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REVIEW ARTICLE

Multidimensional Analyses of Long-Term Clinical Courses of Asthma and Chronic Obstructive Pulmonary Disease

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are chronic respiratory disorders involving obstructive airway defects. There have been many discussions on their similarities and differences. Although airflow limitation expressed as forced expiratory volume in one second (FEV_1) has been considered to be the main diagnostic assessment in both diseases, it does not reflect the functional impairment imparted to the patients by these diseases. Therefore, multidimensional approaches using multiple measurements in assessing disease control or severity have been recommended, and multiple endpoints in addition to FEV_1 have been set recently in clinical trials so as not to miss the overall effects. In particular, as improving symptoms and health status as well as pulmonary function are important goals in the management of asthma and COPD, some patient-reported measurements such as health-related quality of life or dyspnea should be included. Nonetheless, there have been few reviews on the long-term clinical course comparing asthma and COPD as predicted by measurements other than airflow limitation. Here, we therefore analyzed and compared longitudinal changes in both physiological measurements and patient-reported measurements in asthma and COPD. Although both diseases showed similar long-term progressive airflow limitation similarly despite guideline-based therapies, disease progression was different in asthma and COPD. In asthma, patient-reported assessments of health status, disability and psychological status remained clinically stable over time, in contrast to the significant deterioration of these parameters in COPD. Thus, because a single measurement of airflow limitation is insufficient to monitor these diseases, multidimensional analyses are important not only for disease control but also for understanding disease progression in asthma and COPD.

KEY WORDS

asthma, COPD, longitudinal survey, multidimensional analysis, patient-reported outcome

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the two most common respiratory conditions, and have overlapping disease characteristics. At about 45 years ago, these two diseases were considered to belong to the same spectrum of syndromes causing airflow limitation.[1] However, presently, there is an increasing realization that they should be differentiated from each other, although they can coexist.[2] This is not only because their etiological mechanisms differ but also because pharmacotherapeutic strategies depend on the diagnosis.[3] Inhaled corticosteroids (ICSs) are the mainstay for the

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Table 1 Multidimensional analysis of asthma control

Pulmonary function	Asthma symptoms/reliever use
Spirometry	Health status or health-related quality of life
Peak expiratory flow monitoring	Functional status or disability
Minimally invasive markers	Asthma exacerbations
Airway hyperresponsiveness	Unscheduled health care utilization
Fractionated exhaled nitric oxide	Use of additional or emergency medication
Sputum eosinophils	Treatment adherence and side-effects

treatment of asthma, by reducing airway inflammation and hyperresponsiveness, and, in general, with dose reduction as asthma severity decreases. In patients with asthma, bronchodilators are used when anti-inflammatory therapy to prevent episodes of bronchoconstriction fails. In contrast, bronchodilators are the fundamental therapy for symptomatic patients with COPD, and high-dose ICS treatment is reserved for use with severe COPD patients who have frequent exacerbations.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[2] are predicated on the fact that asthma and COPD are inflammatory diseases causing airflow limitation through an interaction involving different sensitizing agents, different cell populations in the airway inflammatory process, and different degrees of reversibility. These two diseases show similarities, transitions and substantial differences, and have been discussed extensively from various perspectives also in this journal.[3-7] However, many features of these diseases including pathogenesis and progression are not fully understood.[8] Regarding the long-term clinical course, the GOLD[2] defines COPD as being characterized by progressive airflow limitation that is not fully reversible. In asthma, although it is not clearly classified as a progressive disorder, inflammation progresses and affects lung mechanics, possibly causing irreversible airflow limitation as a consequence of airway remodeling in the long run.[9]

However, in the management of patients with asthma and COPD, it is indicated that monitoring airflow limitation alone may miss the overall effects of the disease.[10,11] Systemic effects as well as local lung consequences are also reported in both diseases.[12,13] Therefore, in analyzing disease progression, a multidimensional approach with multiple parameters is necessary to assemble a comprehensive picture of the disease process.[8] We have undertaken this approach in patients with asthma and COPD.[14-19] In the present review, we summarize and compare available reports on the long-term clinical course of asthma and COPD in order to assess the similarities and differences between these two diseases.

