

Chapter 12

General discussion

The first part of this thesis focused on patient-reported **knee instability** and biomechanical factors that may play a role in knee stabilization, namely muscle strength, proprioception and laxity of the knee joint, in a clinical cohort of knee OA patient. The relationships between each of these biomechanical factors and structural joint damage, as detected by radiography and/or MRI, were also explored.

In the second part of this thesis, the **effectiveness of exercise therapy** was the central theme. Exercise therapy is a key component of conservative OA management, but effects are still only moderate at best and need to be optimized. A randomized, controlled trial was conducted to evaluate the effectiveness of additional knee joint stabilization training in knee OA patients suffering from knee instability. Data of this trial were also used to evaluate underlying mechanisms and potential barriers of exercise therapy.

It has been suggested that the heterogeneous knee OA population needs to be classified into homogeneous subgroups or phenotypes, in order to better understand the complexity of OA disease and to develop tailor-made interventions for specific phenotypes. Therefore, the third part of this thesis aimed to identify clinically relevant **knee OA phenotypes**.

In the following section, the presented study findings from this thesis will be discussed, and directions for future research will be provided.

Part I. Knee joint instability

Clinical importance of knee joint instability

Knee instability, which is reported by the patient as ‘a feeling of buckling, shifting, or giving way of the knee’, was found to be highly common (65%) in the AMS-OA cohort (1) (**Chapter 2**). This is in line with previous literature (2). Moreover, knee OA patients reporting knee instability were found to have more severe activity limitations than those patients not reporting knee instability, even after controlling for factors like muscle weakness, pain, radiographic severity, body mass index, and age. These results emphasize that patient-reported knee instability may need to be addressed in clinical practice.

Upper leg muscle strength: a dominant factor in knee stabilization

Patient-reported knee instability was significantly associated with reduced upper leg muscle strength, while not with impaired proprioception or increased laxity of the knee (3) (**Chapter 3**). These findings have recently been replicated in a study by Shakoor et al (4), and is in line with a large population-based cohort study (not exclusively knee OA patients) (5). Quadriceps and hamstrings muscles are widely considered to be principal stabilizers of the knee joint (6), but exact pathways have yet to be clarified. Stronger upper leg muscles should be able to control knee joint movements under more challenging conditions, thereby possibly maintaining knee joint stability. This stabilizing role of the upper leg muscles could also explain, at least partly, the well-established association of muscle weakness with activity limitations in knee OA (7;8). Interestingly, knee OA patients with weaker muscles tend to have higher cocontractions of quadriceps and hamstrings muscles during gait (i.e., stiffening of the knee), which might be considered a stabilizing strategy, but could potentially be harmful for the knee joint through higher joint compression (9). This further underlines the importance of strong muscles around the knee joint, although also other muscle functions than maximal strength, such as muscle activation (10), muscle force steadiness (11)), and muscle fatigue could be important for knee stabilization.

Quadriceps (but not hamstrings) weakness was found to be associated with severity of patellofemoral (PF) cartilage loss on both MRI and radiography and presence of joint inflammation on MRI, while not with other structural features (12) (**Chapter 6**). The association with PF cartilage loss is in line with earlier studies (13-16). This may confirm a suggested role of quadriceps weakness in the pathogenesis of PF OA, rather than tibiofemoral (TF) OA, possibly due to changes in the placement or tracking of the patella (16). The association may also suggest that PF joint damage can inhibit quadriceps muscle function (17). The association between quadriceps weakness and joint inflammation is a new and potentially clinically relevant finding, which has recently been confirmed in our AMS-OA

cohort using a systemic inflammatory marker (18). This may imply that muscle weakness in knee OA is partly attributed to inflammatory processes, both locally and systemically.

To conclude, the upper leg muscles seem to play a dominant role in knee stabilization and may also be involved in OA disease process. This implies that the muscles are a crucial target for treatment and that determinants of muscle weakness in knee OA need to be further clarified.

