Improving Outcomes of Chronic Obstructive Pulmonary Disease through the Treatment of Comorbidities: One Step Beyond

The comprehensive and personalized management of chronic obstructive pulmonary disease (COPD) must also include the careful evaluation and treatment of comorbidities (1, 2). The most frequent comorbidities in COPD are cardiovascular, Type 2 diabetes mellitus (T2D), depression, and anxiety (2, 3). There is a complex relationship between COPD and T2D: Patients with COPD have a higher prevalence of T2D, compared with the general population (approximately 20% vs. 10%) (2–4), and patients with T2D are at increased risk of COPD, with an estimated 10% of these patients having COPD (4). Several mechanisms have been implicated in the increased risk of T2D associated with COPD; among these, cigarette smoke, reduced physical activity, increased obesity, disease-related inflammation, corticosteroid exposure, oxidative stress, and hypoxia are probably the most important (4). Furthermore, patients with COPD and T2D are at increased risk of infections, including severe exacerbations, and, eventually, an increased risk of death, compared with patients with COPD without T2D (5–7). On the other hand, the use of high-dose inhaled or systemic corticosteroids in the treatment of either stable or exacerbated COPD is associated with hyperglycemia, poor control of diabetes, and even an increase in the prevalence of T2D in patients with COPD (8, 9).

The interactions among treatment of COPD, risk of infection, T2D, and risk of exacerbations of COPD can be represented as a vicious circle, with several strategies that may help to break this circle having been suggested (Figure 1). With regard to these strategies, some previous studies have suggested that not only adequate control of T2D but also the type of antidiabetic drug used may have an impact on outcomes in COPD (10, 11). Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are drugs for T2D that have shown effects on airway inflammation in asthma models that might also suggest beneficial effects in COPD. In this issue of the *Journal*, Foer and colleagues (pp. 1088–1100) present the results of a retrospective, database study in the United States that analyzed the frequency and risk of exacerbations of COPD in patients with T2D who were treated with different oral antidiabetic medications (12). In particular, they were interested in comparing GLP-1RAs and other therapies. Their results showed that GLP-1RA users had significantly lower exacerbation rates and exacerbation risk compared with users of dipeptidyl peptidase 4 inhibitors (DPP-4is) and sulfonylurea, but no significant differences were observed between GLP-1RA users and sodium-glucose cotransporter 2 inhibitor (SGLT2i) users. The magnitude of the differences was very relevant, with a 48% increased rate of exacerbations with DPP-4i and more than double (109% increase) the rate with sulfonylureas compared with GLP-1RA; and when accounting for baseline glucose control and the body mass index (BMI), severe exacerbation risk almost doubled for DPP-4i and sulfonylurea users compared with GLP-1RA users (12). These results are consistent with the findings of previous observational studies that also showed a reduction in COPD exacerbations with GLP-1RA in comparison with other antidiabetic medications (10, 11). However, the following aspects of this study must be highlighted. First, the diagnosis of COPD was well characterized by a validated algorithm that includes smoking and lung function. Second, the definition of the main outcome (exacerbation of COPD) was also carefully validated, and a sensitivity analysis was conducted that included the use of antibiotics in the definition of exacerbation. Third, there was an accurate selection of covariates, including another sensitivity analysis with metabolic covariates (BMI and glycosylated hemoglobin).

Despite the quality of data and the well-designed and careful data analysis of the study and the consistency between its results and those of previous works, we should not forget that all these studies are observational; even if the analyses have been carefully designed and controlled as much as they can possibly be, it cannot be ruled out that some source of unexpected and/or unknown source of bias may exist, which can only be accounted for in a randomized controlled trial (RCT). Nevertheless, the results of this and previous studies strongly suggest a differential effect on the risk of exacerbations of COPD with the different antidiabetics tested, and this is an important message for clinicians: While we wait for a definitive RCT, it should be considered that, if there are no significant differences in the safety profile and no cost-related issues, GLP-1RA (or SGLT2i) should be preferred to DPP-4i and sulfonylureas for T2D in patients with COPD, particularly if they are frequent exacerbators.

The design of the study does not allow the investigators to ascertain whether there is a real effect of GLP-1RA on the reduction of exacerbation risk or, more unlikely, whether there is an increased risk of exacerbations associated with DPP-4i and sulfonylureas. Moreover, the precise mechanism that explains the possible reduction in exacerbation by GLP-1RA is not completely understood. However, it is interesting that an exploratory analysis accounting for a change in metabolic parameters suggested that GLP-1RA may have a direct effect not attributable to BMI or glucose control. If confirmed, a direct effect of GLP-1RA on the risk of exacerbation may open the door to test the use of GLP-1RA in COPD without comorbid T2D to investigate a possible additive effect on the reduction of exacerbations in addition to the usual respiratory medications. This strategy has been tested with statins, albeit, unfortunately, with negative results (13).

