Archivos de Bronconeumología 59 (2023) 412–413

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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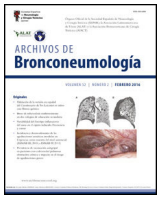

Editorial

Impact of Oral Antidiabetics Agents in the Prevention of COPD Exacerbations

Prevention of exacerbations is a major objective of chronic obstructive pulmonary disease (COPD) treatment. Smoking cessation and long-acting bronchodilators, in some cases combined with inhaled corticosteroids, are the main therapeutic tools used to achieve this goal. Other treatments that have proven useful in this regard, for selected groups of patients, include high-dose N-acetylcysteine, roflumilast, azithromycin and vitamin D. Despite the use of these therapies, some patients continue to suffer from recurrent exacerbations and, in these cases, it is extremely important to identify treatable disorders that may contribute to the persistence of such exacerbations.

Extrapulmonary comorbidities are important conditions that contribute to the risk of exacerbations, and diabetes mellitus (DM), a disease commonly found in patients with COPD, is particularly relevant in this context.[1,2] Increased glucose concentrations impair polymorphonuclear leukocyte function, decreasing their phagocytic function and altering host defense.[3] As a consequence, infections (including those of the lower respiratory tract) are more frequent in patients with DM,[4] especially in those with poorer glycemic control.[5] In reality, the coexistence of COPD and type-2 DM is considered a syndrome with some shared components, such as risk factors (smoking), genes, proteins and pathways (inflammation and oxidative stress), linked through mechanisms that are still not fully clarified.[6] Patients in whom COPD and DM coexist are at greater risk of suffering frequent exacerbations.

Several studies have evaluated the effects of oral antidiabetic agents (OAD) in the prevention of exacerbations in patients with type-2 DM and COPD, with reductions of up to 35% in the relative risk of exacerbations.[7,8] Metformin is the most studied drug. Its effects appear to go beyond simply lowering glucose levels in blood and respiratory tract and, therefore, decreasing the risk of respiratory infection. It activates adenosine monophosphate-associated protein kinase (AMPK), inhibiting inflammatory mechanisms and reducing airway inflammation.[9] In addition, it can reduce oxidative stress.[10] Other OAD like thiazolidinediones, dipeptidyl peptidase-4 and glucagon-like peptidase 1 (GLP-1) receptors agonist, also produce anti-inflammatory effects and may reduce airway hiperresponsiveness.[7,8] The use of Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, whose glycosuric effect can lead to a decrease in glucose concentrations in the tissues (in this case at the lung), has been associated with a decreased risk of lower respiratory tract infections, specifically community-acquired pneumonia.[11] All of these mechanisms could potentially reduce the risk of exacerbations in COPD.[7]

The best combination of OAD in patients with COPD and type-2 DM, with the aim of reducing the incidence of exacerbations, is not entirely clear, and there are some discrepancies between studies, possibly attributable to their observational, retrospective design.[7,8,12] Importantly, some of these studies have failed to adjust for concurrent glycemic control, an important variable in the incidence of adverse outcomes in DM. In addition, it is not clear the profile of COPD patients who may benefit most from these therapies (i.e., type of airway and systemic inflammation, type of exacerbations -infectious versus non infectious-, presence of chronic airway infection). Studies conducted with metformin have shown to inhibit smooth muscle proliferation and reduce eosinophilic inflammation of the airway,[13,14] while the local anti-inflammatory effect of GLP-1 receptors agonists has been shown to reduce bronchial hyperreactivity,[15] which would justify their greater benefit in patients with COPD with a history of concurrent asthma. Consistent with these findings, Wu et al. found a beneficial effect of metformin in patients with asthma-COPD overlap (ACO) but not in "pure" COPD.[16] However, it should be mentioned that ACO was defined in this study based on participants self-report of concurrent diagnosis of asthma, and the definition did not use eosinophilia or any other biomarkers, as should be desirable. Thus, some uncertainty remains about the real meaning of these results. Furthermore, the published studies cannot fully adjust their results for some potential confounding factors, such as therapies used to treat COPD. Inhaled corticosteroids are especially important since, particularly at high doses, they can increase the risk of bacterial airway infection and could worsen metabolic control in patients with DM.

A very intriguing possibility is the hypothesis that OAD could reduce COPD exacerbations in patients without DM. Airway glucose concentrations are increased in stable COPD patients without DM compared with controls, and are further increased in COPD exacerbations.[17] Higher glucose concentrations in the airways correlate with an increase in inflammatory markers and a greater possibility of isolation of *Pseudomonas aeruginosa*.[17] Increased airway glucose levels in the absence of hyperglycemia are possibly related to increased glucose leakage across the inflamed epithelium. Given that metformin has anti-inflammatory properties, and that it can reduce the glucose flux through the lung epithelium,[18] it is plausible that this drug could reduce the risk of airway infection and COPD exacerbation even in patients without DM. In studies conducted in animal models, drugs such as metformin and dapagliflozin reduced glucose concentrations in the respiratory

https://doi.org/10.1016/j.arbres.2022.12.004

tract and inhibited the growth of *S. aureus* or *P. aeruginosa*.[19] However, the only prospective randomized study in humans published to date found no effect of metformin, used as acute treatment in patients without DM hospitalized for COPD exacerbation, on C-reactive protein levels or clinical outcomes, but the study was not powered to detect changes in clinical end-points.[20] Although the safety of metformin have been questioned in COPD due to the theoretical risk of lactic acidosis in patients with hypoxic conditions, the real risk of this complication seems to be very low.[18]

The aforementioned studies, together with other investigations indicating a possible effect of OAD in modulating cellular senescence and reducing lung function decline, suggest a potential role for these drugs in the management of COPD. The cited evidence, although currently inconclusive, suggests that patients with persistent COPD exacerbations might benefit from OAD treatment. Further, adequately powered studies are warranted to investigate the possible role of these drugs in controlling recurrent COPD exacerbations, both in patients with and without DM.

Financial

No financial support has been received for conducting the study or drafting the manuscript.

Conflict of interests

The authors state that they have no conflict of interests.

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