Literature Review

Journal of Syiah Kuala Dentistry Society

e-ISSN 2502-0412
www.jurnal.unsyiah.ac.id/JDS

Association between severity of periodontitis and rheumatoid arthritis

Izzati Chatyarianti **CHANAL**[1], Agus **SUSANTO**[*], Ira **KOMARA**[2]

Department of Periodontology Faculty of Dentistry, Universitas Padjadjaran, Bandung, Jawa Barat, Indonesia
* Corresponding author: e-mail: agus.susanto@fkg.unpad.ac.id

Received; August 12, 2021, Revised, October 11, 2021, Accepted, November 25, 2021

ABSTRACT Many studies have shown a correlation between periodontitis and rheumatoid arthritis, and both are inflammatory diseases that cause damage to their surrounding tissues and have similar characteristics. Periodontitis can cause an increased erythrocyte sedimentation rate and C-reactive protein in rheumatoid arthritis (RA) patients and can cause systemic inflammation in RA. This review aims to assess the association between the severity of periodontitis and rheumatoid arthritis. The method of this study is scoping review. PRISMA method is used as a guideline for searching and selecting articles using four electronic databases with criteria (P: Population) periodontitis and rheumatoid arthritis patients, (C: Concept) Relationship between periodontitis and rheumatoid arthritis, (C: Context) periodontal medicine. Articles selection based on the inclusion criteria: journals published in 2011-2020, research methods using case-control, cohort, or RCT, subjects diagnosed with RA and Periodontitis, and subjects age at least 18 years old and exclusion criteria are subjects were pregnant and issues diagnosed with other diseases. Six articles included one cohort study and five case-control studies. The result showed a positive correlation between periodontitis and RA. There is an association between the severity of periodontitis and rheumatoid arthritis

KEYWORDS: Periodontitis, periodontal disease, rheumatoid arthritis

INTRODUCTION

Periodontitis is an inflammation of the periodontium caused by specific microorganisms, causing progressive damage to the periodontal ligament and alveolar bone, characterized by pocket formation, gingival recession, or both.[1] Based on RISKESDAS 2018, the prevalence of periodontitis in Indonesia reached 74.1%.[2] Periodontitis has multifactorial etiology that consists of genetic, behavioral, environmental, aging, and immunity factors, causing the imbalance of oral bacteria/ periodontopathogens related to hosting responses.[3] In addition, periodontopathogens will induce amino acid arginine changes into amino acid citrulline that plays an essential role in autoimmune mechanisms assisted by peptidyl arginine deaminase (PAD) enzyme.[4] Amino acid citrulline antigen is a dominant target of the autoimmune response in rheumatoid arthritis.[4]

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation and joint hyperplasia, and bone and cartilage damage.[5] RISKESDAS 2018 data shows the prevalence of RA in Indonesia reaches 7.3% and increases every year.[2] Increased levels of IgG and IgA against periodontopathogens colonization (*Porphyromonas gingivalis, Tanerella forsythia, Treponema denticolla, Aggregatibacter actinomycetemcomitans*) are found in synovial membranes of patients with rheumatoid arthritis.[6]

Periodontitis and rheumatoid arthritis have similar characteristics.[6] Both are characterized by chronic inflammation, bone erosion, periosteal soft tissue damage, similar humoral and cellular immune responses, as well as similar immunogenetic history.[6] Periodontitis causes the increase of ESR (Erythrocyte Sedimentation Rate) levels and C-Reactive protein in RA patients with periodontitis.[7] The association between periodontitis and rheumatoid arthritis is still debated. Based on a study by Chou et al., Terao et al., and Ribeiro et al.,

How to cite this article: Chanal IC, Susanto A, Komara I. Association between severity of periodontitis and rheumatoid arthritis. JDS. 2021; 6(2): 113-121

e-ISSN 2502-0412

there is a difference in the number of inflammatory biomarker values in both periodontitis patients with RA and without RA.[8–10] but different from the results obtained by Pinho et al. and Dominguez et al.[11,12] The aim of this review is to determine the association between severity of periodontitis and rheumatoid arthritis.

