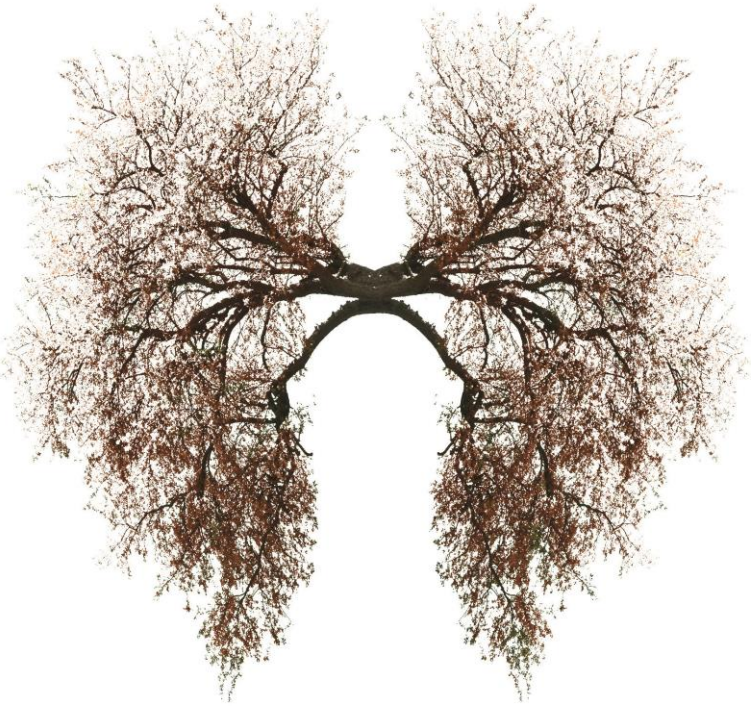
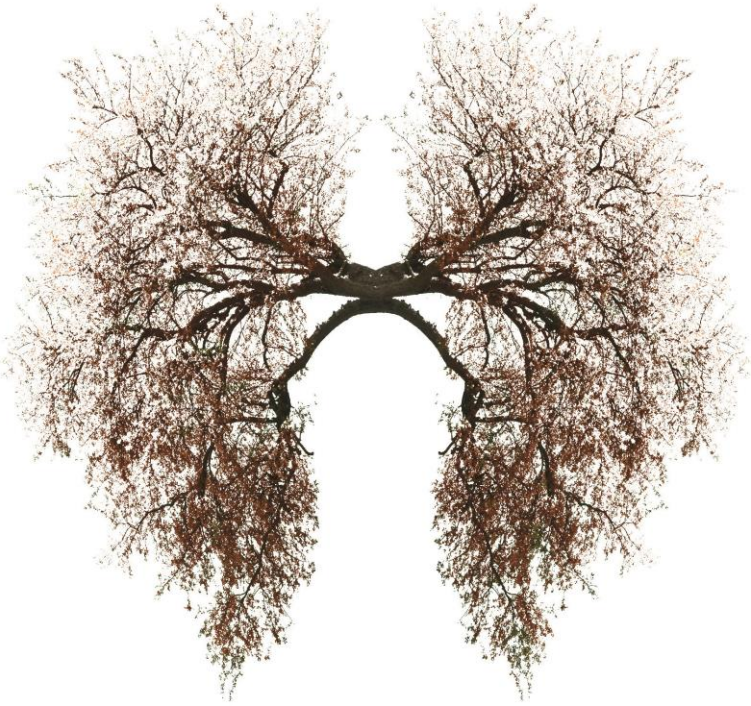
PART 2



The influence of comorbidity on physical therapy practice and outcome in patients with COPD

CHAPTER 3



Therapeutic consequences for physical therapy of comorbidity highly prevalent in COPD: a multi-case study

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ABSTRACT

Introduction

Comorbidities are prevalent in patients with chronic obstructive pulmonary disease (COPD), but current physical therapy guidelines do not incorporate clear actions related to multimorbidity. Comorbidity (e.g. diabetes mellitus) may require adaptations in intervention strategies, as comorbidity negatively affects treatment results of the index disease (e.g. COPD) or treatment for one disease (e.g. cardiopulmonary endurance training for COPD) may negatively interact with the treatment or natural course of a coexisting disease (e.g. severe osteoarthritis of the knee). Therefore, insight of considerations required when applying physical therapy in comorbid-COPD patients and suggestions to enhance and accelerate clinical reasoning may be helpful for health care providers to obtain optimal treatment and results.

Case description

Two case studies illustrated possible consequences of COPD (index disease) and comorbidity for physical therapy in a primary care setting. Avoidable and inescapable problems were both unfolded in different steps in the clinical decision-making process.

One very severe COPD patient (FEV_1=46% predicted, with chronic respiratory failure) with decompensated heart failure, using a beta-adrenergic blocker, demonstrated the danger of missing relevant information about a comorbid condition and related medication during the intake and its consequences for physical therapy. Another mild COPD patient (FEV_1=86% predicted) with multiple inter-related comorbidities showed the importance of monitoring outcomes of multiple diseases and adjustments to the plan-of care and interventions.

Discussion

Dealing with comorbidity in COPD management needs a patient-centred rather than a disease-oriented approach in order to obtain optimal treatment and results. Physical therapists should improve their skills and knowledge of high prevalent comorbidities, be fully informed, monitor more than COPD-outcomes alone and adequately adjust interventions. General practitioners and physicians can improve the level of information given in their referral of a patient to a physical therapist, by providing information on all coexisting diseases and related medication.

INTRODUCTION

In physical therapy, the impact of coexisting diseases other than the primary disease the patients are treated for (index disease), on the treatment and the outcome of an individual patient has become more recognised nowadays. Generally, comorbidity has two definitions. Firstly, it can indicate a medical condition existing simultaneously with but independently of another condition in a patient. Secondly, it can indicate a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient (e.g. due to shared risk factors like smoking).[1]

In patients with chronic obstructive pulmonary disease (COPD) a combination of both definitions seems to apply.[2] Although little is published in the area, comorbidity is highly prevalent in patients with COPD, with studies reporting 73-84% of patients with one or more comorbidities.[3,4] Cardiovascular disease is probably the most frequent comorbidity in COPD patients, because 16% have coronary artery disease and 12% have congestive heart failure. Other comorbidities that occur frequently in combination with COPD include asthma (26%), metabolic syndrome (13% have diabetes) and lung cancer. Additionally, both osteoporosis and depression are major comorbidities, although often under-diagnosed.[2,5]

Twenty-five percent of COPD patients have been treated by physical therapists (PTs) in The Netherlands in 2003.[6] Because comorbidities have a significant influence on prognosis,[2] they should be taken into account routinely. The impact of comorbidities should be clarified, given the implications that comorbidities have for clinical reasoning– the whole thinking and decision-making process by which PTs collect cues, process the information, come to an understanding of a patient' situation, plan and implement interventions, evaluate outcomes and reflect and act on the process.[7,8] Although, it is known that comorbidities are prevalent in COPD, current guidelines hardly reflect or address the multimorbidity issue. Moreover, it is often not feasible or sensible to combine different disease-specific self-contained guidelines in physical therapy, since treatment might interact negatively with the treatment or natural course of a coexisting disease (e.g. high-intensive cardiopulmonary endurance or strength training for COPD might not be possible if there is severe osteoarthritis of the knee[9] or might increase the risk for adverse events).[10]

The aim of this article is to illustrate consequences of COPD and comorbidity for physical therapy using two case examples. Insight in the requirements for physical therapy in comorbid-COPD patients and suggestions to enhance and accelerate clinical reasoning may be helpful for all health care providers to obtain optimal treatment and results.

AN ILLUSTRATION IN PHYSICAL THERAPY PRACTICE

The two individual cases presented, are participants in a cohort study of COPD patients treated in a primary care setting. The first case demonstrates the danger of missing a relevant comorbid condition and its consequences for physical therapy. The second case describes the complexity of interference between different comorbidities and COPD that a PT has to deal with in daily practice.

Case 1

"MB" is a 70-year-old retired woman diagnosed with COPD GOLD IV (diagnosed in 2008). The presenting sign that caused her to seek medical attention from her general practitioner (GP) included a-specific low back pain, which hampered her to walk for five consecutive minutes. She was referred for physical therapy for these complaints. The PT started with collecting initial data, generating patient-identified problems and examination (Table 3.1). Because the patient's primary goal was to be able to sit and walk for thirty minutes without experiencing back pain, the PT firstly aimed at reducing the low back pain and improving the activities of sitting and walking by physical therapy. After an exercise programme of eight weeks– including education, active mobilisation exercises for the lumbar spine and endurance training–goals were evaluated and reassessment took place. The a-specific low back pain was significantly decreased (Table 1). However, during endurance training the patient was not able to walk for more than six minutes continuously or twelve minutes with intervals (alternately walking and resting with intervals of 2-1-2 minutes). At the end of the training she did not complain about low back pain anymore, but about dyspnoea during exercise as the limiting factor in therapy (Table 3.1).

