A possible link between ankylosing spondylitis and periodontitis - A systematic review and meta-analysis

Running header: Ankylosing spondylitis and periodontitis

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Abstract

Objectives

The aim was to examine the link between ankylosing spondylitis (AS) and periodontitis.

Methods

Medline, Embase, Amed, Cinahl, Web of Science and Google Scholar were searched to identify eligible studies which were selected and reviewed independently by at least two authors.

Results

Six case-control studies were included in the review. Study size ranged from 90 to 40,926 participants. The prevalence of periodontitis ranged 38%-88% and 26%-71% in AS patients and controls respectively. As there was low level heterogeneity (I^2=13%), using fixed effect analysis, the overall pooled estimate of the OR for periodontitis was 1.85 (1.72, 1.98). There was no evidence of publication bias.

Conclusion

The results lead to a need for further large study with sufficient statistical power to detect the desired effect size, taking into account potential confounding factors and using validated measures of AS and periodontitis.

Key words: Ankylosing Spondylitis; Periodontitis; epidemiology; prevalence; dental

Introduction

Ankylosing Spondylitis (AS) is defined as a chronic inflammatory rheumatic disease that affects mainly the axial skeleton, causing an inflammation of the spine (spondylitis) or the sacroiliac joints (sacroiliitis). It is characterized by inflammatory back pain (IBP) onset in early adulthood with a progressive reduction in spinal mobility, but can also affect the peripheral joints, eyes, bowel and skin [1]. The median prevalence across studies in Europe is 18.6 per 10,000 with a higher prevalence in males (ratio 3.8 to 1) [2].

Periodontitis is a form of periodontal disease, which is defined as any disorder of the tissue surrounding and supporting the teeth [3]. Mostly, this disorder is characterized by gingival inflammation initiated by pathogenic bacteria in dental plaque [3, 4]. A reversible form of periodontal disease, gingivitis, is highly prevalent among adults (50-90% worldwide) and can be easily reversed by effective oral hygiene [3]. Periodontitis in contrast, affects not only the superficial gingival tissue but extends to the periodontal ligament which leads to loss of connective tissue and alveolar bone [3]. Periodontitis is characterised by loss of periodontal ligament with the formation of soft tissue pockets between the gingiva and the tooth root. It follows an immune response to the chronic presence of plaque bacteria. Periodontitis may proceed asymptomatically and if untreated it can lead to tooth loss [3].

Since the definition of the diagnostic threshold is not clarified yet, the prevalence of periodontitis varies dependent on definition [3, 4]. In epidemiological research there are mainly three criteria used for the clinical diagnosis of periodontitis: clinical attachment loss (CAL), bleeding on probing (BOP) and pocket probing depth (PPD) [4, 5, 6]. Besides insufficient oral hygiene, periodontitis is more common in males and persons of African-American race, is associated with specific gene polymorphisms as well as environmental factors such as smoking and stress [3, 7, 8].

It is well known that the human leukocyte antigen (HLA)-B27 is associated with AS [9]. While no significant association was found between HLA class II antigens and aggressive periodontitis, patients with aggressive periodontitis showed a positive association with HLA-A9 and a negative association with HLA-A2 and HLA-B5, which are not relevant in AS [10]. An association between the occurrence of a single nucleotide polymorphism in the interleukin-10 gene and both chronic and aggressive forms of periodontitis was found, but there are no

such data on AS [11]. Probably, the most important association between AS and periodontitis could be between non-MHC AS genes that can perturb the balance in the cytokines network (IL1,IL6,TNF) involved in both diseases.

Periodontitis is associated with several systemic diseases, e.g. diabetes [7, 12], adverse pregnancy outcomes [13], cardiovascular disease [14] and cancer [15]. While the association between rheumatoid arthritis (RA) and periodontitis is well known [16, 17, 18] for AS however, an association with periodontitis is not clear. Nevertheless, certain similarities between RA and AS are among the main reasons to hypothesise a link between periodontitis and AS may also exist. One feature both rheumatic diseases share is that they are both defined as a chronic inflammatory disease [19], and it is this which may lead them both to be related to periodontitis. The underlying pathogenic process linking periodontitis with RA involve cytokines (TNF-α and interleukin) as well as T and B lymphocytes [19, 20].

