# Two for the price of one: GLP-1 analogues, a new approach in treating severe COPD patients with diabetes

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**Multimorbid severe COPD patients need to be treated with a complementary systemic approach. In this way, the patient, not only the airway disease, will be treated comprehensively, as two effects (metabolic and pulmonary) are better than one.** https://bit.ly/3PHoygt

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She said, "I'm sure we must be perfect for each other
And if you doubt it, you'll be certain when you meet my mother"

*Two for the Price of One* (ABBA, *The Visitors*, 1981)

In COPD patients, the co-occurrence of more diseases potentially sharing pathobiological mechanisms has recently been considered a multimorbid condition, in which a patient-centred rather than a single-disease approach may have relevant implications [1]. In COPD patients, the co-occurrence may be particularly intriguing if associated with a metabolic disorder; the relative impact of these two co-occurring diseases may depend on several factors, such as physical inactivity and systemic inflammation related to a smoking habit, sedentary lifestyle, airway inflammation and obstruction, adipose tissue and inflammatory marker activation [2]. In this context, mounting evidence documents the co-existence of signalling and genetic signature linking patients with COPD and type 2 diabetes mellitus (T2DM) [3]. Clinical data demonstrates that COPD patients with T2DM are at higher risk of severe exacerbation and higher mortality risk overall [4], particularly for respiratory causes [5]. In acute exacerbation of COPD, the presence of T2DM, together with a residual inflammatory response documented at discharge and at least one previous hospitalisation in the past year, may predict who will be readmitted in less than 30 days from discharge [6]. In fact, the use of oral corticosteroids for the treatment of acute exacerbation of COPD is associated with an increased relative risk of acute hyperglycaemia [7]. Therefore, managing COPD patients with T2DM requires some relevant considerations, especially from the therapeutic point of view. The possibility of targeting mechanisms linking COPD and T2DM may help to target pharmacological approaches that intercept common pathways [8].

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine peptide incretin hormone implicated in insulin-mediated glucose homeostasis. Upon postprandial release, the half-life of GLP-1 is 1–2 min, and it is enzymatically degraded by DPP4 [9]. Therefore, in the pharmacological management of insulin regulation *via* incretin hormones, several anti-hyperglycaemic drugs have been designed to either deliver an exogenous analogue of GLP-1 or use inhibition of DPP4 (DPP4i) to sustain levels of endogenous GLP-1 by preventing degradation.

Randomised controlled trials of GLP-1 receptor agonists have shown improvements in lung function in patients with T2DM and obese patients with COPD, including increased forced vital capacity and diffusion

capacity for carbon monoxide [10, 11]. Together with findings from animal models [12], these results suggest a possible functional role for GLP-1 within the lung. In fact, expression of GLP-1 receptors has been observed in the human lung, with an experimental study demonstrating a broncho-relaxant effect observed for human isolated bronchi with activation of the GLP-1 receptor [13]. Previous observational studies in COPD investigating the association between the use of GLP-1 receptor agonists and exacerbation rates have performed retrospective analyses to demonstrate that patients receiving GLP-1 receptor agonists suffered fewer exacerbations when compared to the active-comparator DPP4i [14, 15].

In this issue, See *et al*. [16] interrogated this relationship further by using the TriNetX Analytics Network database to conduct a retrospective, observational analysis of the association between incretin-based therapies and pulmonary outcomes in COPD patients with a concomitant diagnosis of T2DM and receiving single-inhaler triple therapy (SITT). Patients receiving GLP-1 analogues (exposed cohort) were compared to those receiving DPP4i (non-exposed cohort). One of the strengths of this study was the sample size used to generate the authors' results (n= 3502), a similar sample size to at least one previous study [14].

Propensity score matching was used to define the treatment groups, pulmonary outcomes were assessed using the Cox proportional hazards model, whilst a log-rank test compared survival distributions. The authors found that patients using GLP-1 analogues had an 18% lower risk of acute exacerbation (hazard ratio (HR), 0.82 (95% CI 0.71–0.94); p=0.003) and a 40% decreased risk of all-cause mortality (HR, 0.60 (95% CI 0.47–0.77); p<0.001), when compared to DPP4i. In addition, a reduced risk of pneumonia was observed with GLP-1 analogues compared to DPP4i (HR, 0.72 (95% CI 0.61–0.85); p<0.001).

Propensity score matching allows for the formation of matched sets of treated and untreated participants who share a similar propensity score; this method was introduced by Rosenbaum and Rubin [17] in the 1980s and is used in an attempt to remove the effects of confounders in assessing causal relationships. This statistical method is potentially useful for observational studies when assessing treatment effects where controlled randomisation is not possible due to the nature of the study. Propensity score matching attempts remove any bias, leaving remaining differences between groups (here primarily exacerbation rates) attributable to the variable of interest (*i.e.* treatment with GLP-1 analogues) [18].

