Chapter 8

General Discussion

This thesis provides an insight into the contribution of various inflammatory, neuromuscular, biomechanical and behavioral factors to the activity limitations in patients with knee OA. In this chapter, the main findings of the studies will be summarized, placed into clinical context and directions for further research will be suggested.

Contribution of inflammatory factors to activity limitations

Elevated levels of inflammatory markers are one of the clinical factors that have been associated with activity limitations in patients with knee OA (1). The pathway between inflammation and activity limitations is however to date not clearly elucidated. Previous studies have suggested that an increase in activity limitations might be associated with a decrease in muscle strength (2), which might be induced at least partially by elevated levels of inflammatory markers (3). Nevertheless, the scarce evidence about the association between inflammatory markers and muscle strength in patients with OA has shown conflicting results (4;5).

In **chapter 2,** we investigated the cross-sectional association between serum inflammatory markers (i.e., c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and knee muscle strength in a group of patients with knee OA. In this study, elevated markers of CRP and ESR were associated with lower muscle strength. The association found is coherent with findings from previous studies in patients with OA (4), in patients with rheumatoid arthritis (6) and in the general elderly population (7;8). However, the longitudinal relationship of the association between inflammatory markers and muscle strength has not been established in patients with OA. Therefore, in **chapter 3,** this association was evaluated in a subsample of the same study group using a longitudinal design. In this two years follow-up study, results showed that elevated levels of CRP values, but not ESR, at baseline and two years were associated with a lower gain in muscle strength over time compared with patients with not elevated levels at both times of assessment. Though, further longitudinal studies are needed, those results might represent a step forward in understanding the cause and effect association between inflammatory markers and muscle strength.

CRP and ESR levels, studied in **chapters 2 and 3,** have been found elevated in patients with knee OA (9;10). Evidence has shown that these systemic inflammatory

markers might be elevated secondarily to an active inflammatory process but also due to a higher BMI, which is a relevant characteristic in many patients with OA (Figure 1). BMI was an important confounder in the relationship between inflammatory markers and muscle strength studied in **chapter 2**. Previous studies have found a strong association between systemic inflammatory markers and BMI (11;12). Production and secretion of several pro-inflammatory cytokines by the adipose tissue (adipocytokines), and/or a non-hepatic production of CRP stimulated by adipocytes (13;14) might explain this association. In addition, elevated levels of local proinflammatory cytokines such as interleukin 1 beta (IL-1 beta), IL-1 receptor antagonist (IL-1ra) and tumor necrosis factor alpha (TNF- α) have been reported in OA (15), probably associated to synovitis (16).

