Chapter 1

General introduction

Definition and prevalence

Osteoarthritis (OA) is considered the most common form of arthritis affecting synovial joints mostly the knees (6% of all adults) (1). The prevalence of OA is commonly defined radiographically or clinically (2). Radiological OA refers to the morphological or structural changes within the joint visible on X-rays. Those changes are usually defined using the radiological classification of Kellgren-Lawrence (K&L) (3). On this scale, the presence and severity of OA is defined according to intraarticular changes such as osteophyte formation, periarticular ossicles, thinning of the joint cartilage with narrowing of the intraarticular joint space, and formation of pseudo-cystic areas with sclerotic walls (4). In people older than 80 years, 53% of women and 33% of men have radiographic osteoarthritis of the knee, defined as the K&L grade ≥ 2 (5).

Symptomatic OA is considered if in addition to the presence of radiographic changes, the person suffers from joint pain, aching or stiffness (2). Data from the Johnston county osteoarthritis project showed prevalence of symptomatic OA of 16.7% in the knee (6) among adults aged ≥45 years. Currently, the overall prevalence of OA is roughly estimated at 151.4 million people worldwide (7). However, it is estimated that the prevalence of OA will continue rising worldwide, mainly due to the increase in life expectancy and the prevalence of obesity within the population (2).

Pathogenesis

The pathogenesis of OA has long been mainly related to changes initiated in the articular cartilage (Figure 1). However, recent evidence has suggested the participation of subcondral bone and synovial membrane (5) within the disease's development and progression.

The articular cartilage has a unique matrix structure rich in collagen and proteoglycans. It allows to absorb stress forces, to deform under mechanical load and to provide a smooth load bearing surface facilitating the joint's movement (8). Genetic, biomechanical and biochemical factors may alter the normal functioning of chondrocyte cells promoting a disruption of the equilibrium between the continual formation and breakdown of the cartilaginous matrix, and leading to a failure of the homeostatic balance maintenance (1;9). As a consequence, the cartilage becomes part of a vicious

cycle of depletion resulting in progressive loss of the hyaline cartilage within the joint, and eventually leading to underlying subchondral bony changes (1;9;10).

