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Literature Review

Periodontal diseases and its association with disease activity in ankylosing spondylitis/SpA: A systematic review

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Abstract

A close association between periodontal disease (PD) and ankylosing spondylitis (AS) has long been speculated. Both diseases are characterized by dysregulation of the host inflammatory response, leading to further destruction of the soft and hard connective tissue. There is evidence of increased levels of tumor necrosis factor-alpha and various interleukins in both patients of AS and periodontitis. This study aimed to conduct a systematic review exploring the relationship between AS and PD. We searched MEDLINE & Embase databases (from their inception till October 2019) using appropriate combinations of the following search items with limits '(English, Human)': Ankylosing spondylitis, spondyloarthritis, spondyloarthropathies, spondyloarthritides, spinal disease, musculoskeletal disease, rheumatic disease and periodontitis, PD, periodontoses, parodontoses, chronic periodontitis, gum disease, gingivitis, oral health, dental health, plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL). This search was supplemented by the manual search of bibliographies of the selected articles and conference proceedings of the European League against Rheumatism. Only the reviews and observational studies of cross-sectional, cohort, or case-control type on adult patients with AS were selected. Data were extracted from a predesigned PROforma. A total of 984 articles were identified, and 12 were selected for a detailed appraisal. All the identified studies were of the case-control type. The prevalence of periodontitis ranged from 38% to 88% in patients with AS and 26% to 71% in the control group. Of the 12 studies, 2 showed significant changes in PI, 2 showed altered PPD, 3 showed significantly increased CAL, and 2 showed increased BOP. In 7 studies, periodontitis was seen in a significant number of patients with AS ($p<0.05$). All the studies reported that the prevalence of PD in patients with AS was higher than that in patients without AS. Our systematic review found an association between AS and PD. Patients with AS show a higher prevalence of periodontitis and poor oral hygiene than the healthy controls.

Keywords: Ankylosing spondylitis, periodontitis, periodontal diseases, spondyloarthritis

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Introduction

Ankylosing spondylitis (AS) is a chronic, complex, and potentially debilitating disease with an insidious onset, gradually progressing to chronic bilateral sacroiliitis over a few years. A poor quality of life has been observed in all patients with AS because of chronic pain and progressive spinal stiffness (1). Involvement of the bilateral sacroiliac joint, peripheral joints, digits, and entheses are the characteristic features of the disease (2). Postural abnormalities, hip-joint pain, peripheral arthritis, enthesitis, and classical sausage digits (dactylitis) are all associated with AS (2, 3). Acute anterior uveitis, skin psoriasis, and inflammatory bowel disease are the most common extra-articular manifestations in AS (3-5). Periodontal disease (PD) includes a spectrum of diseases affecting the tissue surrounding the teeth (4-6). The disease might lead to the damage of the alveolar bone structures supporting the teeth (5, 6). The classical features of this disease are gingival bleeding, bone loss, pocket formation, periodontal tissue inflammation, and tooth mobility (7-9). Gingivitis is the more prevalent form of PD. It can be reversed easily if the patient maintains an effective oral hygiene. Periodontitis, in contrast to gingivitis, extends up to the periodontal ligament, subsequently loss of alveolar bone and adjacent connective tissue (10, 11).

PD has been linked to various chronic systemic diseases, such as diabetes mellitus and cardiovascular diseases. In a genetically susceptible individual, periodontal pathogens are most likely responsible for the development of AS. Some studies hypothesized a few periodontal pathogens like *Porphyromonas gingivalis* might initiate rheumatoid arthritis by acting as a triggering factor for autoimmunity against the citrullinating proteins in the joints (12). Similarly, other studies have shown an association between AS and PD (13). Few studies have shown increased levels of tumor necrosis factor-alpha (TNF-α) and various interleukins

(ILs) in both patients with AS and periodontitis as well as the pathogenetic role of TNF-α, T-cell response, C-reactive proteins (CRP) levels, IL-6, and IL-2 (12-14).

AS has been related to various other inflammatory connective tissue diseases. However, there is a paucity of data suggesting an association between AS and PD. This systematic review aimed to appraise the available literature exploring the relationship between AS and PD.

Methods

For reporting our review, we followed the universally accepted preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (15).

Search strategy

We searched the MEDLINE and Embase databases using the following medical subject headings terms: Ankylosing spondylitis, periodontitis, periodontal diseases, spondyloarthritis, and spondylitis. In addition, we used keywords spondyloarthritides, spinal disease, musculoskeletal disease, rheumatic disease and periodontitis, periodontal disease, periodontoses, parodontoses, chronic periodontitis, gum disease, gingivitis, oral health, dental health, plaque index, bleeding on probing, probing pocket depth, and clinical attachment loss. We supplemented the above by searching Google scholar with the following terms: ankylosing spondylitis, spondyloarthritis, spondyloarthropathy, periodontal disease, and periodontitis. We searched Google scholar up to 30 pages to avoid a large number of irrelevant articles. Furthermore, we manually searched 1 reputed rheumatology and dental sciences journal each (Annals of the Rheumatic Diseases and Journal of Clinical Periodontology, respectively) for the last 5 years (2015-2019). We also manually scanned the references of the selected full texts.

