Title: The effect of smoking on clinical parameters and structural damage in patients with axial spondyloarthritis: a systematic literature review.

Abstract

Objectives: To evaluate the association between smoking and clinical parameters and structural damage in axial spondyloarthritis (axSpA).

Methods: We systematically searched MEDLINE, EMBASE and Cochrane Library up to November 2015. We selected articles that analysed the smoking impact on disease activity, functional status, structural damage, physical mobility and life quality. Independent extraction of articles by 2 authors using predefined data fields was performed. Studies quality was graded according to the Oxford Level of Evidence scale.

Results: A total of 17 articles were selected for inclusion: 2 case-control, 11 cross sectional and 4 prospective cohort studies, which analysed 4,694 patients. Weak evidence suggested a smoking effect on pain, overall assessment of health, disease activity, physical mobility and life quality in ankylosing spondylitis (AS). Moderate-good evidence revealed higher HAQ-AS among smokers (0.025 units/yr, 95%CI: 0.0071-0.0429, p=0.007). Every additional unit of ASDAS resulted in an increase of 1.9 vs. 0.4 mSASSS units/2 yr in AS smokers vs. non-smokers. Good evidence revealed that cigarette smoking and smoking intensity was associated with spinal radiographic progression in axSpA [mSASSS ≥2 units/2 yr: OR=2.75, 95%CI: 1.25-6.05, p=0.012; mSASSS progression in heavy smokers (> 10 cigarettes/day): OR=3.57, 95%IC: 1.33-9.60, p=0.012].

Conclusions: Published data indicate that smoking has a dose-dependent impact on structural damage progression in axSpA. There is worse HAQ among AS smokers compared to non-smokers. Respect to pain, overall assessment of health, disease activity, physical mobility and life quality, although the evidence level is poor, all evidence points in the same direction: smoking AS patients are worse than non-smoking.

Keywords: Systematic review, smoking, tobacco, spondyloarthritis, ankylosing spondylitis, disease activity, ASDAS, BASDAI, BASFI, BASRI, BASMI, mSASSS, radiographic progression, quality of life, HAQ-S, Euro-QoL, ASQoL.

Introduction

Spondyloarthritis is a family of chronic arthritis diseases characterized by inflammatory back pain, peripheral arthritis and enthesitis [1]. Ankylosing spondylitis (AS) is the typical disease among the family of spondyloarthritis, and it predominantly involves the axial joints and bilateral sacroiliac joints. It is a potentially debilitating disease, which may lead to progressive limitation of the spinal mobility, loss of the functional ability, and reduced quality of life. Inflammatory rheumatic diseases are considered to be due to a complex interaction between environment and genetic factors, which may lead to immune reactions and cause different rheumatic disorders [2]. The environmental factor might be quite important in the development of chronic rheumatic and immune disease.

Cigarette smoking, one of the most serious health problems, has been identified as one of the major environmental risk factor of rheumatic diseases, including rheumatoid arthritis (3-5) and systemic lupus erythematosus [6,7]. Fewer studies have been performed in ankylosing spondylitis, and even less in early axial spondyloarthritis (axSpA). Smoking has been associated with increased disease activity and radiographic severity in established AS in some studies [8]. Current but not previous smoking or smoking intensity has been recently reported to be a major risk factor for incident AS, supporting the hypothesis that smoking may be causally related to the development of AS [9].

The newly developed Assessment of SpondyloArthritis International Society classification criteria for axSpA [10, 11], are more inclusive of patients at an early disease stage. As smoking is a well established risk factor for developing RA and other inflammatory diseases, such as systemic lupus erythematosus and inflammatory bowel disease and has also been associated with phenotypic variations in AS, it would be worthwhile to determine the impact of smoking in the whole axSpA spectrum, particularly in early stage axSpA. The objective of this study was to evaluate the effect of smoking not only on clinical and structural damage but also on functional status and quality of life in patients with axSpA. We made a systematic literature review in the framework of the drawing up of the axSpA and psoriatic arthritis guidelines of the Spanish Society of Rheumatology.

Materials and methods

A systematic review was conducted to identify all studies published up to November 25, 2015 providing information on the association between smoking and clinical parameters, structural damage, functional status and quality of life in patients with axSpA. This review was elaborated according to the PRISMA statement [12]. An expert committee developed the research question and adjusted it according to the PICO (patients, intervention, comparator and outcome) system. This process was supervised by expert methodologists from the Spanish Society of Rheumatology research unit.

