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Summary

Osteoarthritis (OA) is the most common rheumatic disease of the musculoskeletal system, and frequently affects the knee, hip, and hand joints. OA is the sixth primary cause of moderate-to-severe disability and the eighth cause of disease burden in Europe. The development of difficulties in performing daily activities is more pronounced in middle aged and older persons with OA than their contemporaries without this disease. However, the natural course of pain and physical functioning in OA of the knee or hip is highly individual and variable. Some patients improve, while others remain stable, or even deteriorate.

Exercise therapy is a key intervention in the management of patients with knee or hip OA. It is an effective intervention to reduce joint pain and to improve physical functioning in patients with knee or hip OA. Exercise therapy consists of muscle-strength training of the lower limb and aerobic training at a moderate to high training intensity. However, comorbidity is present in 68 to 85% of patients with OA. Comorbidity interferes with exercise therapy, contributes to non-adherence, and may affect the outcome of exercise therapy. The effect of exercise therapy in patients with knee or hip OA and severe comorbidity is not known. Patients with unstable medical conditions, precluding safe participation in an exercise program, are excluded from clinical trials, because of the high risk of comorbidity-induced adverse events. In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy. If accepted into an exercise program, both therapists and patients tend to reduce exercise intensity to a level unlikely to be effective, because of fear of aggravating symptoms of the comorbid disease. There are no guidelines for tailoring exercise to the presence of comorbidity. There is therefore a need for protocols with comorbidity-related adaptations that facilitate the application of exercise therapy and improve the outcome of exercise therapy in patients with knee or hip OA and severe comorbidity.

Chapter 1 provides a general introduction of the research topics of this thesis. The research described in this thesis has two objectives: First, to describe i) the course of pain and physical functioning in patients with knee and hip OA and ii) to give an overview of prognostic factors of pain and physical functioning by systematically summarizing the scientific literature (**Chapter 2, 3**), and second, to develop and evaluate a tailored exercise program for patients with knee OA and comorbidity (**Chapter 4-8**).

In **Chapter 2** the literature on the course of pain and physical functioning in patients with *knee* OA is systematically summarized and an overview is presented of prognostic factors that predict deterioration in pain and physical functioning. A meta-analysis and a qualitative data synthesis were performed. Of the 58 studies included, 39 were of high quality. High heterogeneity in the course of pain and physical functioning across studies and within study populations (as indicated by large standard deviations of change scores)



was found. Strong evidence was found for a number of prognostic factors predicting deterioration in pain (e.g., higher knee pain at baseline, bilateral knee symptoms, and depressive symptoms). Strong evidence was also found for a number of prognostic factors predicting deterioration in physical functioning (e.g., worsening in radiographic OA, worsening of knee pain, lower knee extension strength, lower walking speed, and higher comorbidity count). These factors are summarized in Figure 1 (see general discussion section). For several other studied factors, weak, inconsistent, or inconclusive evidence was found. Knowledge about predictors of pain and physical functioning is important for patients and clinicians. Based on this information, clinicians can identify patients who are at risk of deterioration of pain and physical functioning. More insight into predictors of the course of pain and physical functioning is the basis for improving and targeting treatment to specific subgroups of patients with knee OA.

Chapter 3 presents the results of a second systematic review and meta-analysis on the course of pain and physical functioning in patients with *hip* OA, and prognostic factors that predict deterioration in pain and physical functioning. A meta-analysis and a qualitative data synthesis were performed. Eleven out of the 15 included studies were of high quality. Because of high heterogeneity across studies and within study populations, no conclusions could be drawn with regard to the course of pain and physical functioning. Higher comorbidity count and lower vitality were found to predict deterioration of physical functioning (strong evidence) (see Figure 1). Clinical factors (higher comorbidity count and presence of knee OA), health behaviour factors (no supervised exercise and physical inactivity), and a socio-demographic factor (lower education) were found to predict deterioration of pain (weak evidence). For several other predictive factors, weak evidence was found (e.g., bilateral hip pain, increase in hip pain, bilateral knee pain, presence of knee OA). These findings may guide future research aimed at the identification of subgroups of patients with hip OA.