Types of participants

Types of participants to be included in the review had to be diagnosed with AS according to various criteria for AS, such as New York (NY), modified New York (mNY), Rome criteria (16), or assessment of spondyloarthritis international society (ASAS) criteria (17), or cases, which had been clinically diagnosed by a rheumatologist. Patients who were under the age of 18 years were not included.

Study selection

Study selection was done by 2 independent reviewers (RR and AP); their selections were compared, and a consensus was reached through discussion when there was a case of disagreement. The option of a 3rd reviewer (VR) was available for final opinion in case of any disagreement.

Types of publications

Studies (observational studies of cross-sectional, cohort, or case-control type with adult patients) reporting the prevalence of periodontitis in patients with and without AS were included. Other studies, such as case reports, case series, and randomized controlled trials, were not included. Studies were selected without any language or time limits.

Data extraction

Data were extracted using a well-designed and piloted PROforma. We gathered the information related to study type, year of publication, language used, duration of the disease, sample size, exclusion and inclusion criteria, method of participation, and diagnostic criteria for AS and PD.

Quality assessment

Quality assessment was done by using the Scottish intercollegiate guidelines network methodology checklist (18).

Results

A total of 984 studies were identified initially (Figure 1). A total of 233 duplicate records were

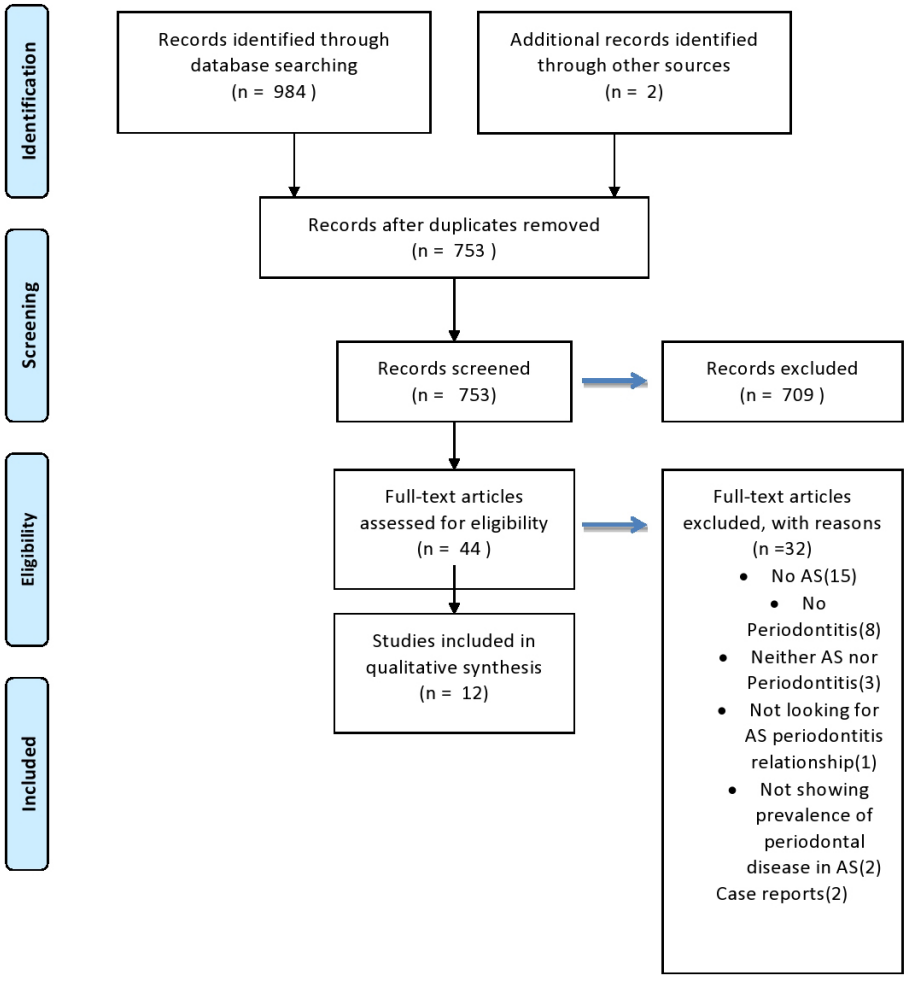

Figure 1. Preferred reporting items for systemic reviews and meta-analyses 2009 flow diagram.

