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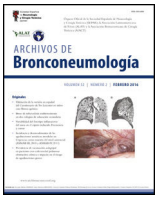

Editorial

Rheumatoid arthritis and smoking☆

Artritis reumatoide y tabaco

Smoking is an epidemic that causes pulmonary and cardiovascular diseases and cancer, but it is also associated with immune system disorders. Cigarette smoke contains a mixture of more than 4000 toxic substances, including nicotine, carcinogens, organic compounds, gaseous substances, and free radicals. These substances affect both innate and adaptive immunity, and play a double role, either by exacerbating pathogenic immune responses or by attenuating defensive immunity, increasing the burden of oxidative stress, inflammation, autoantibody formation, and epigenetic changes.[1] Evidence from epidemiological studies associates smoking with the appearance of certain autoimmune diseases, such as lupus erythematosus, multiple sclerosis, primary biliary cirrhosis, Graves-Basedow disease, and others.[2]

Rheumatoid arthritis (RA) is an autoimmune disease that, in addition to affecting the joints, produces systemic manifestations that are associated with a worse prognosis, such as diffuse interstitial lung disease (ILD).[3] A history of smoking is more common in RA patients with ILD than in RA patients without ILD (25 vs. 5 pack-years, respectively).[4]

RA affects 0.5%–1% of the population and is one of the diseases in which most evidence is available on how the interaction of known external agents in individuals with a genetic predisposition will trigger an autoimmunity process. Autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), may appear in the serum of these patients. The presence of these autoantibodies, especially ACPA, is associated with more severe and persistent RA, and with extra-articular disease. Other autoantibodies against carbamylated proteins and antibodies against peptidyl arginine deaminases (anti-PAD) have also been identified.[5]

The principal genetic determinant for the development of RA is the presence of alterations in the HLA-DRB1 genes. The specific amino acid sequence at positions 70–74 of the HLA-DR®1 chains is called the shared epitope (SE) and is associated with the presence of RA and ACPA levels, but not with RF levels. Furthermore, the risk of developing RA is up to 10 times higher among first-degree relatives. This genetic susceptibility contributes between 50%–60% to the development of RA.[5]

Since the association between smoking and RA was first described in 1987,[6] several retrospective and prospective studies have been published that have shown that smoking is the main avoidable environmental risk factor associated with the development and severity of RA in genetically predisposed individuals. This gene–environment interaction is probably due to smoking-stimulated lung protein citrullination. Moreover, smoking alters the periodontal flora, favoring the growth of bacteria such as *Propionibacterium gingivalis* that synthesizes a PAD enzyme that can induce protein citrullination in the gingival tissue, constituting another source of antigen.[7]

In a large cohort[8] of patients with 1 copy of SE, the relative risk for developing RA was 2.4 (95% CI: 1.4–4.2), and 4.2 (95% CI: 2.1–8.3) when there were 2 copies of SE. In smokers, this risk increased to 5.5 (95% CI: 3–10) with 1 copy of SE and to 15.7 (95% CI: 7.2–34.2) when there were 2 copies of SE. However, this relationship was not found in seronegative RA patients. Subsequent studies have confirmed these findings.[9]

Raised levels of RA-related antibodies (ACPA, RF, anti-PAD, and anti-carbamylates) are present in the bloodstream for 3–5 years before the onset of joint inflammation.[10] This finding suggests that the development of this autoimmunity has an extra-articular origin. Citrullinated protein levels have also been studied in bronchoalveolar lavage (BAL) samples. Concentrations were significantly higher in smokers with pulmonary inflammation than in smokers without lung changes. None of the non-smokers showed these proteins in BAL.[11]

Smoking can also influence the development and therapeutic response of RA.[12] It modifies cytokine production and the effector function of innate immune cells, dendritic cells, macrophages and NK cells. Induction of a systemic inflammatory response is demonstrated by higher levels of cytokines, such as TNF-α, IL-1, and IL-6, that are of particular importance in the pathogenesis of RA. This imbalance in the production of some cytokines such as IL-6 and TNF-α appears to be related with a worse response to treatment among patients with RA who are smokers.[13]

The relationship between smoking and RA depends on the intensity of the habit measured by the pack-year index (PYI), and particularly on the duration. Some studies have observed a dose–response relationship, however, others have found that smoking duration is associated with an increased risk of RA, so that among individuals who have smoked for more than 20 years, the risk of developing RA is the same among those with a PYI of 6–9 as among those with a PYI > 20. On the other hand, the effects of tobacco as a risk factor persist as long as 20 years after the cessation of exposure.[7,9] Passive smoking in children also appears to influence the subsequent development of RA, especially in first-degree relatives.[14] Smoking has been clearly linked to RA, but nicotine gum

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consumption has not.[15] All these data are clearly important for the purposes of prevention and cessation programs.

The treatment of RA constitutes a major economic burden, and this disease affects quality of life and decreases survival. In a genetically predisposed subgroup, smoking is the main agent responsible for both RA development and a worse prognosis. Preventive measures are essential. In addition to the general population, the main target would be genetically predisposed first-degree relatives. Studies in these first-degree relatives show that anti-smoking campaigns and cessation programs delivered via computer applications were helpful for stopping smoking and decreasing the incidence of RA.[16]

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