The impact of nicotine smoking on spondyloarthritis and rheumatoid arthritis

G. El Hasbani[1], J. E Nassar[2], A.M. Elsayed Ali[2], I. Uthman[3], A. Jawad[4]

*[1]Department of Medicine, Hartford HealthCare St. Vincent's Medical Center, Bridgeport, CT, USA;
[2]Faculty of Medicine, American University of Beirut, Lebanon; [3]Department of Internal Medicine, American University of Beirut Medical Center, Lebanon; [4]Department of Rheumatology, Royal London Hospital, UK*

SUMMARY

Objective. Nicotine has major side effects on human health through numerous mechanisms, one of which is the alteration of the immune system and its genetic components. Such alteration can be a predisposing factor for autoimmune diseases such as spondyloarthritis (SpA) and rheumatoid arthritis (RA). This review aims to shed light on the effects of nicotine smoking on the pathophysiology, clinical presentation, and management of SpA and RA.

Methods. This review looked into the studies, excluding case reports and series, which were cited by PubMed/MEDLINE.

Results. Patients with established autoimmune conditions may have a different underlying pathophysiology and disease course when exposed to nicotine through cigarette smoking. Through the involvement of several cytokines, endothelial dysfunction, and epigenetic mechanisms, the severity of SpA is more prominent in smokers. The global health status, pain, and fatigue are worse in SpA patients. The evidence on the effect of nicotine smoking on the treatment of SpA is still limited. Nicotine can contribute to RA *via* the disruption of cellular regulatory activity, inflammatory responses, morphological, physiological, biochemical, and enzymatic responses. As such, smokers with RA have higher disease activity and are more likely to be seropositive through the citrullination of peptides. In addition, these patients are at risk of achieving a suboptimal response to tumor necrosis factor inhibitors.

Conclusions. Cigarette smoking can substantially affect the pathophysiology and clinical presentation of patients with SpA and RA. The impact of nicotine on the management of these diseases still needs to be further studied.

Key words: *Cigarette smoking, autoimmunity, spondyloarthritis, rheumatoid arthritis, pathophysiology, treatment.*

■ INTRODUCTION

Cigarette smoking is a major public concern that causes significant morbidity and mortality (1). Despite the humungous number of health side effects, the number of smokers remains high (1). Nicotine is one of the major components of cigarette smoke (2). The body's immune system reacts to nicotine by producing pro-inflammatory cytokines (3). Interestingly, nicotine can activate the body's anti-inflammatory mechanisms, such as the cholinergic pathway, limiting T cell activation and antibody response (4). As such, nicotine's effects on the immune system and the type of activated cells may seem unpredictable. Nevertheless, nicotine exposure has been associated with an increased number of mutations in distinct signatures, contributing to different extents to various cancers and autoimmune diseases (5).

Apart from the association with certain musculoskeletal and rheumatic diseases, nicotine exposure can alter the metabolism of medications supposed to treat such diseases. For example, liver function can be affected by nicotine, which ultimately affects the metabolism of certain medications, such as bisphosphonates (6, 7).

In this review, we will try to shed light on the role of nicotine exposure in spondyloarthritis (SpA) and rheumatoid arthritis (RA). We will discuss the pathophysiological mechanisms involved. Nevertheless, we will report significant clinical presentations

Corresponding author:
Georges El Hasbani
Department of Medicine,
Hartford HealthCare St. Vincent's Medical
Center,
Bridgeport 06606, CT, USA
E-mail: george.hasbany@lau.edu

that smokers with SpA or RA might have, as well as management aspects that differ from the routine standard of care.

■ SPONDYLOARTHRITIS

Pathophysiology

Nicotine smoking can increase the release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, which are normally elevated in axial SpA (8). IL-23 production, secondary to toxins, converts naïve CD4+ T cells to the T helper (Th)17 phenotype (9). Th17 cells have the potential to release IL-23, IL-17, IL-22, IL-6, and transforming growth factor-β (10). IL-17 specifically may mediate inflammation, vascular activation, extracellular matrix breakdown, and cartilage breakdown (9).