THE NEED FOR MULTIDIMENSIONAL EVALUATION IN ASSESSING DISEASE PROGRESSION

Asthma is characterized by chronic airway inflammation in which many cell types are involved, particularly mast cells, eosinophils and CD4+T-lymphocytes.[2] They release various mediators that contribute to asthma symptoms. Airway remodeling in asthma is thought to cause persistent airflow limitation over time.[9] Long-term research on adult patients with asthma has shown that forced expiratory volume in one second (FEV_1), the "gold standard" of airflow limitation indices, decreases more over the years than in subjects without asthma.[20-22] In the international asthma guidelines[23,24] and the recent joint statement by the American Thoracic Society/European Respiratory Society,[25] periodic monitoring of FEV_1 is recommended in addition to symptom assessment to objectively measure asthma severity and risk of adverse events,[26] because patients with asthma frequently have poor subjective perception of their symptoms or asthma severity.

The ultimate aim of asthma management is to achieve and maintain control of the disease. Reducing airway hyperresponsiveness (AHR) in conjunction with optimizing symptom reduction and lung function leads to more effective control of asthma while alleviating chronic airway inflammation.[27] Thus, monitoring AHR or markers of airway inflammation such as induced sputum plays a role in the long-term management of asthma. However, although tracking FEV_1 or AHR may tell us about the changes in airway inflammatory status or some aspects of disease control, these measurements do not provide data on the functional, social and psychological impairments experienced by patients,[10] indicating that they are clearly not sufficient for understanding the physiological changes that accompany disease progression. To reflect what is important to patients, for example, health status or health-related quality of life is more dependent on the overall impact of the disease rather than on a single measurement.[28] Indeed, the 2007 National Asthma Education and Prevention Program Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma (the 2007 NAEPP guidelines) outline specific measures for periodic assessment (1-6 months intervals) and monitoring of control, including asthma symptoms and quality of life/functional status as well as pulmonary function.[24,29] These patients' own assessments tend to differ from those made by clinicians.[25] Thus, the use of the multidimensional analysis as in Table 1 including patients'

perspectives is important to build up a comprehensive picture of the disease process.

Like asthma, COPD is a chronic respiratory disease characterized by obstructive airway defects. The decline of FEV_1 has traditionally been used to measure disease progression in COPD.[30] The level of FEV_1 was also used as a severity marker, as it was previously considered the most crucial predictor of mortality,[31] an important outcome in COPD, considering that this disease is ranked high as a cause of death worldwide.[2] However, after the year 2000, the situation changed. We have demonstrated that other measurements of exercise capacity, health status and dyspnea, all of which include systemic components, are important mortality predictors independent of FEV_1 in COPD.[32-34] This idea has been applied to multidimensional disease severity grading protocols, such as the BODE index (including body mass index, dyspnea, exercise capacity and airflow limitation)[35] or ADO index (including age, dyspnea and airflow limitation).[36] Other studies indicated systemic measurements such as the presence of anemia[37] or higher C-reactive protein levels[38] are important mortality predictors. Current guidelines such as the GOLD[2] state that COPD should be considered a systemic disorder and be evaluated multidimensionally.

DISEASE MONITORING

ICSs are the mainstay for the therapy of chronic asthma. They improve symptoms, pulmonary function, AHR and health status. It has been demonstrated that the time course of improvement of the different measurements differs after initiating asthma treatment with ICSs.[25,39] For example, based on clinical trials with high-dose ICS,[39] the order of improvement is first, night symptoms, then FEV_1, next minimum waking peak expiratory flow, day-time symptoms, amount of rescue short-acting β-agonist required, and finally AHR. However, in comparison to many short-term studies investigating the effects of drugs such as ICS on various measurements, little information is available about their long-term changes after peak improvements in asthma.

