Summmary

Chapter 1 provides a general introduction for this thesis. Osteoarthritis (OA) is a chronic progressive joint disease. It is estimated that its high prevalence will continue rising worldwide due to the increases in life expectancy and in the prevalence of the obesity within the population. OA has been associated with chronic pain and activity limitations. A wide range of risk factors associated with activity limitations has been identified in this group of patients. However, a risk factor contributes to predict but does not explain activity limitations. The understanding of the mechanisms and processes associated with those risk factors is relevant for the future development of therapeutic and preventive interventions directed to decrease and/or prevent activity limitations in patients with OA. Therefore, the general aim of this thesis was to analyze the contribution of diverse inflammatory, neuromuscular, biomechanical and behavioral factors to the activity limitations in patients with knee OA.

In c**hapter 2**, the cross-sectional association of elevated levels of serum c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with knee muscle strength was studied. Elevated levels of inflammatory markers have been associated with activity limitations in patients with knee OA. The pathway between inflammation and activity limitations has not been clearly elucidated. However, the association between elevated levels of inflammatory markers and lower muscle strength found in this study support the hypothesis that the association between elevated inflammatory markers and activity limitations might rely, at least partially, on changes in muscle strength. It is possible that changes occurred in the 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, further research is needed to clarify the causality of the association between inflammatory markers and activity limitations in patients with knee OA. In addition, the association found was not independent of BMI, which might be explained by the strong association between systemic inflammatory markers and BMI previously documented.

The study in **chapter 3** aimed to examine the longitudinal association of elevated levels of CRP and ESR with change in knee muscle strength in patients with established knee osteoarthritis (OA), over two years. Patients with elevated CRP values at both baseline and two-years follow up exhibited a lower increase in knee muscle strength over two years compared with the group with not elevated levels at both times

of assessment. The association persisted after adjustment for changes in relevant confounders, including BMI. Elevated ESR values at both times of assessment were not significantly associated with change in knee muscle strength. Our results indicate that elevated CRP values are related to a lower gain in muscle strength over time in patients with established knee OA. Although the mechanism to explain this relationship is not fully elucidated, these results suggest inflammation as a relevant factor influencing muscle strength in this group of patients.

In **chapter 4** the longitudinal association between knee muscle strength and activity limitations in patients with established knee OA was studied. 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. The increase in muscle strength and subsequent decrease in activity limitations over time is probably related to the fact that the patients of this study were initially referred to our outpatient rehabilitation centre to receive medical attention. Additionally eighty percent of the study group reported to have received some type of physical therapy intervention during the follow-up period.

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. The results from this study suggest that muscle strength partially explains the between-patients variability over time in activity limitations previously documented in patients with established knee OA.

In **chapter 5** decrease in muscle strength and decrease in proprioceptive inaccuracy, but not self-reported knee instability, were associated with decrease in postural control in patients with knee OA. Moreover, decreased postural control was associated with performance-based activity limitations. The results of this study contribute to an extension of the knowledge about the relevant association of postural control and activity limitations in patients with knee OA, highlighting the importance of incorporating postural control assessment and treatment within the regular care of this population. In addition the one-leg stand test (OLST), used in the present study, may be considered a convenient tool to assess postural control easily in patients with OA.

Chapter 6 aimed to investigate the joint kinematics, kinetics and muscle activity patterns during a stepping-down task in patients with knee osteoarthritis (OA) (early and established) and control subjects, and to assess their associations with self-reported knee instability. During the stepping-down task patients with established knee OA showed greater medial hamstrings activity and vastus lateralis-medial hamstrings co-contraction than controls. Higher vastus medialis-medial hamstrings co-contraction was found in patients with established OA compared with control subjects and with patients with early OA. 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 further joint damage and disease progression. Therefore, neuromuscular and strength training directed to counteract greater muscle activity patterns during the performance of daily life 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. On the other hand, greater muscle co-contraction patterns might be necessary to achieve more effective ambulatory strategies due to its contribution to compensate knee instability and/or avoid knee pain in patients with established OA. Therefore, if treated with the intention to decrease joint compression, functionality may be sacrificed. 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 or muscle activity characteristics studied during the stepping-down task were significantly different between subjects with or without self-reported knee instability. However, muscle weakness was found to be a relevant factor associated with self-reported knee instability in patients with knee OA, which is consistent with the literature.

The systematic review of the literature in **chapter 7** provides an overview of the evidence related to the validity of the avoidance model and/or the relationships between the components of the avoidance model. In knee OA, strong evidence supported the association between avoidance of activities and activity limitations via muscle weakness, as well as strong evidence for the association between muscle weakness and

activity limitations was found. Weak evidence stated that pain and psychological distress are associated with muscle weakness via avoidance of activities. In hip OA, weak evidence was found for the mediation effect of muscle weakness between avoidance of activities and activity limitations; and as well as with knee OA strong evidence was found for the association between muscle weakness and activity limitations. 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

Finally, an overall discussion of the findings of this thesis is presented in **chapter 8**. Main findings, implications for clinical practice, directions for future research and conclusions regarding to the contribution of diverse factors in the activity limitation in patients with knee OA are provided.