Main Points

- This systematic review emphasizes an association between periodontal disease (PD) and ankylosing spondylitis (AS) and a higher incidence of periodontitis in patients with AS.
- The prevalence of periodontitis ranged from 38% to 88% in patients with AS and 26% to 71% in the control group.
- Of the 12 studies, 2 showed significant changes in plaque index, 2 studies showed altered probing pocket depth, 3 showed significantly increased clinical attachment loss, and 2 showed increased bleeding on probing.
- In 7 studies, periodontitis was seen in a significant number of patients with AS ($p<0.05$).
- All the studies reported that the prevalence of PD in patients with AS was higher than that in patients without AS.

removed after screening. Of the 753 remaining articles, only 44 full-text articles were scrutinized. At this point, 44 articles were thoroughly reviewed; 15 of them were removed as they did not have AS in the manuscript, 8 articles did not have periodontitis, and 3 had neither AS nor periodontitis. Furthermore, 1 article did not prove the AS-periodontitis relationship, 2 articles did not show the prevalence of PD in AS, and 2 articles were case reports. A total of 12 studies were taken into consideration for this review (19-30).

Characteristics of these 12 included studies are shown in Tables 1-4. They were all published between 2005 and 2013 (19-30). These studies were conducted in 7 different countries, including Colombia, Korea, New Zealand, Germany, Turkey, Finland, and Taiwan. Most of the pa-

Table 1. Description of cases and controls.

Parameters	Description		
Author, year, reference	Bautista-Maulano et al. (2017) (19)	Kang et al. (2015) (23)	Londoño et al. (2013) (20)
Study type	Case-control	Case-control	Single-arm
Country	Columbia	Korea	Colombia
Source of funding	University EL Bosque Hospital, Militan Central	Abbott Investigator Initiated Research Program Grant and National Institute of Dental and Craniofacial Research	University Militan Hospital Universidad, El Bosque
Diagnostic criteria used for AS	ASAS criteria	1984 mNY criteria	ESSG criteria
Disease duration of AS	5.0 (7.1) years	49 (58.3%) less than 10 years	11.1±8.0 years
Diagnostic criteria used for PD	Criteria by CDC-AAP	3 definitions of chronic periodontitis used by CDC	By 2 experienced periodontists
Study duration	NR	12 months	7 months
Sample size	Cases: 78 Controls: 156	Cases: 84 Controls: 84	Cases: 8
Sex, n (%)	Male Cases: 47 (60.3) Controls: 94 (60.3)	Female Cases: 16 (23.5) Controls: 16 (23.5)	Female Cases: Not specified Controls: Not specified
Age	Cases: 39.6 (11.0)	Cases: 37 (31.0-44.0)	Cases: 41.4±10.7
Mean (±SD) (years)	Controls: 39.5 (11.1)	Controls: 36.5 (30.0-44.0)	
Recruitment	Cases: Rheumatology clinic in Colombia Controls: Random people attending patients in hospital	Cases: Rheumatology clinic, Seoul National University, Bunding Hospital in Seongram Controls: Same geographic area	Cases: Rheumatology department, School of Dentistry, De La Sabena, Colombia
Inclusion criteria	Cases: • Diagnosed with AS by ASAS criteria Controls: • Age, 18-60; years random individuals	Cases and controls: • Age, 19-70 years • AS Criteria for ESSG Age- and sex- matched controls	Cases: Per ESSG criteria
Exclusion criteria	Cases and controls: • Use of antibiotics post 3 months and a history of periodontal and orthodontic therapy	Cases and controls: • Any recent periodontal treatment for at least 6 months • Any antimicrobial therapy • Immunosuppressive drugs • History of diabetes mellitus type 2 or IBD	Cases: • Patient with previous periodontal treatment, receiving TNF-α blocker • Recent use of antibiotics, infection, edentulous with malignancies, on orthodontic treatment
Plaque index (PI)	Cases: 0.4 (0.2) Controls: 0.5 (0.2) p=0.12, NS	Case: 25.45 (13.39-40.99) Control: 23.66 (10.49-36.61) p=0.57, NS	50%
PPD	Cases: 3.3 (1.7) Controls: 3.2 (1.9) p=0.29, NS	NR	2.36%

Table 1. Description of cases and controls. (Continued)

Parameters	Description		
CAL	Cases: 1.9 (0.6) Controls: 2.3 (0.8) p<0.001, S	Cases: 2.58 (2.33-2.89) Controls: 2.60 (2.36-2.96)	23%
BOP	Cases: NR Controls: NR	Cases: 11.56 (7.14-21.16) Controls: 9.70 (6.44-17.11) BOP in >20% site: Cases: 2.2 (26.2) Controls: 17 (20.2)	16.7%
Number of teeth missing	NR	Cases: 5 (2.0-9.0) Controls: 6 (3.0-10.0)	26.6 (95% [25.5-27.7])
Number of teeth present	Cases: 26.1 (4.1) Controls: 25.5 (5.9) p=0.79, NS	NR	NR
Periodontitis	Cases: 44 (56.4%) Controls: 108 (69.2%) p=0.01	Cases: No or mild: 25 (29.8%) Moderate: 50 (59.5%) Severe: 9 (10.7%) Controls: No or mild: 28 (33.3%) Moderate: 40 (47.6%) Severe: 16 (19.0%)	Association between severity of periodontal inflammation in patients with more than 5 years of evolution of disease
Lopez criteria	NR	Cases: 39 (46.4%) Controls: 40 (47.6%)	NR
Average AL value >2.6 mm	NR	Cases: 41 (48.8%) Controls: 42 (50.0%)	NR