Nicotine smoking promotes the growth of *Porphyromonas gingivalis* and *Provetellae* species, which induce citrullination of various extracellular proteins (11). Citrullinated vimentin has been involved hypothetically in the pathophysiology of ankylosing spondylitis (AS) (12) and its radiographic progression (13). However, this hypothesis has not been tested yet.

Gut dysbiosis, a disruption in the intestinal microbiome, has been reported in both smokers (14), and patients with SpA (15). Inflammatory bowel disease (IBD), classically associated with SpA (14), is characterized by a specific microbiota dysbiosis in which the bacterial diversity is limited (16). In healthy human subjects undergoing controlled smoking cessation, there is a significant increase in the phylogenetic diversity of the gut (15). In addition, there is a decrease in *Bacteroidetes,* which are thought to be associated with IBD (17). However, the data relating tobacco use to IBD is still contradictory (18).

Endothelial dysfunction may explain the vascular pathology in SpA (19). For example, some biologic markers of endothelium, such as vascular endothelial growth factor, are elevated in patients with AS and are associated with disease progression (20). On the other hand, nicotine is known to damage endothelial cells in healthy individuals, which may suggest nicotine involvement in SpA smokers (21).

Epigenetic mechanisms, which are dysregulated in SpA, may also be affected by nicotine smoking. For example, sirtuin (SIRT1) is an enzyme in the cell nucleus that deacetylates transcription factors to control epigenetic gene silencing (22). It modulates IL-23/Th 17 pathway, sclerostin/Wnt pathways, and autophagy, which are implicated in SpA (23). Endothelial cells from human umbilical vein exposed to cigarette smoke extracts showed decreased SIRT1 levels, highlighting the possible role of cigarette smoke-mediated oxidative stress in endothelial dysfunction (24).

Among psoriasis patients, a protective effect of nicotine smoking against psoriatic arthritis (PsA) was found, referred to as the smoking paradox, which may be explained by collider bias (25). It is difficult to unravel the independent effect of nicotine smoking, however, since it is related to many other confounders.

Clinical manifestations

There is concordant evidence that nicotine is associated with increased disease severity in SpA, and there are more studies on AS compared to PsA. The limited literature suggests that smokers are at higher risk of developing AS than non-smokers (26). As for PsA, nicotine smokers with no history of psoriasis have a 27% higher risk of developing the disease than non-smokers (25).

Certain evidence suggests that ever-smokers suffer from significantly higher Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, spinal pain, and poorer quality of life than never-smokers (27). In a large cross-sectional analysis of the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis, current nicotine smoking was significantly associated with severe disease, fatigue, depression, and insomnia (28). Since most studies conducted in this field are cross-sectional, it is difficult to draw a causal inference. Interestingly, in a longitudinal study, although smokers with AS had higher disease activity at baseline than non-smokers, they displayed the same

disease progression as non-smokers over time (29). Research on the relationship between smoking and radiographic progression in AS has not been conclusive. There is some evidence that shows a relationship between the presence of syndesmophytes and elevated markers of inflammation which may contribute to radiographic progression in axial SpA (30, 31). However, cigarette smoking was not significantly associated with new syndesmophyte formation (30, 32-34). Therefore, there is not enough evidence to conclude that smoking is independently related to radiographical progression in axial SpA.

The data on the effect of nicotine on PsA clinical outcomes are limited. It appears that affected patients experience worse global health status, pain, fatigue, and more painful areas compared to never-smokers (15). Additionally, smoking has been associated with a poor quality of life, and its cessation may help reduce functional decline (35).

Management

Although nicotine smoking is associated with a poor quality of life and severe structural damage in patients with AS (36), its effect on treatment response is still being explored. AS smokers, especially those with high C-reactive protein (CRP) concentrations, have a diminished response to TNF-α inhibitors compared to non-smokers (37, 38). For patients with PsA, cigarette smoking is associated with poor response and low adherence to treatment (39, 40), leading to early discontinuation (41). PsA smokers had worse baseline patient-reported outcomes, shorter treatment adherence, and a poorer response to anti-TNF agents, especially infliximab and etanercept, compared to non-smokers (40). Secukinumab, a human monoclonal antibody selective for IL-17A, improved the disease activity of PsA patients, including those using cigarette smoking (42).