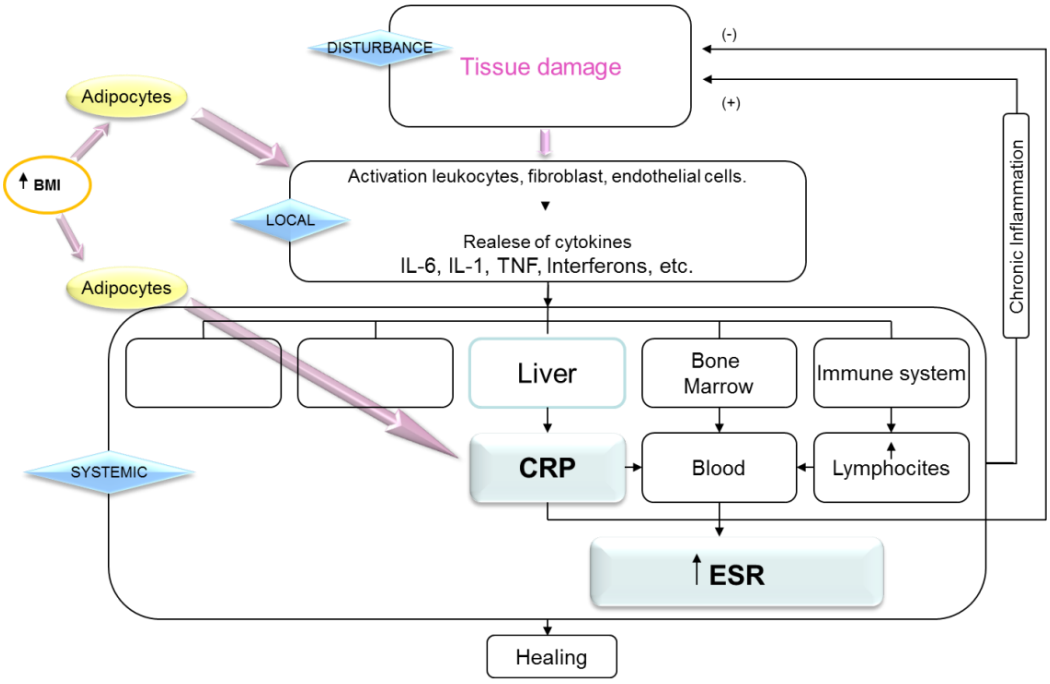

Figure1. Inflammatory response

Source: Adaptation based on Heinrich et al. (17)

Elevated levels of inflammatory markers have been associated not only with lower muscle strength, but also with loss of muscle mass and sarcopenia both in healthy elderly and in patients with rheumatoid arthritis (6-8). Higher levels of inflammation and oxidative stress may interfere with the balance between protein synthesis and breakdown in the skeletal muscle, cause mitochondrial dysfunction, and induce

apoptosis (18). It is been shown that local inflammatory cytokines such as TNF-α are the primary signals that induce cellular apoptosis in the muscle (18), contributing to a reduction in muscle mass and strength. Apoptosis and inflammation are involved in muscle mass and strength reduction. Indeed, the association between elevated markers of inflammation and lower muscle strength might be explained by the catabolic effect of inflammatory markers in muscle tissue (3).

Besides the effect of inflammatory markers in muscle tissue, elevated markers of inflammation at the local level could contribute to muscle inhibition which might translate in lower muscle strength (19). Knee synovitis and effusion, signs of local inflammation, were previously associated with lower average knee muscle strength in patients with OA (20). Effusion of the knee was found to be a potential inhibitor of maximal muscle activation in non-OA studies (21). Previous evidence has suggested that muscle inhibition associated to neurophysiological mechanisms might affect the muscle's capacity to generate force (22). However, the potential inhibitory effect of synovitis and/or effusion as mechanism explaining the association between elevated inflammatory markers and lower muscle strength cannot be concluded from the studies carried out in **chapters 2 and 3**. Further studies are needed to clarify the role of systemic and local inflammatory markers in the decrease of muscle strength in patients with OA.

The results of both the cross-sectional and longitudinal studies of this thesis support the hypothesis that the association between elevated systemic inflammatory markers and activity limitations might rely, at least partially, on changes in muscle strength. It is possible that changes in skeletal muscle secondary to elevated levels of inflammatory markers may contribute to a decrease in muscle strength, and subsequently decrease in muscle strength may lead to activity limitations. However, additional research is required to clarify the causality of the association between inflammation and activity limitations in patients with knee OA.

Contribution of neuromuscular factors to activity limitations

Neuromuscular factors and activity limitations

Previous cross-sectional (23;24), prediction (25;26) and intervention (2;27) studies have reported a linear inverse association between muscle strength and activity limitations in

patients with OA. However, observational studies that analyze the longitudinal association between changes in average knee muscle strength, knee extensor strength, knee flexor strength and changes in activity limitations in patients with established knee OA are missing. Therefore, the association between change in knee muscle strength (average, extensor and flexor separately) and change in activity limitations over two years was studied in **chapter 4** of this thesis.

The results of this study showed an association between increase in knee muscle strength and decrease in activity limitations in patients with established knee OA, over two years. Due to the progressive nature of the disease, a decrease in muscle strength over time is expected in patients with knee OA. However, there was an overall increase in muscle strength over the follow-up period in this study population. This is probably related to the fact that the patients of this study were initially referred to our outpatient rehabilitation centre to receive medical attention, time during which the acute onset of symptoms may have influenced the baseline measures causing a regression to the mean. Additionally, eighty percent of the study group reported to have received some type of physical therapy intervention during the two years follow-up. These aspects may help to explain the unexpected increase in muscle strength, and subsequent improvement in activity limitations over time.

