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Chronic obstructive pulmonary disease : new insights in morning symptoms and physical activity

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Summary



Chapter 1 provided an overview of chronic obstructive pulmonary disease (COPD) in general, morning symptoms in patients with COPD, physical activity in general and physical activity in COPD. The World Health Organisation (WHO) showed in their most recent report on the top ten causes of death that COPD is the third leading cause of death worldwide. There are no curative options for COPD yet. However, COPD is a treatable disease, whereby reduction of symptoms and prevention of acute exacerbations are seen as most important treatment goals. Symptoms can occur during each part of the day, whereby the morning is the most symptomatic part of the day. Exacerbations are defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a sudden worsening of respiratory symptoms that result in additional therapy. COPD can be treated with bronchodilators, inhaled corticosteroids and lifestyle advises such as smoking cessation, exercise training and sufficient physical activity. Physical activity is defined by the WHO as “any bodily movement produced by skeletal muscles that results in energy expenditure.” Unfortunately, physical inactivity is common in COPD. Physical inactivity in COPD is related to high mortality rates, lower quality of life, more dyspnoea and more previous exacerbations. Despite the mentioned treatment options, COPD frequently causes disability. More research is needed in factors that are related with poor outcomes in COPD, such as morning symptoms and physical inactivity. The aim of this thesis was to gain more knowledge about morning symptoms and physical activity in COPD in search of novel treatment options.

In **chapter 2**, the results of a systematic review on the current evidence of the association between morning symptoms and physical activity in patients with COPD were shown. Eight studies were included in this review. Across all COPD stages, 37.0 to 90.6% of patients reported a relation between more morning symptoms and lower self-reported physical activity. All included studies used questionnaires to assess physical activity.

Following the results of the systematic review, we designed the MOrning symptoms in-Depth observationAl Study (MODAS) to evaluate the association between morning symptoms, other patient characteristics and objectively measured physical activity. The MODAS was a single center cross-sectional study that was conducted at the Leiden University Medical Center (LUMC). 80 patients with moderate to very severe COPD were included. Morning symptoms were assessed with the PRO-Morning COPD symptoms questionnaire. Patients ranked the severity of dyspnoea, sputum production, chest tightness, wheezing, cough in the morning and limitations due to symptoms in the morning. The total score of the PRO-Morning COPD symptoms questionnaire ranged from 0 to 60. A low scores indicates less morning symptoms than a high score. Physical activity was objectively measured with an accelerometer that was worn on the lower back for seven consecutive days, 24-hour a day. An accelerometer is a device that measures acceleration in different axes. In **chapter 3**, we showed that patients had a mean morning symptom score of 19.7. We demonstrated

that patients with overall more symptomatic COPD have higher morning symptom scores. Therefore, we concluded that morning symptoms should be carefully assessed in addition to general COPD-specific questionnaires measuring symptoms, especially in those with more symptomatic COPD. Furthermore, lower health status, increased anxiety and depression, lower objectively measured physical activity and lower pulmonary function were associated with an increased morning symptom severity. These factors can be potential targets for intervention to improve morning symptoms. In **chapter 4**, we described physical activity patterns during the course of the day. Patients were divided into two groups of comparable size based on their morning symptom score: 41 patients had low a morning symptom score (total morning symptom score <17.0) and 39 patients had a high morning symptom score (total morning symptom score ≥ 17.0). We showed that patients with low morning symptom scores took more steps in the morning and afternoon than patients with high morning symptom scores. There was no significant difference in number of steps during the evening and night between patients with low and high morning symptoms scores. This was the first study that investigated activity patterns in patients with COPD during the course of the day, while taking morning symptoms into account. However, causality between morning symptoms and physical activity during different parts of the day could not be proven, due to the cross-sectional design of the study. We speculated that physical activity programs in the evening instead of the morning or afternoon might be helpful for COPD patients with morning symptoms, as the evening seems to be the most suitable part of the day for increasing physical activity.