In the era of the personalized treatment of COPD (1, 14), this personalization should not be restricted to respiratory medications, and we must explore whether extending this personalized approach to the treatment of comorbidities may result in better outcomes. In this context, the study by Foer and colleagues (12) suggests that GLP-1RA should be the first-choice treatment for patients with COPD, frequent exacerbators, and patients with comorbid T2D, but despite not being the objective of the study, their results also suggest that SGLT2i could be a good alternative to GLP-1RA, with SGLT2i even showing significantly better results than GLP-1RA in overweight

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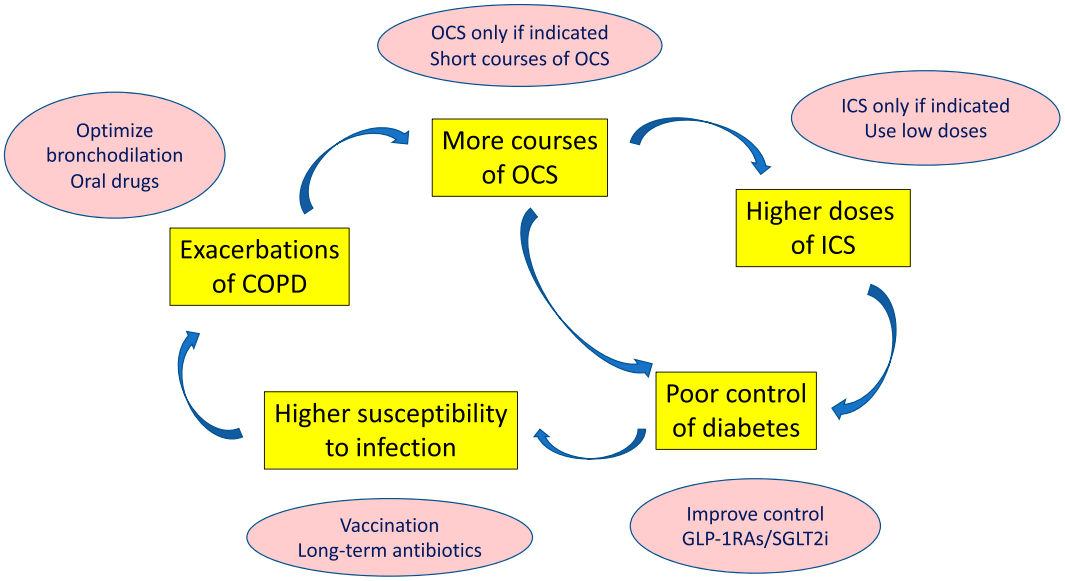

Figure 1. Representation of the vicious circle of infection, exacerbations, corticosteroid treatment, and Type 2 diabetes mellitus. Pale red circles indicate strategies that may help breaking the vicious circle. COPD = chronic obstructive pulmonary disease; GLP-1RAs = glucagon-like peptide 1 receptor agonists; ICS = inhaled corticosteroid; OCS = oral corticosteroid; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

patients and in Grade 1 COPD (12). These results must be taken with caution because of the small sample size of these specific comparisons, but they could represent a further step in personalized treatment. In summary, although the final answer will only be provided by adequately designed RCTs, clinicians must be aware that "one size does not fit all" in patients with COPD who have T2D. ■

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References

1. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, *et al.* Global Initiative for Chronic Obstructive Lung Disease 2023 report: GOLD executive summary. *Am J Respir Crit Care Med* 2023;207:819–837.
2. Lopez-Campos JL, Almagro P, Gómez JT, Chiner E, Palacios L, Hernández C, *et al.*; en nombre del equipo de trabajo de GesEPOC 2021. Actualización de la Guía Española de la EPOC (GesEPOC): comorbilidades, automanejo y cuidados paliativos [Spanish COPD guideline (GesEPOC) update: comorbidities, self-management and palliative care]. *Arch Bronconeumol* 2022;58:334–344.
3. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, *et al.*; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–161.
4. Cazzola M, Rogliani P, Calzetta L, Lauro D, Page C, Matera MG. Targeting mechanisms linking COPD to type 2 diabetes mellitus. *Trends Pharmacol Sci* 2017;38:940–951.
5. Castañ-Abad MT, Montserrat-Capdevila J, Godoy P, Marsal JR, Ortega M, Alsedà M, *et al.* Diabetes as a risk factor for severe exacerbation and death in patients with COPD: a prospective cohort study. *Eur J Public Health* 2020;30:822–827.
6. Chen G, Lin Q, Zhuo D, Cui J. Elevated blood glucose is associated with severe exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2022;17:2453–2459.
7. Figueira Gonçalves JM, García Bello MÁ, Golpe R, Alonso Jerez JL, García-Talavera I. Impact of diabetes mellitus on the risk of severe exacerbation in patients with chronic obstructive pulmonary disease. *Clin Respir J* 2020;14:1208–1211.
8. Miravitlles M, Auladell-Rispau A, Monteagudo M, Vázquez-Niebla JC, Mohammed J, Nuñez A, *et al.* Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. *Eur Respir Rev* 2021;30:210075.
9. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, *et al.* Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017;49: 1600791.
10. Albogami Y, Cusi K, Daniels MJ, Wei YJ, Winterstein AG. Glucagon-like peptide 1 receptor agonists and chronic lower respiratory disease exacerbations among patients with type 2 diabetes. *Diabetes Care* 2021;44:1344–1352.
11. Pradhan R, Lu S, Yin H, Yu OHY, Ernst P, Suissa S, *et al.* Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ* 2022;379:e071380.
12. Foer D, Strasser ZH, Cui J, Cahill KN, Boyce JA, Murphy SN, *et al.* Association of GLP-1 receptor agonists with COPD exacerbations among patients with type 2 diabetes. *Am J Respir Crit Care Med* 2023; 203:831–840.
13. Criner GJ, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, *et al.*; COPD Clinical Research Network; Canadian Institutes of Health Research. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014;370:2201–2210.
14. Miravitlles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros JA, *et al.* Spanish COPD guidelines (GesEPOC) 2021: updated pharmacological treatment of stable COPD. *Arch Bronconeumol* 2022; 58:69–81.