■ RHEUMATOID ARTHRITIS

Pathophysiology

RA is characterized by persistent synovitis and the generation of autoantibodies against several factors, such as rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) (43). Consequently, the synovium is continuously inflamed, leading to the degeneration of the joints (43).

Cigarette smoking has been cited as a significant risk factor for RA, especially in RF-positive patients (44, 45). This specifically happens through mechanisms of oxidative stress, inflammation, and autoantibody formation (44) (Figure 1).

Regarding oxidative stress, there are two phases of smoke: the particulate (tar) and the gaseous (vapour) phases, both of which have extremely high levels of free radicals (46). It is also known that cigarette smoke releases free radicals from within the body, which are a major component in the pathogenesis of RA through the damage they impose on the antioxidant systems, exacerbating rheumatoid inflammation (46).

Smoking causes a systemic proinflammatory state by influencing the immune system's cellular and humoral components (47). Chronic cigarette smoking appears to disrupt cellular regulatory activity, inflammatory responses, and morphological, physiological, biochemical, and enzymatic responses through its impact on innate and adaptive immune responses (47). Cigarette smoking increases the expression of matrix metalloproteinase (MMP)-12, which is involved in the pathophysiology of RA (48). Additionally, pro-MMP-9, which is regularly produced by synovial fibroblasts and contributes directly to joint degeneration, shows higher concentrations in smokers (49). In addition, nicotine can decrease natural killer cell activity, permitting the induction of an inflammatory response through higher levels of pro-inflammatory cytokines (47, 50).

As for autoantibody formation, citrullination is a post-translational modification where the amino acid arginine in a protein is changed into citrulline, which is not one of the 20 conventional amino acids provided by DNA in the genetic code (51).

Individuals with the *HLA-DRB1* shared epitope (SE) have increased susceptibility to RA regardless of anti-CCP antibody or RF status (52). Smoking is known to cause im-
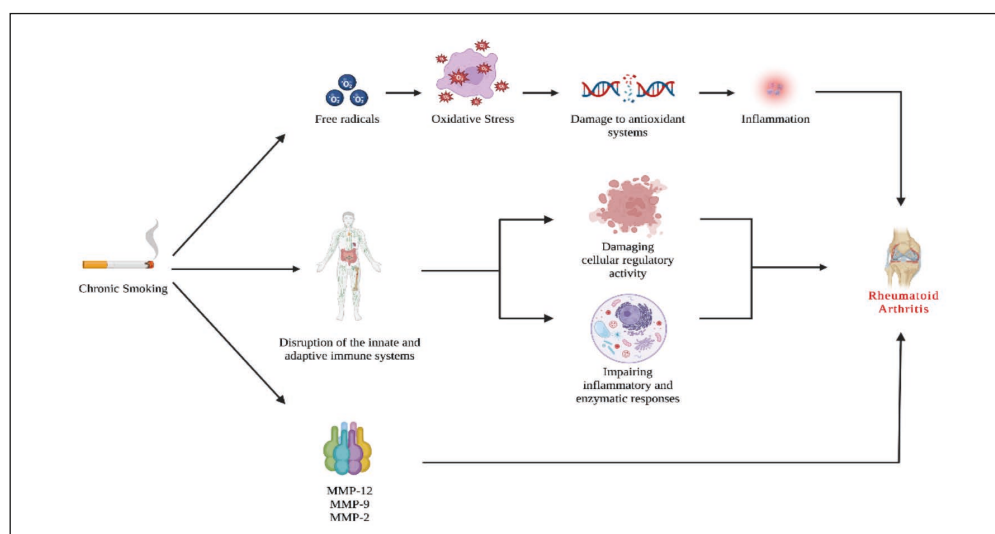
Figure 1 - A summary of certain pathophysiological mechanisms that can link cigarette smoking to rheumatoid arthritis. MMP, matrix metalloproteinase.

munological responses that are HLA-DR-restricted to autoantigens with citrullination modifications (53). Nevertheless, anti-CCP antibody formation is strongly influenced by SE status, with a gene-dose effect (53).