In long-term large-scale studies assessing the effects of medical treatment, multidimensional approaches have been used in both asthma and COPD. In the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study investigating the effectiveness of early intervention with ICSs on long-term asthma control,[40,41] asthma-related events, use of additional asthma medications, asthma symptoms, restriction in daily activities and sleep problems caused by asthma were measured in addition to the change in lung function measured as FEV_1. In COPD, large-scale long-term clinical trials lasting 3-4 years to investigate the effects of ICSs,[42-46] the salmeterol/fluticasone propionate combination,[47,48] or long-acting anticholinergic agents[49,50] have been reported after 1999. Although, at first, the major endpoints for these studies were the rates of decline in FEV_1, other outcomes such as change in health status, mortality and the number of exacerbations have also begun to be assessed as primary or additional endpoints as in the Towards a Revolution in COPD Health (TORCH) trial[47,48] and the Understanding Potential Long-Term Impact on Function with Tiotropium (UPLIFT) trial.[49,50] Thus, unlike the traditional measurement of disease progression using the decline in FEV_1,[30] in light of a better understanding of the multidimensional nature of COPD, progression has been measured by the rate of change of other outcomes. Halpin and Tashkin have recently reported that surrogate markers of progression could include those of (a) pathobiology, (b) physiologic indices, (c) patient-centered outcomes, and, ultimately, (d) mortality.[51] The working group suggested that the definition of disease modification should be: an improvement in, or stabilization of, structural or functional parameters as a result of reduction in the rate of progression of those parameters occurring while an intervention is applied and which may persist even if the intervention is withdrawn.[51]

In the clinical trials investigating the efficacy of drugs, physicians' freedom to apply clinical judgment to change a patient's medication might be restricted due to the rigorous study protocols. We therefore planned a study to reflect routine clinical practice as closely as possible by permitting individual judgment to maximize disease control. We recruited 87 consecutive patients with stable asthma[15,16] and 137 consecutive patients with stable COPD,[18,19] all of whom had been regularly treated previously for at least 6 months in order not to assess the abrupt changes just after the start of treatment. We then evaluated the patients with asthma multidimensionally every year, and the COPD patients every 6 months, both over a period of 5 years. Pulmonary function, health status, disability and psychological status were assessed in both diseases, AHR only in asthma, and exercise capacity only in COPD. Thus, we obtained information on the multidimensional effects of maintaining asthma or COPD control over a longer time period than usually reported.

LONG-TERM CHANGES IN AIRFLOW LIMITATION

Patients with asthma experience an accelerated and progressive loss of lung function over time.[20-22] ICS improves FEV_1 only for a short period. In contrast, although long-term treatment with ICS may be associated to some degree with a smaller decline in FEV_1, ICS cannot prevent the development of airflow limitation in some cases of asthma.[52-55] There are several possible reasons for this, airway remodeling being one candidate[9] because the effect of ICS on airway remodeling is less evident as compared to its beneficial

Table 2 Baseline data and annual changes in clinical measurements over a 5-year clinical course of 87 patients with stable asthma and 137 patients with stable COPD

	Asthma		COPD	
	Baseline	Annual change	Baseline	Annual change
Age, years	50 ± 2		69 ± 1	
FEV_1, l	2.25 ± 0.09	-0.053 ± 0.011***	1.22 ± 0.04	-0.025 ± 0.006***
FEV_1, %predicted	81.7 ± 1.9	-1.1 ± 0.3**	45.9 ± 1.3	-0.9 ± 0.2**
Log (PD_{20}-FEV_1), c.u.	1.57 ± 0.07	0.07 ± 0.02***		
Peak $\dot{V}o_2$, ml/min/kg			14.8 ± 0.3	-0.5 ± 0.1***
SGRQ total (0-100)	20.3 ± 1.4	-0.3 ± 0.5	36.2 ± 1.4	1.9 ± 0.3***
MRC (0-4)	0.3 ± 0.1	0.01 ± 0.02	1.1 ± 0.1	0.14 ± 0.02***
HADS anxiety (0-21)	3.4 ± 0.3	-0.04 ± 0.11	4.7 ± 0.3	0.16 ± 0.08*
HADS depression (0-21)	3.3 ± 0.3	0.03 ± 0.09	3.9 ± 0.3	0.17 ± 0.07*