The relationship between increase in muscle strength and decrease in activity limitations might be explained by the important role of muscle function around the knee joint which controls motion, adds stability, redistributes loads and compensates against gravity (26). We analyzed the association between changes in isokinetic concentric muscle strength and changes in activity limitations over two years. The results showed that an increase in average knee muscle strength and knee flexor muscle strength were associated with decrease in self-reported activity limitations and decrease in performance-based activity limitations; while increase in extensor muscle strength was only associated with decrease in time performing the stair test.

Besides the concentric muscle strength analyzed in our study, the analysis of eccentric muscle strength could contribute to a further understanding of the association between muscle strength and activity limitations according with their level of exigency. For example, concentric extensor muscle strength might be highly required to climb

stairs, while eccentric contraction of the same muscle group could be required when descending stairs. In addition, the bi-articular function of the muscles assessed could influence the performance of the task through flexion or extension of hip. Indeed, concentric as well as eccentric evaluation of knee muscle strength (average, extensor and flexor separately) might give a comprehensive view of the association between muscle strength and activity limitations in patients with established knee OA. Further information about this association, together with a clear definition of the thresholds of muscle strength problematic for activity limitations, could help to design intervention programs according to specific tasks and particular needs in daily life within this group of patients. In addition, data related with optimal velocity of contraction and endurance capacity might contribute to reach this goal.

According to the neuromuscular model proposed by Dekker et al. (28), besides low muscle strength, knee instability may also contribute to activity limitations (see Figure 2, chapter 1). The association between the presence of knee instability, lower muscle strength and increased activity limitations has been previous documented in patients with knee OA (29). However, studies have focused mainly on the analysis of the average (30) and extensor (31) knee muscle strength and their association with knee instability. In **chapter 6** of this thesis, the associations of self-reported knee instability with average knee muscle strength, but also knee extensor and flexor were analysed separately. The present results showed that self-reported knee instability in patients with knee OA was associated with (isokinetic and isometric) average knee muscle strength, flexor knee muscle strength and extensor muscle strength. We concluded that muscle strength training could be a potential effective mechanism to counteract self-reported knee instability in patients with OA. Subsequently, a decrease in self-reported knee instability might contribute to a decrease in activity limitations.

In patients with OA, evidence has shown an increase (1), no change or even a decrease (26;32) in activity limitations over time. In addition, high between-patients variability in the course of activity limitations in patients with OA which need to be further explored has been reported (25;33). The results from the study in **chapter 4** suggest that muscle strength partially explains the between-patients variability in activity limitations previously documented in patients with established knee OA.

Overall, our results suggest that muscle strength plays a relevant role within the development of activity limitations and self-reported knee instability in patients with knee OA.

Postural control and activity limitations

Postural control (balance) is required for the maintenance of the body position while standing and/or while performing activities of daily living. It has been considered an important component of performance for transfer, ambulatory tasks and activity limitations (34). Impairments of postural control might lead to a loss of movement, increase in activity limitations and decrease in quality of life.

Postural control is a multifactorious task that involves diverse sensorimotor information (i.e. vision, vestibular function) integrated at the central level. Those processes translate into a coordinated neuromuscular response at the peripheral level (i.e. muscle strength, proprioception) (35). Postural control deficits, which have been previously reported in patients with OA (36), have been associated with lower muscle strength and proprioceptive inaccuracy (37;38). However, the association between decreased postural control and knee instability has not been clearly established, and only limited studies have reported the association between postural control deficits and increased activity limitations in this group of patients (35;38). Therefore, the association of postural control with muscle strength, proprioception, self-reported knee instability and activity limitations in patients with OA was studied in **chapter 5**.