CDC-AAP: Centre for Disease Control and Prevention-American Academy of Periodontology; ASAS: Assessment of SpondyloArthritis International Society; mNY: modified New York; ESSG: European spondyloarthritis study group; SD: standard deviation; PI: plaque index; PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; NR: not relevant; AS: ankylosing spondylitis; PD: periodontal disease; AL: attachment loss; NS: not significant; S: significant.

Table 2. Description of cases and controls.

Parameters	Description		
Author, year, reference	Bisanz et al. (2016) (21)	Schmalz et al. (2018) (30)	Ziebolz et al. (2018) (29)
Study type	Case-control	Cross-sectional	Cross-sectional
Country	New Zealand	Germany	Germany
Source of funding	New Zealand Dental Association	NR	NR
Diagnostic criteria used for AS	ASAS criteria for AS	mNY criteria	Clinical diagnosis by a rheumatologist
Disease duration of AS (years)	NR	10.92±10.55	Median: 6 (IQR: 11.5)
Diagnostic criteria used for PD	PPD≥4 mm at ≥4 sites	DMF-T, PPD, and CAL at 6 point per tooth	PPD, BOP, and CAL were evaluated on 6 teeth
Study duration	NR	NR	NR
Sample size	Cases: 17 Controls: 22	Cases: 50 Controls: 50	Cases: 52 Controls: 52
Sex, n (%)	Female Cases: 6 (35.3) Controls: 7 (31.8)	Male Cases: 26 (52) Controls: 23 (46)	Female Cases: 24 (46) Controls: 24 (46)

Table 2. Description of cases and controls. (Continued)

Parameters	Description		
Age mean (±SD) (years)	Cases: 38 (12.8) Controls: 37 (12.7)	Cases: 47.18±15.67 Controls: 55.82±10.56	Median age (IQR) Cases: 49.5 (25) Controls: 48.0 (20)
Recruitment	Cases: • Rheumatology Department of Dunedin Hospital, New Zealand Controls: • Elected from Electoral hall	Cases: • Department of Nephrology Controls: • Rheumatology, University Medical Centre, Goettingam, Germany	Cases: • Department of Nephrology, Rheumatology, University Medical Centre, Goettingam, Germany Controls: • Department of Preventive Dentistry Periodontology & Cardiology
Inclusion criteria	Cases: • Axial spondyloarthritis per the ASAS criteria Controls: • Individually matched to AxSPA patients on age, sex, and ethnicity	Cases: • Diagnosed with AS by rheumatologistand 6 remaining teeth according to mNY criteria; age, 18-79 years Controls: • Department of Preventive Dentistry, Periodontology & Cardiology	Cases: • Diagnosis of AS by a pharmacologist and age more than 18 years Controls: • Healthy patient matched for age, sex, and smoking behavior
Exclusion criteria	Cases: • Not fulfilling ASAS criteria Controls: • Unable to provide informed consent • Pregnancy • History of malignancy • Taking anticoagulants • Previous history of periodontal treatment, edentulous, history of inflamed arthritis (including AxSPA), osteoporosis, CVD, DM, or IBD	Cases and controls: • Poor general health condition, organ transplant, other autoimmune disease, existence of hepatitis A, B, and C; TBC; HIV; and other chronic disease	Cases and controls: • Poor general condition (morbidity) • Organ transplant, diagnosed other autoimmune diseases and other chronic diseases
PI, n (%)	Cases: 1.0 (0.4) Controls: 0.6 (0.4)	Cases: NR Controls: NR	Cases: NR Controls: NR
PPD, n (%)	Cases: 5.6 (5.1) Controls: 5.1 (11.5) p=0.146, NS	Cases: NR Controls: NR	Median: Cases: 2.4 (1.2) Controls: 1.8 (1.0) p<0.01, S
CAL, n (%)	Cases: 10.1 (13.4) Controls: 12.6 (25.1) p=0.318, NS	Cases: NR Controls: NR	Median: Cases: 2.4 (1.2) Controls: 1.8 (1.0)
BOP, n (%)	Cases: 36.6 (21.3) Controls: 23.6 (17.6) p=0.041, S	Cases: NR Controls: NR	Median: Cases: 42 (52) Controls: NR
Number of teeth missing	Cases: 13.1 (7.6) Controls: 9.9 (7.6) p=0.210, NS	Cases: 3.54±4.29 Controls: 4.10±4.07	Cases: NR Controls: NR
Number of teeth present	NR	NR	NR