MATERIALS AND METHODS

This study was conducted by scoping review method. The study questions were designed based on the PCC Framework concept as follows: (P: Population) periodontitis and rheumatoid arthritis patients, (C: Concept) Association between periodontitis and rheumatoid arthritis, (C: Context) periodontal medicine. Articles collection and selection were conducted following the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Article searches were carried out through four electronic databases, PubMed, The Cochrane Library, Scopus, and OpenGrey, with keywords on Boolean operators as follows: ((Periodontitis) OR (Periodontal Disease)) AND (Rheumatoid Arthritis). Figure 1 shows the PRISMA flowchart as the article selection process. After reading all articles, the exclusion and inclusion criteria had been set. Inclusion criteria were all journals published in 2011-2020, all study methods using case control, cohort, or RCT methods, subjects diagnosed with RA and periodontitis, and subjects aged at least 18 years. Exclusion criteria were female subjects who were pregnant and the study population with other diseases diagnoses.

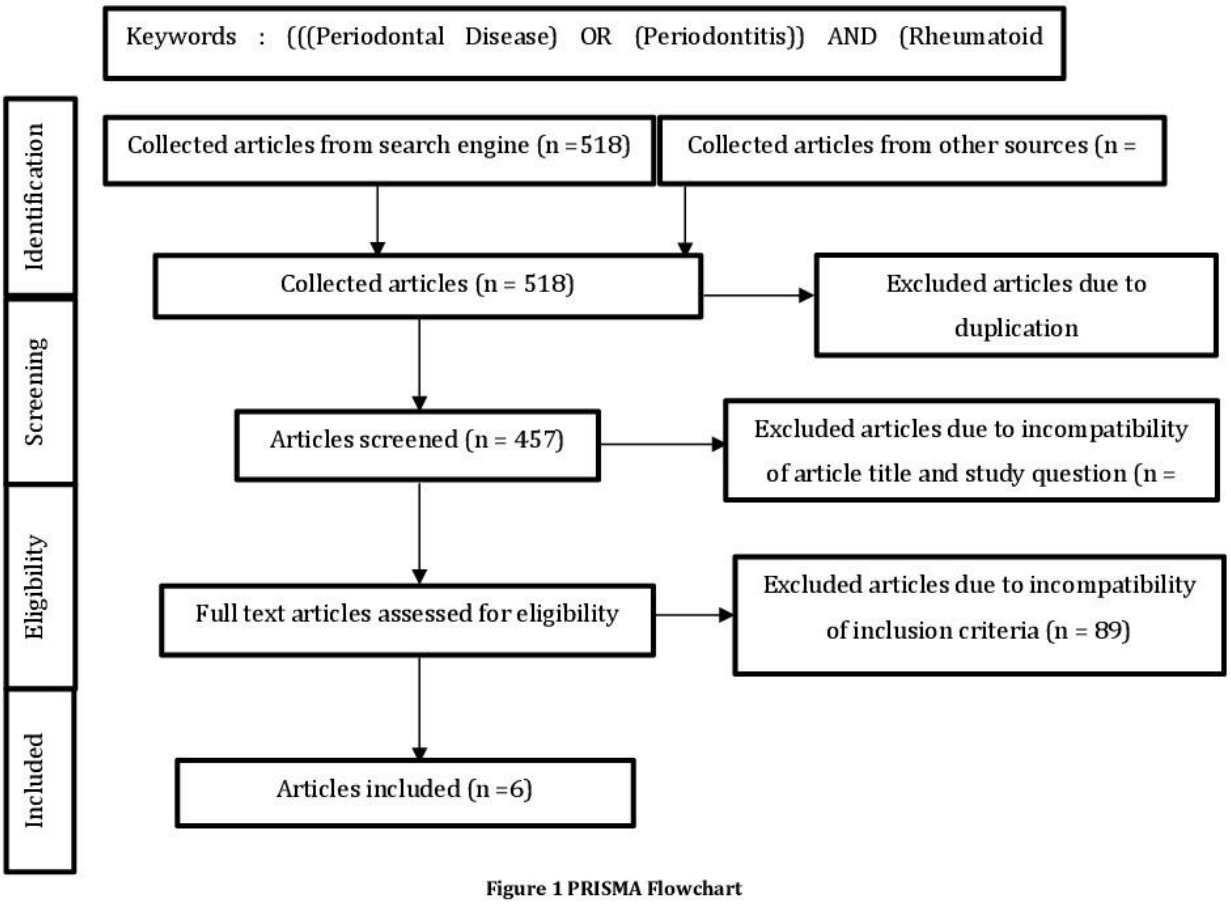

Figure 1 PRISMA Flowchart

RESULTS

Table 1. Data Extraction

No	Title	Author	Sample	Method	Results	Conclusion
1	Periodontal Health and Oral Microbiota in Patients with Rheumatoid Arthritis (2019)	Eriksson, Kaja, *et.al*.[13]	n = 20 age 29 – 80 years old with chronic arthritis	Cohort	Moderate/severe periodontitis was commonly found in RA patients (75%), especially in ACPA-positive patients. ACPA-positive patients had more severe periodontitis than ACPA-negative patients (86%), was no significant difference between no/mild and moderate/severe groups for DAS28, serum CRP and salivary CRP levels. Inflammatory mediators were higher in patients with moderate/severe periodontitis.	There is a relationship between periodontitis and RA. Severe periodontitis is associated with increased ACPA and systemic and oral inflammatory mediators.
2	Association Between Chronic Periodontitis and Rheumatoid Arthritis : a hospital-based case-control study (2013)	Joseph, Rosamma, *et.al*.[14]	n = 212 n(RA) = 100 age (mean) = 46,54 n(NRA) = 112 age (mean) = 45,91	Case control	Overall average of OHI-S for the RA and control groups was moderate (fair status) that statistically there is a significant difference. The average of GI score in all groups was mild gingivitis that might be due to the consumption of NSAIDs. In RA group, more teeth were lost. Although both groups had moderate OHI-S scores and mild gingivitis, but both of them had higher PPD and CAL scores indicating that RA causes more severe periodontal damage. 100% of the RA group had periodontitis, with moderate/severe periodontal status. There was no relationship between RA activities and the severity of periodontal disease that might be due to DMARDs consumption. The RA group had higher	There is an association between RA and chronic periodontitis. Evidence showed that RA affects a person's periodontal condition.