In the study carried out in **chapter 5** of the present thesis, decreased postural control was associated with a decrease in muscle strength and proprioceptive inaccuracy, but not with self-reported knee instability. Moreover, even after adjusting for relevant confounders (i.e. knee muscle strength) decreased postural control was associated with performance-based activity limitations, but not with self-reported activity limitations. This may be due to the potential influence of diverse psychosocial factors involved in the self-assessment. The results of this study contribute to an extension of the knowledge about the relevant association between postural control and activity limitations in patients with OA, suggesting the importance of incorporating postural control assessment and treatment within the regular care of these patients.

Traditionally, in patients with OA, postural controls has been assessed using complex and expensive equipment which are not always available in the clinical settings (38). Therefore, the identification of a simple clinical test, such as the one-leg stand test (OLST) used in **chapter 5**, to assess postural control easily in this group of patients might be of clinical relevance.

Contribution of biomechanical factors to activity limitations

Studies which analyze the biomechanical characteristics of patients with knee OA during the performance of activities of the daily living, different from gait level and stair climbing, such as stepping-down from a sidewalk are still needed. Moreover, the analysis of those variables in patients with diverse stage of the disease might contribute to a better understanding of the disease development and/or progression. Therefore, in **chapter 6** knee kinematics, kinetics and muscle activity patterns during a stepping-down task in patients with early joint degeneration based on the classification of Luyten et al. (39) versus more established knee osteoarthritis (OA) and control subjects were studied.

Patients with knee osteoarthritis (OA) often complain of knee instability (31;40). Failure to control the knee usually occurs during dynamic activities such as gait and stairs climbing/descending (29). However, due to the difficulty to clinically measure dynamic knee instability, the assessment of joint instability has been mainly limited to the self-reported knee instability questionnaire. Identification of objective biomechanical and/or neuromuscular performance characteristics associated with knee instability is needed in order to develop appropriate strategies oriented to counteract instability in those patients. Therefore, the biomechanical characteristics and muscle activity during a stepping-down task were further compared between patients with and without self-reported knee instability in **chapter 6**.

During the stepping-down task patients with established knee OA showed greater medial hamstrings activity than controls; as well as greater vastus medialis-medial hamstrings co-contraction than early OA and control subjects. As it has been reported in previous studies during the performance of gait and stairs climbing, greater muscle activity in the medial compartment of the knee might suggest an attempt to compensate greater knee laxity usually present in patients with established OA

(29;41;42). In addition, in the present study, larger vastus lateralis-medial hamstrings co-contraction was found in patients with established OA compared with control subjects. This finding suggests an overall increase in the compressive load through the knee surface in the patients with more severe disease. Greater muscle activity might suggest a less efficient use of knee muscles or an attempt to compensate greater knee laxity usually present in patients with established OA.

Increased muscle co-contraction patterns might contribute to increase the joint compression, leading to a further joint damage and disease progression. Rehabilitation strategies such as neuromuscular and strength training might contribute to counteract abnormal co-contraction patterns in this group of patients. On the other hand, greater muscle co-contraction patterns in combination with other movement modifications, such as decrease in knee flexion angles and excursion during activities, are thought contributed to stiffness of the joint in order to compensate knee instability and/or avoid knee pain in patients with established OA. Therefore, those performance characteristics might be necessary to achieve more effective ambulatory strategies, and functionality may be sacrificed if they treated with the intention to decrease joint compression. Further studies are needed to clarify the different perspectives mentioned and to accurately propose the intervention most suitable for each particular case.

None of the biomechanical performance-based characteristics recorded during the stepping-down task studied were significantly different between subjects with or without self-reported knee instability. This might be due to the small number of patients who reported at least an episode of knee instability during the past three months. Additionally, none of our subjects reported to have the feeling of knee instability during the stepping-down test in our laboratory. Therefore, we can conclude that probably the analysis of the biomechanical characteristics during the performance of a more challenging task might be required in order to find differences in biomechanical parameters between patients with and without self-reported knee instability.