After reassessing outcomes and achievement of the short-term goals (pain relief and improving functions of sitting and walking), a new working hypothesis of reduction of dyspnoea due to COPD and improvement of exercise capacity and physical activity became the primary goal of interest. Again, the PT collected data and registered all coexisting diseases and medication with the help of the patient (Table 3.1). "MB" told the PT that she suffered from hypotension and depression and used a white/red-coloured anti-depressive drug. Apart from a pink-coloured vitamin pill, "MB" believed she used a white-coloured stomach protector. The physical therapy intervention consisted of exercise training twice a week (interval training for eight weeks until she managed to walk/cycle for more than ten consecutive minutes on a treadmill or ergometer) in combination with strength training (lower and upper extremities) and counselling.

Nine weeks after the start of the COPD training programme, "MB" started endurance treadmill/cycle training, while the PT monitored heart rate and SpO_2. Taking into account an intensity of 70% of the patient's predicted heart rate, "MB" was

encouraged to raise her pace (as her heart rate was around 90 beats per minute, i.e. 60% of her predicted heart rate). After 20 minutes signs of cyanosis appeared in "MB's" hands and spread directly to her lips and angina was present. When the PT measured SpO_2, a rapid drop until 78% forced the PT to stop the patient immediately for safety reasons.

Table 3.1 Collected data and assessment data of case 1.

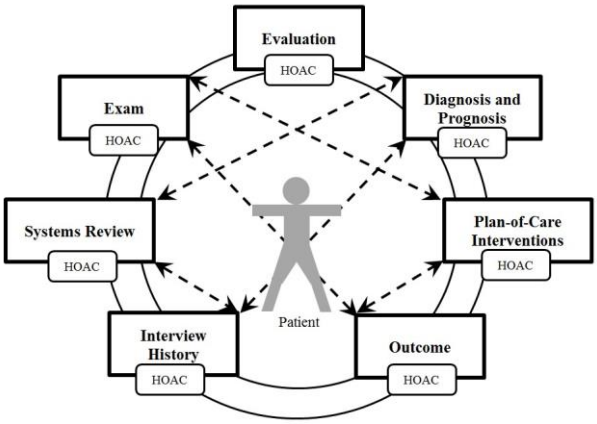
Assessment in time	Interview/history-taking	Related PT goals	Emerging problems during PT‡
0 weeks	A-specific low back pain, VAS=7/10 Walking <5 min	Reduce pain, VAS<7 Sit and walk >30 min	Non-reported dyspnoea overlooked; not all comorbidities and medication known to PT.
8 weeks	A-specific low back pain, VAS=1/10 Walking ≤6 min Dyspnoea, MRC=4/5		
8 weeks*	COPD GOLD IV - FEV_1/FVC=0.41 - FEV_1%pred=46% of predicted, chronic respiratory failure - Resting SpO_2=95% - Dyspnoea, MRC=4/5 - Walking ≤6 min - Nicotine addiction, 67.5 pack years - Physical activity, daily walking 15 min Depression Hypotension, 79/53 mmHg, resting heart rate =57 beats/min Medication: - Oral corticosteroids - Bronchodilators - Long term oxygen therapy (2.0 l/min) - Anti-depressive drug - Vitamin pill - Stomach protective drug	Reduce dyspnoea, MRC <4 Improve exercise capacity & physical activity in daily life, walk >30 min	Patient information as source for comorbidity and medication is not sufficient → information from referring physician and pharmacy needed!
9 weeks†	Exercise SpO_2=78% Decompensated heart failure: stomach protective drug = beta-adrenergic blocker!		Patient information on medication not checked by PT → pharmacy records or drug packing material.

*Reassessment at 8 weeks due to unattained goals (walk ≤6 min); †Serious adverse event during exercise happened at 9 weeks; ‡ Emerging problems during PT due to failures in the communica on and the clinical decision-making process.

Abbreviations: PT = Physical Therapist, VAS = Visual Analogue Scale, min = minute, MRC = Medical Research Council Dyspnoea scale, COPD = Chronic Obstructive Pulmonary Disease, GOLD IV = very severe COPD, FEV_1/FVC = Forced Expiratory Ratio, FEV_1%pred = % Forced Expiratory Volume in one second of predicted, SpO_2 = Transcutaneous Oxygen saturation.

Analysis of case 1

The PT adequately noticed that the index disease shifted from a-specific low back pain to COPD (the first hypothesis was not viable anymore and some steps in the hypothesis-oriented algorithm for clinicians (HOAC) were redone, Figure 3.1).[11] However, if the PT had followed the complete HOAC, the PT would not only have addressed the patient's goal (a-specific low back pain and related limitation in activities), but would also have searched for non-reported complaints by the patient and related viable goals.[11] The PT could then have taken the limitation in exercise capacity due to COPD into account and monitor more symptoms from the beginning (also dyspnoea and SpO_2). Moreover, the PT missed that the dyspnoea, which presented acutely during the treadmill exercise could also have been caused by comorbidity. "MB" had stable COPD in combination with hypotension, depression and decompensated heart failure (the white-coloured drug was actually a beta-adrenergic blocker). Therefore, limited increase in heart rate and acute presentation of increased dyspnoea on exertion was present (best measured with the modified Borg scale (0-10) in this case). The PT could have known these responses if the medication regimen had been checked from a more reliable source. This case illustrated that GP's and physicians should provide a PT with information on all coexisting diseases and related medication, when they refer a patient to a PT for only one complaint/disease. The PT could have collected the data more thoroughly by asking the patient's permission for a complete drug overview from the GP or pharmacist. Another option was to ask the patient to bring all packing material of used drugs. In patients with circulatory problems, saturation may decline in a late stage of the exercise. In this case the PT was not supposed to take heart rate as an indicator for exercise intensity. The physical therapy' intensity should have been individually tailored based on the results of a maximal cardiopulmonary exercise test (CPET) with gas analysis under monitoring of electrocardiography (ECG), SpO_2 and blood pressure. Unfortunately, this test was never executed in the hospital, whereas enough indicators for the necessity of a CPET were present, like angina and desaturation <90%.[12] A (minor) alternative method to tailor exercise intensity on the treadmill could have been using 70% of the walking speed during the six-minute walk test and controlling dyspnoea and fatigue with the Borg scale.



Abbreviations: HAOC = Hypothesis-Oriented Algorithm Clinicians. Adapted from Schenkman et al.[13]
Figure 3.1 Simplified overview of the unifying framework demonstrating the steps in the clinical decisionmaking process.

Case 2

"MK" is a 65-year-old retired woman diagnosed with COPD GOLD I in combination with asthma (diagnosed in 2005). Although she was treated by a PT for her COPD, after a thorough interview/ history-taking and systems review (HOAC, Figure 3.1),[13] the PT was aware of all other comorbidities (and medication) she had when she started with physical therapy (Table 3.2). "MK" participated in a graded exercise programme to reduce dyspnoea, improve mucus clearance, reach increased exercise capacity and improved physical activity in daily life. The programme consisted of endurance training on a treadmill (starting with an intensity of 60% of the walking speed during the six-minute walk test) and cycle-ergometry (starting with an intensity of 60% of maximum wattage based on the results of a CPET), peripheral muscle training of upper and lower extremities (starting with an intensity of 60% of maximal voluntary contraction), relaxation therapy, breathing exercises and lifestyle advises (stimulating exercise and following the diet by her dietician). After 12 weeks, re-evaluation showed that she had not lost weight and her dyspnoea remained (Table 3.2). "MK" experienced three severe COPD exacerbations in one year. State-of-the-art treatment was a 10-day dose of Prednisolone and this helped to reduce the infection. However, she gained weight as a result of the Prednisolone. The PT noticed "MK's" absence from the therapy several times a year. It appeared that "MK" fell a lot as a result of hypoglycaemia, caused by intentionally eating less food in order to lose weight. The PT referred her to her dietician. The PT measured blood pressure and blood glucose level at the start of every training session, but "MK" often experienced hypoglycaemia or hyperglycaemia leading to many interruptions during the training programme. According to the internal

medicine physician, her Diabetes remained unstable due to the combination of COPD and Diabetes Mellitus type 2 (DM II). Another problem during physical activity was her reduced work capacity and experienced pain resulting from osteoarthritis of her right knee. Total knee replacement, which was indicated by the severity of the osteoarthritis, was contraindicated due to "MK's" reduced peripheral blood flow (DM II) and pulmonary capacity (COPD) precluding anaesthesia. Therefore, the PT advised her to start swimming as a regular sport activity. However, after a few weeks "MK" was too afraid to continue, because of the risk of a hypoglycaemia during swimming. In the same year, an additional comorbidity appeared. "MK" showed depression and suicidal thoughts, increased by the disappointment that she could not undergo surgery for her right knee (Table 3.2). She visited a psychologist.

Table 3.2 Collected data and assessment data of case 2.