Knee joint proprioception: new measurements needed

Knee joint proprioception (i.e., knee motion sense) was not found to be associated with patient-reported knee instability, even not in an interaction term with muscle strength (3) (**Chapter 3**). This was unexpected, as proprioception is presumed to be essential for knee protection and stabilization, and frequently been related to pain and activity limitations, as described in a review study (19) (**Chapter 4**). It should be noted that in a study by Collins et al (20) in 38 knee OA patients, an association between knee joint proprioception (i.e., knee position sense) and patient-reported knee instability was found. Position and motion sense tests are the 2 most commonly used measures for proprioception, but correlate poorly with each other. Position sense tests are less reliable but presumed to be more likely to stimulate muscle spindles, which are considered the most important proprioceptive receptors, compared to motion sense tests. This could explain the different study results in this thesis compared to Collins et al.

Both position and motion sense tests have been criticized because of poor reliability and excessive variability, potential confounding by patient memory, reaction time, concentration, and joint pain during testing (21), and a possible learning effect. Recently, a more reliable proprioceptive test has been introduced, namely a vibratory perception threshold test (21). However, this measure was not found to be associated with patient-reported knee instability (4). All existing proprioceptive tests are assessed under unloading, non-functional conditions, which is presumably not closely linked to proprioception necessary during daily activities. Therefore, a new and reliable measurement technique within a loading and functional context should be developed, and could be more closely linked to patient-reported knee instability.

Loss of proprioception is a well-known symptom in knee OA, but causal factors of these deficits are unknown (19) (**Chapter 4**). Several possible causes have been suggested, including dysfunction of articular mechanoreceptors, loss of muscle spindles due to muscle weakness, inflammatory processes, and injuries in menisci or ACL. Reduced proprioception was found to be associated with medial meniscal abnormalities in the AMS-OA cohort (22) (**Chapter 5**), which is a new finding, while not with inflammation or any other MRI feature (12) (**Chapter 6**). Interestingly, proprioception may not only depend on local factors, but may

also be a generalized process. Patients with knee OA do not only have proprioceptive deficits in their affected knee, but also in the contralateral knee (23-25), as well as other joints (e.g., shoulder) (26). Longitudinal studies may unravel which factors (local and/or generalized) are involved in reduced proprioception of the knee joint, and whether proprioception plays a role in OA disease process.

To conclude, new measurements of knee proprioception need to be developed that are more closely linked to proprioception necessary in daily life. With such a measure, determinants of reduced proprioception in knee OA, of which meniscal damage seems to be one, may be identified.

Knee joint laxity and instability: different constructs?

Several studies (9;27-29), including one in this thesis (3) (**Chapter 3**), were not able to find an association between knee joint laxity and instability. This might be surprising, as traditionally, knee joint laxity was considered a synonym for instability and frequently used as a measure for instability. Apparently, active structures are dominant over the passive structures in their function to stabilize the knee joint. Furthermore, passive knee joint laxity assessed in unloaded position and episodes of knee instability during daily life could be two different constructs. However, an alternative laxity measure, assessing knee joint stiffness (resistance) rather than range of motion of the passive restraint, has recently been introduced and found to be related to knee instability in knee OA patients (i.e., reduced stiffness was associated with severity of patient-reported knee instability) (30). This finding needs to be replicated in future studies.

Laxity of the knee joint was found to be associated to cartilage loss and osteophyte formation on MRI and/or radiography,), although associations were weak and fluctuated in direction (12) (**Chapter 6**). While cartilage loss in the LTF compartment was associated with higher laxity, possibly reflecting 'pseudo-laxity' (i.e., a reduction in tension on the passive restraint due to joint space narrowing (31)), cartilage loss in the MTF compartment was associated with lower laxity, possibly reflecting an 'ankylosing' or 'bone-to-bone' effect of end-stage cartilage loss. The association between laxity and structural joint damage may therefore depend on the stage of OA disease. It has also been suggested that the presence of laxity may contribute to the development and progression of knee OA. Lax knees may allow abrupt motion inside the joint, which could affect articular cartilage and other tissues (31). However, this could not be demonstrated in a longitudinal study (32).

To conclude, knee joint laxity has found to be unrelated to patient-reported knee instability. The role of laxity in OA disease process is still unclear and needs to be unraveled in future longitudinal studies.