Since physical inactivity is already present in mild and moderate COPD, we focussed in **chapter 5** on physical activity and associated characteristics in non-severe COPD patients. We used baseline data from the Netherlands Epidemiology of Obesity (NEO) study, a large population-based cohort study that was conducted from 2008 to 2012 in the greater area of Leiden, the Netherlands. Patients were included in the analyses if they had physician diagnosed COPD with an International Classification of Primary Care (ICPC) code for COPD (R95) or if patients met our criteria for newly diagnosed COPD. 323 patients were included, of which 77 met the criteria for physician diagnosed COPD and 246 met the criteria for newly diagnosed COPD. We showed that pulmonary function was positively associated with self-reported physical activity in patients with non-severe COPD. The presence of a physician diagnosed COPD and the use of nearly all pulmonary medication were associated with less self-reported physical activity. In this study, we found no association between increased symptoms in the morning and self-reported physical activity. We concluded that prospective intervention studies are needed to determine whether early pharmacological interventions and/or physical activity could slow down COPD progression in non-severe COPD. It is important to include patients with non-severe COPD in studies, because there is room for improvement in this specific patient group.

In **chapter 6**, we evaluated a novel systematic approach for patients with (suspected) asthma and COPD referred to secondary care pulmonology. Patients visited the outpatient clinic of the department of pulmonology at the LUMC. The systematic approach consisted of a predefined systematic diagnostic evaluation. An internet-based self-management support system was a non-obligatory part of the systematic approach. Outcomes were compared to usual care. 125 patients were included in the study, of which 22 (21.4%) were evaluated with the systematic approach. Patients who were evaluated with the systematic approach underwent more diagnostic tests when compared to usual care. There were no differences in the final diagnoses. This suggests that only a part of the diagnostic tests that were included in the systematic approach are regularly needed to make specific diagnosis. More lifestyle advice, symptom scores and individual care plans were electronically recorded. Furthermore, more patients were referred back to primary care when compared to usual care. We showed in our study that it is possible to use a systematic approach in secondary care pulmonology and that this stimulates physicians to record lifestyle advice, symptoms and individual care plans. Further research is needed to evaluate the impact of this systematic approach on disease control, quality of life, lifestyle changes and costs.

In **chapter 7**, we provided a general summary, we discussed hypotheses based on the studies in this thesis and gave directions for future research and clinical practice. We started the discussion with methodological considerations. We concluded that different study populations, morning symptom questionnaires, tools to assess physical activity and study designs contributed to differences in study outcomes. Thereafter, we discussed the question whether morning symptoms cause physical inactivity, or is it the other way around. There is a relation between morning symptoms and physical activity as shown in the MODAS and previous studies. We believe that it is twofold; morning symptoms can cause physical inactivity, but physical inactivity can cause morning symptoms as well. Yet, it is not possible to prove causality between morning symptoms and physical activity since prospective studies are lacking. Therefore, we have to search for (a combination of) interventions that target morning symptoms as well physical activity. Then, we discussed the question whether morning symptoms are a distinct phenotype in COPD. A phenotype in COPD has been defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes." We concluded that morning symptoms are related to other factors that are associated with poor outcomes in COPD. However, it is not possible yet to state that morning symptoms are a distinct phenotype in COPD since we should first know the effects of morning symptoms on long term. Thereafter, we discussed the question whether pulmonologists need a systematic approach to diagnose obstructive lung diseases and improve treatment plans. We concluded that a systematic approach is not necessary to make specific diagnoses, but it can be used as a tool to pay attention for patient characteristics that can be overlooked

in clinical practice. In this thesis we argued for the implementation of the assessment of morning symptoms and objectively measured physical activity in systematic approaches. The studies in this thesis highlighted the importance of morning symptoms and physical inactivity in patients with COPD. With our research, we gained new insights in morning symptoms and physical activity in COPD. These factors can be used as targets for therapy in future interventional studies. Combining interventions can potentially result in even greater positive effects, but this needs also to be studied in future studies.

LIST OF ABBREVIATIONS AND EXPLANATIONS

Accelerometer: a device that measures acceleration in different axes

COPD: chronic obstructive pulmonary disease

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICPC: International Classification of Primary Care

LUMC: Leiden University Medical Center

MODAS: MORning symptoms in-Depth observationAI Study

NEO study: Netherlands Epidemiology of Obesity study

Phenotype: "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes"

Physical activity: "any bodily movement produced by skeletal muscles that results in energy expenditure"

WHO: World Health Organisation