Assessment in time	Interview/history-taking	Related PT goals	Emerging problems during PT†
0 weeks	COPD GOLD I (2005) - FEV_1/FVC=0.69 - FEV_1%pred=86% of predicted - Dyspnoea, MRC=4/5 - Walking ≤10 min - Never smoked - Physical activity, 3x/week → not anymore Diabetes type 2 (1998) - No-proliferative retinopathy, lase eyesurgery in 2004 and 2011 - Sensory neuropathy in both feet Obesity, BMI=42.3 kg/m^2 (2008) Hypercholesterolemia (2008) Severe osteoarthritis right knee, Kellgren-Lawrence score=grade 4 (2008) Multiple falls per year	Reduce dyspnoea, MRC <4 Improve mucus clearance Improve exercise capacity and physical activity in daily life, walk >30 min	COPD exacerbations → prednisolone → weight gain → less eating → hypoglycaemia → multiple falls. Combination COPD & DM → instable DM → interruptions in training programme and physical activity in daily life. Physical activity ↑ → osteoarthritis ↑ → work capacity ↓ and pain ↑ in knee. Total knee replacement ↔ contraindicated by COPD & DM → depression.
12 weeks*	Dyspnoea due to COPD, MRC=4/5 3 COPD exacerbations/year Walking ≤15 min No weight loss, BMI=42.3>kg/m^2 Depression		

*Reassessment at 12 weeks; †Emerging problems during PT due to complex system interrelationships. Abbreviations: PT = Physical Therapist, COPD = Chronic Obstructive Pulmonary Disease, GOLD I = mild COPD, FEV_1/FVC = Forced Expiratory Ratio, FEV_1%pred = % Forced Expiratory Volume in one second of predicted, MRC = Medical Research Council Dyspnoea scale, min = minute, BMI = Body Mass Index, DM = Diabetes Mellitus.

Analysis of case 2

According to the guidelines, the physical therapy programme would suite a patient with COPD. However, the number, type and severity of comorbidities that this patient suffered from made the training programme very complex. Even in this case—where the patient was directly referred for PT as part of pulmonary rehabilitation and thorough history, assessment and evaluation revealed all present comorbidities— complex system interrelationships make it difficult for PTs to achieve the treatment goals. All comorbidities might have been responsible for the programme's reduced effectiveness. This case demonstrated that not only are patients with severe airflow limitation susceptible to comorbidities, but also patients with mild airflow limitation are susceptible to comorbidities.[14] The training programme had to be adjusted to the physical and mental state of the patient every week. Cognitive therapy in an earlier stage was probably useful, given her kinesiophobia in relations to her multimorbidity and inadequate interpretations of body signals. However, she refused to admit to her need for psychological help until she was informed about the contraindications for a total knee replacement. In line with the HOAC,[11] adjustments could be carried out at different steps in the clinical decision-making process: checking implementation of tactics (e.g. eating and medication intake before training), appropriateness of tactics used (e.g. reduction of intensity because increasing to 80% of maximal voluntary contraction was not possible), type of exercises (more cycling than walking), duration of a session (more resting and counselling were necessary concerning physical activity in daily life, eating and depressive feelings), plan strategy (e.g. interval instead of endurance training) or adjusting viable goals (e.g. cycling three times 10 minutes instead of 30 consecutive minutes in daily life).[11] The patient could only continue with the physical therapy programme, because the PT assessed and continued to monitor blood pressure, glucose level, reduced muscle capacity and pain in the right knee, and three-monthly questionnaires addressing depression and social inhibition, apart from the standard COPD outcomes like oxygen saturation, dyspnoea, fatigue and functional capacity. Moreover, multidisciplinary evaluations with the GP, dietician, psychologist, internal medicine physician and pulmonologist were necessary.

Weighing comorbidity in clinical reasoning

Once a PT knows all coexisting diseases and medication use of a patient, not often will this information be transformed into a useful overview. Researchers have developed indexes to standardise the weight or value of comorbid conditions. A review in 2003 concluded that the Charlson index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexisting Disease (ICED) and the Kaplan Index are valid an reliable methods to measure comorbidity or multimorbidity.[15] Although researchers have validated such lists, no one index is as yet recognised as a standard. The DO-IT task force (a group of researchers from four different universities in The Netherlands emerging from the

project Designing Optimal Interventions for physical Therapy, DO-IT) reached consensus on the use of the CIRS for physical therapy research and clinical practice, based on literature.[15-18] The CIRS registers co-occurrence of multiple chronic or acute diseases and medical conditions within one person in 13 categories and weights its severity (from 0 to 4). For the case examples in this article a CIRS score of 7 (case 1: cardiac=2; vascular=1; and respiratory=4) and a score of 10 (case 2: respiratory=2; ear/nose/throat/eye=1; musculoskeletal/skin=3; psychiatric=2; and endocrine=2) could be assigned.

DISCUSSION

Physical therapy, advices and clinimetric methods may contradict in patients with COPD and comorbidity (e.g. state-of-the-art therapy for COPD includes promotion of physical activity, but might not be possible if the patient suffers from severe osteoarthritis of the knee).[10] Both cases illustrated the importance of careful consideration of the impact of co-morbidities on the process of clinical reasoning in physical therapy in patients with COPD as the index disease. In the case examples of this article, three steps in the clinical decision-making process can be recognised where a PT should be increasingly aware regarding comorbidities of patients with COPD.[13] First, thorough identification of all coexisting diseases during physical therapy interview/history-taking and systems review is crucial in clinical reasoning (Figure 3.1). Additionally, PTs should recognise and explain to the patient that there might be other non-reported complaints, which can lead to viable treatment goals. For PTs it is a delicate task to acquire all information of all comorbid conditions of a patient and stay informed, as it is an on-going process. A PT should not always solely trust patients' knowledge of diseases and related medication, as case one clearly demonstrated. Physical therapists are advised to collect additional thorough information from the referring physician and pharmacy records. The CIRS may be of help in categorising the multi-morbid conditions and grading the severity. On the other hand, physicians should be aware that only referring a COPD patient for physical therapy is insufficient and additional information on comorbidities, like medication use, severity, complications and any other cues that may hamper clinical reasoning is necessary. Comparably, guidelines on acute lower respiratory tract infections recommend restrictive use of antibiotics and therefore GPs need to know the patients' relevant comorbid conditions.[19] A tool to evaluate the patients' comorbidities, like the CIRS, should be part of a request form from a referring physician, similar to other standardised tools to evaluate the patients' health (e.g. lung functions, MRC or the Clinical COPD Questionnaire).[20] Importantly, a PT does not only have to be familiar with the name of drug treatments used by the patient for comorbidities, but needs to know whether the drug components influence the relation between physical activity and

exercise physiology (heart rate response, glycaemic response or peripheral blood flow). In most COPD patients (all with desaturation >4% during exercise) a CPET is needed for safety issues, but is also useful for establishing the limiting factors of the patient (pulmonary, cardiovascular, diffusion, peripheral or mental factors).[21] In the case of absence of a CPET, a PT is advised to request such a test from the referring physician.[21] Even better would be to make a CPET part of the usual-care policy in COPD patients who are referred for an exercise training intervention, because of the major benefits regarding safety considerations in PT practices and effectiveness of the training programme (i.e. determination exercise intensity).

Second, monitoring outcomes of the index disease and outcomes of comorbidities (exam, evaluation and outcome) are a crucial step in treating chronic conditions in a physical therapy practice (Figure 3.1). In every training session, depending on the comorbidities extensive monitoring of the patient is needed (such as measuring pain and impairments in activities due to osteoarthritis of the hip or knee, measuring blood pressure in hypertensive patients or glucose level in patients with DM). Moreover, one should be alert to hidden comorbidities, as important comorbidities in COPD patients can be easily overlooked because their symptoms are also associated with COPD (e.g. heart failure and lung cancer (dyspnoea and weight loss) or depression (fatigue and reduced physical activity)).[2] Physical therapists can play a key role in recognizing comorbid symptoms in patients, as they observe patients for long periods during exercise training. It is important that a PT refers a patient back to the GP when a comorbid condition is suspected. Good monitoring of comorbidity is a prerequisite for successful physical therapy in COPD. Not only has physical therapy proven to be effective in improving health related quality of life, improving exercise capacity and reducing the risk of mortality in COPD patients[22] and in COPD patients with comorbidities,[23] physical therapy (in term of increasing physical activity) may also play a role in reducing the risk of comorbidity.[2]

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Third, monitoring may reveal the need for adjustments of the plan-of-care and interventions (Figure 3.1) due to comorbidities regarding the FITT factors (Frequency, Intensity, Time and Type of training). Current guidelines for PTs treating COPD, for example, do not stress very clearly how to handle a COPD patient with DM II or how to treat a patient with COPD, cardiac failure, osteoarthritis and depression.[24] These guidelines largely depend on scientific evidence for treatments and lifestyle advice. However, the underlying scientific studies are mostly executed in homogenous study populations, as comorbidity is treated as an exclusion or correction factor due to methodological difficulties.[25] Therefore, not a disease but the individual patient needs to be the starting point in physical therapy, as no other patient has the exact same comorbidities and the same drug and other medical treatments.