Table 2. Description of cases and controls. (Continued)

Parameters	Description		
Periodontitis, n (%)	Cases: 1 (0.1) Controls: 2 (0.1)	Cases: No or mild: 2 (4) Moderate: 25 (50) Severe: 23 (46) Controls: No or mild: 11 (22) Moderate: 26 (52) Severe: 13 (26) p=0.01, S	Cases: No or mild: 2 (4) Moderate: 26 (51) Severe: 23 (45) Controls: No or mild: 13 (25) Moderate: 34 (65) Severe: 5 (10) p=0.01, S
Lopez criteria	NR	NR	NR
Average AL value >2.6 mm	NR	NR	NR

ASAS: Assessment of SpondyloArthritis International Society; mNY: modified New York; ESSG: European spondyloarthritis study group; SD: standard deviation; PI: plaque index; PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; NR: not relevant; DM: diabetes mellitus; CVD: cardiovascular disease; IBD: inflammatory bowel disease; AS: ankylosing spondylitis; PD: periodontal disease; AL: attachment Loss; AxSpA: axial spondyloarthritis; NS: not significant; S: significant.

Table 3. Description of cases and controls.

Parameters	Description		
Author, year, reference	Helenius et al. (2005) (22)	Pischon et al. (2010) (24)	Sezer et al. (2012) (25)
Study type	Case-control	Case-control	Case-control
Country	Finland	Germany	Turkey
Source of funding	Helsinki University Central Hospital, Orion Research Foundation, Finnish Dental Association, Finnish Women's Dental Association	German Research Foundation and Habilitation Fellowship from Charite Universitatsmedizin	NR
Diagnostic criteria used for AS	mNY	mNY	mNY
Disease duration of AS (years)	14.7 (8.9%)	11.7 (7.4)	5.04 (6.13)
Diagnostic criteria used for PD	CPI score ≥3 (PPD≥4 mm)	Mean CAL >3 mm	1999 consensus classification of periodontal disease; at least 4 teeth with PPD>5 mm+CAL ≥ 2 mm at the same time
Study duration	NR	36	6
Sample size	Cases: 18 Controls: 77	Cases: 48 Controls: 48	Cases: 48 Controls: 48
Sex, n (%)	Female Cases: 6 (33.3) Controls: 50 (64.9)	Female Cases: 14 (29.2) Controls: 14 (29.2)	Female Cases: 13 (27.1) Controls: 13 (27.1)
Age mean (±SD) (years)	Cases: 42.4 (11.6) Controls: 42.2 (12.7)	Cases: 40.4 (11.7) Controls: 39.8 (12.1)	Cases: 34.27 (9.73) Controls: 33.33 (9.67)
Recruitment	Cases: Rheumatology Outpatient Department, Meilahti Hospital, Helsinki University Central Hospital Controls: Institute of Dentistry, University of Helsinki	Cases: Department of Rheumatology and Clinical Immunology, Charite-Universitatsmedizin Controls: General Dental Office	Cases: Department of Rheumatology, Gaziantep University, Faculty of Medicine Controls: Gaziantep University, Faculty of Dentistry

Table 3. Description of cases and controls. (Continued)

Parameters	Description		
Inclusion criteria	Cases: • Meeting the current classification criteria related to AS Controls: • Randomly selected volunteer dental patients, no AS	Cases: • Individuals with prevalent AS who attended for routine examination Controls: • Healthy individuals attending a general dental office	Cases: • Individuals with AS diagnosed by 2 rheumatologists Controls: • Systemically healthy individuals
Exclusion criteria	Cases: • NR Controls: • History of diabetes, rheumatic disease, or any other disease affect the masticatory system	Cases and controls: • History of periodontal therapy or use of antibiotics during the last 3 months prior to examination, pregnancy, or lactation	Cases and controls: • History of systemic diseases or conditions, periodontal treatment within the last 6 months, antibiotic or corticosteroid medication within the last 3 months, <18 teeth, current smoker
PI	NR	Cases: 0.55 (0.37) Controls: 0.32 (0.19) p<0.001, S	Cases: 1.60 (0.61) Controls: 1.53 (0.52) p=0.547, NS
PPD	NR	Cases: 3.06 (0.71) Controls: 2.67 (0.49) p=0.002, S	Cases: 3.17 (0.82) Controls: 3.15 (0.90) p=0.91, NS
CAL	NR	Cases: 3.20 (0.74) Controls: 2.73 (0.50) p<0.001, S	Cases: 2.35 (1.93) Controls: 2.04 (1.81) p=0.419, NS
BOP	NR	Cases: 56.5 (23.0) Controls: 25.0 (37.09) p<0.001, S	Cases: 46.77 (3.17) Controls: 33.09 (2.98) p<0.001, S
Number of teeth missing	Cases: 3.44 (3.17) Controls: 2.13 (2.01) p=0.108, NS	Cases: 1.95 (2.31) Controls: 2.44 (2.62) p=0.362, NS	NR
Number of teeth present	NR	NR	NR
Periodontitis, n (%)	Cases: 10 (56) Controls: 20 (26) p=0.015, S	Cases: 23 (47.9) Controls: 15 (31.3) p=0.095, NS	Cases: 18 (37.5) Controls: 14 (29.2) p=0.386, NS
Lopez criteria	NR	NR	NR
Average AL value >2.6 mm	NR	NR	NR