The pathogenic role of tumour necrosis factor-alpha (TNF- α) and an immunologic T-cell response is considered to be present in AS [21] and there is evidence of significantly elevated levels of interleukin-6 (IL-6), IL-2 and TNF-α in AS patients [22]. Additionally AS and periodontitis both share increased levels of C-reactive protein (CRP) levels [22,23] although the increase is greater in the case of periodontis than AS. Moreover studies found a significant reduction of disease activity measured by the erythrocyte sedimentation rate (ESR) and a decrease of TNF-α levels in RA patients undergoing treatment for periodontitis [24,25].

The aim of this systematic review was therefore to examine whether there is a relationship between AS and periodontitis.

Materials and methods

The protocol for the review was registered with the international register of systematic reviews PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). We followed PRISMA guidelines for reporting the review [26].

Types of publications

To be included in this systematic review, the studies had to be reviews or observational studies of cross-sectional, case-control or cohort design. Randomised controlled trials, case reports and case series were excluded. There were no restrictions on publication date or publication status.

Types of participants

Participants of the studies had to be diagnosed with AS either based on recognised international criteria (New York [27], modified New York (mNY) [27], Rome [27] or ASAS criteria [28]) or based on clinical diagnosis by a rheumatologist. Studies which included individuals younger than 18 years were not eligible.

Types of outcome measures

For a study to be considered eligible a prevalence of periodontal disease had to be reported in AS patients and also available for a non-AS population.

Search strategy

The electronic search consisted of literature search in several databases including EMBASE, MEDLINE, AMED, CINAHL and Web of Science. The search strategy was internally peer-reviewed and included the following search terms: (ankylosing spondylitis, spondyloarthritis, spondylarthritis, spondyloarthritides, spondyloarthropathies, spondylarthropathies, musculoskeletal disease, rheumatic diseases, spinal disease) AND (periodontal disease, periodontitis, aggressive periodontitis, chronic periodontitis, gingivitis, parodontoses, parodontosis, periodontosis, gum diseases, gingival diseases, pyorrhea alveolaris, oral health, dental health, plaque index, probing pocket depth, bleeding on probing, clinical attachment loss).

Additionally, Google Scholar was searched using the following search terms: "ankylosing spondylitis AND periodontal". Due to the large amount of results when using Google Scholar a cut-off point of 25 pages to be searched was defined, after which the results were deemed irrelevant. Two rheumatology and two dental journals for the last 5 years (January 2009 – December 2013) were manually searched, including the Annals of the Rheumatic Diseases, Rheumatology, the Journal of Dental Research and the Journal of Clinical Periodontology.

Furthermore the references of the found full texts were scanned for any studies missed. Authors were contacted to obtain the missing information if the publications were thought to be eligible. The whole search was limited to human where possible and there was no language limitation. The last search was run on the 5th March 2014.

Study selection

Selection was made by two independent reviewers. At every step the two reviewers' selections were compared and in the case of disagreement a consensus was reached. If necessary a third person would have been consulted to make a decision.

Data extraction

Data were extracted using a specially designed and piloted data extraction form. Information was gathered on (1) the characteristics of the publication (year, language, study type, size and duration and source of funding as well as method of participant recruitment, inclusion and exclusion criteria and diagnostic criteria used for AS and periodontitis and methods for dealing with confounding factors), (2) characteristics of the participants (mean age, gender and disease duration in AS-patients) and (3) information on periodontal parameters (prevalence of periodontitis in participants, types of periodontal parameters measured, determined odds ratios and type of analysis used).

Quality assessment

Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist [29] was used to evaluate the risk of bias in the included studies. The assessment was undertaken by two reviewers independently and was compared afterwards. In the case of disagreement a consensus was reached and if necessary a third author was consulted to make a decision.

Statistical analysis

Where medians and interquartile ranges (IQR) were presented, these were converted to mean and standard deviation (SD) to allow comparison across studies, under assumption of normality. T-test and chi-square test were used to compare outcomes between cases and controls within each study as appropriate. If an Odds Ratio (OR) was not presented it was calculated from raw data.