Knee instability: development of an objective measure

In this thesis, a subjective measure of knee instability based on questionnaires from Irrgang et al (33) and Felson et al (5) (i.e., 'a feeling of buckling, shifting, or giving way of the knee', reported by the patient) was considered golden standard. However, some patients were found to have difficulty interpreting this question. Ideally, an objective measure can detect and differentiate different forms of actual episodes of instability. Such a measure could be combined with electromyography (EMG) in order to clarify the role of the muscles in knee stabilization. In the recent years, innovative techniques have been developed to assess three-dimensional knee motions under dynamic conditions by using accelerometers (34) (Fig. 1) or stereo X-ray technology (35). These measures need to be related to patient-reported knee instability for validation.

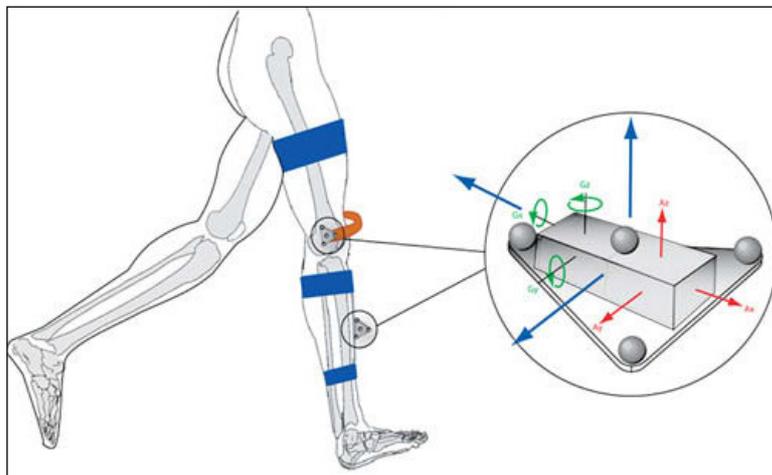


Fig. 1. Knee acceleration measure assessing accelerations of femur with respect to tibia, in anterior-posterior and medial-lateral directions as an estimate for knee instability, and in proximal-distal direction as an estimate for load transmission (34) (printed with permission)

Part II. Optimizing effectiveness of exercise therapy

Knee joint stabilization training: no added value

In a large randomized, controlled trial (STABILITY-trial), initial knee stabilization training, in addition to strength and functional training was not found to be effective compared to a control program of strength and functional training only (36) (**Chapter 7**). This was unexpected, as we specifically included patients suffering from knee instability. On the other hand, it is in line with other recent studies (37-39), in which additional ‘neuromuscular training’ was not effective over strength training only. Knee stabilization training may only be necessary in specific subgroups of patients with knee instability, whereas in the large majority, strength training could be sufficient. In subgroup-analyses, initial knee stabilization training did show added value in participants with knee instability and higher upper leg muscle strength at baseline, whereas participants with the lowest upper leg muscle strength improved more following the control program (40) (**Chapter 8**). This suggests that exercises should first aim at muscle strengthening, prior to knee stabilization.

The unexpected negative result of the STABILITY-trial could also be explained by the small contrast between interventions and a difference in training intensity in favor of the control group. Firstly, the only difference between programs was the addition of initial knee joint stabilization training, as this component was expected to be essential in the targeted group of patients suffering from knee instability. This design would have ensured that a difference in effectiveness was attributable to the knee stabilization training. Secondly, we found that patients from the control group exercised with a higher intensity compared to patients from the experimental program in the last phase of the exercise program. Possibly, extensively focusing on quality of performance of exercises, as part of the knee joint stabilization training, may have limited an intended increase in training intensity in the experimental group.

Success factors of exercise therapy

Both exercise programs from the STABILITY-trial were found to be highly effective, with effects at the higher end of the spectrum compared to other studies (Table 1). The success of our exercise therapy is likely attributable to the following factors:

Type of exercises. We incorporated all components recommended in (inter)national guidelines (51-54), including strength training, training of daily activities (i.e., task-specific), aerobic training, and patient education. Furthermore, most exercises were in weightbearing position and incorporated parts of daily activities like walking, rising and sitting from a chair, and stair-climbing, thereby presumably influencing daily functioning more directly.