SD: standard deviation; PI: plaque index; PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; NR: not relevant; mNY: modified New York; AS: ankylosing spondylitis; PD: periodontal disease; AL: attachment loss; NS: not significant; S: significant.

tients were recruited from rheumatology clinics, whereas in a few studies, the controls came from dental and nephrology departments. A total number of 7,340 patients and 34,764 controls were included in these 12 studies.

Definition of AS

Of the 12 studies, 2 used ASAS classification criteria (19, 21) for diagnosing AS, whereas 6 used mNY criteria (22-25, 27, 30). Londoño et al. (20) used the European Spondyloarthritis Study Group (ESSG) criteria, whereas Ziebolz et al. (29) depended on rheumatologists' clinical acumen to include patients who were diagnosed clinically. Keller et al. (28) did the same and included patients diagnosed by a rheumatologist. Chang et al. (26) did not mention the diagnostic criteria of AS in their study.

Definition of periodontitis

An interesting point was the high variability in both the terminology and the definition of periodontitis in all these studies. A few authors used the term periodontitis in their studies, whereas others used PD as well as chronic periodontitis (25, 28). In all the studies, the primary outcome was the prevalence of PD. Other outcomes reported were bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment loss (CAL), plaque index (PI), and number of missing teeth. For diagnosing periodontitis, a few studies used diagnostic criteria by the Center for Disease Control (CDC) (19, 23), whereas others used clinical parameters, such as PI, PPD, BOP, and CAL (21, 24, 25, 27, 29). Of the 12 studies, 4 distinguished the severity of periodontitis using the definition proposed by the CDC (20, 23, 29, 30).

Prevalence of periodontitis in AS

The prevalence of periodontitis in AS was between 38% and 88% in patients with AS,

Table 4. Description of cases and controls.

Parameters	Description		
Author, year, reference	Suppiah et al. (2013) (27)	Keller et al. (2013) (28)	Chang et al. (2013) (26)
Study type	Case-control	Case-control	Case-control
Country	New Zealand	Taiwan	Korea
Source of funding	Research Grant from the New Zealand Dental Association, Research Foundation	NR	NR
Diagnostic criteria used for AS	mNY	ICD-9-CM codes 720 or 720.0; clinical diagnosis by a rheumatologist	NR
Disease duration of AS (years)	9.1 (8.6)	NR	NR
Diagnostic criteria used for PD	2 or more sites with at least 4 mm CAL	ICD-9-CM code 523.4; at least 2 principal diagnoses based on diagnostic test and clinical examination; PPD≥3 mm	Clinical case definition proposed by the CDC
Study duration	12	108	3
Sample size	Cases: 41 Controls: 49	Cases: 6,821 Controls: 34,105	Cases: 75 Controls: 73
Sex	Female Cases: 12 (29.3%) Controls: 13 (26.5%)	Female Cases: 2,839 (41.6%) Controls: 14,195 (41.6%)	NR
Age mean (±SD) (years)	42.5 (13.7)	27.2 (19.4)	NR
Recruitment	Cases: Rheumatology Department, Dunedin Public Hospital and School of Dentistry Controls: South Dunedin Electoral Poll	Longitudinal Health Insurance Database, 2000	NR
Inclusion criteria	Cases: • AS Controls: • Disease-free individuals matched, individually to cases for age and gender	Cases: • All patients of age >18 years with - a first time diagnosis of AS in ambulatory care visits between January 2001 and December 2009 Controls: • Inclusion in the Longitudinal Insurance Database 2000	NR
Exclusion criteria	Cases: • Being unable to give written consent, pregnancy, malignancy, taking anticoagulants or having a bleeding disorder, requirement for prophylactic antibiotic, being fully edentulous Controls: • Same as cases and a history of periodontal treatment, cardiovascular disease or diabetes mellitus	Cases: • Age <18 years, diagnosis of RA or SLE Controls: • Same as cases and a diagnosis of AS, RA, and SLE since 1995	NR
PI	NR	NR	Cases: 20.92 (27.55%) Controls: 19.21 (23.65%) p=0.24, NS