Meta-analysis was performed for prevalence of periodontitis and mean PPD, CAL, BOP and number of missing teeth using Comprehensive Meta Analysis software version 2.2.064 [30]. Forest plot was used to illustrate the results and I^2 statistics was used to evaluate heterogeneity between studies. Funnel plot and Kendall's tau b were used to examine publication bias.

Results

Search results

Figure 1 shows the results of the study selection. Of a total of 853 texts found across 5 databases and Google Scholar, 60 (7.03%) were considered potentially relevant studies by reading their titles and abstracts. After removing duplicates (n=31) and having found three papers by manually searching the journals, 32 potential studies remained to be evaluated for inclusion using full texts. At this point 25 papers had to be discarded for not meeting the eligibility criteria, 11 of which were removed because they did not investigate AS whilst three studies did not investigate periodontitis and five studies were neither about AS nor about periodontitis. Furthermore three studies were excluded for not reporting a relationship between AS and periodontitis, one for not reporting prevalence of periodontitis in AS and one for being a case series. A further study had to be discarded because the diagnosis of AS was only based on self-reported data. Of the 7 remaining papers, there were two different abstracts concerning to the same study. Therefore in total 6 studies were deemed to be eligible for inclusion in this review [31,32,33,34,35,36,37].

Included studies

Tables 1 and 2 show the included studies' characteristics and design. All studies were case-control and were published between 2005 and 2013, four in rheumatology journals and two in dental journals. For two of the studies only the abstracts were available [34,35,36]. The study size ranged from 90 to 40,926 participants. The study by Helenius et al [31] was a matched case-control study with 77 cases and 77 controls. However, while there were only 18 cases of AS among cases, information was available on all 77 controls, therefore in our review we compared 18 AS cases and 77 controls as a non-matched case-control study. The

studies were conducted in six different countries around the world (Finland, Germany, Turkey, New Zealand, Taiwan and Korea).

Most studies recruited cases from rheumatology departments, while in three studies controls came from dental clinics. One study recruited controls using the electoral register [35,36]. The study by Keller et al [37] obtained both cases and controls from a large insurance database.

Definition of AS

Four studies used the mNY criteria while Keller et al included patients with a clinical diagnosis by a rheumatologist based on the ICD-9 classification. Mean disease duration ranged from 5 years to 14.7 years (Table 1).

Definition of periodontitis

There was a large variability in definition of periodontitis (Table 1). The terms the authors used for periodontitis were "periodontitis" in two studies, while Sezer et al and Keller et al referred to periodontitis as "chronic periodontitis" and Chang et al and Pischon et al focused on "periodontal disease" in general. Five of six studies stated the prevalence of periodontal disease as the primary outcome. Other oral health measures reported most often were BOP, PPD, CAL, plaque index (PI) and number of missing teeth. The study by Chang et al [34] was the only to distinguish between mild, moderate and severe periodontitis using case definition for surveillance of periodontitis proposed by the Centers for Disease Control and Prevention (CDC) [38].

Relationship between AS and periodontitis

The determined prevalence rates of periodontitis in AS patients ranged from 37.5% to 87.8% versus a range from 25.9% to 71.4% in controls. The studies show a consistency regarding the presence and direction of association; each study found the prevalence of periodontitis in AS patients to be higher than in non-AS patients. However only the results obtained by Keller et al and Helenius et al reached statistical significance (Chi-square test $P<0.05$, Table 3).

Weighted mean and combined SD were calculated for all 77 controls for age for the study by Helenius et al [31] and for the average number of missing teeth for both cases and controls for the studies by Helenius et al [31] and Pischon et al [32] using subgroup information in the original publications. Odds Ratios (OR) were calculated from raw data for the studies by Helenius et al [31], Sezer et al [33] and Chang et al [34].

Among five studies (excluding study by Keller et al because it had a different data collection procedure) and among all six studies combined (including Keller et al) there was low level of heterogeneity (I^2=27% and 13% respectively). Using fixed effect analysis, the overall pooled estimate of the OR for periodontitis was 2.07 (95% CI 1.34, 3.21) for five studies and 1.85 (1.72, 1.98) for all six studies (Figure 2). The funnel plot did not show evidence of publication bias (Tau=0.4, P=0.26).