Table 1. Effectiveness of exercise programs in STABILITY-trial compared to other randomized, controlled trials on exercise therapy in knee OA patients (with $n > 50$ in exercise group)

study	intervention	n	effectiveness	
			pain	activity limitations
<u>Knoop et al, 2013 (36)</u>	12-week exercise program with 2 supervised sessions of 60 minutes weekly (experimental group)	80	41%*	31%#
<u>Knoop et al, 2013 (36)</u>	12-week exercise program with 2 supervised sessions of 60 minutes weekly (control group)	79	36%*	27%#
van Baar et al, 1998 (41)	12-week exercise program with 1 to 3 sessions weekly	99	49%*	6% ^{††}
Farr et al, 2010 (42)	9-month exercise program with 3 supervised sessions of 60 minutes weekly	52	42% [†]	-
Fitzgerald et al, 2011 (38)	6-8 week exercise program with 12 supervised sessions in (agility and perturbation group)	91	26%*	34%#
Abbott et al, 2013 (43)	16-week exercise program with 9 supervised sessions of 50 minutes	51	27%*	31% ^{**}
Messier et al, 2013 (44)	18-month exercise program with 3 partially supervised sessions of 60 minutes weekly	150	28% [†]	24%#
Maurer et al, 1999 (45)	8-week exercise program with 3 supervised sessions weekly	57	25% [†]	16%#
Fitzgerald et al, 2011 (38)	6-8 week exercise program with 12 supervised sessions in (standard exercise group)	92	7%*	24%#
O'Reilly et al, 1999 (46)	6-month home-based exercise program with 5 exercises each day	113	22% [†]	17%#
Veenhof et al, 2006 (47)	12-week exercise program with maximal 18 supervised sessions	90	14%*	21%#
Péloquin et al, 1999 (48)	12-week exercise program with 3 supervised sessions of 60 minutes weekly	59	19% [‡]	-
Hopman-Rock and Westhoff, 2000 (49)	6-week exercise + health education program of one supervised session of 120 minutes weekly	56	18%*	-
Messier et al, 2004 (50)	18-month exercise program with 3 partially supervised sessions of 60 minutes weekly	80	6% [†]	12%#

* NRS or VAS score; † WOMAC subscale pain; ‡ Knee joint tenderness score; # WOMAC subscale physical function; ** WOMAC total score (including subscales pain, stiffness, and physical function); †† IRGL subscale disability.

Gradual increase in intensity. Both programs started with a 4-week low-intensity phase with hydrotherapy in week 1 and low-intensity land-based exercises in week 2-4. This would enable the knee joint to adapt at loading, thereby preventing overload-related injuries, especially in the targeted group of patients suffering from knee instability. From week 5 towards the end of the program, training intensity gradually increased in order to optimize training effects.

Professional supervision. Each group of patients was supervised by two professionally trained physical therapists with experience in exercise therapy and rheumatic diseases. Their knowledge and experience enabled them to adequately monitor exercise performance and professionally guide patients.

Group-based sessions. By providing group-based sessions, patients could interact with each other during the treatment, e.g., exchanging experiences, motivating each other. This may have facilitated enjoyment during exercises and compliance to the exercise regimen, thereby possibly influencing treatment outcome as well. Although the literature does not support a superiority of group-based vs. individual exercise sessions in knee OA (55), both patients and therapists in the STABILITY-trial were positive towards these group-based sessions.

High adherence. Participants in the STABILITY-trial were in general highly motivated and adherent to the exercise protocol, not only during but also after the treatment period. As a part of the treatment, participants were encouraged to seek for alternatives to keep perform exercises and remain physically active after discharge. This may have enabled them to better incorporate an exercise behavior in their daily activities. The high level of adherence might have been crucial for the sustainment of effects over time, which usually decline (56).

Physical therapists have various attitudes and beliefs regarding exercise in OA (57), although existing guidelines strongly recommend exercise therapy. Furthermore, exercise therapy is ignored as a treatment strategy by many medical practitioners (58;59). In the STABILITY-trial, an exceptionally large number of candidates enrolled ($n=539$), of which most reported not being (adequately) treated, reflecting the 'underuse' of exercise therapy. Therefore, implementation of effective exercise programs, in addition to more adequate referral to exercise professionals by medical practitioners, will likely have positive effects on the conservative management of OA.

Importance of strength training

Strength training: an essential component of exercise therapy. Multiple findings in this thesis consistently underline the key role of strength training in OA management. Firstly, strength training (in addition to functional training) was equivalent in effect to a program with additional knee joint stabilization training, not only in reducing activity limitations and pain, but also in restoring knee stability (36) (**Chapter 7**). This seems also in line with the cross-sectional association found between lower muscle strength and knee instability (3) (**Chapter 3**).