P. gingivalis has been associated with CCP-positive RA (54), *via* the presence of peptidylarginine deiminase, which may generate citrullinated proteins cross-reactive with anti-citrullinated peptide antibodies (55). On the contrary, some evidence found the presence of *P. gingivalis*, as determined by pyrosequencing of subgingival biofilm, to be associated with the severity of periodontitis but not with RA (56). While nicotine exposure may be associated with both *P. gingivalis* infection and RA, nicotine does not increase the risk of RA solely through its association with *P. gingivalis* (56).

Clinical manifestations

The effect of nicotine use on the activity of RA is yet to be deciphered, as the literature data are still contradictory. Some evidence suggests no association between smoking status and disease activity (57, 58), compared to other evidence that suggests RA patients who smoke have a more active disease (59). Despite having no effect on clinical disease activity, smoking might reduce radiologic disease progression (58).

Extra-articular manifestations (EAM) of RA, such as interstitial lung disease, appear in 20% to 45% of RA patients (60). Studies that examined the connection between nicotine smoking and the EAM of RA demonstrated worse presentations of RA in patients who smoke, leading to early disability (61). Moreover, smoking, alcohol consumption, and positive anti-CCP antibodies were also associated with worse presentations and more severe EAM (62). A history of smoking was associated with an increased risk of mortality in RA-interstitial lung disease (63).

In addition, patients with RA who develop severe EAM are more likely to be active smokers, and their baseline CRP, functional impairment, and mean disease activity score are all greater than their non-smoking counterparts (64). Besides, cigarette smoking is a well-known risk factor for cardiovascular disease in general and in RA specifically, with an increased risk of mortality and morbidity (65). Smoking cessation can reduce the risk of cardiovascular mortality in such patients (65).

Management

RA smokers exhibit a decreased clinical response to the anti-TNF-α infliximab (66). Both the patients' smoking status at the ini-

Table I - The effect of nicotine smoking on the pathophysiology, clinical presentation, and management of rheumatoid arthritis and spondyloarthritis.

Disease associated with nicotine smoking	Pathophysiology	Clinical manifestations	Management
Spondyloarthritis	- Increased levels of several interleukins - Endothelial dysfunction - Deacetylation of several transcription factors	- Higher disease incidence - Increased severity, fatigue, depression, and insomnia - Limited data on the relationship with PsA	Diminished response to TNFi in AS and PsA
Rheumatoid Arthritis	- Increased oxidative stress - Altered cellular and humoral components of immunity - *HLA-DRB1* shared epitope activation for autoantibody production - Increased risk of *P. gingivalis* infection	- Inconclusive data on disease activity - Higher rate of extra-articular manifestations - Increased cardiovascular mortality	Lower response rate to TNFi

TNFi, tumour necrosis factor inhibitors; AS, ankylosing spondylitis; PsA, psoriatic arthritis.

tiation of infliximab and their pack-year history of smoking are related to their poor response to the medication (67). Moreover, RA smokers starting infliximab have a lower likelihood of achieving remission based on the European League Against Rheumatism response criteria (68). Some mechanisms have tried to explain the suboptimal response of RA patients to TNF inhibitors. High titters of RF and anti-CCP antibodies have been linked to poor responsiveness (69, 70).

Since smoking is associated with high concentrations of inflammatory cytokines (71), these cytokines can contribute largely to the suboptimal response to treatment. Mechanistically, the intensity and duration of smoking are related to greater TNF-α/soluble TNF receptors (sTNFR) ratios and enhanced TNF-α production by T cells. Smokers' increased TNF-α levels or ratios of TNF-α/sTNFR may be linked to their resistance to treatment with TNF-α antagonists (71). Additionally, since IL-2 induces TNF-α production by activated human T cells (72), the significantly higher levels of serum soluble IL-2 receptors (sIL-2R) produced in smokers play a role in the slower response to infliximab compared to non-smokers, who experience a more rapid response due to their lower sIL-2R levels (73). The lowered response to treatment in smokers has also been attributed to the higher basal metabolic rates, suggesting that the accelerated metabolism of anti-rheumatic drugs might impact the treatment outcome (74).