Three studies reported other oral health measures (BOP, PPD, CAL, PI) [32,33,34] and only two studies reported the number of missing teeth [31,32]. Pischon et al reported statistically significant differences between AS cases and controls for all the above measurements except missing teeth (Table 3). Two other studies found significant differences between cases and controls for BOP [33, 35,36], but only Sezer et al reported the actual data. On meta-analysis, there was a high level of heterogeneity (I^2>80%) between studies for PPD, CAL and BOP. The only significant difference was found for BOP (using random effect model, the combined mean difference between cases and controls was 14.05 (95% CI 4.16, 23.94, P=0.005). We did not attempt to perform a meta-analysis for PI and missing teeth due to non-uniform reporting of the results.

Quality assessment

The validity of only five of the six studies could be evaluated (Table 4) as there was not enough information in the abstract by Chang et al [34]. All studies addressed an appropriate and clearly focused question, however only two studies recruited cases and controls from comparable populations. Only Suppiah et al [35,36] reported the participation rate in cases and controls. With the exception of the study conducted by Sezer et al [33] which was assigned to a high quality level (++), all studies had acceptable level of minimising bias and confounding (+). Only the two studies that reported a significant association were considered to have shown distinct evidence of an association between AS and periodontitis.

Discussion

This is the first systematic review to examine the association between AS and periodontitis. Meta-analysis showed an important (almost double) and statistically significant risk of AS associated with periodontitis.

However, this estimate is based on only a few, generally small and recent, studies. Sezer et al [30] conducted the first study to evaluate the relationship and the potential role of clinical parameters and pro-inflammatory cytokines while the study by Helenius et al [31] is the first to investigate oral health and saliva in patients suffering from different types of rheumatic disease. The strengths of the study conducted by Keller et al [37] are the large sample size and the selection of participants from a population-based database.

Although there is some consistency in measures of association, there are clear differences in rates of periodontitis reported in the included studies. These differences might be due to different levels of oral health between countries. Moreover the factor "age", associated with loss of periodontal support, is an important determinant of prevalence [4]. The results show that the three studies with participants of a mean age >39 years detected a higher prevalence of periodontitis in AS patients than the two studies with a participant mean age of <35 years. However, no such difference was noted in controls. Other environmental factors affecting the prevalence of periodontal disease include smoking. However the majority of the papers included in this systematic review excluded smoking participants whilst only Pischon et al [32] adjusted for smoking.

The studies conducted had differing diagnostic thresholds to identify periodontitis. Linden et al [39] encountered this problem while reviewing the association of periodontitis with several systemic diseases. This problem is most likely to be one of the aspects responsible for the differing prevalence rates of periodontal disease across the studies. An indication of the importance of how periodontitis should be defined is given by the results concerning the CPI score detected by Helenius et al [31]. It was shown that out of 154 participants, 65 had a CPI score of 3 or more. The other 89 participants all had a CPI score of 2 (defined as gingivitis), which means that 100% of the participants had some kind of periodontal disease.

This is not surprising given the high prevalence [4]. What is important about this however is that as soon as the diagnostic threshold is changed, for instance from a PPD of ≥ 4mm to ≥ 3mm, a large proportion of individuals previously diagnosed with gingivitis, would subsequently be characterised as having periodontitis. Additionally it should be noted that because there is no consensus on the definition of periodontitis, there is also no consensus for gingivitis. Thus it is not possible to distinguish the periodontitis patients for example from Keller et al [37], who investigated "chronic periodontitis" and Pischon et al [32], who investigated "periodontal disease".