How to cite this article: Chanal IC, Susanto A, Komara I. Association between severity of periodontitis and rheumatoid arthritis. JDS. 2021; 6(2): 113-121

e-ISSN 2502-0412

					ESR and CRP values.	
3	Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients (2019)	Rodriguez-Lozano, Beatriz, *et.al*.[15]	n(RA) = 187 age (mean) = 54,4 n(NRA) = 157 age (mean) = 55,5	Case-control	The prevalence of severe periodontitis was high in RA patients (44.92%), with a high majority in NRA (12.1%). An association was found between the severity of periodontitis (development of CAL) and RA disease activities. In patients with remission and low activity of DAS28, there were more patients without periodontitis, while in patients with moderate and high activity of DAS28, they tend to have moderate/ severe periodontitis. The relationship between the severity of periodontitis in RA patients was not affected by DMARDs. However, no association was found between the immunity characteristics of RA (anti-CCP) and periodontitis.	There is an association between RA and periodontitis.
4	Prevalence and Severity of Periodontitis in Indonesian Patients with rheumatoid arthritis (2013)	Susanto, Hendri, *et.al*.[7]	n(RA) = 75 age (mean) = 45,5 n(NRA) = 75 age (mean) = 46,9	Case control	The prevalence of RA patients with moderate/ severe periodontitis was high (71%), and there was no significant difference compared to the control group (69%). There was a tendency for CRP values of RA patients with moderate/ severe periodontitis to be higher than those of no/mild periodontitis. There was no difference in CRP values between groups with periodontitis and without periodontitis in the NRA group.	There is a possible association between periodontitis and RA. The prevalence and severity of periodontitis with RA in Indonesia differed much from the control group. Still, there was a tendency for higher levels of inflammation in the RA group with severe periodontitis.
5	The association between rheumatoid arthritis and periodontal disease in a population based	Renvert, Stefan, *et.al*.[16]	n(RA) = 132 age (mean) = 70 n(NRA)= 249 age (mean) = 70	Case control	A population-based study in elderly RA patients found that RA was associated with periodontitis. Most (63%) of the RA group was included in remission or low RA disease activity. PPD, BOP, and decreased alveolar bone were more commonly found in the RA group.	Rheumatoid arthritis is related to periodontitis status.