The effects of nicotine exposure do not only affect the response to biological disease-modifying agents but also conventional treatments. For example, smoking has been associated with methotrexate failure (75). The clinical effect of hydroxychloroquine in connective tissue diseases has been shown not to be affected by smoking (76), although no data is available in the context of RA.

■ CONCLUSIONS

Table I summarizes the effect of nicotine smoking on the pathophysiology, clinical presentation, and management of RA and SpA. Cigarette smoking may contribute to the occurrence of autoimmunity or alteration of the pathophysiology and disease course of certain established autoimmune diseases, such as SpA or RA. By substantiating the release of cytokines, the disease activity may be worse, as measured by different scores. EAM have been shown to be more prominent. A suboptimal response to TNF inhibitors may be seen in RA patients. The data on the effect of cigarette smoking on the novel treatments for SpA is still unclear.

Contributions
GEH, JN, AS, searched the literature, assisted with the organization of the manuscript, interpreted and collected data, and wrote and edited the review; AJ, IU, interpreted and collected data, helped to design the figure and panel, and wrote and edited the review.

Conflict of interest
The authors declare no potential conflict of interest.

**Ethics approval and consent
to participate**
Not applicable.

Funding
None.

Availability of data and materials
Data available from the corresponding author.

■ REFERENCES

1. Marom-Haham L, Shulman A. Cigarette smoking and hormones. Current Opin Obstet Gynecol 2016; 28: 230-5.
2. Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: nicotine addiction. Sci Adv 2019; 5: eaay9763.
3. Yu H, Yang YH, Rajaiah R, Moudgil KD. Nicotine-induced differential modulation of autoimmune arthritis in the Lewis rat involves changes in interleukin-17 and anti-cyclic citrullinated peptide antibodies. Arthritis Rheum 2011; 63: 981-91.
4. Geng Y, Savage SM, Johnson LJ, Seagrave J, Sopori ML. Effects of nicotine on the immune response. I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. Toxicol Appl Pharmacol 1995; 135: 268-78.
5. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. Mutational signatures associated with tobacco smoking in human cancer. Science 2016; 354: 618-22.
6. Al-Bogami M, Alkhorayef MA, Akanle OA, Jawad A, Mageed R. The effects of smoking on response of osteoporosis treatment using dual energy X-ray absorptiometry scans, invited. Transactions of the American Nuclear Society 2013; 109: 51-2.
7. Mueck AO, Seeger H. Smoking, estradiol metabolism and hormone replacement therapy. Current Med Chem Cardiovasc Hematol Agents 2005; 3: 45-54.
8. Madej M, Nowak B, Świerkot J, Sokolik R, Chlebicki A, Korman L, et al. Cytokine profiles in axial spondyloarthritis. Reumatologia 2015; 53: 9-13.
9. Wendling D, Guillot X, Prati C. The IL-23/Th 17 pathway in spondyloarthritis: the royal road? Joint Bone Spine 2015; 82: 1-4.
10. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 pathway in rheumatic diseases: an overview. Front Immunol 2021; 12: 637829.
11. Berthelot JM, Le Goff B. Rheumatoid arthritis and periodontal disease. Joint Bone Spine 2010; 77: 537-41.
12. Bodnár N, Szekanecz Z, Prohászka Z, Kemény-Beke A, Némethné-Gyurcsik Z, Gulyás K, et al. Anti-mutated citrullinated vimentin (anti-MCV) and anti-65 kDa heat shock protein (anti-hsp65): new biomarkers in ankylosing spondylitis. Joint Bone Spine 2012; 79: 63-6.
13. Bay-Jensen AC, Karsdal MA, Vassiliadis E, Wichuk S, Marcher-Mikkelsen K, Lories R, et al. Circulating citrullinated vimentin fragments reflect disease burden in ankylosing spondylitis and have prognostic capacity for radiographic progression. Arthritis Rheum 2013; 65: 972-80.
14. Wendling D, Vuitton L, Koch S, Prati C. Spondyloarthritis and the gut: a new look. Joint Bone Spine 2015; 82: 77-9.
15. Biedermann L, Brülisauer K, Zeitz J, Frei P, Scharl M, Vavricka SR, et al. Smoking cessation alters intestinal microbiota: insights from quantitative investigations on human fecal samples using FISH. Inflamm Bowel Dis 2014; 20: 1496-501.
16. Schaeverbeke T, Truchetet ME, Richez C. Gut metagenome and spondyloarthritis. Joint Bone Spine 2013; 80: 349-52.
17. Quaglio AEV, Grillo TG, De Oliveira ECS, Di Stasi LC, Sassaki LY. Gut microbiota, inflammatory bowel disease and colorectal cancer. World J Gastroenterol 2022; 28: 4053-60.
18. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015; 12: 205-17.
19. Prati C, Demougeot C, Guillot X, Godfrin-Valnet M, Wendling D. Endothelial dysfunction in joint disease. Joint Bone Spine 2014; 81: 386-91.
20. Poddubnyy D, Conrad K, Haibel H, Syrbe U, Appel H, Braun J, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis 2014; 73: 2137-43.
21. Miyata S, Noda A, Ito Y, Iizuka R, Shimokata K. Smoking acutely impaired endothelial function in healthy college students. Acta Cardiol 2015; 70: 282-5.
22. Fujita Y, Yamashita T. Sirtuins in neuroendocrine regulation and neurological diseases. Front Neurosci 2018; 12: 778.
23. Wendling D, Prati C. Smoking and spondyloarthritis: a bad connection. Rheumatol Int 2015; 35: 1951-3.
24. Arunachalam G, Yao H, Sundar IK, Caito S, Rahman I. SIRT1 regulates oxidant- and cigarette smoke-induced eNOS acetylation in endothelial cells: role of resveratrol. Biochem Biophys Res Commun 2010; 393: 66-72.
25. Nguyen UDT, Zhang Y, Lu N, Louie-Gao Q, Niu J, Ogdie A, et al. Smoking paradox in the development of psoriatic arthritis among patients with psoriasis: a population-based study. Ann Rheum Dis 2018; 77: 119-23.