Several other aspects that may have an influence on the possible link between the two diseases are still not clarified. For instance both Keller et al [37] and Sezer et al [33] came to the conclusion that the explanation for the underlying mechanism of the association must in great part be attributed to a factor, other than inflammatory contribution. Furthermore Sezer et al found that the periodontal status of AS patients might be affected by IL-6 levels and Keller et al reported that the association between periodontitis and AS was reduced by having had a gingivectomy or periodontal flap surgery. After excluding participants who had undergone a gingivectomy or periodontal flap surgery, they found the adjusted OR to have been increased to 2.04 (95%CI 1.93, 2.15). Suppiah et al [35,36] detected a positive gradient between disease activity in AS and periodontal disease severity. Pischon et al [32] also tested for that but there was no evidence of an association. Moreover, it appears that disease modifying anti-rheumatic drugs (DMARDs) used for the treatment of chronic inflammatory rheumatic diseases may affect the risk of periodontitis, which was not only highlighted by Sezer et al [33] but by Pischon et al [32] as well. However Sezer et al [33] further pointed out that, although anti-TNF drugs and NSAIDs have been demonstrated to be beneficial not only in the treatment of AS but also of periodontitis, the effects of these drugs in the combination of both AS and periodontitis are still unknown. TNF-alpha blocker usage was not associated with prevalence of PD or outcome of periodontal treatment in Chang et al [34] and Pischon et al [32] did not find an association between periodontitis and medication (NSAIDS and TNF-α blockers).

There are several factors, Sezer et al and Pischon et al have in common. They may have defined differing thresholds for periodontitis, but Sezer et al provided the required data to calculate a prevalence of a CAL > 3mm in AS patients and controls, which is the diagnostic

threshold Pischon et al used to identify periodontitis. Thus it is possible to directly compare the results of the two studies concerning this parameter. First the prevalence was calculated, which revealed that 41.7% of the AS patients had a CAL > 3mm vs. 29.2% of the controls (Pischon et al determined a prevalence of 47.92% for the AS group and 31.25% for the controls). Both studies determined a modestly higher prevalence in AS than in non-AS patients but are limited by the small number of participants (both n=96) and hence low statistical power.

Among the limitations of this systematic review is the fact that there is very scarce literature on the topic this review addresses. This problem is increased by the heterogeneity among the few eligible studies in geographic location, and different diagnostic tools and criteria were used to define periodontitis or AS. However this is also partially strength of this systematic review, because similar results were found across a variety of study locations with different diagnostic tools. Moreover the review's results might be prone to publication bias however we did not find evidence of this. The proposed association was hypothesis driven based on an already observed relationship with RA.

Conclusion

These results suggest that an association may exist between AS and periodontal disease. Such an association would be important since the knowledge of an effect of periodontal treatment on AS disease activity or vice versa would lead to a need for close collaboration between rheumatologists and dentists when treating the diseases. Moreover, since studies have shown that both periodontal disease and AS come along with a decrease of quality of life, an essential factor to consider would be how strongly a patient's quality of life would be influenced by suffering from both periodontal disease and AS. However given the small studies with important methodological weaknesses there is a need for a study with sufficient statistical power to detect the desired effect size, taking into account potential confounding factors and using validated measures of AS and periodontitis. Such study would involve collaboration between rheumatologists, dentists and epidemiologists.

Rheumatology key messages

- Periodontitis is associated with an increased risk of AS in case-control studies

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Conflicts of interest

The authors declare no conflicts of interest.

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Figure 1: Flow diagram of study selection process

