Knee joint instability and exercise therapy in patients with osteoarthritis of the knee

Osteoarthritis of the knee is a highly prevalent disease with a large impact on daily functioning. Management of knee OA, in which exercise therapy is a cornerstone treatment, is sub-optimal, with effects of recommended treatments being only moderate at best. For optimization of exercise therapy in knee OA , innovative treatments that are tailored to specific subgroups of patients (e.g., those suffering from knee instability) need to be developed. Furthermore, the content of exercise therapy could be improved by better understanding its underlying working mechanisms and potential barriers.

After a short introduction on the scope of this thesis (**Chapter 1**), the first part of this thesis focused on knee joint instability (**Chapters 2-6**). In the second part, the central theme was the effectiveness of exercise therapy (**Chapters 7-10**). In the third part, the aim was to identify homogeneous and clinically relevant phenotypes from the heterogeneous population of knee OA patients (**Chapter 11**). In the General discussion, the main study findings are discussed, and directions for future research are provided (**Chapter 12**).

Part I. Knee joint instability

In **Chapter 2**, patient-reported knee instability was found to be highly common (65%) in a large cohort of knee OA patients from a clinical setting (Amsterdam Osteoarthritis [AMS-OA] cohort). In addition, patient-reported knee instability was consistently associated with multiple measures of activity limitations, even after adjusting for pain and muscle weakness. These findings emphasize the importance of knee instability in clinical practice.

Knee stability is presumed to depend on upper leg muscle strength, knee joint proprioception and laxity of the knee joint. As reported in **Chapter 3**, patient-reported knee instability was significantly associated with weakness of the upper leg muscles, while not with reduced knee proprioception or high laxity. These findings may indicate that the muscles around the knee are the dominant factor in knee stabilization.

Chapter 4 gives a comprehensive overview of the literature on knee proprioception in knee OA. Proprioceptive deficits have frequently been reported in knee OA patients compared to age-matched healthy controls, and associated with pain and activity limitations (both cross-sectionally and longitudinally), which highlights the importance of proprioception in knee OA. However, causal factors are poorly understood. Proprioception may not only be locally affected, but could also be a generalized process, as indicated by proprioceptive deficits also present in other joints as well in knee OA patients. As described in Chapter 4, many different measurement techniques for knee proprioception are used, which are poorly related with each other and all under passive, non-functional conditions.

Ideally, a new reliable measurement protocol needs to be developed that is more closely linked to daily functioning than existing techniques.

In **Chapter 5**, the association of proprioception with meniscal damage, which was suggested to be a potential causal factor, was determined. This study was the first to focus on and report a significant association between reduced proprioception and medial meniscal abnormalities on MRI in a knee OA cohort. This provides new insight in understanding proprioceptive deficits in knee OA.

In an explorative study, MRI-detected tissue abnormalities (including cartilage loss, osteophytes, bone marrow lesions, effusion, and synovitis) were found to be generally not associated with upper leg muscle strength, proprioception, or laxity (**Chapter 6**). On the other hand, quadriceps weakness was found to be associated with knee joint inflammation (i.e., effusion and synovitis), which could potentially be a clinically relevant finding.

Part II. Optimizing effectiveness of exercise therapy

In **Chapter 7**, a large randomized controlled trial (STABILITY-trial) was conducted to test the hypothesis that patients suffering from knee instability benefit more from an exercise program consisting of knee stabilization training prior to strength and functional training (experimental program), compared to strength and functional training only (control program). Both programs were found to be highly effective in reducing pain (40% improvement), activity limitations (30%) and knee instability (30%). However, knee stabilization training did not show any added value.

Based on this result of the STABILITY-trial, subgroup-analyses were performed to determine whether knee stabilization training may only have added value in specific subgroups of patients with knee instability (**Chapter 8**). This study revealed that knee stabilization training may have added value in knee OA patients with knee instability and strong muscles. This could imply that exercises should first target muscle strength, prior to knee stabilization.

In Chapter 9 and 10, data was used from both exercise groups of the STABILITY-trial together (as one 'exercise-cohort'), since both exercise programs were similarly effective. In **Chapter 9**, improvement in upper leg muscle strength following exercise therapy was found to be associated with reductions in pain and activity limitations, and might be an underlying mechanism of the effectiveness of exercise. No role was found for improvement in knee joint proprioception. These findings emphasize the importance of upper leg muscle strengthening in knee OA treatment.

In **Chapter 10**, an explorative study was performed on the role of OA severity (detected on MRI) on the effectiveness of exercise therapy. Outcome of exercise therapy was found to be independent of OA severity in multiple MRI features (including bone

marrow lesions, inflammation, and meniscal abnormalities), with the exception of patellofemoral (PF) cartilage loss and PF osteophytes, which were related to reduced effects. This suggests that all grades of knee OA, even 'end-stage' OA, can benefit from exercise therapy, which is a clinically highly important finding. In patients with advanced PF OA, exercises may need to be adapted in an attempt to optimize treatment effects in this particular subgroup.

Part III. Knee OA phenotypes

In **Chapter 11**, a cluster analysis technique was used to identify clinically relevant phenotypes from a large and heterogeneous knee OA population. Five phenotypes could be identified based on easily obtainable patient characteristics. These phenotypes (i.e., 'mild OA', 'strong muscle', 'non-obese weak muscle', 'obese weak muscle' and 'depressive phenotype') were found to differ in level of pain and activity limitations and possibly represent different etiological OA subtypes, which may need to be treated differently.

The following directions for future research were suggested in the General discussion (**Chapter 12**):

- to develop and validate an objective measure for knee instability;
- to develop a new and reliable measurement technique for knee joint proprioception within a functional setting;
- to unravel the role of the upper leg muscles in knee stabilization and determinants of muscle weakness in knee OA;
- to clarify the potential longitudinal (cause-consequence) relationships between knee joint damage and biomechanical impairments (muscle weakness, reduced proprioception, and laxity);
- to evaluate the effectiveness (and safety) of innovative exercise programs, e.g., exercise therapy with higher intensity levels, exercises in combination with vitamin D, pain medication or anti-inflammatory medication, or adapted exercises for PF OA patients;
- to unravel the controversy on the impact of exercise therapy on knee OA progression (protective vs. destructive impact of exercising);
- to identify clinically relevant knee OA phenotypes which may need specific treatment.