26. Videm V, Cortes A, Thomas R, Brown MA. Current smoking is associated with incident ankylosing spondylitis - the HUNT population-based Norwegian health study. J Rheumatol 2014; 41: 2041-8.

27. Zhao S, Challoner B, Khattak M, Moots RJ, Goodson NJ. Increasing smoking intensity is associated with increased disease activity in axial spondyloarthritis. Rheumatol Int 2017; 37: 239-44.

28. Zhao S, Jones GT, Macfarlane GJ, Hughes DM, Dean LE, Moots RJ, et al. Associations between smoking and extra-axial manifestations and disease severity in axial spondyloarthritis: results from the BSR Biologics Register for Ankylosing Spondylitis (BSRBR-AS). Rheumatology (Oxford) 2019; 58: 811-9.

29. Ciurea A, Finckh A. Smoking and spondyloarthritis. Joint Bone Spine 2013; 80: 234-5.

30. Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012; 64: 1388-98.

31. Zhao SS, Goodson NJ, Robertson S, Gaffney K. Smoking in spondyloarthritis: unravelling the complexities. Rheumatology (Oxford) 2020; 59: 1472-81.

32. Braun J, Baraliakos X, Hermann KG, Xu S, Hsu B. Serum C-reactive protein levels demonstrate predictive value for radiographic and magnetic resonance imaging outcomes in patients with active ankylosing spondylitis treated with golimumab. J Rheumatol 2016; 43: 1704-12.

33. Kim HR, Hong YS, Park SH, Ju JH, Kang KY. Low bone mineral density predicts the formation of new syndesmophytes in patients with axial spondyloarthritis. Arthritis Res Ther 2018; 20:231.

34. Min HK, Lee J, Ju JH, Park SH, Kwok SK. Alcohol consumption as a predictor of the progression of spinal structural damage in axial spondyloarthritis: data from the Catholic Axial Spondyloarthritis COhort (CASCO). Arthritis Res Ther 2019; 21: 187.

35. Bremander A, Jacobsson LT, Bergman S, Haglund E, Löfvendahl S, Petersson IF. Smoking is associated with a worse self-reported health status in patients with psoriatic arthritis: data from a Swedish population-based cohort. Clin Rheumatol 2015; 34: 579-83.