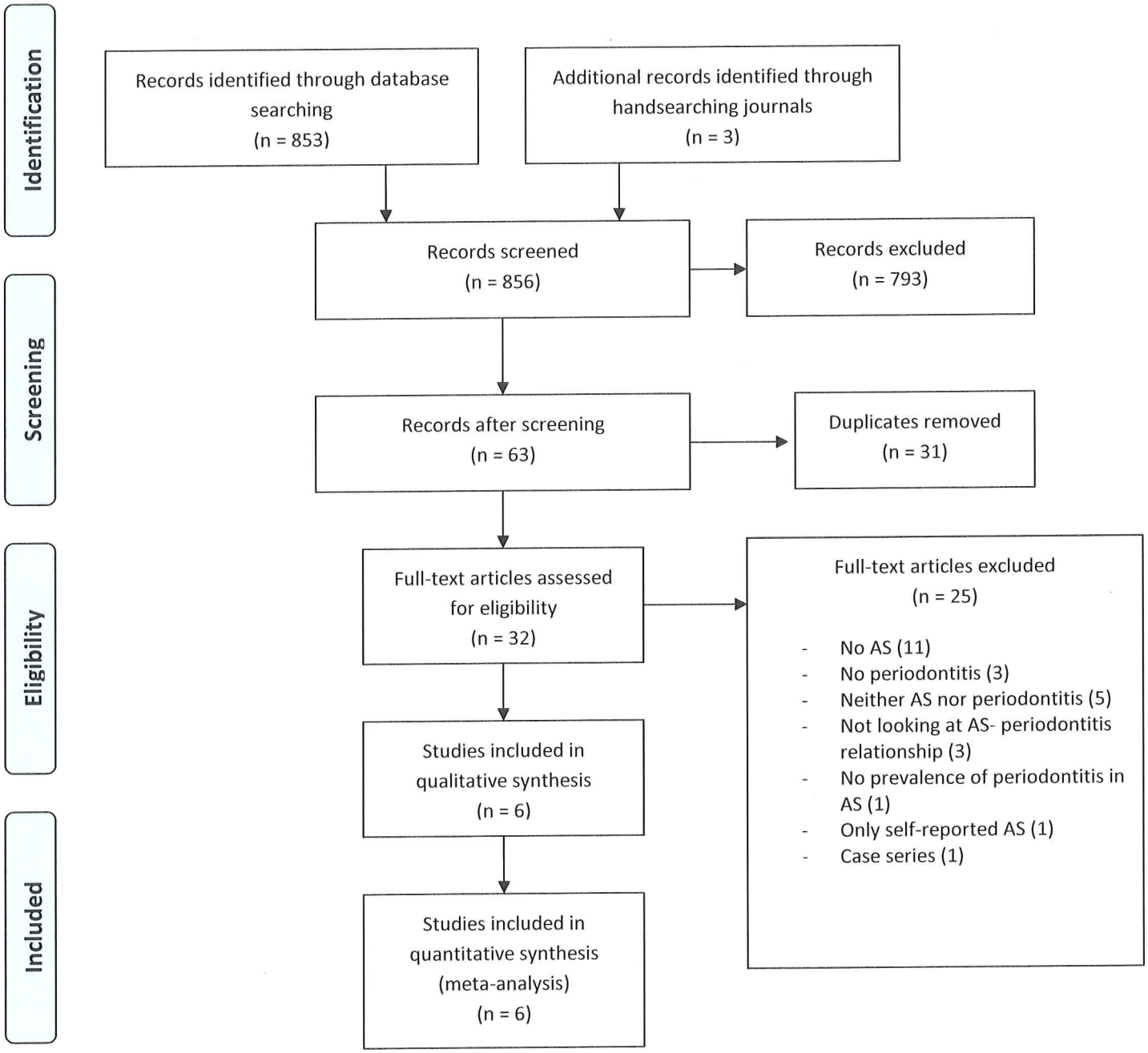

Table 1. Description of the included studies

Study description	First author, publication year					
	Helenius, 2005	**Pischon, 2010**	**Sezer, 2012**	**Suppiah, 2012/2013**	**Keller, 2013**	**Chang, 2013**
Study type	Case-control	Case-control [b]	Case-control [b]	Case-control [c]	Case-control [a]	Case-control [b]
Country	Finland	Germany	Turkey	New Zealand	Taiwan	Korea
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 Charité Universitätsmedizin	NR	Research grant from the New Zealand Dental Association Research Foundation	NR	NR
Diagnostic criteria used for AS	Modified New York	Modified New York	Modified New York	Modified New York	ICD-9-CM codes 720 or 720.0; Clinical diagnosis by a rheumatologist	NR
Mean (SD) disease duration (AS) in years	14.7 (8.9)	11.7 (7.4)	5.04 (6.13)	9.1 (8.6)	NR	NR
Diagnostic criteria used for periodontitis	Community Index of Periodontal Treatment Need (CPI) score of 3 or more (PPD ≥ 4mm)	Mean CAL > 3mm	1999 Consensus Classification of periodontal Disease At least 4 teeth with PPD ≥ 5mm + CAL ≥ 2mm at the same time	≥ 2 sites with at least 4mm CAL	ICD-9-CM code 523.4; At least two principal diagnoses based on diagnostic test and clinical examination PPD ≥ 3mm	Clinical case definition proposed by the Centers for Disease Control and Prevention
Study duration (months)	NR	36	6	12	108	3

a Matched by age in intervals of 10 years, gender, urbanization level and index year (5 controls per case)
[b] Matched by age and gender [c] Matched by age, gender and ethnicity NR Not relevant