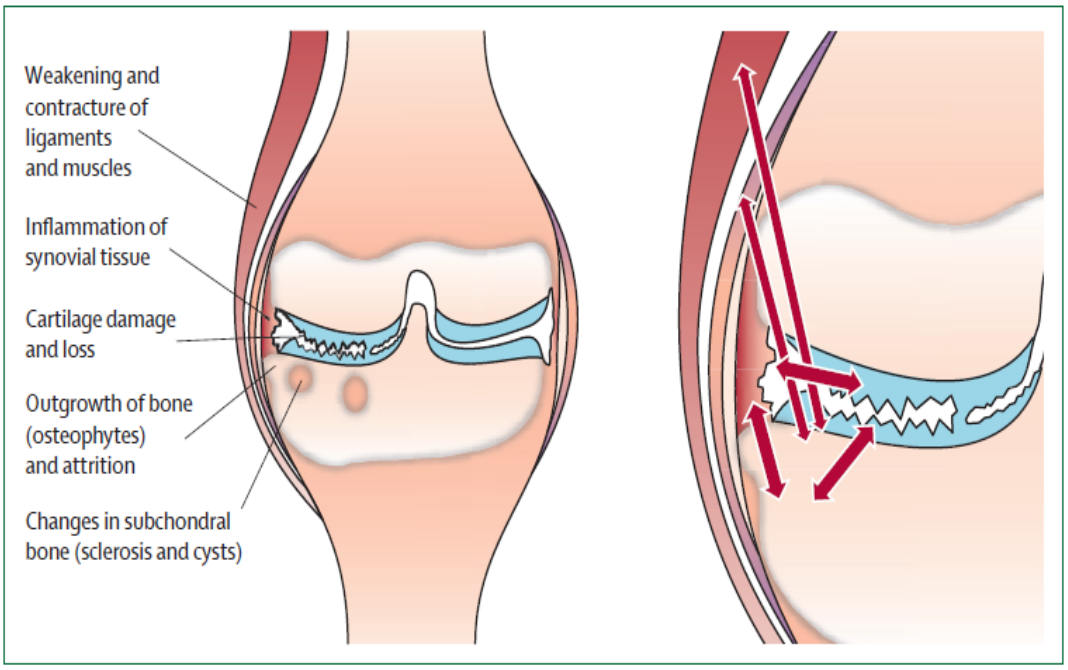

Figure 1. Schematic drawing of an osteoarthritic joint

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Osteochondral changes characteristic of OA disease may occur early during the development of OA and accentuate during the disease progression. Recent evidence suggests subchondral bone changes as possible precursor of the cartilage damage rather than as consequence of it (5;8). Moreover, it is suggested that the integrity of the cartilage depends on the mechanical properties of its bony underlying. Therefore, the bone's loss of effective capacity to absorb forces (stiffening of subchrondral bone) caused by repetitive micro-fractures may affect the cartilage's overlay integrity (8). According to Intema et al. (11), thinning of the subchondral plate is related to cartilage degeneration while trabecular bone changes are related to mechanical loading.

Synovial inflammation may occur as a consequence of posttraumatic joint injury (9) or secondary to the chemical process associated with early or late phases of OA. It usually corresponds to clinical symptoms of joint swelling and pain (5). The

inflammatory component is characterised by the release of catabolic and proinflammatory mediators from the synovial membrane which might promote the cartilage degeneration (12), due to the excessive production of the proteolytic enzymes responsible for cartilage breakdown (13).

Joint damage in OA can be influenced by various factors, which have been grouped into systemic factors and local mechanical factors (10). Systemic factors are considered to predispose patients to the development of the disease such as older age (3;5), female gender (2;14), genetic predisposition (10;15), Chinese and African American race/ethnicity (16;17), vitamin D deficiency (18) and obesity (19). Local mechanical factors, which are thought to influence the disease's distribution and severity, include previous joint injury (20), high impact physical activity (21) and some occupational activities (22), muscle weakness (23) and malalignment (2).

Symptoms, signs and diagnostic criteria

Chronic joint pain is the main clinical symptom that leads to the initial visit to the clinician in patients with OA (2). Stiffness present in the morning, in the evening or after periods of inactivity which lasts for a short period of time is considered another OA symptom (24). Additional signs related to OA include bony enlargement, impaired range of joint motion, crepitus on motion, tenderness on pressure, joint effusion, malalignment and/or joint deformity (2;8). The American College of Rheumatology (ACR) has published classification guidelines presenting the diagnostic criteria for clinical and radiographic osteoarthritis of the knee (table 1) (25).

Table 1. American College of Rheumatology criteria for knee OA

Knee (clinical)
Osteoarthritis if 1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5 are present:
1. Knee pain for most days of previous month 2. Crepitus on active joint motion 3. Morning stiffness lasting 30 min or less 4. Age 38 years or older 5. Bony enlargement of the knee on examination

Knee (clinical and radiographic)

Osteoarthritis if 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6 are present:

1. Knee pain for most days of previous month
2. Osteophytes at joint margins on radiographs
3. Synovial fluid typical of osteoarthritis (laboratory)
4. Age 40 years or older
5. Crepitus on active joint motion
6. Morning stiffness lasting 30 min or less

Based on Bijlsma JW et al. (5)

A wide range of risk factors associated with activity limitations has been identified in patients with knee OA including socio-demographic factors (older age, female gender), physical impartments (muscle weakness, poor joint proprioception, etc), comorbidity and overweight, psychological and social factors, and health behaviors (31). Variation in those risk factors, or a combination of them, might contribute to further clarification of the between-patients variation in activity limitations over time. However, a risk factor contributes to prediction but does not explain activity limitations. Therefore, 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 (31). In this thesis we study some of the *inflammatory, neuromuscular, biomechanical and behavioral* factors contributing to activity limitations in OA.

