



The association between inhaled corticosteroid and osteoporosis and fracture

To the Editor:

We read with great interest the study investigating the association between inhaled corticosteroid (ICS) and the risk of osteoporosis and fracture among COPD patients [1]. Multivariate analysis in this study demonstrated a significant dose–effect relationship between ICS and the risk of osteoporosis-related events. Compared to non-ICS users, high-dose ICS treatment was significantly associated with any osteoporosis-related event (risk ratio 1.52, 95% CI 1.24–1.62; while the corresponding estimate for low-dose ICS was 1.27, 95% CI 1.13–1.56) [1]. Overall, it is a well-designed study; however, we have one major and two minor concerns about the findings of this study.

The major concern was the confounding effect of disease severity of COPD. For COPD patients requiring high-dose ICS, they could carry high risk of exacerbation. In contrast, ICS was not indicated for COPD patients with low risk of exacerbation. Compared to patients with low risk of exacerbation, frequent exacerbator could have less physical activity caused by their decrease muscle strength and endurance due to oxidative stress, hypoxaemia, hormone abnormality, deficiency of nutrients such as protein and vitamin D, and the use of systemic corticosteroid [2]. Moreover, a correlation between systemic inflammation and osteoporosis should be taken into consideration because previous studies demonstrate a stronger correlation in frequent compared to non-frequent exacerbators [3–5]. These findings suggest that COPD exacerbation itself might be associated with osteoporosis. To overcome this confounding effect, their results should be better adjusted according to the risk of COPD exacerbation. Finally, patients with ≥ 1 dispensation of oral corticosteroids (OCS) at any time point from 2000 to 2014 were excluded from the study [1]. Although this strategy leads to the exclusion of the major confounding factor (use of systemic corticosteroid), it converts the study population to a non-representative sample regarding the severity and the frequency of COPD exacerbations.

The first minor concern was whether the effect of different corticosteroids used in the equivalent dose may be associated with different degrees of risk of osteoporosis. Taking pneumonia as an example, many studies have demonstrated that the intra-class difference among commonly used ICSs on the risk of pneumonia can vary, in which fluticasone-based ICS was associated with a higher risk of pneumonia or tuberculosis than non-fluticasone-based ICS [6–10]. Although this study excluded the use of systemic corticosteroid, many other medications could be possible confounding factors. Medications such as proton pump inhibitors, statins, thiazide diuretics, histamine-receptor antagonists, hormone therapy, contraceptives and cyclosporine A are well-known contributors to osteoporosis. Because COPD patients could have multiple comorbidities and have high opportunity to take these medications, their confounding effect needed to be re-evaluated in this study.

Although we raised some concerns regarding the study reported by JANSON *et al.* [1], this study still provided useful information. However, as ICS is an important and commonly used medication for COPD patients at risk of exacerbation, more detailed assessment is warranted.



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More analysis is needed to assess the impact of inhaled corticosteroid on osteoporosis

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Cheng-Yi Wang¹ and Chih-Cheng Lai²

¹Dept of Internal Medicine, Cardinal Tien Hospital and School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan. ²Dept of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan.

Correspondence: Chih-Cheng Lai, Dept of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan 71051, Taiwan. E-mail: dtmed141@gmail.com

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