Generally speaking, current literature suggests that the importance of comorbidities should not alter COPD treatment and vice versa; comorbidities should be treated as if the

patient did not have COPD.[2] From a physical therapists' perspective, this recommendation is insufficient and it is often not possible to execute, as is the case with disease-specific guidelines. Dealing with comorbidity needs a patient-centred rather than a disease-oriented approach.[10] For physical therapy this means a qualitative improvement in skills and knowledge (PTs need to combine different medical areas in order to meet comorbidity knowledge requirements). In patients where the index disease is related to the comorbidity, with or without a mutual risk factor, disease-specific guidelines can be used to direct management,[10] as long as all applicable guidelines are laid side by side. In patients with coexisting chronic morbidity without any known causal relation to the index disease, problems with disease-specific guidelines emerge, especially in aging-related diseases when comorbidity is linked to frailty.[26] In general, the PT curriculum in The Netherlands does not yet underscore the need for a more advanced understanding of complex system interrelationships regarding multiple-morbidities. The curriculum can place more emphasis on the possible effects of comorbidities on exercise physiology and related pharmacotherapy. In the future, guidelines for PTs, where physical therapy treatment and monitoring of outcomes of COPD is guided on the basis of the coexistence of different comorbidities therapy, may be desirable. Therefore, research is needed where comorbidity is not seen as an exclusion or correction factor but as a variable of interest.

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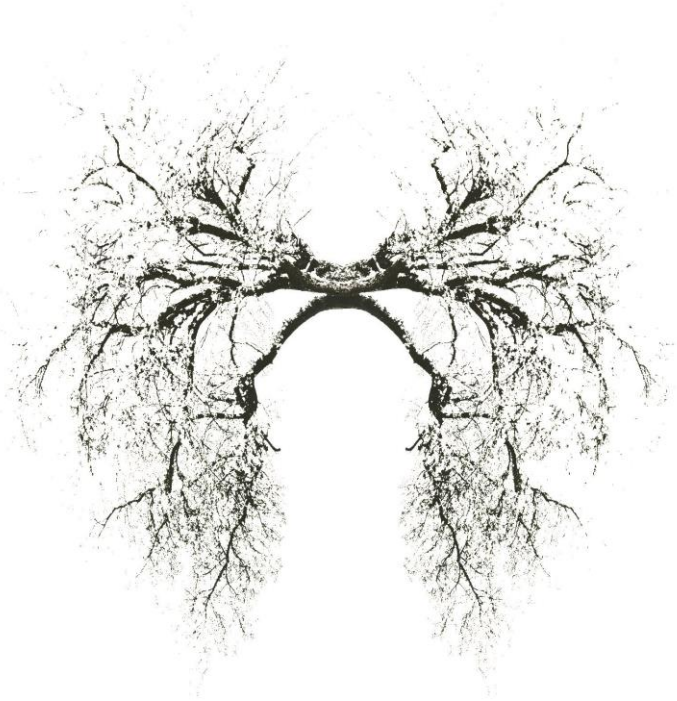
CHAPTER 4



Influence of comorbidity on improvements of functional exercise capacity in patients with COPD receiving physical therapy

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Submitted

ABSTRACT

Introduction
Comorbidities are common in patients with COPD. Although, comorbidities do not preclude access to rehabilitation, they seem to affect physical therapy outcomes in patients with COPD. However, the extent to which comorbidity impacts on physical therapy outcomes over time remains unclear, especially in

primary care. This study investigates the influence of comorbidity on the progression of change in functional exercise capacity during physical therapy in patients with COPD in a primary care setting.

Methods
A prospective cohort study included patients receiving long-term guideline-directed physical therapy for COPD. Functional exercise capacity was measured by six-minute walk distance (6MWD). Comorbidity was registered with the Cumulative Illness Rating Scale (CIRS). To study the influence of comorbidities on repeated assessments of 6MWD over time random slope mixed model analyses with an AR(1) correlations structure was used.

Results
In 158 patients, GOLD I-IV, 1301 measurements of 6MWD were analysed. Median treatment duration was 27 months (*CI*:7-65). Comorbid conditions in the categories 'endocrine, metabolic, lymphatic, immune', 'cardiovascular' and 'muscle, bone, skin' were most prevalent. With every additional comorbid condition the 6MWD was significantly lower at the start of physical therapy (23m, *CI*:31.49-13.91). Besides, with every extra condition the progression of 6MWD over time decreased with 7m in 1,000 days (*CI*:13.21-0.72) during physical therapy. By analysing each disease category individually for its impact on the 6MWD, three different profiles were noted. Corrected for the confounding influence of the other fixed comorbidity variables, cardiac, hepatic and psychiatric disease had the strongest negative interactions with time, with a significant correlation of sequential 6MWT measurements (r=0.33, SE=0.045).

Conclusion
Both reduced starting point and reduced improvements of functional exercise capacity by comorbidity in patients with COPD receiving physical therapy were statistically significant and clinically meaningful. This is the first long-term follow-up study in COPD to illustrate the influence of comorbidity on exercise capacity during primary care physical therapy within prognostic profiles.

INTRODUCTION

Comorbidities are highly prevalent in patients with COPD,[1] increase with age and disease severity[2,3] and are more prevalent in men than in women.[3,4] Given that studies report 73-84% of patients having one or more comorbidities,[5,6] a patient with COPD without any comorbid condition is a rarity.[7] Although the prevalence of each single comorbidity varies across studies,[8] cardiovascular disease is a major comorbidity in patients with COPD, both in frequency as well as impact.[9] Also osteoporosis and depression, while often under-diagnosed, are major comorbidities given their association with poor health status and prognosis.[9] Other comorbid conditions in patients with COPD are skeletal muscle dysfunction, metabolic syndrome, anxiety and lung cancer.[9-11]

Comorbidities can occur in patients with mild, moderate and severe airway obstruction, significantly increase the overall burden of disease in individual patients[9] and may predict mortality in COPD.[3,12,13] Therefore, healthcare professionals should actively take comorbidities into account.[7] However, how comorbidity should be taken into account is unclear, both concerning therapeutic adaptations to be made and prognostic profiling of patients.[14]

4

Previous studies already demonstrated that physical exercise training in pulmonary rehabilitation (PR)[9] has important benefits for patients, such as improved exercise capacity and health-related quality of life.[15-17] In accordance with McCarthy et al. (2015) physical therapy qualifies as PR, since exercise training for at least four weeks with or without education and/or psychological support is included.[16] The monodisease character of current clinical guidelines demonstrates the difficulty of protocollised care for patients with comorbidities besides the index disease.[18,19] For physical therapists the presence of comorbidity often implies that their guidelinedirected treatment must be adjusted in terms of content, duration, frequency and intensity.[9,20] Thus, physical therapists should offer an individually-tailored programme that tries to match the physical therapy clinical guidelines for COPD and other comorbid conditions in order to obtain optimal treatment and results.[7,14]

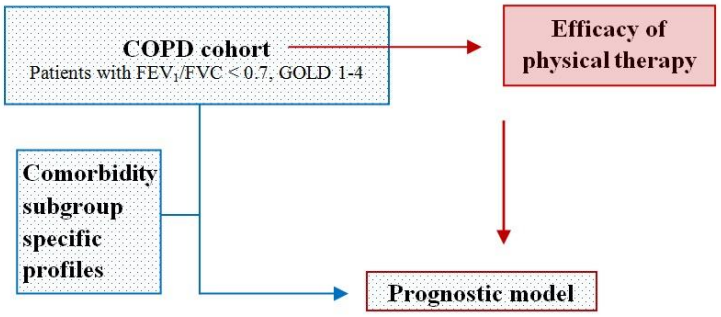
Although, the presence of comorbidities does not preclude access to rehabilitation,[11] comorbidities have been suggested to affect outcomes of PR in patients with COPD, but conflicting results have been found so far.[21] A cross-sectional study concluded that the distance walked by the patients decreased with increasing comorbidity count.[22] A large retrospective single-centre study found that higher scores on the Charlson Index and the presence of metabolic and heart diseases reduced the probability to improve outcomes of rehabilitation (exercise tolerance (six-minute walk distance (6MWD)) and health-related quality of life (St George's Respiratory Questionnaire).[11] The same research group showed in a subsequent prospective study that only the presence of osteoporosis was associated with a poorer 6MWD.[23] In contrast with the previous studies, two retrospective and a small prospective cohort study established that

responders in exercise capacity (6MWD) were more likely to have metabolic disease,[24,25] or a higher body mass index.[26] A cohort study found respiratory failure, ischemic heart disease and anxiety/depression to negatively influence improvement in health status and dyspnoea, but did not find comorbidity as an independent predictor of response in 6MWD.[27] Apart from the conflicting results, these previous studies demonstrate three important points. First, treatment duration along with the period to establish comorbidities' influence is relatively short. The length of the supervised exercise programmes was unclear in most studies, but seemed to range between 2-8 weeks. Whereas comorbid conditions progress slowly, like cor pulmonale,[28] and their influence on rehabilitation outcomes is likely to manifest over the long-term rather than a few weeks. Second, populations studied are patients with COPD who received rehabilitation in secondary or tertiary centers. The population rehabilitating in primary care is especially interesting to study because they more closely reflect the general COPD population, increasing the external validity of the results. Patients who rehabilitate at primary care centers are not exclusively patients referred by a pulmonologist, but are a natural mixture of patients (GOLD I-IV) either referred by a general practitioner or pulmonologist or patients who enter rehabilitation by direct access to physical therapy.[29] Third, the number of comorbid conditions involved was mostly small (the presence of musculoskeletal, cardiac, metabolic diseases and anxiety/depression). One recent prospective study included a larger number, 13 comorbidities and 5 comorbidity clusters at baseline, and concluded that comorbidity did not, in general, influenced the likelihood of having a clinically meaningful change in exercise capacity (6MWD). However, it concerned only an 8 to14-week therapy programme again in a tertiary setting.[8] The impact of comorbidity on long-term (14 weeks>) modification of functional exercise capacity in COPD patients following PR like physical therapy in primary care, however, remains unclear.[21] Moreover, most studies have analysed the influence of comorbidity on exercise capacity cross-sectionally by multiple logistic regression analyses,[21,25,26] instead of longitudinally including multiple measurement moments of exercise capacity during rehabilitation. Therefore, the aim of the present study was to investigate the influence of single comorbidities as well as clusters of comorbidity on ongoing long-term changes in functional exercise capacity (6MWD) during physical therapy in patients with COPD in a primary care setting.