Results are shown as mean ± SE. The numbers in parentheses indicate the theoretical score range. *$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$. Adapted and modified from references 15, 16, 18 and 19.

effect on airway inflammation.[56,57] Nonetheless, to achieve improvement in airway remodeling after ICS therapy, early and long-term persistent treatment seems to be important even in patients with relatively mild asthma.[40,41,57]

Regarding COPD, few drugs have been found which demonstrated statistically significant effects on pulmonary function decline, although recent reports suggest that salmeterol plus fluticasone propionate or tiotropium significantly reduced the rate of decline in postbronchodilator FEV_1 by 16 ml/year and 6 ml/year, respectively, as compared to placebo.[48,50] Consistent with the above-mentioned studies, also in our experience,[15,18] FEV_1 declined significantly over 5 years in both asthma and COPD despite continued treatment to control disease (Table 2, Fig. 1).

LONG-TERM CHANGES IN AHR IN ASTHMA

Previous studies indicate that, after the initiation of ICS treatment, AHR continues to improve slowly over many months, although lung function and symptoms improve relatively more quickly. It is thought that AHR may reflect both airway inflammation and remodeling.[57] From the long-term point of view, two studies demonstrated that AHR continued to improve over a 3-year period in patients who were following asthma treatment guidelines.[14,58] Our study[15] added data on this issue by showing that an improvement in AHR peaked after approximately 3 years, but slowly deteriorated thereafter (Table 2, Fig. 1). However, it must be borne in mind that the time-scale of changes in the provocative concentration/dose to cause a certain degree of airway narrowing (e.g. 20% fall in FEV_1: PC_{20}, PD_{20}) in response to ICS therapy can vary with the challenge test.[25] The recent joint statement referred to above[25] promulgates the notion that AHR should be regarded as an integrative disease marker, reflecting multiple pathophysiological mechanisms, and can be used as a predictor of future risk of exacerbations and decline in lung function in longitudinal studies. Thus, long-term treatment of asthma patients will be needed to ensure and maintain improvement in AHR even after asthma symptoms have improved.

LONG-TERM CHANGES IN EXERCISE CAPACITY IN COPD

In patients with COPD, the degree of activity limitation assessed by an accelerometer worsens with disease progression,[59] and reduced exercise capacity has significant correlations with mortality.[33] In our study,[18] exercise capacity measured by peak oxygen uptake ($\dot{V}o_2$) on progressive cycle ergometry deteriorated significantly, which might be even more prominent than FEV_1 (Table 2, Fig. 1). Analyses predicting its decline revealed that the deterioration in ventilatory related factors due to impaired respiratory mechanics or ventilatory muscle dysfunction played the most important role.[18] Casanova *et al.* also reported that exercise capacity measured by 6 minute walking distance deteriorated over time in patients with COPD.[60] These deteriorations in exercise capacity were not strongly correlated with the decline in FEV_1, but would lead to a worsening of exertional dyspnea or health. Therefore, physical inactivity is an important therapeutic target in COPD, especially with the increasing attention being paid to pulmonary rehabilitation in recent guidelines.[61]

LONG-TERM CHANGES IN HEALTH STATUS

Usually, health status is not correlated with physiological measurements, and represents disease severity other than what is reflected in pulmonary function in asthma and COPD.[62] Health status is a patient-reported measure that represents the overall impact of the level of disease control and exacerbations on quality of life. Thus, in both diseases, it is now used in addition to pulmonary function to optimize patient management strategies and to evaluate the effects of therapeutic interventions.