Search strategy

A librarian (MG) designed a search strategy for the following biomedical databases: MEDLINE (PubMed) (1950-November 25, 2015), EMBASE (1980-November 25, 2015) and the Cochrane Library (Wiley Online) (up to November 25, 2015). Initially, key

search terms in natural language were identified and assessed using the PICO format to frame the question. A generic search strategy was then designed, consisting of exploited controlled vocabulary (Medical Subject Headings-MeSH, Emtree, and other thesauri) and free language. This was later adjusted to redefine the most relevant terms. The strategy was complemented by field identifiers, wild cards, proximity operators and Boolean operators. This strategy was adopted for the various resources selected. The searches were conducted with a language restriction (English, French and Spanish), but without time or geographical limits. Finally, a hand search was performed by reviewing the references of the included studies and the abstracts of the ACR congress (2013, 2014 and 2015) and the EULAR congress (2013, 2014 and 2015). A description of the search strategy is shown in Appendix 1 in Supplementary Material.

Inclusion criteria

The studies retrieved with the above strategies were finally included if they met the following predefined criteria: 1) adult patients fulfilling at least one of the following classification criteria for axSpA or AS: the modified New York criteria [13], European Spondyloarthropathy Study Group criteria [14], Amor criteria [15] or Assessment of SpondyloArthritis International Society classification criteria for axSpA [10,11]; 2) smoking status, 3) comparison with non-smokers patients; 4) outcomes measures: swollen and tender joints count; enthesitis; pain (visual analogue scale, NRS, etc.); morning stiffness (minutes); overall assessment of health (VAS, Bath Ankylosing Spondylitis Patient Global Score, etc.); disease activity assessed using both the Bath Ankylosing Spondylitis Disease activity Index (BASDAI) [16] and the Ankylosing Spondylitis Disease Activity Score (ASDAS) [17]; patient's physical mobility (measured by the Bath Ankylosing Spondylitis metrology index (BASMI) [18], etc.); functional status assessed using both the Bath ankylosing Spondylitis Functional Index (BASFI) [19] and the Health Assessment Questionnaire for Ankylosing Spondylitis (HAQ-AS) [20]; structural damage evaluated with the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) [21], the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [22] and sacroiliitis grading (New York criteria) as established by conventional radiography (grade 2: minimal, grade 3: moderate and grade 4: ankylosis; quality of life measured by the AS Quality of Life (ASQoL) (23), Short Form 36 (SF-36) [24], Short Form 12 (SF-12) [25] and Evaluation of AS Quality of Life (EASi-QoL) [26]. Any type of study except case series or case reports was eligible. There was no limitation with regard to the number of patients included in the studies.

Selection of studies and data collection

EndNote X7® software was used to manage the records retrieved by searches of the different electronic databases and manual search methods. Articles were selected, according to the inclusion criteria, by two independent reviewers (VVG and TCI). Firstly, articles were selected according to title and abstract, followed by a full-text reading. If any discrepancy arose in either of the two selection phases, consensus was reached with the aid of a third reviewer (DS). Articles with incomplete data or which did not comply with the inclusion criteria were excluded. Authors were contacted when the full article was not available. Supplementary information was obtained for one of the studies. A reviewer (VVG) compiled the information on the studies included using

standardized forms. When the data were not included in the text, they were extracted from the tables and figure to obtain the necessary information.

Assessment of the methodological quality and data analysis

The Oxford Level of Evidence rating scale was used to evaluate the methodological quality of the studies [27]. Due to the small number of studies and their design, we focused on describing the studies in evidence tables, their results and a qualitative synthesis rather than a meta-analysis.

Results

The search identified 509 studies related to smoking effect on clinical and structural damage in AS and axSpA patients published between 1961 and November 2015 and was screened for inclusion in the study. Of these, 26 were duplicated studies, so potentially eligible citations were assessed and 24 studies met eligibility for data extraction. An additional 7 studies were later excluded for the following reasons: low quality (1), did not meet study design eligibility (4), letter to the editor (1), review (1). The remaining 17 studies: 2 case-control, 11 cross-sectional and 4 prospective cohort studies, met the criteria to be included in this review (Fig.1). In total, 4,878 patients were analysed. The main characteristics of the studies included in the analysis are shown in Table 1 and Table 2. A list of excluded studies and reasons for their exclusion are shown in Table 3.

Swollen and tender joints count and enthesitis

None of the included studies evaluated the smoking effect on swollen and tender joints count and enthesitis.