METHODS

Study design

A dynamic prospective cohort study was conducted from January 2009 to January 2016, to study the influence of comorbidity on functional exercise capacity during physical therapy within prognostic profiles (Figure 4.1).



Abbreviations: COPD = Chronic Obstructive Pulmonary Disease, FEV1 = Forced Expiratory Volume in one second*, FVC = Forced Vital Capacity*, GOLD = the Global Initiative for Chronic Obstructive Lung Disease. *All lung functions are post-bronchodilator values.

Figure 4.1 Framework of the study.

Study population

Patients who were treated for COPD in a primary care physical therapy practice in the south of The Netherlands were included in the cohort according to the eligibility criteria in Table 4.1. The only exclusion criterion was a condition that would prevent the patient from participating in the therapeutic process and executing the 6MWT. Informed consent was obtained prior to inclusion. This study was embedded in a larger study approved by the ethics committee of Maastricht University/Hospital (NL28718.068.09). Detailed information of this overarching study was published earlier.[30]

Table 4.1 Eligibility criteria for patients with COPD to enter the cohort.

A general practitioner/pulmonologist diagnosed COPD in GOLD stage 1, 2, 3 or 4 (confirmed by a postbronchodilator $FEV_1/FVC < 0.7$).
Having an adequate and optimal medication (inhalation) regimen.
Competent to speak and understand the Dutch language.

Abbreviations: COPD = chronic obstructive pulmonary disease, GOLD stages: II = moderate COPD, FEV_1/FVC <0.7 and 50% ≤FEV_1<80% of predicted; III = severe COPD, FEV_1/FVC <0.7 and 30% ≤ FEV_1<50% of predicted; IV = very severe COPD, FEV_1/FVC <0.7 and FEV_1<30% of predicted *or* FEV_1<50% of predicted plus chronic respiratory failure, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second.

Physical therapy intervention

The entire cohort received usual physical therapy care for patients with COPD in The Netherlands, besides multidisciplinary COPD care; at least being monitored by a general practitioner or pulmonologist and mostly taking medication. The physical therapy programme was based on the guidelines of the Royal Dutch Society for Physical Therapy (KNGF) for COPD,[18] including an exercise programme with whole body endurance and/or interval exercise training, as well as peripheral muscle strength training. When indicated, the therapy included respiratory muscle training and breathing exercises. Patients in the cohort continuously followed physical

therapy in a primary care practice for one hour, twice a week (maintenance programme). The programme lasted as long as the patient was willing to participate and as long as their referring physician prolonged the physical therapy indication. In addition, patients were encouraged to increase their total physical activity in daily life. At least 30 minutes of moderately intense physical activity on at least five days a week was the considered current recommended level by the Dutch Standard for Healthy Exercise (NNGB). For non-active people, with or without physical limitations, all extra physical exercise was considered significant, regardless of intensity, duration, frequency and type.[18,31]

Outcome measures

The outcome of interest was functional exercise capacity, measured by the standardised six-minute walk test (6MWT).[32] The 6MWT is recommended as a reliable, valid, and responsive test to measure functional exercise capacity in adults with COPD.[32-34] Guidelines do not specify how often the six-minute walk distance (6MWD) should be measured during rehabilitation in patients with COPD.[18] Therefore, all tests conducted during the period 2009-2016 were taken into account. The 6MWD was generally measured every 12 weeks. So, the total number of 6MWD measurements taken into account depended on the duration that an individual patient followed physical therapy in the cohort.

Comorbidity at the start of physical therapy was recorded with the Cumulative Illness Rating Scale (CIRS), a comorbidity measure that includes all possible disease categories

and severity.[35] Thus, the CIRS allows a more in depth analysis of comorbidity in COPD than other outcome measures,[36] while differentiating between 13 organ systems
(Table 4.2).

Table 4.2 The Cumulative Illness Rating Scale (CIRS)[20, 35, 36] with examples of how disease conditions were placed in the categories in this study.

Cardio-vascular-respiratory system 1. cardiac diseases *(e.g. myocardial infarction)* 2. vascular diseases *(e.g. hypertension)* 3. respiratory diseases *(e.g. COPD, asthma)* 4. eye, ear, nose, throat and larynx diseases *(e.g. impaired vision, deafness)* Gastrointestinal system 5. diseases of the upper gastrointestinal system *(e.g. ulcer)* diseases of the lower gastrointestinal system (*e.g. Crohn's disease*) 6. hepatic diseases *(e.g. hepatitis)* Genitourinary system 7. renal diseases *(e.g. renal insufficiency)* 8. other genitourinary diseases *(e.g. incontinence)* Musculo-skeletal-integumentary system 9. muscle, bone and skin diseases *(e.g. fibromyalgia, osteoarthritis, rheumatoid arthritis, decubitus ulcer, eczema)* Neuropsychiatric system 10. neurological diseases *(e.g. Parkinson's disease, Cerebra Vascular Accident, epilepsy, sleep apnoea, migraine)* 11. psychiatric diseases *(depression, anxiety disorder, psychosis, dementia, addiction, stress or insomnia for which specific drugs is prescribed)* General system 12. endocrine and metabolic diseases and lymphatic/immune system *(e.g. Diabetes Mellitus, obesity,*	All systems were weighted from 0-4: 0 none 1 mild – does not or little interfere with normal activity; prognosis is excellent 2 moderate – interferes with normal activity; treatment is needed; prognosis is good 3 severe – is disabling, treatment is urgently needed; prognosis is good 4 extremely severe – lifethreatening; treatment is urgent or of no avail; prognosis is grave

hypercholesterolemia, hypo/hyperthyroid, malignancy)

Every comorbid condition of a patient, based on available information by the patient and (referring) physician, was assigned to one of the categorical organ systems by the physical therapist and checked by the researcher, in accordance with the measurement protocol.[20,36] A training (guideline, explanation and case study) was provided to the physical therapists who filled out the CIRS. The CIRS in this study covers an active history of comorbidity, meaning that comorbid conditions older than 5 years that do not interfere with normal activities in the patients' daily life or did not involve medical treatment were scored zero.[20] The researcher performed the scoring on the different

categories. Weighting the severity of the comorbid condition within each category (0 (none) to 4 (extremely severe)) was based on the information provided by the patient and physical therapist.[20,36]

Besides comorbidities, the following characteristics of each cohort patient were registered at the start of physical therapy: sex, age, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), GOLD stage, smoking status (never smoked, ex-smoker or smoker), smoking history (pack years), exacerbation history (patientreported number of treated events in the previous year), and disease-specific healthrelated quality of life (Clinical COPD Questionnaire (CCQ) total, symptom, mental health and functional scores)[18]. All data was measured by the attending physical therapists by standardised procedures, monitored by the researchers. The researcher continuously collected all data from the patient files in the physical therapy practices, including medical information in the patient files available in the practice.

Data analysis

Descriptive variables were presented quantitatively as means (± standard deviation) or medians (25^{th}-75^{th} percentiles) for the continuous variables, depending on the data distribution; as percentages for the dichotomous variables gender and the presence (0/1) of the different disease categories; and as categorical variables for GOLD stage, smoking status and morbidity count.

In the case of absence of information on comorbidity (CIRS) or absence of any 6MWT data, the patient was case-wise deleted. Because all patients suffered from COPD and this disease was considered the index disease, CIRS category #3 (respiratory diseases) was excluded from the analyses. Indices of comorbidity that were derived from the CIRS were the presence (0/1) of the different disease categories, morbidity count (the number of comorbid diseases on which the patients scored 1 or higher) and the severity index (sum score on the CIRS: 0-48 divided by morbidity count).

In the analyses the morbidity count and the presence (0/1) of the different disease categories at the start of physical therapy were involved. The severity index was considered a secondary outcome.