	cross-sectional case control study (2020)					
6	Periodontal disease in Chinese patients with rheumatoid arthritis : A case-control study (2019)	Zhao, Rui, *et.al.*[17]	n(RA) = 128 n(NRA) = 109 age (mean) = 44,36	Case control	This study showed that patients with RA are at higher risk for periodontal disease and moderate periodontitis, and this relationship is independent of age, socioeconomic level, smoking status, and BMI. Anti-CCP and RF were detected more in RA patients with periodontitis than RA patients without periodontitis. PD has a strong association with DAS28 and ESR.	The prevalence of periodontitis and gingivitis is increased in RA patients.

*RA: Rheumatoid Arthritis; NRA: Non-Rheumatoid Arthritis; ACPA: *Anti Citrullinated Protein Antibody*; Anti-CCP: *Anti-Cyclic Citrullinated Protein Antibody*; CRP: C-Reactive Protein, DAS28: *Disease activity score-28*; PPD: *Probing Periodontal Depth*; CAL: *Clinical Attachment loss*; BOP: *Bleeding on Probing;* PD*: Periodontal disease;* OHI-S: *Oral Hygiene Index – Simplified;* GI: *Gingival Index*; NSAID: *Non-Steroidal Anti Inflammation Drug*s; DMARD*: Disease-modifying anti-rheumatic drug*

Table 2. Characteristic of Periodontitis

Author	Periodontal status (n)		PPD mm (Mean±SD)	CAL mm (mean±SD)	BOP% (mean±SD)	Plaque Index (mean±SD)
	No/mild	Moderate/severe				
Eriksson[13]	10 (25%)	30 (75%)	-	-	-	-
Joseph[14]						
n(RA)	42 (42%)	104 (92,8%)	2,48±0,65	2,88±0,65	-	-
n(NRA)	58 (58%)	8 (7,2%)	1,95±0,48	0,98±1,04	-	-
Rodriguez-L[15]						
n(RA)	5 (2,67%)	182 (97,33%)	3,08±0,63	3,99±1,27	63±23	74±48
n(NRA)	53 (33,76%)	104 (66,24%)	2,69±0,48	3,34±1,03	42±26	56±40
Susanto[7]						
n(RA)	22 (29,3%)	53 (70,6%)	1,7±0,4	2,0±0,8	-	-
n(NRA)	23 (30%)	52(69,3%)	1,8±0,4	2,1±0,8	-	-
Renvert[16]						
n(RA)	-	-	3,3±6,2	-	24,5±22,6	32,5±23,9
n(NRA)	-	-	2,7±5,4	-	21,8±16,8	32,4±21,9

Zhao[17]							
n(RA)	-		-	3,62±1,38	3,57±1,59	23±16	41±14
n(NRA)	-	-		2,03±0,93	2,11±1,13	13±8	32±11

*RA: Rheumatoid Arthritis; N(RA): Non-rheumatoid arthritis; PPD: Probing Pocket Depth; CAL: Clinical Attachment Loss; BOP : Bleeding on Probing; SD : Standard deviation