Secondly, a significant effect modification by upper leg muscle strength indicated that persons with lower baseline muscle strength tend to benefit more from the control program, whereas persons with higher baseline muscle strength improve more following the experimental program (40) (**Chapter 8**). This suggests that also in a group of knee OA patients suffering from knee instability, the primary goal of exercise therapy needs to be

muscle strengthening, while in a second phase, other components, e.g., specific knee stabilization training, could be added.

Thirdly, improvement in upper leg muscle strength was found to be consistently associated with reductions in pain and activity limitations following exercise therapy (60) (**Chapter 9**). Upper leg muscle strengthening (for both quadriceps and hamstrings) seems to be an important underlying mechanism of the beneficial effects of exercise therapy. Stronger muscles could enable the patient to better perform daily activities like walking and stair negotiating, thereby reducing activity limitations and possibly pain. Furthermore, muscle strengthening may not only influence daily functioning directly, but also indirectly via changes in knee joint structures (e.g., cartilage quality (61), inflammation (62)), psychosocial factors (63), and comorbidity-related symptoms (63). More studies are needed focusing on underlying mechanisms of the effectiveness of exercise therapy. These studies should use data from (previous) trials on exercise therapy with a non-exercise group as control group.

Strength training: all OA grades can benefit. Some clinicians may argue that exercise therapy is ineffective (if not harmful) in patients with severe knee OA. In contrast, we included patients of all grades of knee OA severity (ranging from K/L grade 0-4) in the STABILITY-trial and found that the severity of knee OA on MRI was not of importance for treatment outcome (64) (**Chapter 10**). This implies that professionally supervised exercise therapy is effective and safe in patients of all grades of OA severity, and that, instead of referral for total knee arthroplasty (TKA), exercise therapy could be considered in patients with 'end-stage' knee OA. TKAs are the main contributor to the direct health-care costs in OA management (65). Therefore, more consistent referral to exercise therapy is likely to significantly reduce the economic burden of OA. Furthermore, in a substantial group of candidates for surgery, TKA is contra-indicated (because of comorbidities) or not preferable (due to high risks for complications), while half of the patients that undergo TKA do not perceive any improvement in symptoms (66). For these patients, exercise therapy could be an effective treatment and should be considered.

It should be noted that the effect of exercise therapy on structural changes in the knee joint is still controversial. Muscle strengthening may decelerate OA disease, based on the shock-attenuating and stabilizing capacity of the muscles (58). On the other hand, muscle strengthening could theoretically accelerate OA disease as well, if accompanied with higher axial compression that may place the cartilage in an environment of excessive and prolonged load (67). Due to this controversy, clinicians and patients may have doubts about exercise therapy as an effective and safe treatment. However, multiple studies failed to demonstrate a destructive impact of exercise therapy (50;68;69), whereas some evidence suggests a positive impact (61;62). Future studies need to unravel the controversy on the impact of exercise therapy on OA disease.

Strength training: further optimization. Based on findings in this thesis, optimization of exercise programs might be possible by aiming at higher levels of muscle strengthening. Therefore, a gradual increase towards maximal intensity of the exercises may need to be pursued. In future studies, exercise programs with higher intensity levels need to be evaluated on effectiveness and safety. Furthermore, strength improvements may be facilitated through adding vitamin D (70) or anti-inflammatory medication (71). Patients with high pain levels may benefit from a combined treatment of exercises and strong pain medication, to enable them to effectively perform exercises without having pain flares. Finally, for patients with advanced PF OA, exercises may need to be adapted, as this subgroup was found to benefit less from the exercise therapy (64) (**Chapter 10**). By minimizing patellofemoral contact forces and knee loading during exercising (58), or by providing PF taping or bracing during exercising, effectiveness might be optimized.