In **Chapter 4** the relationship between specific comorbid diseases, activity limitations, and pain in patients with OA of the hip or knee is described. A cross-sectional cohort study among 288 older adults (50–85 years of age) with OA of hip or knee was conducted. Subjects were recruited from three rehabilitation centres and two hospitals. The results of this study showed that 18 comorbidities occurred in >5% of the sample (e.g., chronic back pain, arthritis of the hands or feet, hypertension, asthma or COPD, diabetes, severe cardiac disorders, overweight or obesity, hearing or vision impairment and chronic cystitis). In addition, the results showed that the following comorbid diseases are associated with activity limitations: chronic back pain or hernia, arthritis of the hand or feet, and other chronic rheumatic diseases (all musculoskeletal disorders); diabetes and chronic cystitis (non-musculoskeletal disorders); hearing impairments in a face-to-face conversation, vision impairments in long distances, dizziness in combination with falling (all sensory impairments); and overweight and obesity. Comorbid diseases associated with pain were arthritis of the hand or feet and other chronic rheumatic diseases (musculoskeletal disorders), and diabetes (non-musculoskeletal disorder).

In **Chapter 5** restrictions and contraindications for exercise therapy are described for common comorbidities (cardiac diseases, hypertension, type 2 diabetes, obesity, chronic obstructive pulmonary disease (COPD), depression, chronic pain, low back pain (LBP), visual or hearing impairments, and chronic cystitis) in hip and knee OA patients. These were identified by performing a narrative review of the scientific literature. Restrictions limit the application of exercise therapy, necessitating adaptations to the therapeutic protocol. If a contraindication is present, however, exercise therapy is not an option and the patient should be excluded from exercise therapy. We found that cardiac diseases, hypertension, type 2 diabetes, COPD, and chronic cystitis are associated with restrictions resulting from physiological impairments. Conversely, LBP, chronic pain syndromes, and depression were associated with psychological and behavioural restrictions to exercise therapy. Visual and hearing impairments resulted predominantly in environmental restrictions to exercise. Obesity was associated with restrictions resulting from physiological and psychological impairments and behavioural barriers. In addition, several absolute contraindications exist and patient safety cannot be guaranteed when these are not taken into account during exercise therapy. This overview is helpful in decisions on the treatment of patients and will be instrumental in the development of a protocol for comorbidity-related adaptations in exercise therapy for OA patients.

Chapter 6 describes the development of adapted exercise protocols for patients with knee OA and comorbidity. Based on literature and expert opinion, comorbidity-adapted protocols were developed for highly prevalent comorbidities in OA. Field-testing showed that the protocols provided guidance in clinical decision making in both the diagnostic and the treatment phase. Because of overlap, the number of exercise protocols could be reduced to three: one requiring physiological adaptations (coronary disease, heart failure, hypertension, diabetes type 2, chronic obstructive pulmonary diseases, obesity), one requiring behavioural adaptations (chronic aspecific pain, nonspecific low back pain, depression), and one requiring environmental adaptations (visual or hearing impairments). Evaluation of patient outcomes after treatment showed significant ($P < 0.05$) and clinically relevant improvements in pain and physical functioning. It was concluded that a randomized controlled trial should be performed to evaluate the effectiveness of treatment in line with our protocols.

In **Chapter 7** the results of a randomized controlled trial about the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee OA and comorbidities are described. In this study, 126 participants with a clinical diagnosis of knee OA and at least one of the following target comorbidities were included: coronary disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease, or obesity (body mass index $\geq 30 \text{ kg/m}^2$), with severity score ≥ 2 of the comorbidity on the Cumulative Illness Rating Scale. The intervention group received a 20-week, individualized, comorbidity-adapted exercise program consisting of aerobic and strength training. The control group received their current medical care for knee osteoarthritis and was placed on a waiting list for exercise therapy. The primary outcome measure was



physical functioning, measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale physical functioning and 6-minute walking test (6-MWT). Measurements were performed at baseline, at 20-weeks post-treatment, and at 3-months post-treatment. The results showed that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with knee OA and severe comorbidities. The intervention group performed better on physical functioning over time. These differences were statistically significant. At 3-months follow-up, the mean improvement in the intervention group was 33% on the WOMAC scale and 15% on the 6-MWT. This improvement is of clinical relevance. No serious adverse events occurred during the intervention. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee OA, even in the presence of severe comorbidity.

In **Chapter 8** an innovative strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease is presented. This strategy is derived from our previous work developing comorbidity-related adaptations to exercise therapy in OA. We now broaden this approach into a general strategy for the development of comorbidity-related adaptations to exercise therapy in an index disease. The i3-S strategy consists of four steps. The first three steps involve creating inventories of 1) comorbid diseases, 2) contraindications and restrictions on exercise therapy, and 3) potential adaptations to exercise therapy. In the fourth step, this information is synthesized into guidance on comorbidity-related adaptations to exercise therapy in the index disease. The adaptations concern physiological, behavioural, and environmental factors. We recommend using and evaluating the i3-S strategy in future research.

Finally, in **Chapter 9** the main results of this thesis are summarized and discussed and directions for further research are provided.