severity of periodontitis in Indonesian patients with RA is comparable to controls but with less healthy pocket epithelium than in controls and a tendency toward a higher inflammatory state in patients with RA and severe periodontitis. Future research should focus on whether periodontitis contributes to the increased inflammatory state observed in patients with RA and periodontitis and whether periodontitis thereby contributes to increased severity of RA.

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