Contribution of inflammatory factors to activity limitations

Pain, stiffness, radiographic damage and presence of comorbidities have been identified as relevant factors contributing to activity limitations in patients with knee OA (27). Additionally, previous studies have found an association between activity limitations and elevated levels of inflammatory markers (32;33). It has been suggested that the association between elevated levels of inflammatory markers and activity limitation might rely, at least partially, on changes in muscle strength (34).

Recent evidence has shown a low grade of inflammation in patients with OA, mainly associated with synovitis (35). A slight or moderate elevation of inflammatory markers (i.e. erythrocyte sedimentation rate (ESR), c-reactive protein (CRP)) have been reported in this group of patients (36;37) without differentiation of the stage of the

disease (early or established). There is scarce and contradictory evidence about the association between inflammation and muscle strength in patients with OA (38;39). However, previous studies carried out in older adults have reported an association of increased levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factors (TNF), with sarcopenia and muscle weakness (40;41). The associations found might be explained by the catabolic effect of inflammatory markers on muscle tissue (32).

The association between elevated levels of inflammatory markers and decreased muscle strength in patients with knee OA is studied in the **chapters 2** and **3.** The study results might potentially contribute to explaining the muscle weakness usually found in this group of patients. Secondarily, those results might contribute to the design of better treatment interventions directed to the improvement in muscle strength and subsequent decrease in activity limitations. Further understanding of the role of inflammation on muscle weakness might lead to new targets of assessment and treatment in patients with knee OA.

Contribution of neuromuscular factors to activity limitations

Neuromuscular factors and activity limitations

Muscle weakness has been reported in patients with knee OA, probably associated to diverse factors including decrease/lack in physical activity and the aging process (sarcopenia). The contribution of muscle weakness to activity limitations in patients with knee OA has been previously established (42). Low muscle strength has been associated with activity limitations (43), and earlier prediction studies have shown higher baseline muscle strength as potential protective factor for activity limitations in the long term (29;44). Additionally, strength training interventions have shown an association between increase in muscle strength and a decrease in activity limitations (45-47). Nevertheless, in patients with established OA, there is scarce evidence about the longitudinal association between muscle strength and activity limitations which motivates the research question of **chapter 4**.

The inverse relationship between muscle strength and activity limitations might be explained by the important role of muscle function around the knee, which directly controls the joint motion and secondarily adds stability to the joint (29). In addition to

low muscle strength, poor proprioception (48), higher laxity (49) and higher varus-valgus knee motion (50) may also contribute to activity limitations probably through knee instability (Figure 2). Patients with knee osteoarthritis (OA) often complain of knee instability, defined as the sensation of buckling, shifting or giving way (51). Previous studies have estimated that between 12% and 65% of this group of patients have reported at least one episode of knee instability during the past three months (51;52). The association between presence of knee instability and increased activity limitations has been previous documented in patients with knee OA (53).