Profiles of different comorbidities were linked to the clinical outcome 6MWD and their prognostic value was revealed by a special linear mixed model: the random slope model. A polynomial model was abandoned in favour of a linear random slope model. The 6MWD observations of each patient were considered as a separate cluster. The relations of these distances with time-since-start-of-the-programme were modelled as a patient specific linear relation, hence the random slope model. The AR(1) correlation structure (sequential measurements represented by an autocorrelation structure of order 1) was used.[37]

The analyses were performed in three phases.
Phase 1 included a random slope model with X_{total} – the absolute number of comorbidities – in order to relate the morbidity count to the 6MWD. A graph was presented with estimates of fixed effects for those patients without any comorbidity, for those patients with one comorbid condition, for those with two comorbid conditions, etcetera.
Phase 2 involved the effect of the presence (0/1) of each different disease category on 6MWD using a random slope model. Each disease category was analysed individually for its impact on the 6MWD, resulting in different profiles. Each profile represented a different kind of influence of the specific comorbid condition on 6MWD in patients with COPD with a specific comorbid condition compared to patients with COPD without that specific comorbid condition. However, these models were not corrected for the confounding influence of the other comorbidities and not corrected for the influence by unbalanced distribution in other disease categories between the group that has the specific comorbid condition and the group that is without the specific comorbid condition.

Finally, phase 3 gave the optimal random slope model that contains a combination of comorbid diseases to predict 6MWD. Taking into account all twelve different disease categories 2^12 = 4096 disease combinations were possible. It was not feasible to include this large number of disease combinations in a model. Therefore, a random slope model was used with backward stepwise regression analysis starting with all twelve comorbidities (X's) and including all twelve X*time interaction terms. The best model was adjusted for undue influence of other fixed comorbidity variables.

RESULTS

One hundred and fifty-nine patients were monitored in 18 primary care physical therapy practices in the south of The Netherlands. In one patient the outcome of interest was not measured because this person refused to execute the 6MWT. Outcomes were presented over a large variety in the numbers of observed 6MWDs in patients. Data density was most optimal over a period of the first 5.5 years after the start of physical therapy, since most patients ended their therapy after this time (91.6 percentile). Therefore data was shown in graphs over a maximum period of 2000 days. All patients were continuously following the physical therapy intervention at least twice a week for one hour, with median treatment duration of 27 months (25th-75th percentiles: 7 to 65 months). All patients received a combination of, at least, endurance or interval exercise training and peripheral muscle strength training with a training intensity of 60-80% of 6MWT or one-repetition maximum, along with ratings of perceived exertion and dyspnoea of five and higher on the modified

Borg-scale (0-10). In 158 patients 1301 measurements of the 6MWT were present; varying from one 6MWT to 36 6MWTs per person.

Table 4.3 presents demographic and clinical patient characteristics. Missing data in patient characteristics were considered in this table (n=14 missing FEV_1/FVC; n=15 missing FEV_1; n=4 missing GOLD stage; n=11 missing smoking status; n=57 missing smoking history; n=48 missing exacerbations history; and n=10 missing disease-specific health-related quality of life). All continuous variables were distributed normally (*z*-scores<3.29), except for smoking and exacerbation history, CCQ data and severity index that showed a positively skewed and leptokurtic distribution (*z*-scores>3.29).

Table 4.3 Baseline Characteristics of the subjects (n=158)

Characteristic	At the start of PT
Gender, *n* male (%)	84 (53)
Age *(yr),* mean (SD)	62.3 (8.8)
FEV1 (%pred), mean (SD)	60.0 (18.7)
FEV_1/FVC *(%)*, mean (SD)	50.6 (12.5)
GOLD Stage, *n* (%)	
I	21 (14)
II	79 (51)
III	41 (27)
IV	13 (8)
Smoking status, *n* (%)	
Never smoked	19 (13)
Ex-smoker	94 (64)
Current smoker	34 (23)
Smoking history *(pack-yr)*, median (25^{th}-75^{th} percentiles)	39.5 (20.7-57.3)#
Exacerbation frequency over 12m-retrospectively, median (25^{th}-75^{th} percentiles)	1.0 (0.0-2.0)#
CCQ total, median (25^{th}-75^{th} percentiles)	2.1 (1.5-2.9)#
CCQ symptom	2.5 (1.8-3.5)#
CCQ mental health	1.0 (1.0-2.0)#
CCQ functional scores	2.25 (1.3-3.3)#
Morbidity count, *n* (%)	
0	18 (11)
1	31 (20)
2	29 (18)
3	33 (21)
4	26 (17)
5	13 (8)
≥ 6	8 (5)

Abbreviations: PT = physical therapy, FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; GOLD = the Global Initiative for Chronic Obstructive Lung Disease, GOLD stages: II = moderate COPD, FEV_1/FVC <0.7 and 50% ≤ FEV_1 <80% of predicted; III = severe COPD, FEV_1/FVC <0.7 and 30% ≤ FEV_1 <50% of predicted; IV = very severe COPD, FEV_1/FVC <0.7 and FEV_1 <30% of predicted *or* FEV_1 <50% of predicted plus chronic respiratory failure, CCQ = Clinical COPD Questionnaire. * p<0.05, # non-normal distribution.

In all 158 patients comorbidities were registered at the start of physical therapy with an average morbidity count of 2.6 (1.7) and a median severity index of 2.0 (2.0-2.0). Figure 4.2 shows the presence of the different disease categories in 158 patients at the start of physical therapy. Comorbid conditions in the category endocrine, metabolic, lymphatic and immune system and cardiovascular conditions in a combined category were the most common ailments in all patients, closely followed by muscle, bone and skin diseases. Psychiatric and vascular diseases were the third and fourth most prevalent categories, before cardiac and eye, ear, nose, throat and larynx diseases. All other categories had a lower prevalence.

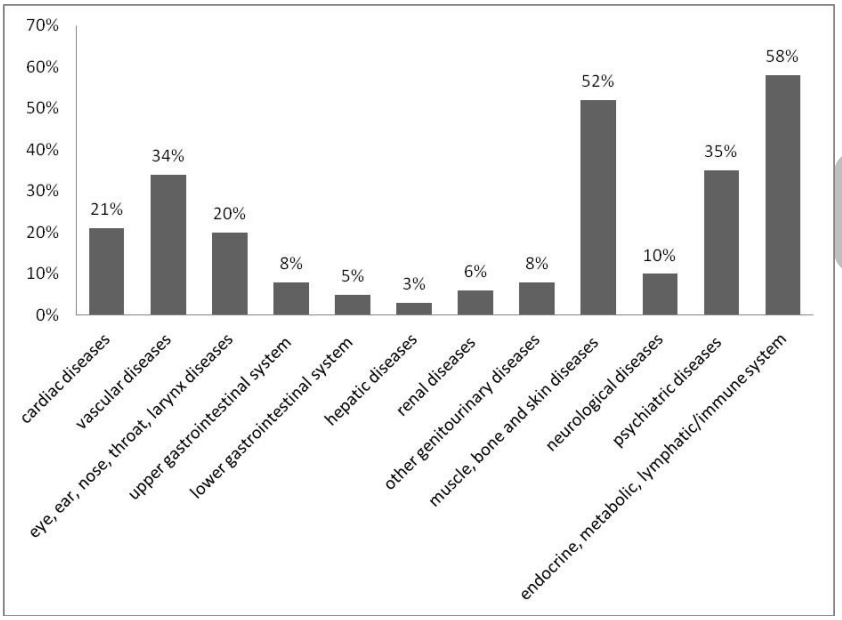


Figure 4.2 Presence of comorbid conditions in the cohort at the start of physical therapy.

Phase 1: Morbidity count, despite the disease category, had a significant twofold influence on 6MWD in patients receiving physical therapy. Estimates of fixed effects showed that with every additional comorbid condition the 6MWD was 23 metres lower at the start of physical therapy compared to a person with one less comorbid condition (-22.70 (*95%CI*: -31.49 to -13.91), $t(159)= -5.10$, $p<0.01$). Besides, the progression of 6MWD in time decreased with 7 metres in 1,000 days (-7.00 (*95%CI*: -13.21 to -0.72), $t(56)= -2.23$, $p=0.029$).
Figure 4.3 shows the influence of comorbidity count on the 6MWD over a total of 5.5 years (2,000 days). In this figure it can be seen that the starting level on the 6MWT

in patients with COPD without any comorbidity was on average 527 metres (*95%CI*: 500 to 554) and they more or less increased gradually with 12 metres (12.00 (*95%CI*: -9.28 to 32.46) per 1,000 days during physical therapy. This positive progression is reduced to 5 metres in patients with COPD and one comorbid condition, to -2 metres for those with two comorbid conditions, to -9 metres for those with three comorbid conditions, etcetera. The tipping point of a gradual decrease instead of a gradual increase in 6MWD over time is noticed in patients with two comorbidities (or more), in addition to the reduced starting level on the 6MWT when patients visit the physical therapist for the first time (y-axis at 0 days in Figure 4.3).