Table 4. Description of cases and controls. (Continued)

Parameters	Description		
PPD	NR	NR	Cases: 2.54 (0.36%) Controls: 2.58 (0.30%) p=0.645, NS
CAL	NR	NR	Cases: 2.62 (0.36%) Controls: 2.66 (0.40%) p=0.523, NS
BOP	NR	NR	Cases: 14.87 (11.47%) Controls: 11.98 (8.35%) p=0.081, NS
Number of teeth missing	NR	NR	NR
Number of teeth present	-	-	-
Periodontitis, n (%)	Cases: 36 (87.8) Controls: 35 (71.4) p=0.058, NS	Cases: 2,830 (41.5) Controls: 8,820 (25.9) p<0.001, S	Cases: 51 (68) Controls: 43 (58.9) p=0.250, S
Lopez criteria	NR	NR	NR
Average AL value >2.6 mm	NR	NR	NR

CDC: Centre for Disease Control and Prevention; ICD: International Code of Diseases; SD: standard deviation; mNY: modified New York; PI: plaque index; PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; NR: not relevant; AS: ankylosing spondylitis; PD: periodontal disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; AL: attachment loss; NS: not significant; S: significant.

whereas it was between 26% and 71 % in the control group. Of the 12 studies, 2 showed significant changes in PI (20, 24), 2 showed altered PPD (24, 29), 2 showed significant increase in CAL (19, 24), and 4 showed increased BOP (21, 23-25). In 7 studies, periodontitis was seen in a significant number of patients with AS (p<0.05) (19, 22, 23, 26, 28-30). All the 12 studies reported that the prevalence of PD was higher in patients with AS than in those without AS.

Quality assessment

Quality assessment on the basis of the Scottish intercollegiate guidelines network methodology checklist (18) is shown in Table 5. The studies were not of uniformly good quality.

Discussion

Studies have shown that the periodontal pathogens have been implicated in the pathogenesis of AS in individuals who are genetically predisposed. Human leukocyte antigen-B27 (HLA-B27) is responsible for CD8+ T-cells being presented with the endogenous peptides. A very popular arthritogenic peptide theory postulates that B27 is directly responsible for the pathogenesis of AS. HLA-B27-specific antigenic peptides are shared among different arthritis-causing pathogens, and subsequently, these peptides also cross-react with autoantigens. Therefore, when *P. gingivalis* peptidyl arginine deiminase infect an HLA-B27-positive individual, a cytotoxic T-cell-mediated autoimmune response would be initiated in the joints (31).

We expanded on an older systematic review of 6 studies, which showed a positive correlation between PD and AS severity and the risk of AS in PD being almost double in the meta-analysis despite no significant difference in PPD and CAL. A significant association was seen in BOP in patients with AS (p=0.0005) (32). In this study, we included those studies as well as the studies conducted after 2015 till date and included 7,340 patients and 34,764 controls.

Of the 12 studies, only 1 by Londoño et al. (20) was a single-arm study, whereas all the others were case-control studies. We could only get an abstract of Suppiah et al. (27), but we were able to generate a substantial amount of information from it. In nearly all the studies, the duration of AS was between 5 and 20 years with a variable duration in each study. The authors used different criteria for the diagnosis of AS. The ASAS criteria were used in 2 studies (19, 21) and mNY criteria by 5 authors (22-25, 27, 30). The study by Londoño et al. (20) used the ESSG criteria for diagnosing AS. Ziebolz et al. (29) depended on the rheumatologist's clinical acumen for diagnosing the AS, Keller et al. (28) used ICD-9-CM codes 720 or 720.0, and Chang et al. (26) did not use any diagnostic criteria.

In a study conducted by Helenius et al. (22), a serious periodontal condition was noticed in 45% patients with Spondyloarthritis (SpA), with a community periodontal index score of 3-4. Pischon et al. (24) included patients with a high prevalence of AS, although the duration and severity of the disease varied. Sezer et al. (25) showed that the serum concentrations of IL-6, TNF-α, and CRP were significantly higher in the AS group (p<0.001). Keller et al. (28) found that patients were 1.70 (95% confidence interval, 1.56-1.89) times higher than the control group to have undergone a periodontal flap operation or gingivectomy.

Bisanz et al. (21) concluded that patients with axial Spondyloarthritis (AxSpA) had a high Bath ankylosing spondylitis disease activity index of 4.1±2.1 (mean±SD) and a significantly higher prevalence of PD than the control group. Bautista-Maulano et al. (19) also established the clinical periodontal variables; however, they could not find any significant increase in the frequency of any periodontal variable.

Schmalz et al. (30) showed worse oral-health-related quality of life (OHRQoL) in patients with AS than that of healthy controls, irrespective of the oral status. This may be due to the high disease burden of AS affecting OHRQoL in such patients, necessitating increased attention and care of such patients in dental care, especially considering the psychological aspects.