Table 3. Characteristic of Rheumatoid Arthritis

Author	DAS28				Anti-CCP (n)	CRP mg/dL (mean±SD)	ESR mm^3/hr (mean±SD)
	Remission (x ≤ 2,6)	Low (2,6 – 3,2)	Moderate (2,6 – 3,2)	High (x > 5,1)			
Eriksson[13]							
No/Mild PD	4 (44%)	0 (0%)	5 (56%)	0 (0%)	5 (50%)	0,51±0,73	-
Moderate/Severe PD	10 (37%)	4 (15%)	9 (33%)	4 (15%)	25 (86%)	0,42±0,52	-
Joseph[14]							
No/Mild PD	-	24 (57,1%)	18 (42,8%)	0 (0%)	-	1,80±1,93	47,10±28,80
Moderate/Severe PD	-	40 (62,5%)	14 (43,7%)	4 (8%)		2,29±3,65	46,30±28,01
Rodriguez-L[15]							
No/Mild PD	27 (26%)	27 (26%)	39 (38%)	9 (8%)	114 (67,86%)	0,44±0,23	21,8±7,46
Moderate/Severe PD	11 (13%)	12 (14%)	46 (54%)	16 (18%)		0,48±0,52	25,86±16,68
Susanto[7]					**RU/mL (mean)**		
n(RA)							
no/mild PD	-	-	-	-	1,3	0,41	29
moderate PD	-	-	-	-	0	0,33	36
severe PD	-	-	-	-	1,6	1,54	41,5
n(NRA)							
no/mild PD	-	-	-	-	0	0,09	20
moderate PD	-	-	-	-	0	0,12	25,5
severe PD	-	-	-	-	0	0,24	21,0
Renvert[16]	40,5%	22,2%	31%	5,6%	124 (66%)	0,9±0,8	19±15
Zhao[17]							
No/Mild PD		mean 3,64±1,46			19,51%	0,92±0,81	23,39±20,66
Moderate/Severe PD		mean 4,03±1,38			67,82%	1,29±1,51	27,01±23,24

DISCUSSION

Periodontopathogens produce PAD enzymes that induce hyper-citrullination. The amino acid citrulline is considered an antigen, so the specific antibodies (ACPA/anti-CCP) will be formed and found in the serum of patients with rheumatoid arthritis.[5,18] The severity of RA may be seen from its biomarkers such as CRP, ESR, anti-CCP, and DAS28.[19] There were many studies about the relationship between periodontal disease and rheumatoid arthritis. Several studies described that there is a relationship between periodontitis and rheumatoid arthritis.[8–10] However, some authors claimed that no connection had been found between both diseases.[11,12] This raises whether there is a true association between periodontitis and rheumatoid arthritis. Therefore, we further investigated to determine this association between the severity of periodontitis and rheumatoid arthritis.

Based on the results of this review, there is a relationship between periodontitis and rheumatoid arthritis that in line with the statements of Chou et al., Terao et al., and Ribeiro et al. [8–10] It was also proven in the study conducted by Joseph, et al., by dividing participants into two groups, namely RA and Non-RA groups. It was found that most of the subjects in the RA group had moderate/severe periodontitis. The PPD and CAL values were higher in the RA group, indicating more severe periodontal destruction in RA subjects. [14] The same result was found in the study conducted by Rodriguez-L et al., Renvert et al., and Zhao et al. [15–17] The study result by Eriksson et al. with 40 RA participants was obtained that 30 of them had severe/moderate periodontitis.[13] However, no association was found between RA activity and BOP that might be due to DMARDs or NSAIDs consumptions. BOP is not an appropriate predictor for clinical markers of periodontal disease progression.[16] In contrast to the study result by Susanto et al., there was no difference in periodontitis status in RA and NRA groups due to the high prevalence of periodontitis in Indonesia.[7] This may be due to the increased production of pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), which is not balanced by the production of anti-inflammatory cytokines (IL-10 and TGF-β) in periodontitis and RA.[14] Cytokines together with a low level of tissue inhibitors of metalloproteinases (TIMPs) and high level of matrix metalloproteinases (MMPs) as well as prostaglandin E2 (PGE2) cause tissue damage in periodontitis and RA.[7,14]