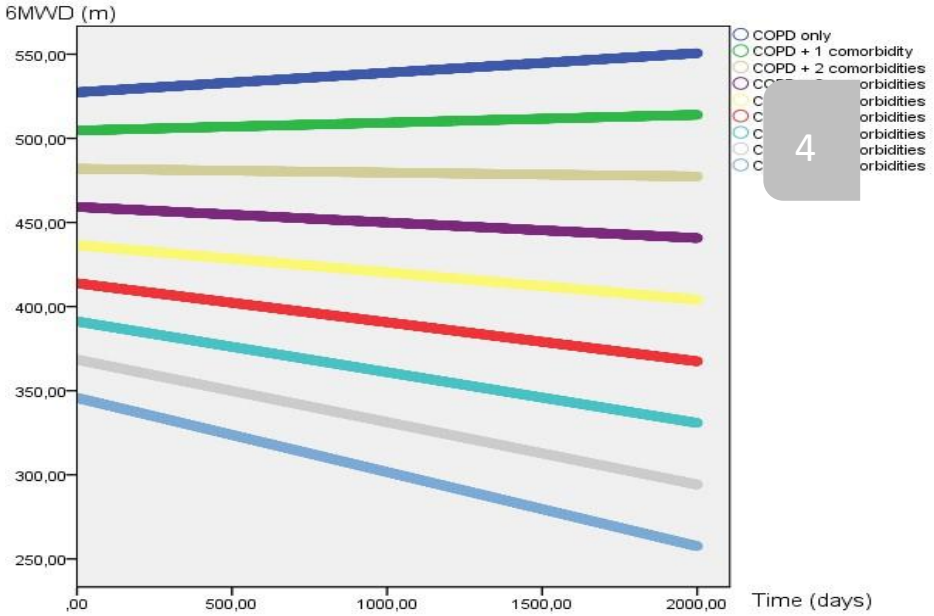


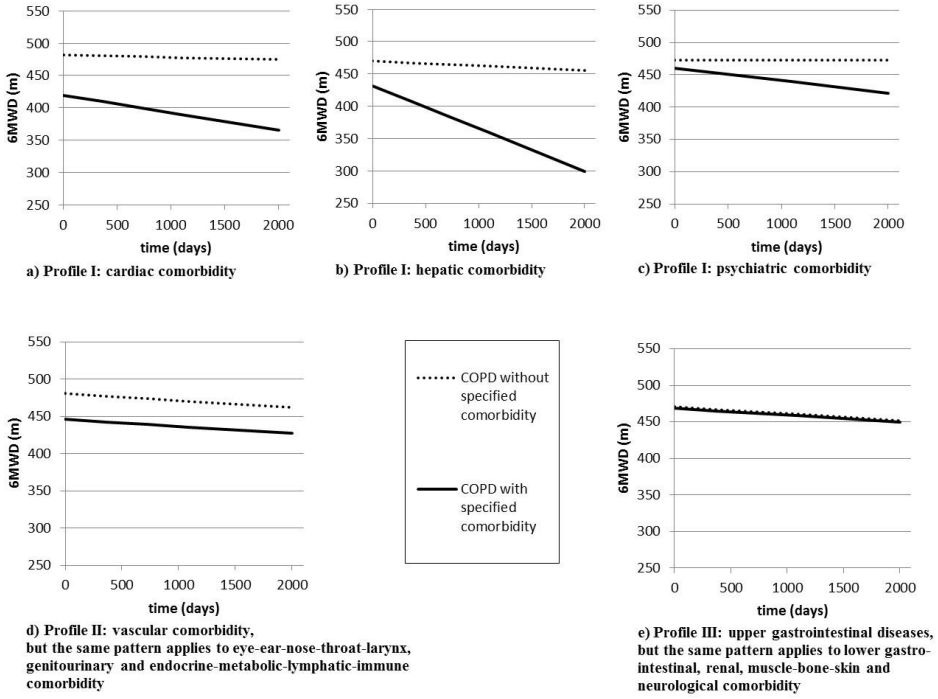
Figure 4.3 Influence of morbidity count on start level and progression of functional exercise capacity (sixminute walk distance (6MWD)).

Phase 2: Each disease category had a different kind of influence on functional exercise capacity. By analysing each disease category individually for its impact on the 6MWD, three different profiles were disentangled (univariate models). Profile I: For cardiac diseases, hepatic diseases and psychiatric diseases a significant influence on both the starting level and on the progression of the 6MWD was found in patients with COPD with that specific comorbidity compared to patients without that specific comorbidity (Figure 4.4a). Patients with *cardiac comorbidity* walked 62 metres less on the 6MWT at the start of physical therapy (-61.95 (*95%CI*: -100.26 to -23.64)). They also showed a

more rapid decline of 24 metres in 1,000 days compared to patients with COPD without cardiac comorbidity (-23.81 (*95%CI*: -43.59 to -40.31), *t*(49)= -2.42, *p*=0.019). In patients with *hepatic diseases* the starting level was reduced by 39m along with a 59m decline over time (*p*=0.005). Patients with *psychiatric diseases* started with 12m less and declined 19m over time (*p*=0.032). Profile II: For vascular diseases, eye-earnose-throat-larynx diseases, genitourinary diseases (other than renal) and endocrinemetabolic-lymphatic-immune diseases a significant influence on the starting level was found. But no difference in 6MWD decline for those with COPD with that specific comorbidity compared to patients without that specific comorbidity was shown (parallel slopes) (Figure 4.4b). Patients with *vascular comorbidity* walked 35 metres less on the 6MWT at the start of physical therapy (-34.62 (*95%CI*: -67.68 to -1.55)). Over time patients showed a decline of 9 metres in 1,000 days (-9.21 (*95%CI*: -17.73 to -0.67), *t*(43)= -2.18, *p*=0.035) regardless whether they had the comorbid condition or not. The same pattern was seen in patients with *eye-ear-nose-throat-larynx diseases* with a 75m reduced starting level and a non-differential 9m decline (*p*=0.042), in patients with *genitourinary diseases* with a 95m reduced starting level and a nondifferential 9m decline (*p*=0.036), and in patients with endocrine-metabolic-lymphaticimmune diseases with a 63m reduced starting level and a non-differential 10m decline (*p*=0.020). Profile III: For patients with upper gastrointestinal diseases, lower gastrointestinal diseases, renal diseases, muscle-bone-skin diseases and neurological diseases the same 6MWD starting level and the same decline over time was found compared to those without that specific comorbidity (parallel slopes and lines cross y-axis at same height) (Figure 4.4c). For example, patients with COPD with or without *upper gastrointestinal diseases* all started with an average of 469m on the 6MWT and all showed a progression of -9m over time (*p*=0.037).

Phase 3: Taking into account all twelve different disease categories the optimal random slope model was fitted to the data: *6MWD = 521 – 45 (in case of present cardiac disease) – 57 (in case of present eye-ear-nose-throat-larynx disease) + 64 (in case of present hepatic disease) – 81 (in case of present genitourinary disease) + 0.8 (in case of present psychiatric disease) – 48 (in case of present endocrine-metabolic-lymphaticimmune disease) + 0.007*number of days after starting physical therapy – 0.023*number of days after starting physical therapy (in case of present cardiac disease) – 0.047*number of days after starting physical therapy (in case of present hepatic disease) – 0.019*number of days after starting physical therapy (in case of present psychiatric disease).* This model including interactions between time and cardiac, hepatic and psychiatric disease in patients with COPD was the best combined model. It was corrected for the confounding influence of the other fixed comorbidity variables and corrected for undue influence of unbalanced distribution in other disease categories. This AR(1) model, with r=0.33 (SE=0.045), was very significant for the correlation of sequential 6MWT measurements (*z*-score>3.29). Moreover, in terms of the accuracy of the optimal model, all of the comorbid disease categories in profile I

are consistently present in this model. The disease categories from profile III and vascular diseases from profile II did not recur in this model. For the other disease categories from profile II, only their main effect on the 6WMD starting level could be found in the final model.



a) Profile I: cardiac comorbidity
b) Profile I: hepatic comorbidity
c) Profile I: psychiatric comorbidity
d) Profile II: vascular comorbidity, but the same pattern applies to eye-ear-nose-throat-larynx, genitourinary and endocrine-metabolic-lymphatic-immune comorbidity
e) Profile III: upper gastrointestinal diseases, but the same pattern applies to lower gastro-intestinal, renal, muscle-bone-skin and neurological comorbidity

Figure 4.4 Influence of different comorbidity categories on start level and progression of functional exercise capacity (six-minute walk distance (6MWD)), represented by three different profiles.

DISCUSSION

This study showed a clear influence of comorbidity on change in functional exercise capacity (6MWD) in patients with COPD who received physical therapy in a primary care setting. Besides a significant influence of absolute morbidity count on 6MWD, the influence of the different comorbid disease categories could be assigned to three profiles, each with a different kind of prognostic linear model. Comorbidities within the cardiac, hepatic and psychiatric category have the most negative influence on 6MWD represented by a linear model that best fits the data.

Patients with COPD without any comorbidity that visit a physical therapist for treatment may expect to start with a 6MWD of 527 metre and may or may not improve on functional exercise capacity over time (-9m to 32m). When the number of comorbid conditions is two or more, not only the patients' starting 6MWD will be significantly reduced, but also progression will deteriorate significantly over time.

Having a cardiac disease, hepatic disease or a psychiatric disease besides COPD, will have a negative influence on the patients' starting 6MWD as well as a more rapid decline of 6MWD over time. Suffering from vascular, eye-ear-nose-throat-larynx, genitourinary and endocrine-metabolic-lymphatic-immune diseases (profile II) does not influence the progression of 6MWD. For patients with upper and lower gastrointestinal, renal, muscle-bone-skin and neurological

diseases (profile III), neither the starting level nor the progression of 6MWD was altered compared to those without that specific comorbidity.