36. Villaverde-García V, Cobo-Ibáñez T, Candelas-Rodríguez G, Seoane-Mato D, Campo-Fontecha PDD, Guerra M, et al. The effect of smoking on clinical and structural damage in patients with axial spondyloarthritis: a systematic literature review. Semin Arthritis Rheum 2017; 46: 569-83.

37. Ciurea A, Scherer A, Weber U, Exer P, Bernhard J, Tamborrini G, et al. Impaired response to treatment with tumour necrosis factor α inhibitors in smokers with axial spondyloarthritis. Ann Rheum Dis 2016; 75: 532-9.

38. Zurita Prada PA, Urrego Laurín CL, Guillén Astete CA, Kanaffo Caltelblanco S, Navarro-Compán V. Influence of smoking and obesity on treatment response in patients with axial spondyloarthritis: a systematic literature review. Clin Rheumatol 2021; 40: 1673-86.

39. Pezzolo E, Naldi L. The relationship between smoking, psoriasis and psoriatic arthritis. Expert Rev Clin Immunol 2019; 15: 41-8.

40. Højgaard P, Glintborg B, Hetland ML, Hansen TH, Lage-Hansen PR, Petersen MH, et al. Association between tobacco smoking and response to tumour necrosis factor α inhibitor treatment in psoriatic arthritis: results from the DANBIO registry. Ann Rheum Dis 2015; 74: 2130-6.

41. Haddad A, Gazitt T, Feldhamer I, Feld J, Cohen AD, Lavi I, et al. Treatment persistence of biologics among patients with psoriatic arthritis. Arthritis Res Ther 2021; 23: 44.

42. Riechers E, Kiltz U, Brandt-Juergens J, Kästner P, Peterlik D, Tony HP. Does smoking affect secukinumab treatment outcomes and safety in patients with psoriatic arthritis? - Real world data from the German Aquila study. Ann Rheum Dis 2020; 79: 1711.

43. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376: 1094-108.

44. Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin JI. Smoking and rheumatoid arthritis. Int J Mol Sci 2014; 15: 22279-95.

45. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010; 69: 70-81.

46. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. Ann NY Acad Sci 1993; 686: 12-27; discussion 27-8.

47. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol 2002; 2: 372-7.

48. Bracke K, Cataldo D, Maes T, Gueders M, Noël A, Foidart JM, et al. Matrix metalloproteinase-12 and cathepsin D expression in pulmonary macrophages and dendritic cells of cigarette smoke-exposed mice. Int Arch Allergy Immunol 2005; 138: 169-79.

49. Raitio A, Tuomas H, Kokkonen N, Salo T, Sorsa T, Hanemaaijer R, et al. Levels of matrix metalloproteinase-2, -9 and -8 in the skin, serum and saliva of smokers and non-smokers. Arch Dermatol Res 2005; 297: 242-8.

50. Shegarfi H, Naddafi F, Mirshafiey A. Natural killer cells and their role in rheumatoid arthri-

tis: friend or foe?. Scientific World Journal 2012; 2012: 491974.

51. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, et al. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev 2010; 233: 34-54.

52. Bang SY, Lee KH, Cho SK, Lee HS, Lee KW, Bae SC. Smoking increases rheumatoid arthritis susceptibility in individuals carrying the HLA-DRB1 shared epitope, regardless of rheumatoid factor or anti-cyclic citrullinated peptide antibody status. Arthritis Rheum 2010; 62: 369-77.

53. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006; 54: 38-46.

54. Hitchon CA, Chandad F, Ferucci ED, Willemze A, Ioan-Facsinay A, van der Woude D, et al. Antibodies to porphyromonas gingivalis are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. J Rheumatol 2010; 37: 1105-12.

55. Fisher BA, Cartwright AJ, Quirke AM, de Pablo P, Romaguera D, Panico S, et al. Smoking, Porphyromonas gingivalis and the immune response to citrullinated autoantigens before the clinical onset of rheumatoid arthritis in a Southern European nested case-control study. BMC Musculoskelet Disord 2015; 16: 331. Erratum in: BMC Musculoskelet Disord 2016; 17: 62.