Table 5. Quality assessment.

Item		First author, publication year, reference											
		Helenius et al. (2005) (22)	Sezer et al. (2012) (25)	Chang et al. (2013) (26)	Keller et al. (2013) (28)	Pischon et al. (2010) (24)	Londoño et al. (2013) (20)	Suppiah et al. (2013) (27)	Bisanz et al. (2016) (21)	Bautista-Maulano et al. (2017) (19)	Kang et al. (2015) (23)	Schmalz et al. (2018) (30)	Ziebolz et al. (2018) (29)
1.1	The study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2	The cases and controls are taken from comparable populations	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
1.3	The same exclusion criteria are used for both cases and controls	Cannot say	Yes	Cannot say	Cannot say	Yes	No	No	No	Yes	Yes	Yes	Yes
1.4	What percentage of each group (cases and controls) participated in the study?	Cannot say	Cannot say	Cannot say	Not applicable	Cannot say	Cannot say	Cases: 72.1%; controls: 34.7%	Cannot say	Cannot say	Cannot say	Cannot say	Cannot say
1.5	Comparison is made between participants and non-participants to establish their similarities or differences	No	No	No	Not applicable	No	No	No	Not applicable	Not applicable	Not applicable	No	No
1.6	Cases are clearly defined and differentiated from controls	Yes	Yes	Yes	Yes	Yes	Cannot say	Yes	Yes	Yes	Yes	Yes	Yes
1.7	It is clearly established that controls are non-cases	Yes	Yes	Cannot say	Yes	Cannot say	Cannot say	Yes	Yes	Yes	Yes	Yes	Yes
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	Cannot say	No	Cannot say	Not applicable	No	Cannot say	Cannot say	Cannot say	Cannot say	Cannot say	Cannot say	Cannot say
1.9	Exposure status is measured in a standard, valid and reliable way	Yes	Yes	Cannot say	Yes	Yes	Cannot say	Yes	Yes	Yes	Yes	Yes	Yes
1.10	The main potential confounders are identified and taken into account in the design and analysis	No	Yes	Cannot say	Yes	Yes	Yes	Cannot say	Yes	Yes	Yes	Yes	Yes
1.11	Confidence intervals are provided	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.12	How well was the study done to minimize the risk of bias or confounding?	+	++	-	+	+	-	+	+	+	+	+	+
1.13	Do you think there is clear evidence of an association between the exposure group and outcome?	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
1.14	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

In a study by Ziebolz et al. (29), a higher number of decayed teeth was noted in patients with AS than in healthy controls (HC). Prevalence of *Parvimonas micra, Eubacterium nodatum*, and *Eikenella corrodens* was seen as a significant difference between patients with AS and HC. The Bath ankylosing spondylitis metrology index and disease duration showed significant associations with PPD

and CAL ($p<0.001$). This signifies that the prevalence of bacteria related to improper maintenance of oral hygiene was higher in patients with AS. It also affects the periodontal burden.

The most common exclusion criteria used in all the studies was the use of antibiotics for more than 3 months or having received any treatment for periodontitis. Majority of the studies reported missing teeth between 3 and 6 in number. Studies conducted by Helenius et al. (22) and Pischon et al. (24) reported a comparable incidence of the number of missing teeth between cases and controls ($p>0.05$).

Bautista-Maulano et al. (19) reported the incidence of periodontitis in 56.4% cases and 69.2% controls, with a significantly higher incidence in the controls ($p=0.01$). The study by Bisanz et al. (21) also reported a higher incidence in controls; whereas studies by Helenius et al. (22), Keller et al. (28), Ziebolz et al. (29), and Schmalz et al. (30), reported a significantly higher incidence of severe periodontitis than in the controls ($p<0.05$).

The limitation of this systematic review is the scarcity of literature on the topic this review. Because of the different diagnostic tools and criteria defining AS and PD used in various studies and the heterogeneity among the very few available studies, the review could not gather a substantial amount of information. A similar review done by Ratz et al. (32) could not justify the proposed association owing to the low number of studies and the fact that the study was a hypothesis based on an already observed relationship with rheumatoid arthritis.

In conclusion, although the studies are heterogeneous in nature, according to our systematic review, there appears to be an association between AS and PD. Studies have also noted a higher incidence of periodontitis in patients with AS. Overall, this review underscores the need for a close collaboration between dentists treating PDs and rheumatologists. It is important for patients with AS to undergo dental examination, which could be triggered by rheumatologists, eliciting the basic history of dental problems in AS. Studies have shown that both PD and AS affect the quality of life (30), and an important factor to consider would be how strongly a patient's quality of life is affected by both AS and PD. In future, there should be more case-control studies on this topic. Furthermore, a collaborative approach between rheumatologists and dentists is necessary for the management of AS.

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