Pain

Specific information on smoking effect on pain level in AS patients was reported in three cross-sectional studies [32, 33, 36]. Mattey et al. [32] found that there was no significant difference between those who had never smoked and past smokers and only current smokers showed significantly higher pain scores than those had never smoked ($p<0.05$), using a 10 cm numerical rating scale (NRS; 0=no pain, 10=most severe pain). Averns et al. [36] did not find significant differences between non-smokers, ex-smokers and smokers (pain was assessed using a visual analogue scale), but Zhang et al. [33], found that compared to non-smoking patients those with tobacco use scored significantly higher in nocturnal pain (visual analogue scale) and total back pain (visual analogue scale), ($p<0.05$).

A cross-sectional analysis of the DESIR cohort [8], showed that smoking was independently associated with earlier onset of inflammatory back pain in patients with axSpA ($B=-1.46$, $p=0.04$).

Morning-stiffness

The association between smoking and morning-stiffness was reported in only one cross-sectional study [33]. Zhang et al. [33] did not find statistically significant

differences between smokers and non-smokers patients with regard to morning-stiffness (14.0±26.3 vs. 9.9±17.6; p=0.30).

Overall assessment of health

The smoking effect on overall assessment of health in AS patients was evaluated in three studies (1 case-control, 2 cross-sectional studies) [28, 30, 33]. The value of BAS-G was higher in smoking AS patients than those with non-smoking, but this difference did not show statistical significance (5.20±2.62 vs. 4.46±2.69; p=0.305) [28]. However, Reed et al. [30] found significant difference between smokers and non-smokers in BAS-G (regression coefficient 1.94, 95%IC: 0.75-3.13; p= 0.02).

Compared to non-smoking patients, those with tobacco use scored significantly higher in overall assessment of health (VAS), (6.6±2.7 vs. 5.6±3.3; p=0.00) [33].

Global disease activity

The effect of smoking on disease activity in AS patients was examined in eight cross-sectional studies [8, 9, 28-33]. The disease activity was evaluated with *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) in all of them. According to these reports, current smokers had significantly higher BASDAI scores than non-current smokers, and current smoking was an independent variable for higher BASDAI after adjusting for confounding factors in the majority of the studies. No difference in BASDAI score between ever smokers and never smokers, and no correlation with pack years, was found in Reed et al. [30] and Sakellariou et al. [9]. Furthermore, Mattey et al. [32] and Sakellariou et al. [9] reported that current smokers but not ever smokers had higher BASDAI score compared to never smokers and, despite the significant correlation between pack years and BASDAI, only current smoking and not pack years was significantly associated with BASDAI ≥ 4 in the multivariate analyses.

Smoking was independently associated with higher disease activity (measured by BASDAI) in patients with axSpA (B=0.50, p=0.003) in the DESIR cohort [8].

Physical mobility

The association between smoking and physical mobility in AS patients was evaluated in six cross-sectional studies [8, 28, 29, 31, 33, 36]. The measures that were used to examine the physical mobility were: the Bath Ankylosing Spondylitis Metrology Index (BASMI) in three studies [8, 29, 33] and physical examinations [tragus to wall distance (cm), modified Schöber's index (cm), intermalleolar distance (cm), cervical rotation (degree), lateral lumbar flexion (cm), fingertip to floor distance (cm), chest expansion (cm) and occiput to wall distance (cm)] in the other three studies [29, 31, 36]. Compared to the non-smokers, smoking patients had significantly higher BASMI [8,29,33] but no correlation with pack years, was found by Fallahi el al. [29]. Among the physical mobility parameters, it is of interest that modified Schöber's index, cervical rotation, lateral lumbar flexion and chest expansion were significantly reduced in smoking AS patients as than those with non-smoking. In addition, occiput to wall distances were significantly increased in smoking patients than those with non-smoking. Taken together, smoking AS patients showed relatively poor physical mobility than those with non-smoking [28, 31, 36].

Functional status

Functional status in AS patients, was reported in 10 studies: 9 cross-sectional studies [8, 9, 28, 30-34, 37] and 1 longitudinal study [38]. Two measures of functional limitations were used: the Bath AS Functional Index (BASFI) in nine studies [8, 9, 28, 30-34, 37] and the Health Assessment Questionnaire modified for the Spondyloarthropaties (HAQ-AS) in three studies [8, 34, 38]. Regarding function, ever smokers had significantly higher BASFI scores than never smokers and there was a significant positive association between smoking pack years and BASFI. In 5 studies, current smoking, ever smoking or increasing smoking intensity was an independent variable for higher levels of functional limitation in AS [9, 28, 29, 32, 34]. Functional disability in AS (HAQ-AS) progressed more rapidly in smokers. Smoking was also associated with the progression of functional disability in the subgroup of patients who had AS for less than 10 years [38].