Bateman *et al.* reported that in well-controlled

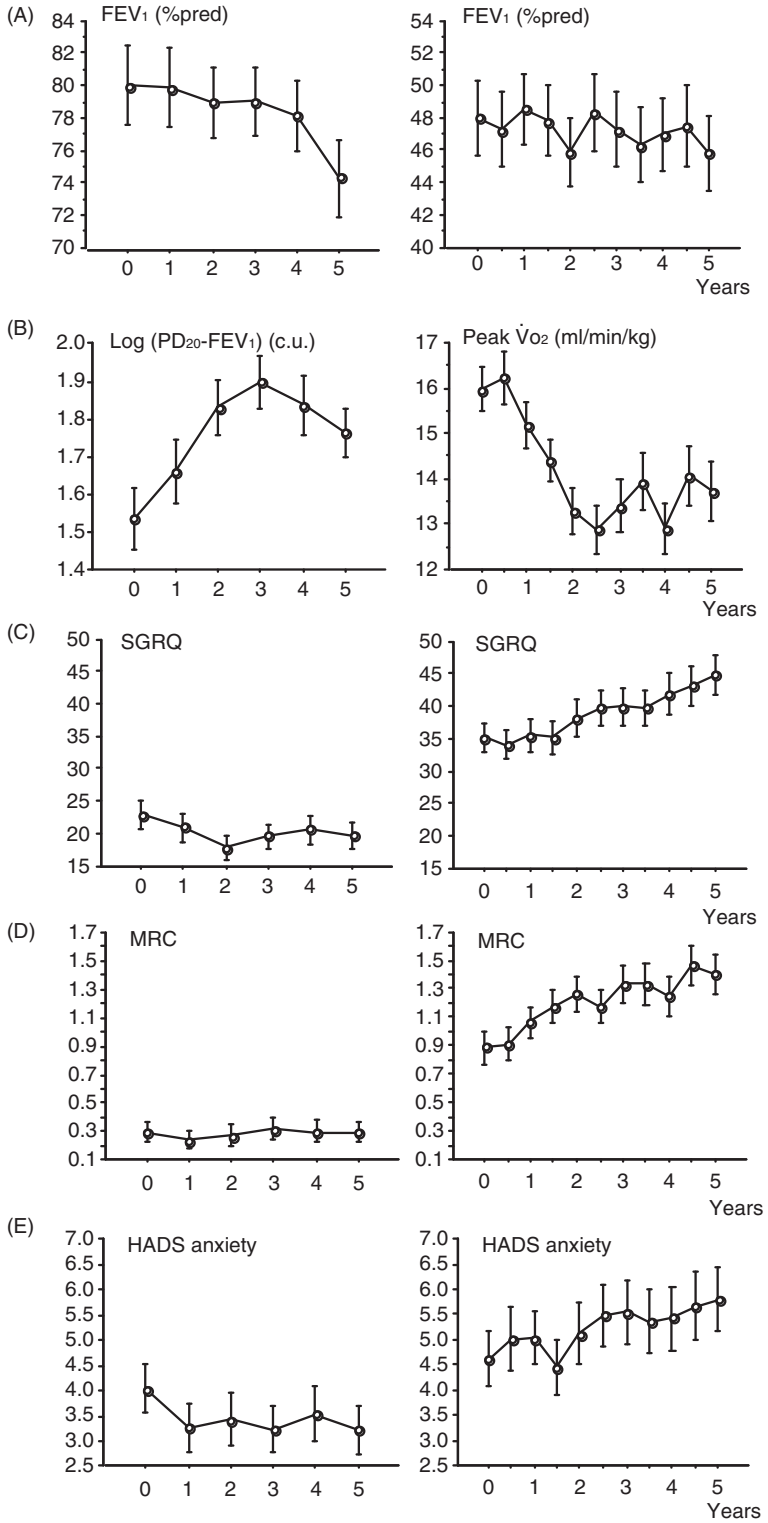

Fig. 1 Longitudinal changes in (**A**) FEV_1, (**B**) log (PD_{20}-FEV_1) and peak $\dot{V}O_2$, (**C**) SGRQ score, (**D**) MRC score, and (**E**) HADS anxiety score in 44 asthma patients (left-hand side) and 45 COPD patients (right-hand side) who had complete data sets with no missing data. Higher scores on the SGRQ, MRC and HADS indicate a worse status. Results are shown as mean ± SE. Adapted and modified from references 15, 16, 18 and 19.