Contribution of behavioral factors to activity limitations

According to the theoretical framework of the avoidance model, a behavioral mechanism may cause activity limitations in patients with knee OA and hip OA (43). Different components are considered to influence the association between avoidance of

activity and activity limitations (see Figure 3 in Chapter 1). Initially, it is thought that pain and psychological distress (i.e. anxiety, depression, low vitality and fatigue) lead the individual to avoid the performance of activities. Subsequently, avoidance of activities will result in muscle weakness and thus in an increase of activity limitations. In **chapter 7**, a systematic review of the evidence from observational studies related to the validity of the avoidance model and/or the relationships between the components of it was carried out.

In patients with knee OA, strong evidence supported the association between avoidance of activities and activity limitations via muscle weakness (mediation of muscle strength) (43;44), and the association between muscle weakness and activity limitations was also supported (26;45). However, evidence showed that the strength of the association between muscle weakness and activity limitations could be influenced by other impairments such as proprioceptive inaccuracy and high laxity of the knee (46-48). In patients with hip OA, weak evidence was found for the mediation effect of muscle weakness between avoidance of activities and activity limitations; and strong evidence (49;50) was found for the association between muscle weakness and activity limitations. Muscle weakness in hip OA is believed to be a manifestation of general physical deconditioning, and it is therefore directly associated with activity limitations. Overall, these results emphasize the importance of muscle strength in the maintenance of activities.

Besides the indirect association between avoidance of activities and activity limitations via muscle strength, a direct association was also found. This direct association indicates that muscle weakness is not the only mechanism explaining the association between avoidance of activities and activity limitations (51). Weak evidence stated that pain and psychological distress are associated with muscle weakness via avoidance of activities (mediation of avoidance). The assumed mechanism underlying these associations is that pain during activities leads to avoidance and subsequently muscle weakness. Also, fear of pain through the expectation that renewed activity results in more pain may be the cause of avoidance of activities and consequently muscle weakness (51). It has been reported that fear of pain is more disabling that pain itself (52). However, further research is needed to establish the impact of pain and fear of pain in the avoidance of activities. Overall, the results of studies that examined the

consecutive associations between pain or psychological distress and avoidance of activities were inconsistent, which can be explained by differences in study populations, covariable adjustment, model building strategies, and measurement instruments. To improve the quality and comparability of results, the use of a smaller set of reliable and valid measurement instruments is recommended. Event monitoring and use of accelerometers have the potential to provide better evidence for the validity of the avoidance model.

Evidence from longitudinal studies was only found for the association between muscle weakness and activity limitations in patients with knee OA. Therefore, from the studies included in the review no causal inferences can be drawn for the different pathways of the model. There is a clear need for longitudinal research on associations between changes in all consecutive components of the avoidance model in both patients with knee OA and patients with hip OA. In addition, more research is needed on the consecutive associations between pain or psychological distress, avoidance of activities and muscle strength, and to confirm causal relationships within the avoidance model.

Implications for clinical practice

The studies presented in this thesis have some implications for the therapeutic management of knee OA, which could help to avoid and/or counteract activity limitations in patients this group of patients.

The relevant role of muscle strength within the development of activity limitations has been directly or indirectly confirmed in all of the studies. From a clinical perspective, muscle strength training interventions that incorporate equally knee extensor and knee flexors muscles should be emphasized in order to decrease activity limitations in patients with knee OA. Additionally, increase in muscle strength could contribute to counteract knee instability and to improve postural control. Decrease in knee instability as well an improvement in postural control will secondarily contribute to a decrease in activity limitations, through different pathways. In the same line, our results highlight the importance of including assessment and training of postural control in patients with OA. The OLST might be recommended as an evaluation tool for the assessment of postural control in patients with knee OA, as this represents a simple and easy to perform clinical test.