Propensity scores in this study were based on the predictor variables, in particular age, sex, race, tobacco use, body mass index, haemoglobin A1c, eosinophil count, forced expiratory volume in 1 s, long term use of steroids, oxygen dependence and pre-existing comorbidities, as well as medication use for cardiovascular, diabetic and pulmonary diseases. Propensity scores assume that the predictor variables are the most important variables that may confound the results (*i.e.* the primary outcome: exacerbation rates). One potential flaw in the use of propensity score matching for pre-existing datasets is that scores are limited to existing variables only. Although one cannot be exhaustive in including all potential predictor variables, the lack of prior exacerbation history may be, in this context, a major confounder. This aspect is particularly true given that exacerbation history is one of the most important predictors of future exacerbations in COPD [19]. The authors rightly comment on this as a limitation imposed by data availability, stating that the use of azithromycin and steroids, the number of hospital admissions and ICU admissions were also included in propensity score matching. However, this leads us to further discussion on the method of identification of COPD exacerbations in observational research.

In this study, exacerbations were defined using the International Classification of Diseases (ICD) codes. Elsewhere, an audit of confirmed clinical diagnoses of COPD exacerbation found that only 64% of patients were correctly classified using ICD codes and misclassification was usually attributed to admission due to other concomitant diseases, including admissions of a cardiovascular nature [20]. Nevertheless, clinical diagnoses of COPD exacerbations may also be subjective in classification. Overall, we will soon be relying on more precise definitions of COPD exacerbations, as suggested recently in the Rome proposal and a Lancet commission, paving the way for better-characterised exacerbations in future [21, 22].

An 18% relative reduction in mortality was observed in patients treated with GLP-1 inhibitors, which is interesting, particularly given that the population studied already received optimal treatment with SITT. SITT has been demonstrated to reduce mortality in randomised controlled trials, with a 42–46% relative reduction in all-cause mortality as compared to long-acting $\beta_2$ agonist/long-acting muscarinic antagonist [23, 24]. Furthermore, the reduction in all-cause mortality with SITT in these studies may be attributed to a reduction in cardiovascular-associated mortality. See *et al*. [16] suggest that the mortality benefits observed for patients treated with GLP-1 analogues may also be attributed to cardiovascular benefits and weight loss effects. Elsewhere, anti-inflammatory effects of GLP-1 agonists have also been reported [25], in addition to an improvement in oxidative stress. From the results presented here, GLP-1 analogues may

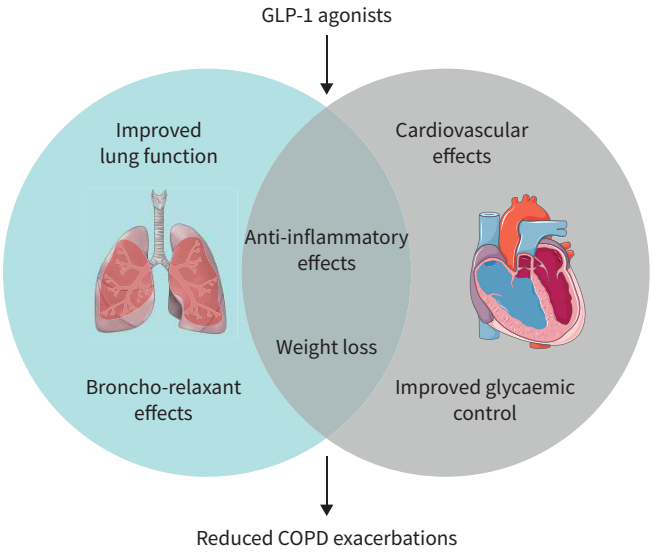


FIGURE 1 Potential mechanisms of action of GLP-1 agonists in exacerbation reduction in COPD. GLP-1: glucagon-like peptide-1.

improve prognosis further in COPD patients treated with SITT and concomitant T2DM and in this observational study the efficacy was documented without significant gastrointestinal severe events. Interestingly, the reported benefits on the risk of mortality (and other endpoints) are related to the effects of exogenous GLP-1 compared to indirect sustentation of endogenous GLP-1 *via* DPP4i, rather than placebo. GLP-1 analogues have been reported to have a higher glycaemic efficiency than DPP4i [26]; therefore, the more significant effect of GLP-1 agonists is likely attributed to the drug's potency. A schematic demonstrating some plausible mechanisms for the observed improvement in exacerbations with GLP-1 agonists can be seen in figure 1.

In conclusion, the article from See *et al*. [16] assumes a precious value in the context of severe and complex COPD patients, for which we may conventionally propose a pivotal and maximal inhalation therapy for management. The possibility of intercepting different pathways by a new pharmacological approach to improving relevant pulmonary outcomes, which are generally difficult to reach for these patients, confirms the need to move our vision in different future directions. Multimorbid severe COPD patients need to be treated with a complementary systemic approach and not only *via* inhalation therapies. In this way, we will comprehensively treat the patient, not only the (airway) disease; two effects, metabolic and pulmonary, are better than one.

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