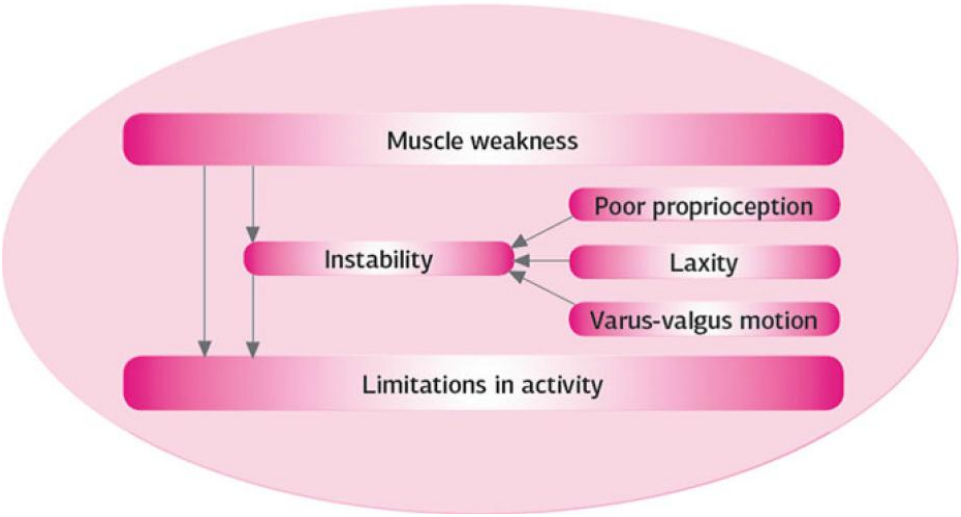

Figure 2. Activity limitations and neuromuscular factors (54)
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Postural control and activity limitations

Postural control (balance) allows the maintenance of posture when carrying out activities, and is essential for the prevention of serious injuries due to falls. It involves numerous body systems working together and leading to a coordinated neuromuscular response at the peripheral level. Neuromuscular disorders present in patients with OA, such as muscle weakness (55) and poor proprioception (56), as well as knee instability (57) might contribute to a decrease in postural control. In turn a decrease in postural control may lead to activity limitations. Postural control deficits, reported in patients with OA (58), have been associated with lower muscle strength and proprioceptive inaccuracy (59;60). However, the association between decreased postural control and knee instability has not been clearly established. Additionally, only limited studies have

reported the association between postural control deficits and activity limitations in this group of patients (46;60).

In patients with knee OA, postural control has been assessed using complex and expensive equipments which are not always available in the clinical settings (60). In contrast, the one-leg stand test (OLST) is a well-recognized tool for the evaluation of postural control, mainly used in studies with older adults (61). Nevertheless, this quick, cheap and easy-to perform test has not been widely used for to assessment of postural control in patients with knee OA. The identification of a simple clinical test, such as the OLST, to assess postural control easily in patients with OA might be of clinical relevance.

In this respect, in **Chapter 5** postural control has been assessed by means of the one-leg stand test. The association of postural control with diverse neuromuscular characteristics such as muscle strength, proprioception and knee instability is studied in patients with knee OA. Additionally, the association between postural control and activity limitations is analyzed.

Contribution of biomechanical factors to activity limitations

The kinematic and kinetic characteristics during the performance of daily activities such as gait and stairs climbing have been extensively studied in patients with OA (62). Evidence has shown the use of compensatory movement strategies such as decreased knee angle excursion (63), increased knee adduction moment (64) and increased muscle activity patterns (65), especially in the medial compartment of the knee, during the performance of activities (66). Results from previous studies have suggested that those variations could interfere with the distribution of the load on the knee joint, leading to further joint damage and disease progression (66). However, studies that analyze the kinematic and kinetic characteristics during the performance of other activities like descending from the sidewalk on the street are still needed. In addition, the analysis and comparison of diverse biomechanical characteristics during the performance of activities between patients in different stages of OA (early and established) might contribute to a further understanding of the disease development and progression.

Self-reported knee instability has been associated with deficiency in diverse neuromuscular factors mainly with muscle weakness in patients with knee OA (52). Recently, some studies have aimed to identify the objective biomechanical characteristics associated with knee instability in this group of patients. Those have reported an association between greater knee adduction moment and medial knee laxity during gait (64), and greater medial knee muscle co-contraction during platform perturbations (67). However, further evidence about biomechanical characteristics involved in the performance of diverse daily activities and self-reported knee instability is required.

The stepping-down task might be considered similar to common activities of daily living, such as descending from the sidewalk on the street. This task challenges muscle strength and neuromuscular control of the lower limb. Therefore, it has been considered helpful for the analyses of the knee under load-bearing conditions during a dynamic activity. Additionally, the stepping-down task has been used for the study of movement strategies in elders (68) and dynamic knee instability in a patient with anterior cruciate ligament deficiency (69).

In **chapter 6,** biomechanical and neuromuscular adaptations during the performance of a stepping-down task are studied in patients with early or established knee OA. Furthermore, the associations of biomechanical and muscle activity characteristics gathered with self-reported knee instability are explored.