The levels of specific immunoglobulins IgG and IgA against periodontal bacteria were found to be elevated in the synovial fluid of RA patients, suggesting a possible important role of antibodies against periodontal bacteria as the cause of RA.[20] This may be seen from the formation of more anti-CCP antibodies in RA patients with moderate/ severe periodontitis than no/ mild periodontitis.[13,17] Likewise with the study of Renvert et al. which stated that 124 individuals in the RA group (66%) were anti-CCP positive. Rodriguez-Lozano et al. said that 114 individuals (67.86%) from the RA group were anti-CCP positive. Still, there was no significant difference in anti-CCP concentrations from the no/mild periodontitis group compared to moderate/severe periodontitis in the RA group.[15]

Rheumatoid arthritis and periodontitis are chronic inflammatory diseases, and there is an increase in inflammatory markers such as CRP and ESR.[6] Joseph et al. found higher CRP and ESR values in the RA group compared to the NRA group, which may be due to the combined effect of underlying RA inflammation and periodontitis.[14] However, when the RA group with no/mild periodontitis compared to RA with moderate/severe periodontitis, there was no significant difference in CRP and ESR concentrations.[14] A study by Eriksson et al. and Rodriguez et al. stated the same results.[13,15] Susanto et al. described that the mean of CRP and ESR in RA patients with moderate/severe periodontitis was higher than the RA group with no/mild periodontitis.[7] Otherwise, Zhao et al. found a significant difference between the no/mild periodontitis group and moderate/severe periodontitis in RA subjects.[17] DAS28 is a measuring tool used to measure the severity of rheumatoid arthritis through the number of joints that have inflammation and pain, the concentration of ESR or CRP, and the Global Health Assessment.[21] Rodriguez-Lazano et al. and Zhao et al. stated that the RA group with moderate/severe periodontitis had a higher DAS28 score than the no/mild periodontitis group.[15,17] Contrary to a study by Eriksson et al., Joseph et al., and Renvert et al., who did not find an association between periodontitis and the DAS28 score, it might be due to the consumption of DMARDs or NSAIDs causing the decrease in RA activities.[13,14,16]

The evidence of the association between the severity of periodontitis and rheumatoid arthritis was confirmed by other researchers on their study results, such as by Joseph et al., Rodriguez-Lozano,

How to cite this article: Chanal IC, Susanto A, Komara I. Association between severity of periodontitis and rheumatoid arthritis. JDS. 2021; 6(2): 113-121

e-ISSN 2502-0412

et al., and Zhao et al., that characterized by higher mean of PPD and CAL values in RA than non-RA patients.[14–17] It was also stated in the study results of Eriksson et.al. That most RA patients had moderate/severe periodontitis.[13] Anti-CCP antibodies were found, CRP and ESR values were higher in RA patients with moderate/ severe periodontitis.[7,16,17] Although it was not proven that periodontitis affects DAS28, this may be due to taking anti-rheumatoid drugs such as DMARDs and NSAIDs.

CONCLUSION

This study concludes an association between the severity of periodontitis and rheumatoid arthritis, which can be observed from higher anti-CCP, CRP, and ESR values in RA patients with periodontitis compared to RA patients without periodontitis. Periodontitis conditions in RA subjects are more severe compared to non-RA subjects.