Table 2. Description of cases and controls

Characteristic	First author, publication year					
	Helenius, 2005	**Pischon, 2010**	**Sezer, 2012**	**Suppiah, 2012/2013**	**Keller, 2013**	**Chang, 2013**
Study size (n)						
Cases	18	48	48	41	6,821	75
Controls	77	48	48	49	34,105	73
Gender (n, % Females)						
Cases	6 (33.3)	14 (29.2)	13 (27.1)	12 (29.3)	2,839 (41.6)	
Controls	50 (64.9)	14 (29.2)	13 (27.1)	13 (26.5)	14,195 (41.6)	NR
Age (years) (Mean (SD))						
Cases	42.4 (11.6)	40.4 (11.7)	34.27 (9.73)	42.5 (13.7)	27.2 (19.4)	NR
Controls	42.2 (12.7)	39.8 (12.1)	33.33 (9.67)			
Recruitment						NR
Cases	Rheumatology Outpatient Department, Meilahti Hospital, Helsinki University Central Hospital	Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin	Department of Rheumatology, Gaziantep University, Faculty of Medicine	Rheumatology Department, Dunedin Public Hospital and School of Dentistry	Longitudinal Health Insurance Database 2000	
Controls	Institute of Dentistry, University of Helsinki	General dental office	Gaziantep University, Faculty of Dentistry	South Dunedin Electoral Roll		
Inclusion criteria						NR
Cases	Meeting the current classification criteria relating to AS	Individuals with prevalent AS who attended for routine examination	Individuals with AS diagnosis by 2 rheumatologists	AS	All patients ≥ 18 years with first time diagnosis of AS in ambulatory care visits between Jan 2001 and Dec 2009	
Controls	Randomly selected volunteer dental patients, no AS	Healthy individuals attending a general dental office	Systemically healthy individuals	Disease free individuals matched individually to cases for age and gender	Inclusion in the Longitudinal Health Insurance Database 2000	

Exclusion criteria						
Cases	NR	History of periodontal therapy or use of antibiotics during the last 3 months prior to examination, pregnancy or lactation,	History of systemic diseases or conditions, of periodontal treatment within last 6 months, of antibiotic or corticosteroid medication within last 3 months, <18 teeth, current smokers	Being unable to give written consent, pregnancy, malignancy, taking anticoagulants or having a bleeding disorder, requirement for prophylactic antibiotic cover to collect clinical data, being fully edentulous	age <18 years, diagnosis of RA or SLE	NR
Controls	History of diabetes, rheumatic disease or any other disease affecting the masticatory system	Same as cases	Same as cases	Same as cases + history of periodontal treatment, cardiovascular disease or diabetes mellitus	Same as cases and diagnosis of AS, RA, SLE since 1995	