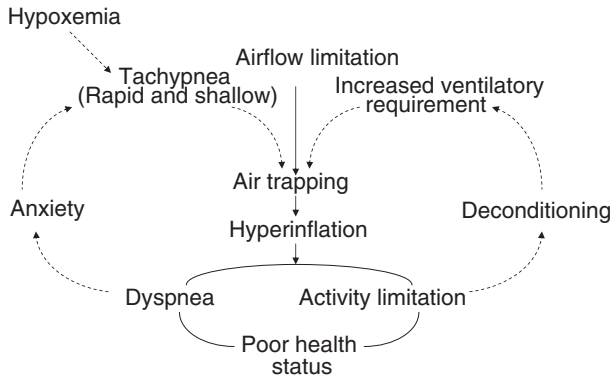

Fig. 2 Two vicious circle theory of air trapping linking pathophysiology and patient-reported outcomes in COPD. Adapted and modified from reference 61.

asthma, maximal or near-maximal Asthma Quality of Life Questionnaire (AQLQ) scores were attainable, and concluded that guideline-based asthma control is beneficial, facilitating greater improvements in health status.[28] Our study[15] also supports this conclusion by our finding that the St. George's Respiratory Questionnaire (SGRQ) score remains unchanged for 5 years as a result of guideline-based therapy of asthma patients (Table 2, Fig. 1). Of note, although airflow limitation progressed over time, health status was maintained at a high level. Periodic assessment of health status is recommended in the 2007 NAEPP guidelines,[24] and generic and asthma-specific validated instruments or simple questions are recommended for ongoing monitoring.[29]

In contrast, in patients with COPD, previous studies from the last 2 years,[63,64] using generic health status questionnaires such as the Nottingham Health Profile, or in patients with mild COPD[64,65] did not find significant changes in health status. However, disease severity of the enrolled patients, questionnaires used and study duration seemed to affect the long-term changes in health status. In the inhaled steroids in obstructive lung disease (ISOLDE) trial,[46] deterioration in health status was demonstrated in moderate to severe COPD patients over 3 years using the disease-specific questionnaire of the SGRQ and the generic one of the Medical Outcomes Study Short Form 36-Items Health Survey (SF-36). We have also shown that health status measured by SGRQ and Chronic Respiratory Disease Questionnaire (CRQ) deteriorated over 5 years independently of progression of airflow limitation (Table 2, Fig. 1).[19] Recent trials of new COPD therapies have of course included the long-term improvement of health status as outcomes.

LONG-TERM CHANGES IN DISABILITY

Both asthma and COPD can cause disability. Now, disability includes impairment, activity limitation and participation restriction.[66] In COPD, it is the major symptom. In contrast, asthma may cause disability both through dyspnea-induced exercise limitation and through the effects of the disease or the impact of the environment on the patients' ability to participate in the activities of their choice or play a full role in their family and society at large. Although there are no specific respiratory disability questionnaires, the Medical Research Council (MRC) dyspnea scale might be the simplest and most popular. Disability can be measured as a component of health status questionnaires.[66] The activity limitations domain of the AQLQ or the activity and impacts components of the SGRQ also reflect disability, as they are concerned with activity limitation and participation due to diseases.