Contribution of behavioral factors to activity limitations

The avoidance model is a theoretical model that explains how behavioral mechanisms may cause activity limitations in people with OA of the knee (70). According to this model (Figure 3), pain experienced by the patient during activities motivates the avoidance of activities. In the short term, avoidance of activities diminishes the pain due to the decreased load on the symptomatic joint. However, in the long term, lack of activity leads to further muscle weakness. Subsequently, muscle weakness contributes to an increase in activity limitations. In addition, it is hypothesized that psychological distress (i.e. anxiety, depression, low vitality and fatigue) also enhances the tendency to avoid activities, leading to muscle weakness and activity limitations (71).

A systematic review of the evidence related to the validity of the avoidance model and/or the relationships between the components of it, in patients with knee and hip OA, is presented in **chapter 7** of the present thesis.

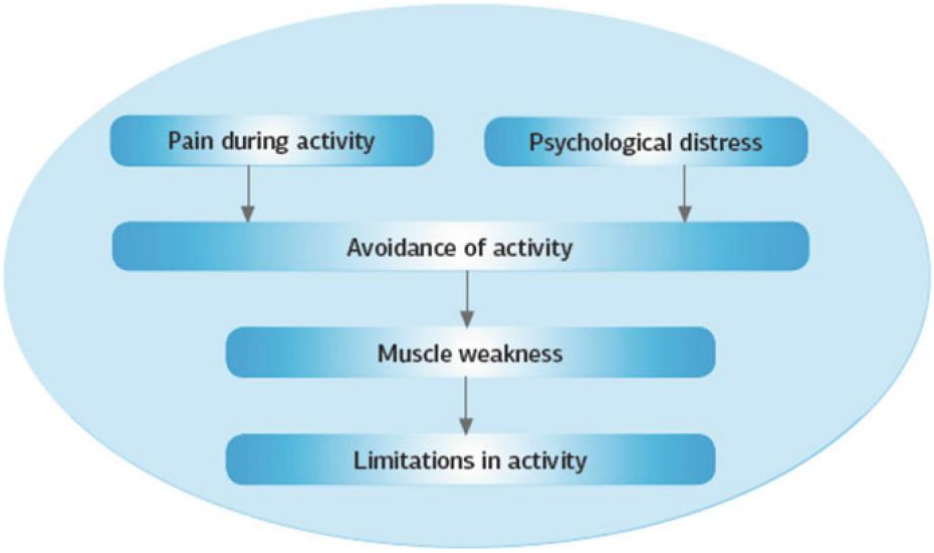

Figure 3. Activity limitations and behavioral factors: The avoidance model (54) (printed with permission)

Aim and scope of this thesis

The aim of this thesis is to explore further the contribution of inflammatory, neuromuscular, biomechanical and behavioral factors to activity limitations in patients with knee OA. The study results may lead to a better understanding of the mechanisms involved in the development of activity limitations in patients with OA. A total of six research questions will be addressed:

1. Do elevated levels of c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) explain some of the decrease in muscle strength that is usually found in patients with knee OA? **(chapter 2)**.

2. Do elevated levels of c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) both at baseline and at two-years follow up associate with lower muscle strength over two years in patients with knee OA? **(chapter 3)**.

3. Is change in muscle strength associated with change in activity limitations over two years in patients with knee OA? **(chapter 4)**.

4. Is postural control associated with muscle strength, proprioception, self-reported knee instability and activity limitations in patients with knee OA? **(chapter 5)**.

5. Are the biomechanical and neuromuscular adaptations during the stepping-down task different in patients with early or established knee OA compared to control subjects? And are these adaptations related to self-reported knee instability? **(chapter 6)**.

6. What is the scientific evidence available to support the validity of the avoidance model as a behavioral mechanism leading to activity limitations in patients with knee and/or hip osteoarthritis (OA)? **(chapter 7)**.

An overall discussion of the findings of the thesis is presented in the **chapter 8**.

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