Part III. Knee OA phenotypes

From one heterogeneous population to multiple homogeneous phenotypes

Five clinically relevant phenotypes were identified from a large and heterogeneous knee OA cohort, based on easily obtainable patient characteristics (i.e., radiographic severity of knee OA, body mass index, muscle strength, and depressive mood) (**Chapter 11**) (72). In an unpublished study, this phenotype identification could be replicated in the AMS-OA cohort. The 5 phenotypes potentially represent different subtypes of OA in which phenotype-specific interventions are needed. For instance, the ‘depressive phenotype’, which was found to be the clinically most affected phenotype, may not benefit from usual pain medication and standard exercises, but needs exercise therapy with a behavioral approach, combined with antidepressant medications and/or psychotherapy.

We would like to challenge other research groups to use our clustering technique for replication as well as for identification of other clinically relevant phenotypes. As an example, Conaghan (73) hypothesized the existence of 3 subgroups that could be identified by MRI and may benefit from pathology-targeted therapies. Firstly, a phenotype of patients with isolated cartilage lesions in the early stage of OA disease may benefit from (mesenchymal) stem cell therapy for cartilage regeneration. Secondly, in a phenotype with extensive synovitis, cytokine inhibition (anti-TNF therapy) might be successful. Thirdly, a phenotype of patients with bone marrow lesions may need antiresorptive bone therapy. Phenotype identification should receive priority in OA research as tailoring of interventions is essential to optimize the effectiveness of OA treatments.

Conclusions

In summary, the following conclusions can be drawn from this thesis.

- Knee instability is highly prevalent among knee OA patients and associated with more severe activity limitations.
- Upper leg muscle strength seems to be a dominant factor in knee stabilization in knee OA patients, whereas knee proprioception and varus-valgus laxity could not be linked to knee instability.
- Knee proprioception is reduced in knee OA and associated with pain and activity limitations. Causal factors (local and systemic) of proprioceptive deficits in knee OA are unclear, although evidence suggests a role of meniscal damage.
- Quadriceps weakness was found to be associated with PF cartilage defects and knee joint inflammation.
- In knee OA patients suffering from knee instability, initial knee stabilization training, in addition to strength and functional training was not found to be effective over strength and functional training only. However, subgroup-analyses revealed that knee stabilization training may have added value in patients with knee instability and stronger muscles.
- Strength training is an essential component of exercise therapy and muscle strengthening following exercise therapy seems to be an underlying mechanism of the effectiveness of exercise therapy.
- Patients from all grades of OA severity can benefit from professionally supervised exercise therapy.
- Identification of clinically relevant phenotypes may facilitate the development of targeted, phenotype-specific interventions.

Directions for future research

Based on the study findings in this thesis, the following directions for future research can be suggested.

Firstly, an objective measure for knee instability that is able to detect and distinguish different forms of instability (i.e., buckling, shifting, giving way) needs to be developed and validated.

Secondly, a new measurement technique for knee joint proprioception needs to be developed that is both reliable and closely linked to proprioception in daily activities, for example by measuring in weightbearing position under dynamic conditions.

Thirdly, future research needs to unravel the role of upper leg muscles in knee stabilization. A minimal level of strength necessary to stabilize the knee could possibly be estimated. Moreover, because of the important role of the muscles in knee stabilization and potentially in OA disease as well, determinants of muscle weakness in knee OA need to be further clarified.

Fourthly, longitudinal studies are needed focusing on the relationship between biomechanical impairments (i.e., muscle weakness, reduced proprioception, laxity) and structural damage in the knee joint.

Fifthly, future studies need to evaluate the effectiveness of innovative, tailor-made exercises programs, for instance exercise therapy adapted for PF OA patients. Exercise programs consisting of high-intensity exercises (with a gradual increase) or combined with additional treatments (i.e., vitamin D, pain or anti-inflammatory medication) could result in larger strength improvements, but need to be evaluated for effectiveness and safety.

Sixthly, the controversy on the impact of exercising on structural damage of the knee joint needs to be unraveled, by comparing progression of knee OA over time between patients treated with long-lasting exercise therapy and patients not exercising at all. Other potential barriers to prescribe (or perform) exercise therapy, besides this controversy, need to be identified, in order to approach the 'underuse' of exercise therapy as an effective, conservative treatment option in knee OA.

Finally, more studies need to aim at identifying clinically relevant phenotypes from the heterogeneous knee OA population. This may help understanding the OA disease and could open opportunities for targeted treatments. Future randomized, controlled trials should ideally be conducted in specific phenotypes.

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