56. Scher JU, Ubeda C, Equinda M, Khanin R, Buischi Y, Viale A, et al. Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis. Arthritis Rheum 2012; 64: 3083-94.

57. Gudelj Gracanin A, Markovic I, Golob M, Lucijanic M, Valetic AM, Morovic-Vergles J. The effect of smoking on disease activity in rheumatoid arthritis - our experience. Acta Clin Croat 2020; 59: 312-7.

58. Vesperini V, Lukas C, Fautrel B, Le Loet X, Rincheval N, Combe B. Association of tobacco exposure and reduction of radiographic progression in early rheumatoid arthritis: results from a French multicenter cohort. Arthritis Care Res (Hoboken) 2013; 65: 1899-906.

59. Söderlin MK, Petersson IF, Bergman S, Svensson B. Smoking at onset of rheumatoid arthritis (RA) and its effect on disease activity and functional status: experiences from BARFOT, a long-term observational study on early RA. Scand J Rheumatol 2011; 40: 249-55.

60. Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. Scand J Rheumatol 2004; 33: 65-72.

61. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 2003; 62: 722-7.

62. Kim SK, Park SH, Shin IH, Choe JY. Anti-cyclic citrullinated peptide antibody, smoking, alcohol consumption, and disease duration as risk factors for extraarticular manifestations in Korean patients with rheumatoid arthritis. J Rheumatol 2008; 35: 995-1001.

63. Qiu M, Jiang J, Nian X, Wang Y, Yu P, Song J, et al. Factors associated with mortality in rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. Respir Res 2021; 22: 264.

64. Nyhäll-Wåhlin BM, Petersson IF, Nilsson JA, Jacobsson LT, Turesson C. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. Rheumatology (Oxford) 2009; 48: 416-20.

65. Popescu D, Rezus E, Badescu MC, Dima N, Seritean Isac PN, Dragoi IT, et al. Cardiovascular risk assessment in rheumatoid arthritis: accelerated atherosclerosis, new biomarkers, and the effects of biological therapy. Life (Basel) 2023; 13: 319.

66. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006; 45: 1558-65.

67. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009; 36: 1180-7.

68. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol 2010; 16: 15-8.

69. Bobbio-Pallavicini F, Caporali R, Alpini C, Avalle S, Epis OM, Klersy C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis 2007; 66: 302-7.

70. Braun-Moscovici Y, Markovits D, Zinder O, Schapira D, Rozin A, Ehrenburg M, et al. Anti-cyclic citrullinated protein antibodies as a predictor of response to anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis. J Rheumatol 2006; 33: 497-500.

71. Glossop JR, Dawes PT, Mattey DL. Association between cigarette smoking and release of tumour necrosis factor alpha and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatology (Oxford) 2006; 45: 1223-9.

72. Lorré K, Fransen L, Ceuppens JL. Interleukin-2 induces tumor necrosis factor-alpha production by activated human T cells via a cyclosporin-sensitive pathway. Eur Cytokine Netw 1992; 3: 321-30.

73. Park SJ, Shin JI. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug: comments on the article by Söderlin et al. Scand J Rheumatol 2012; 41: 411-2.

74. Metsios GS, Stavropoulos-Kalinoglou A, Nevill AM, Douglas KM, Koutedakis Y, Kitas GD. Cigarette smoking significantly increases basal metabolic rate in patients with rheumatoid arthritis. Ann Rheum Dis 2008; 67: 70-3.

75. Siddiqui A, Totonchian A, Jabar Ali JB, Ahmad I, Kumar J, Shiwlani S, et al. Risk Factors associated with non-respondence to methotrexate in rheumatoid arthritis patients. Cureus 2021; 13: e18112.

76. Leroux G, Costedoat-Chalumeau N, Hulot JS, Amoura Z, Francès C, Aymard G, et al. Relationship between blood hydroxychloroquine and desethylchloroquine concentrations and cigarette smoking in treated patients with connective tissue diseases. Ann Rheum Dis 2007; 66: 1547-8.