The impact of nicotine smoking on spondyloarthritis and rheumatoid arthritis

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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
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 Prevotella 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/Th17 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-
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**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-
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 titers 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 rheumatoid arthritis and spondyloarthritis.

<table>
<thead>
<tr>
<th>Disease associated with nicotine smoking</th>
<th>Pathophysiology</th>
<th>Clinical manifestations</th>
<th>Management</th>
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| 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 TNF 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 TNF |

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

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**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.
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