A cross-sectional analysis of the DESIR cohort [8], showed that smoking was independently associated with worse functional status (measured by BASFI) in patients with axSpA (B=0.38, p=0.02).

Structural damage

Structural damage was reported in 5 cross-sectional studies [8, 9, 29, 35, 37] and three prospective cohort study [40-42]. The Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s), the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and the New York criteria were used to evaluate the radiographic damage.

Fallahi et al. [29] compared sacroiliitis grading (minimal: 2, moderate: 3 and ankylosis: 4) between current and non-current smokers and ankylosis was significantly more common in current AS smokers (p=0.001). The pack-years of smoking was higher for the AS patients with sacroiliac ankylosis than for those with moderate or minimal sacroiliiitis. Radiographic severity (scored by BASRI-s) was associated with current smoker (OR=4.72, 95% CI: 2.16-10.30; p<0.0001) [35]. There was an independent positive association between smoking pack years and mSASSS (B=0.26; SE= 0.32, 95% IC: 0.08 to 0.43; p=0.005) [9]. Ramiro et al. [40] found that every additional unit of ASDAS resulted in an increase of 1.9 versus 0.4 mSASSS units/2-years in AS smokers versus non-smokers. The influence of smoking on the association between ASDAS and radiographic progression was statistically stronger than the effect of job type on this relationship in this study (data from OASIS cohort). A cross-sectional analysis of another cohort (DESIR cohort) [8], showed that smoking was independently associated with an increased axial inflammation on MRI (OR=1.57; p=0.02), increased axial structural damage on MRI (OR=1.54; p=0.03) and radiographs scored by mSASSS (B=0.54; p=0.03).

Poddubnyy et al. [41] evaluated prospectively the rates and the predictors of spinal radiographic progression scored by mSASSS over 2 years in a cohort of patients with early axSpA. Spinal radiographic progression was independently associated with cigarette smoking (OR= 2.75, p= 0.012). The same authors, in a more recent study, found that not only smoking but also smoking intensity (>10 cigarettes a day), was associated with mSASSS progression: ≥2 points (OR=3.57, 95%CI: 1.33-9.60, p=0.012) after adjustment for baseline syndesmophytes, C-reactive protein level,

gender, presence of definite radiographic sacroiliitis, use of non-steroidal anti-inflammatory drugs and tumour necrosis factor blockers (OR=3.48, 95%CI: 1.06-11.42, p=0.039). Heavy smoking versus non-smoking, was associated too with formation of new syndesmophytes over 2 years after adjustment for all factors mentioned above (OR=4.17, 95%CI: 0.79-22.02, p=0.093) [42].

Quality of life

We included 4 cross-sectional studies [29, 30, 32, 39] in which the correlation between smoking and quality of life in patients with AS, was investigated. Three measures of quality of life were used: the AS Quality of Life (ASQoL), Short Form-36 (SF-36) and Evaluation of AS Quality of Life (EASi-QoL). Fallahi et al. [29] found that the pack-years of smoking were positively and independently associated with the higher ASQoL scores [regression coefficient (B) =0.11, standard error (SE) 0.05, 95% CI: 0.21 to 0.003; p=0.04]. Reed et al. [30] found a decrease in quality of life associated with current smoking (B=4.24, 95% CI: 2.16 to 6.32; p<0.0001). There was, however, no relation between cumulative exposure (pack-years) and composite indices (data were not shown). Regarding SF-36 subscale scores, there was no significant difference between smokers and non-smokers [39]. Quality of life was shown to be significantly worse in those who had ever smoked compared to those who had never smoked, as measured by EASi-QoL (all 4 domains) [32]. Poor quality of life measures were associated more closely with increasing pack-year history too (p<0.05).

Smoking was also associated with poorer quality of life scored by Euro-Qol (B=1.38, p<0.001), short form 36 physical (B=-4.89; p<0.001) and mental component score (B= -5.90; p<0.001) in patients with axSpA [8].

Discussion

We conducted a systematic review of the scientific literature to analyse the association between smoking and clinical, functional status, structural damage and quality of life in patients with axSpA.