REFERENCES

[1]. Carranza FA, Newman MG, Takei HH, Klokkevold PR, editors. Carranza's Clinical Periodontology. 12th ed. Elsevier Inc.; 2016. 50-59.
[2]. Badan Penelitian dan Pengembangan Kesehatan RI. Laporan Nasional Riset Kesehatan Dasar. Kementrian Kesehat RI. 2018;1–582.
[3]. Kilian M, Chapple ILC, Hannig M, Marsh PD, Meuric V, Pedersen AML, et al. The oral microbiome - An update for oral healthcare professionals. Br Dent J. 2016;221(10):657–66.
[4]. Bay-Jensen AC, Sand JMB, Genovese F, Siebuhr AS, Nielsen MJ, Leeming DJ, et al. Structural Biomarkers [Internet]. Biochemistry of Collagens, Laminins and Elastin: Structure, Function and Biomarkers. Elsevier Inc.; 2016. 203–233 p. Available from: http://dx.doi.org/10.1016/B978-0-12-809847-9.00031-3
[5]. Leech MT, Bartold PM. The association between rheumatoid arthritis and periodontitis. Best Pract Res Clin Rheumatol [Internet]. 2015;29(2):189–201. Available from: http://dx.doi.org/10.1016/j.berh.2015.03.001
[6]. Routsias JG, Goules JD, Goules A, Charalampakis G, Pikazis D. Autopathogenic correlation of periodontitis and rheumatoid arthritis. Rheumatology. 2011;50(7):1189–93
[7]. Susanto H, Nesse W, Kertia N, Soeroso J, Huijser van Reenen Y, Hoedemaker E, et al. Prevalence and Severity of Periodontitis in Indonesian Patients With Rheumatoid Arthritis. J Periodontol. 2013 Aug;84(8):1067–74.
[8]. Chou YY, Lai KL, Chen DY, Lin CH, Chen HH. Rheumatoid arthritis risk associated with periodontitis exposure: A nationwide, population-based cohort study. PLoS One. 2015;10(10):1–10.
[9]. Terao C, Asai K, Hashimoto M, Yamazaki T, Ohmura K, Yamaguchi A, et al. Significant association of periodontal disease with anti-citrullinated peptide antibody in a Japanese healthy population - The Nagahama study. J Autoimmun. 2015;59:85–90.
[10]. Ribeiro J, Leão A, Novaes AB. Periodontal infection as a possible severity factor for rheumatoid arthritis. J Clin Periodontol. 2005;32(4):412–6.
[11]. Pinho M de N, Oliveira RDR, Novaes AB, Voltarelli JC. Relationship between periodontitis and rheumatoid arthritis and the effect of non-surgical periodontal treatment. Braz Dent J. 2009;20(5):355–64.
[12]. Domínguez-Pérez RA, Loyola-Rodriguez JP, Abud-Mendoza C, Alpuche-Solis AG, Ayala-Herrera JL, Martínez-Martínez RE. Association of cytokines polymorphisms with chronic peridontitis and rheumatoid arthritis in a Mexican population. Acta Odontol Scand. 2017;75(4):243–8.
[13]. Eriksson K, Fei G, Lundmark A, Benchimol D, Lee L, Hu YOO, et al. Periodontal Health and Oral Microbiota in Patients with Rheumatoid Arthritis. J Clin Med [Internet]. 2019 May 8 [cited 2021 Apr 14];8(5):630. Available from: https://pubmed.ncbi.nlm.nih.gov/31072030/
[14]. Joseph R, Rajappan S, Nath SG, Paul BJ. Association between chronic periodontitis and rheumatoid arthritis : a hospital-based case – control study. 2013;103–9.
[15]. Rodríguez-lozano B, González-febles J, Garnier-rodríguez JL, Dadlani S, Bustabad-reyes S, Sanz M, et al. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients : a case – control study. 2019;1–12.

[16]. Renvert S, Berglund JS, Persson GR, Söderlin MK. The association between rheumatoid arthritis and periodontal disease in a control study. 2020;1–8.
[17]. Zhao R, Gu C, Zhang Q, Zhou W, Feng G, Feng X, et al. Periodontal disease in Chinese patients with rheumatoid arthritis: A case–control study. Oral Dis [Internet]. 2019 Nov 1 [cited 2021 Apr 14];25(8):2003–9. Available from: https://pubmed.ncbi.nlm.nih.gov/31411781/
[18]. Mariano FS, Sardi J de CO, Duque C, Hõfling JF, Gonçalves RB. The role of immune system in the development of periodontal disease: a brief review. Rev Odonto Ciência. 2010;25(3):300–5.
[19]. Emery P. Atlas of Rheumatoid Arthritis. Atlas of Rheumatoid Arthritis. 2015. 1-18.
[20]. Nickles K, Scharf S, Röllke L, Mayer I, Mayer M, Eickholz P. Detection of subgingival periodontal pathogens—comparison of two sampling strategies. Clin Oral Investig. 2016;20(3):571–9.
[21]. National Rheumatoid Arthritis Society. DAS28 Score [Internet]. NRAS. 2020. Available from: https://nras.org.uk/resource/the-das28-score/