NR Not relevant

Table 3. Relationship between AS and periodontitis

First author, publication year	**Plaque Index** Mean (SD) (T-=test P-value)	**Pocket probing depth (mm)** Mean (SD) (T-=test P-value)	**Clinical attachment loss (mm)** Mean (SD) (T-=test P-value)	**Bleeding on probing (%)** Mean (SD) (T-=test P-value)	**Missing teeth per patient** Mean (SD) (T-=test P-value)	**Periodontitis** N (%) (Chi-square test P-value)	**OR (95% CI)**
Helenius, 2005 Cases (n=18) Controls (n=77)	NR	NR	NR	NR	3.44 (3.17) # 2.13 (2.01) P=0.108	10 (56) 20 (26) P=0.015	Crude: 3.56 (1.23, 10.28) #
Pischon, 2010 Cases (n=48) Controls (n=48)	0.55 (0.37) # 0.32 (0.19) P<0.001	3.06 (0.71) # 2.67 (0.49) P=0.002	3.20 (0.74) # 2.73 (0.50) P<0.001	56.5 (23.00) # 25.0 (37.09) P<0.001	1.95 (2.31) # 2.44 (2.62) P=0.362	23 (47.9) 15 (31.3) P=0.095	Crude: 2.93 (1.25, 6.86) Adjusted [b]:5.48 (1.37, 22.00)
Sezer, 2012 Cases (n=48) Controls (n=48)	1.60 (0.61) 1.53 (0.52) P=0.547	3.17 (0.82) 3.15 (0.90) P=0.91	2.35 (1.93) 2.04 (1.81) P=0.419	46.77 (3.17) 33.09 (2.98) P<0.001	NR	18 (37.5) 14 (29.2) P=0.386	Crude: 1.46 (0.62, 3.42) #
Suppiah, 2012/13 Cases (n=41) Controls (n=49)	NR	NR	NR	NR	NR	36 (87.8) 35 (71.4) P=0.058	Crude: 6.2 (0.7, 52.2)
Keller, 2013 Cases (n=6,821) Controls (n=34,105)	NR	NR	NR	NR	NR	2,830 (41.5) 8,820 (25.9) P<0.001	Crude: 1.86 (1.76, 1.97) Adjusted [a]: 1.84 (1.74, 1.98)
Chang, 2013 Cases (n=75) Controls (n=73)	27.55% (20.92) # 23.65% (19.21) P=0.24	2.54 (0.36) # 2.58 (0.30) P=0.645	2.62 (0.36) # 2.66 (0.40) P=0.523	14.87 (11.47) # 11.98 (8.35) P=0.081	NR	51 (68) 43 (58.9) P=0.250	Crude: 1.48 (0.76, 2.91) #

Calculated from data in publication

a Adjusted for monthly income and geographic location

b Adjusted for age, education and plaque index

NR Not relevant

Table 4. Quality assessment

Item	First author, publication year				
	Helenius, 2005	**Pischon, 2010**	**Sezer, 2012**	**Suppiah, 2012/2013**	**Keller, 2013**
1.1 The study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes	Yes
1.2 The cases and controls are taken from comparable populations	No	No	No	Yes	Yes
1.3 The same exclusion criteria are used for both cases and controls	Can't say	Yes	Yes	No	Can't say
1.4 What percentage of each group (cases and controls) participated in the study?	Can't say	Can't say	Can't say	Cases: 72.1% Controls: 34.7%	Not applicable
1.5 Comparison is made between participants and non-participants to establish their similarities or differences	No	No	No	No	Not applicable
1.6 Cases are clearly defined and differentiated from controls	Yes	Yes	Yes	Yes	Yes
1.7 It is clearly established that controls are non-cases	Yes	Can't say	Yes	Yes	Yes
1.8 Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	Can't say	No	No	Can't say	Not applicable
1.9 Exposure status is measured in a standard, valid and reliable way	Yes	Yes	Yes	Yes	Yes
1.10 The main potential confounders are identified and taken into account in the design and analysis	No	Yes	Yes	Can't say	Yes
1.11 Confidence intervals are provided	Yes	Yes	Yes	Yes	Yes
2.1 How well has the study done to minimise the risk of bias or confounding?	+	+	++	+	+
2.2 Do you think there is clear evidence of an association between exposure group and outcome?	No	Yes	No	No	Yes
2.3 Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes	Yes	Yes	Yes

Figure 2. Meta analysis

Model	Group by Comparison	Study name	Comparison	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	1.00	Helenius et al.	1	2005.00	3.56	1.23	10.29	2.34	0.02
	1.00	Pischon et al.	1	2010.00	5.48	1.37	21.96	2.40	0.02
	1.00	Sezer et al.	1	2012.00	1.46	0.62	3.43	0.87	0.39
	1.00	Suppiah et al.	1	2012.00	6.20	0.72	53.54	1.66	0.10
	1.00	Chang et al.	1	2013.00	1.48	0.76	2.90	1.14	0.25
Fixed	1.00				2.07	1.34	3.21	3.25	0.00
	2.00	Keller et al.	2	2013.00	1.84	1.71	1.97	16.98	0.00
Fixed	2.00				1.84	1.71	1.97	16.98	0.00
Fixed	Overall				1.85	1.72	1.98	17.28	0.00