In our study, the scores on MRC dyspnea scale remained unchanged for 5 years in patients with asthma (Table 2, Fig. 1). This holds true both in the activity and impacts components of the SGRQ.[15] In contrast, in the ISOLDE, the disability worsens over time in COPD using the SGRQ and the SF-36.[46] Also in our study, this was confirmed using the MRC, and activity and impacts components of the SGRQ in COPD over 5 years (Table 2, Fig. 1). In our previous analysis,[19] the change in the MRC score was weakly related to the progression in FEV_1 (r [correlation coefficient] = -0.37) and exercise capacity (r = -0.35). Cooper explains this progressing disability of COPD on the basis of the two vicious circles theory where air trapping and hyperinflation play a central role (Fig. 2).[61] The first vicious circle results from activity limitation, leading to deconditioning, then causing increased ventilatory requirement, a significant factor worsening air trapping and hyperinflation. COPD exacerbations modify this by worsening airflow limitation and causing hyperinflation. The second vicious circle revolves around increased respiratory rate and shortened exhalation time, leading to incomplete lung emptying, i.e. worsened air trapping and hyperinflation, exacerbated by anxiety or hypoxemia.

LONG-TERM PROGRESSION IN PSYCHOLOGICAL STATUS

Psychological disturbance such as anxiety and depression are often addressed both in studies of asthma and COPD.[67] They are reported to be significantly related to important clinical outcomes such as mortality or increased health care utilization. We assessed their 5-year longitudinal changes using the Hospital Anxiety and Depression Scale (HADS). In asthma, anxiety and depression scores remained unchanged over 5 years (Table 2, Fig. 1).[16] However, the baseline score significantly predicted subsequent changes, indicating that, in asthma, the psychological disturbance may progress not as a result of disease progression, but rather because of the individual's underlying psychological state.

This finding contrasted with the changes in the

HADS scores in COPD,[19] where anxiety and depression scores worsened over time, and were significantly associated with changes in health status scores or dyspnea scores. Psychological disturbance is very common especially in patients with severe COPD, and might be relatively easy to assess using validated questionnaires. These symptoms of anxiety or depression overlap with symptoms of COPD. Thus, paying attention to this outcome might also have beneficial effects on other aspects of COPD assessment.[68]

DIFFICULTIES IN LONG-TERM STUDIES

In analyzing long-term studies, how to deal with dropouts is a headache. In our long-term studies of asthma[15] and COPD,[19] 32% and 47% of the patients failed to attend the last 5-year evaluation. Especially in COPD, the sickest patients are reported to be the most likely to withdraw,[69] and differing rates of withdrawal can compromise primary outcomes in some large drug treatment studies.[70] Therefore, in statistical analyses, including dropout data is necessary so as not to underestimate the changes in the measurements. We used random effects models and estimated their changes.[71,72] However, the dropout reasons are complex, and one statistical method is not necessarily ideal for all studies, which makes such long-term studies difficult to perform, analyze and interpret.

Regarding the above-mentioned study-withdrawals, experiencing exacerbations is one of the main explanations for the differences in dropout rates.[73] Exacerbations can affect the long-term changes in measurements. Jones created a model of the relationship between COPD exacerbations and health status decline based on the ISOLDE data.[73,74] That model of health status changes over time described two types of patients, one with no exacerbations and one with a single exacerbation per year. Failure to recover only a very small amount of the acute effect was found to produce the cumulative effect implied by the faster rate of deterioration that occurs in patients who experience exacerbations only once per year, rather than in patients with no exacerbations.[74] In addition to exacerbations, comorbidities may affect long-term clinical changes in both asthma and COPD.[75] Thus, in analyzing longitudinal data, how to assess and include such confounders is also a big problem.

CONCLUSIONS

Here we review and compare multidimensional longitudinal changes in asthma and COPD. We found that, although asthma and COPD patients both suffer long-term progressive airflow limitation, overall disease progression seems to be very different, which highlights the differences between the two diseases. However, these attempts at analyzing and comparing long-term changes multidimensionally have just begun, and approaches could be improved in future by investigating more appropriate parameters or analytical models, which will clarify the progression of both diseases.

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