Most of the included studies were cross-sectional studies with low quality. Four studies (2 EA, 2 axSpA) were prospective cohort studies with appropriate follow-up periods and moderate-good methodological quality. Studies varied substantially in terms of design, outcomes measures and the smoking habit evaluation (some studies evaluated two patients groups: current smoker and non-smoker, other studies analysed three groups: current smoker, ex-smokers and non-smokers, past-smokers and non-smokers were grouped together in various studies but former smokers were included in the current smokers group in two studies. Quantity of smoking (pack-years) was defined in six studies.

In our systematic review, we found weak evidence on the smoking effect on pain level and overall assessment of health in AS patients in three studies.The association between smoking and morning-stiffness was reported in only one cross-sectional study. Although this study suggested that smokers had worse morning-stiffness compared to non-smoking patients, the level of evidence is weak and based on a low quality study.

The effect of smoking on disease activity in AS patients was examined in eight of the studies. According to these reports, current smokers had higher scores than non-current smokers. Current smoking was an independent variable for higher BASDAI after adjusting for confounding factors. No correlation between BASDAI and quantity of smoking (pack-years) was found in the studies. However, the evidence level is weak. All the studies were cross-sectional, being impossible to directly address the effect of smoking cessation on disease activity measures. There were also differences between the studies respect to smoking habit evaluation. Chen et al. [28] included current smokers and past smokers in the same group, while Fallahi et al. [29] and Zhang et al. [33] included past smokers in the non-smokers group. Most of the studies collected smoking habit by face-to-face interview, but the data on smoking were retrospective in Zhang et al. [33], which may have caused misclassification of some patients and it was not possible to determine whether there were differences in smoking status between participants and non-participants in Mattey et al. [32] study, because data were collected from a questionnaire that patients completed at home and returned by mail and no information was obtained on patients failing to respond the questionnaire.

Respect to physical mobility, although the studies design was heterogeneous and the measures used to determine patient mobility were different, all evidence points in the same direction: smoking AS patients had poor physical mobility than those with non-smoking. No correlation with smoking quantity was found [29].

Our systematic review showed some evidence focused on smoking effect on functional status in AS patients. HAQ-AS progressed more rapidly in smokers. Smoking was also associated with the progression of functional disability in the subgroup of patients who had AS for less than 10 years. The evidence level is moderate and based on a moderate-good quality study. Although this study design was prospective with moderately long follow-up, the sample was large and a wide variety of predictors were examined, the generally slow rate of progression may have decreased the statistical power to detect associations with some predictors.

Current smoking and smoking quantity (pack-years) were significantly associated with worse structural damage. However, the measures to evaluate structural damage in AS patients were different (only two studies used the same measure: BASRI), the quality of these studies was low and AS activity or certain clinical features such as non-steroidal anti-inflammatory drug use and potential prognostic factors due to the absence of complete historical data, were not examined. Regarding the smoking effect in patients with axSpA, the strongest level of evidence is based on two very good-quality studies [41, 42], where spinal radiographic progression scored by mSASSS, was independently associated with cigarette smoking and smoking intensity.

This review found poor evidence respect to the correlation between smoking and quality of life. Current smoking and smoking quantity (pack-years) were positively and independently associated with higher ASQoL and EASi-QoL scores, but there was no significant difference between smokers and non-smokers regarding SF-36 subscale score. Although these studies suggested that smoking has a negative impact on quality of life in AS patients, all of them were cross-sectional low-quality studies, being not possible to directly address the smoking cessation impact on life quality measures.

Conclusion

Published data indicate with good level of evidence, that smoking has a dose-dependent impact on structural damage progression in axSpA. There is higher HAQ among AS smokers compared to non-smokers too. Respect to overall assessment of health, global disease activity, physical mobility and quality of life, although the studies design is heterogeneous and the level of evidence is poor, all evidence points in the same direction: smoking AS patients are worse than non-smoking.

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Compliance with ethical standards

Conflict of interest

Author V. Villaverde has received a speaker honorarium from Company Abbvie and Roche.
Author T. Cobo-Ibañez has received a speaker honorarium from Company Abbvie and Pfizer.
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Author JD. Cañete has received consultancy honorarium from Company Abbvie, Boehringer, Celgene, MSD, Novartis, Novo-Nordisk, Pfizer and UCB.
Author D. Seoane-Mato, M. Guerra and P. Diaz del Campo have received Sponsorship contract from company Abbvie.
Author G. Candelas declares that she has no conflict of interest.

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