Moreover, this study confirmed that most patients with COPD undergoing physical therapy, alike pulmonary rehabilitation, have one or more comorbidities.[11] The number of patients in this cohort who had one or more comorbidities is, with 89%, on the top end of the 51%-84% range mentioned in other studies.[5,6,11,25] However, these other studies included a smaller number of comorbid conditions than is captured by the CIRS. A more comprehensive study in a tertiary setting by van Fleteren et al. (2013) reported a total of 97.7% of all patients with COPD having one or more comorbidities.[8] A recent literature review showed that, overall, the prevalence of the single disease categories in our cohort was similar or somewhat lower than those reported in other studies in secondary or tertiary care settings.[21]

Potential explanations for study findings

As suggested by the literature, the reason behind reduced improvement in functional exercise capacity might be the higher degree of impairment in comorbid patients who are generally more dyspnoeic[38] and less physically active[21].
Of the three comorbid categories that showed a very significant negative influence as a single comorbid condition (Profile I) as well as a combination of comorbidities encountered in the final model, both cardiac diseases (21%) and psychiatric diseases (35%) were in the top five of comorbidity prevalence in this cohort. The observation that patients with cardiac diseases besides COPD have reduced exercise capacity is in line with the literature.[39] However, since physical therapy included aerobic endurance training, which is the core component of cardiac rehabilitation programmes, an improvement of functional capacity could equally well be expected.[39] An explanation for the lack of functional capacity improvement in this study might be the long-term (maintenance) exercise programme duration (up to 5.5 years, with a median of 27 months). After cardiac rehabilitation programmes up to 6-12 weeks[39] and after

pulmonary rehabilitation programmes up to 8-12 weeks[16] improvements of functional capacity have been reported in patients with respectively cardiac disease or COPD. But when patients are followed during a long-term (maintenance) programme, as in this study, the deconditioning that comes with prolonged COPD[16] may catch up with the improvements in walking capacity as the disease progresses. The observed clear negative influence of psychiatric diseases might be explained by findings that COPD patients' perceptions about their illness before rehabilitation influence exercise capacity after treatment.[40] Hepatic diseases also had a significant influence, despite its relative low prevalence of 3%. For cirrhosis, this might be explained by a significant reduction in exercise capacity and muscle strength that is present in patients with cirrhosis compared to healthy controls.[41]

On the other hand endocrine-metabolic-lymphatic-immune diseases with a prevalence of 58% and vascular diseases with a prevalence of 35% had no influence on functional exercise capacity progression (Profile II). Literature showed by cross-sectional analysis that walking capacity is impaired in patients with peripheral artery diseases,[42] which can be observed in this study by the lower 6MWD at the start of physical therapy. A reason that metabolic and vascular conditions had no statistically significant influence on functional exercise capacity over time may be explained by a link between different comorbidity categories. Metabolic activity of the abdominal aorta and visceral fat is increased in COPD patients. Since, the degree of visceral fat metabolic activity is associated with aortic inflammation one comorbid condition (metabolic comorbidity) has a role in the development of another comorbid condition (vascular comorbidity) in COPD.[43] Such a link between comorbid conditions may also be true for other disease categories. There may also be a mutual physiological cause for reduced exercise capacity as a consequence of different comorbid diseases that may explain the observed associations. For example heart disease, hypertension and diabetes are all associated with increased systemic inflammation,[38] and systemic inflammation and oxidative stress have a prominent role in COPD and atherosclerosis to understand the link between COPD and cardiovascular disease.[44] Depending on the diagnosed comorbid condition in one patient despite the mutual underlying cause, the total contribution of one comorbid condition in this study may have more negative influence than another comorbid condition. This means that the classification does not necessarily indicate a causal relationship between one comorbid condition and reduced improvement of functional exercise capacity, but rather indicates a causal relationship between a mutual underlying factor and reduced exercise capacity. Still, the presence of two of the most influential categories in this study (cardiac and psychiatric) was in line with the clusters of comorbid conditions as identified by van Fleteren et al. (2013). They mention five comorbidity clusters in total: (1) less comorbidity, (2) cardiovascular, (3) cachectic, (4) metabolic, and (5) psychological.[8] Surprisingly, patients with muscle-bone-skin diseases with a prevalence of 52% showed no different 6MWD at the start of physical therapy nor a worsened decline over time

compared to those without muscle-bone-skin diseases (Profile III). One reason for the lack of influence might be the composition of the categories making many different ailments responsible for the lack of influence. Psoriasis for which a patient used skin cream clearly should have less influence on functional exercise capacity than severe knee osteoarthritis or a very recent total knee replacement (both scored 1 for presence in the category muscle-bone-skin diseases, making differentiations difficult).[35] Another explanation may be a direct positive influence of exercise training on muscle function,[16] preventing more profound 6MWD decline in patients with muscle deconditioningrelated comorbidity.

Measurement considerations

In our study the CIRS was used to record comorbidity in patients with COPD. There are other indices that capture comorbidity, such as the less detailed Kaplan-Feinstein Index[45] or the Charlson Comorbidity Index[46] that misses many important prognostic disorders. The CIRS appeared to be a reliable and valid instrument in a primary care context in former studies.[47]
Table 4.2 in this article was extended with examples of diseases to show what kind of conditions were recorded in each category, since the thirteen categories of the CIRS alone leaves room for interpretation. Ninety-five percent of all cases of hypertension is essential hypertension, which is a heterogeneous disorder regarding causal factors and has a positive correlation with both cardiac and (peripheral) vascular diseases.[48] In this study, physical therapists assigned hypertension to the vascular disease category and not to the cardiac or renal category for the sake of consistency (Table 4.2).[49] In most studies using the CIRS it is not clear where different types of cancers were registered.[36] In this study malignancy was registered in category #13 (endocrine and metabolic diseases and diseases related to the generic *lymphatic*/immune system) for consistency reasons, like in the Kaplan-Feinstein Index, not in separate categories depending on the tumour location. This allocation can be supported by recent studies with animal models implicating that breast cancer can be seen as a systemic disease.[50]

Study limitations

Since systemic inflammation plays a prominent role in the link between COPD and several comorbid conditions,[38] that occurrence of acute exacerbations during physical therapy may have reduced the observed 6MWD. Not taking exacerbation rate into account as a covariate in the analyses can be considered a limitation, as the median exacerbation history in this population was 1.0 (25^{th}-75^{th} percentile: 0.0-2.0). However, the random slope model analyses allowed for all observed 6MWD to be captured in the model, reducing the influence of an acute exacerbation at one point in time during physical therapy.

This study had an observational design. Therefore it cannot be stated with certainty that there was no influence of comorbidity on 6MWD progression of disease in profile II or on starting 6MWD and progression of 6MWD in profile III. For such a statement an experimental design is appropriate. Of course comorbid disease cannot be (randomly) allocated to patients with COPD, therefore this study design and mixed model analyses was the best choice to study the influence of comorbidities on the physical therapy outcome.

For the analyses of the single disease categories (phase 2), the three profiles of univariate models were not corrected for influence by unbalanced distribution in other disease categories between the group that has the comorbid condition and the group that is without the comorbid condition. In phase 3, however, the model that was corrected showed that the influences of other comorbid conditions proved to be captured in the influence of cardiac, hepatic, psychiatric, eye-ear-nose-throat-larynx, genitourinary and endocrine-metabolic-lymphatic-immune diseases.

The advantage of this type of statistical analysis (mixed model analysis) is that all repeated measures of the random factor 6MWD over a long period of time can be incorporated, despite the different numbers and the irregular measurement moments in time. This irregularity in measurement moments is inevitable in health care settings where not all tests can be realised at the planned moment in time, for example due to limited time to measure by physical therapists or unplanned patient absence following hospitalisation. Infrequent measurements of the 6MWD in time are subordinated by the analyses method used and there was large data density in the first 5.5 years.

Moreover, the sample size in our study (n=158) was within the range of earlier published prospective studies in the field (n=85-316),[8,23,25,27] but the first in a primary care population. With 1301 measurements of the 6MWT, it had sufficient power to establish a reliable AR(1) model with very significant interactions (r=0.33, SE=0.045).

Clinical implications

Patients with COPD suffering from a cardiac, hepatic or psychiatric disease for example are likely to show a negative change of respectively 30m, 54m and 26m on the 6MWT over a period of 1,000 days (following the final model in phase 3), which is more than the most recent established minimal clinical important change (25m) on a 30m-course.[51] Although not investigated in our study by including a control group, patients with COPD and comorbid conditions who do not follow an exercise programme like physical therapy are expected to show a larger decline in health outcomes such as exercise capacity.[16]

Not only does this study have clinical implications, it also makes clear that comorbidity should not be excluded from a scientific study that measure functional exercise capacity as an outcome, when its goal is to generalise the results to clinical practice.

In conclusion, comorbidity reduced improvements of functional exercise capacity in patients with COPD receiving physical therapy in primary care both statistically significant and clinically meaningful. The more comorbid conditions were present the _____ more exercise capacity reduced over time. Depending on the comorbid disease category one of three different prognostic profiles could be assigned to predict functional exercise capacity, with cardiac, hepatic and psychiatric diseases having the most negative influence.

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4