EDITORIAL

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Is Osteoporosis a Common Comorbidity in Different Chronic Airway Diseases?

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Although a recent genome-wide association study to prove "Dutch hypothesis," meaning that both asthma and chronic obstructive pulmonary disease (COPD) share a genetic background, has failed to show a common genetic component between the two[1], considerable number of patients have clinical features of both asthma and COPD[2-4]. Some patients with COPD may have eosinophilic airway inflammation or bronchodilator response and some asthmatics may have neutrophilic airway inflammation or fixed airflow limitation. Such condition has been termed asthma-COPD overlap syndrome. However, the use of "syndrome" in asthma-COPD overlap (ACO) is now being challenged because such overlap includes several different phenotypes caused by various underlying mechanisms rather than a single disease entity[5].

Nevertheless, recognition and diagnosis of ACO are important as ACO has different clinical features compared to asthma or COPD alone. More frequent exacerbation, poorer quality of life, more rapid decline in lung function, and more utilization of healthcare resources have been reported in ACO than in traditional chronic airway diseases[6-8]. Epidemiologic studies have reported that the prevalence of ACO ranges from 15% to 55% depending on criteria used by different investigators[9,10]. Recent studies have reported a relatively consistent prevalence rate; approximately 15% of patients with COPD are categorized as ACO both in a large Spanish cohort and COPD Gene consortium[11,12]. It has been shown that the prevalence of ACO is increased with age.[2]

Less is known about comorbidities of ACO. In this issue of *Tuberculosis and Respiratory Diseases*, Oh et al.[13] reported results of a retrospective cross-sectional study of 321 patients. They investigated the prevalence of osteoporosis or bone mineral density (BMD) in patients with asthma, COPD, and ACO[13]. Although they failed to demonstrate different prevalence of osteoporosis among three chronic airway diseases, they found that patients with ACO had significantly lower BMD compared to patients with asthma or COPD alone. In addition, they showed that the use of inhaled corticosteroid (ICS) was not associated with low BMD in their population by multivariate analysis[13].

Regarding comorbidome in ACO, van Boven et al.[14] have reported comprehensive results about its pattern and clinical impact on hospitalization risk using a large Spanish cohort. They showed that allergic rhinitis (odds ratio [OR], 1.81), anxiety (OR, 1.18), and gastroesophageal reflux disease (OR, 1.18) were more prevalent in patients with ACO compared to those in patients with COPD. Moreover, osteoporosis was also more frequent in ACO (OR, 1.14). Interestingly, they reported that chronic kidney disease (OR, 0.79) and ischemic heart disease (OR, 0.88) were less frequent in ACO while cardiovascular diseases were associated with hospitalization risk of patients with ACO[14]. Using 2009 Korean National Health Insurance database, Rhee et al.[3] have also reported that a variety of comorbidities including diabetes, hypertension, ischemic heart disease, depression, and osteoporosis are more frequent in patients with ACO compared to those in patients with COPD without asthma. Although the study of Oh et al.[13] could not find significant higher prevalence of osteoporosis in patients with ACO, their results suggest that lower BMD in patients with ACO compared to patients with asthma or COPD alone could be a characteristic of the overlap, consistent with results of two aforementioned studies[3,14].

Interestingly, in this particular study, the use of ICS was not associated with low BMD. Although the association between ICS use and prevalence of osteoporosis remains controversial,

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evidences suggest that using ICS for treating chronic airway diseases may not be harmful or even beneficial from the viewpoint of osteoporosis. Two systematic reviews have demonstrated that long-term ICS use does not have a significant impact on bone mineral density[15,16]. Moreover, a recent study has reported that the incidence of osteoporosis in ICS users is significantly lower than that in non-ICS users (hazard ratio, 0.73) in female patients with COPD[17]. In that study, higher ICS dose is associated with lower risk of osteoporosis (p for trend=0.0023) after adjusting for age, income, and medications[17]. How can we explain these phenomena? First, ICS can reduce systemic inflammation which might be associated with increased osteoporosis in chronic airway diseases[18,19]. Evidences support that pro-inflammatory cytokines including tumor necrosis factor-α and interleukin-6 are associated with increased risk of osteoporosis[7,20]. Second, regular use of ICS can prevent osteoporosis by preventing acute exacerbation of COPD characterized by surge of both pulmonary and systemic inflammation. A previous study has demonstrated that acute exacerbation of COPD is independently associated with progression of osteoporosis[21]. Third, improved symptoms, lung function, and quality of life by regular use of ICS may prevent immobility-associated bone loss via increased physical activity.

Although a relatively small number of ACO patients were included, this particular study provides insight into comorbidome among different chronic airway diseases[13]. Future investigations should encompass the impact of treatment including ICS on pro-inflammatory cytokines or bone turnover markers and on the development or progression of osteoporosis as well as influence of osteoporosis to the risk of fracture and quality of life in patients with ACO using a large population.

ACO is still an area of unknown. Its pathophysiology, biomarker, clinical characteristics should be elucidated. Identifying ACO is important so that appropriate treatment can be selected. Unfortunately, there is scant information on the optimal treatment for ACO because most previous large clinical trials on asthma or COPD have excluded ACO cases. Although somewhat late, efforts to find potentially beneficial new drugs, ranging from small kinase blocker to monoclonal antibodies for this overlap, are now ongoing[22]. Recent positive results on mepolizumab, a monoclonal antibody against interleukin-5 for patients with eosinophilic COPD, are shedding light on those efforts[23].

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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