We found a relevant association between elevated inflammatory markers and lower muscle strength in patients with knee OA. Although further evidence is needed, theoretically controlling inflammation and reducing overweight in patients with knee OA might contribute to better results in rehabilitation programs, adding to the improvement of muscle strength and subsequent decrease in activity limitations. It is possible that targeting low-grade inflammation by pharmacological, nutritional and/or lifestyle factors (53) might contribute to limiting sarcopenia and decrease in muscle strength in patients with knee OA. On the other hand, it is also possible that an increase in muscle strength (through muscle training) might contribute to a decrease in circulating inflammatory markers in patients with OA (54). It is also feasible that both mechanisms are involved. Further tailored intervention studies to confirm those statements are recommended.

From the biomechanical perspective, rehabilitation strategies directed to counteract greater muscle co-contraction patterns during the performance of daily activities might help to decrease knee loading in patients with knee OA. This may potentially help to protect the knee joint from further damage and disease progression. Nevertheless, it is important to consider that alteration of the compensatory mechanisms developed by the patients to increase knee stability, including the increase in muscle co-activity patterns, might secondarily contribute to an increase in activity limitations.

It is important to consider the potential influence of pain within the development and progression of activity limitations in patients with knee OA. Joint pain is the main reason for the initial visit to the general practitioner. Pain is described as a continuous dull or aching pain, which is interspersed with unpredictable short episodes of high intensity. Typically, this pain increases during weight-bearing activities and is relieved with rest. In later stages, pain occurs at gradually shorter walking distances and may finally even occur in rest and at night. In order to avoid episodes of pain, patients with OA may decrease the load in the symptomatic joint avoiding the performance of activities. However, as suggested in the avoidance model, the avoidance of movement leads to muscle weakness and subsequent increase in activity limitations in the long term. In addition, presence of pain could bias the assessment of muscle strength and activity limitations in patients with OA. Excessive joint pain may also prevent the

patients from fully engage in rehabilitation programs. Therefore, it is important to implement mechanisms, such as the use of pain medicines and pain coping technics, directed to an effective management of the joint pain present in this group of patients. An appropriate pain control is relevant for better assessment and treatment in patients with knee OA.

Directions for further research

Based on the experiences gained from the studies carried out during the elaboration of this thesis a number of recommendations for further research could be formulated.

It was concluded from the results of the studies that an optimal level of muscle strength contributes to a decrease in activity limitations in patients with knee OA. However, due to the lack of conclusive evidence about the most optimal muscle training interventions, further studies which aim to identify the right type and amount of muscle training that should be incorporated within the intervention programs are recommended. Additionally, our results suggested inflammation as a relevant factor influencing muscle strength in this group of patients. Nevertheless, future studies which involve the use of local markers of inflammation (i.e., IL-1, IL-6, Tumor Necrosis Factor (TNF)), instead of systemic inflammatory markers, together with studies involving controlled and tailored interventions and/or studies with animal models might be needed to further understand the causal pathway of this association, and to find out the best course of treatment.

In order to decrease knee loading and protect the joint from further damage, previous studies have suggested a need to control higher muscle co-contraction present in patients with knee OA. Therefore, further studies which target muscle co-contraction in the knees of patients with OA, through neuromuscular and/or strength training, might be recommended. The results of those studies could contribute to objectively elucidate the long term effect of changes in muscle activity patterns within the disease development and progression, and their influence in the course of activity limitations. In addition, we found no difference in the kinematics, kinetics and muscle activity patterns during the performance of the stepping-down task between patients with and without self-reported knee instability. However, a further study of those biomechanical characteristics during the performance of diverse, and probably more challenging,

activities of daily living in a larger sample of patients with self-reported knee instability might contribute to a better understanding of the objective characteristics associated with the sensation of instability in patients with knee OA.

From the behavioral perspective, additional studies which analyze the associations of pain and psychological distress with avoidance of activities, and subsequently with muscle strength are needed. Moreover, the causal relationships within the avoidance model still need to be further studied and determined.

Conclusions

This thesis provides data which contribute to a better understanding of the mechanisms and processes associated to the inflammatory, neuromuscular, biomechanical and behavioral risk factors involved in the development of activity limitations in patients with knee OA. This information may contribute to a more targeted treatment in clinical practice.

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