Chapter 1

General introduction
Osteoarthritis of the knee joint

Osteoarthritis (OA) is the most common rheumatic disease of the musculoskeletal system, with the knee being the most commonly affected joint. It is estimated that about 150 million people worldwide are affected with OA, and approximately 1.2 million in the Netherlands. OA is also responsible for a substantial economic burden, accounting for $128 billion per year in direct and indirect costs in the United States alone. The number of people affected with OA is likely to increase due to the ageing society and the obesity epidemic. This suggests that the clinical and economic burden of OA is anticipated to increase and will remain a major medical and socio-economic problem in the future.

OA is diagnosed radiographically and/or clinically. The Kellgren-Lawrence (KL) grade is the most commonly used radiologic grading system for knee OA and evaluates the severity of radiographic OA based on the presence and degree of osteophytosis, joint-space narrowing (JSN), sclerosis and cysts. The KL grade scales OA severity on a scale of 0-4 with ≥2 defining radiographic knee OA.

The clinical diagnosis of knee OA is mainly based on the American College of Rheumatology (ACR) criteria. According to the ACR criteria, knee OA is diagnosed if knee pain is present and three of the following six parameters are present: age > 50 years, morning stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement and no palpable warmth. It is recognized that some persons suffer from severe pain without evident radiographic damage, while other persons have evident radiographic damage and only mild or no symptoms. Because clinical symptoms and not radiographic changes are leading in treatment decision-making, studies of OA in persons with clinically diagnosed OA may be more relevant from the clinical perspective.

The pathogenesis of the disease is not fully understood, but appears to result from a complex interplay between mechanical, cellular and biochemical factors. The disease occurs when the balance between the breakdown and repair of joint tissues becomes disrupted, often when the mechanical loads applied exceed those tolerated by the joint tissue. Although knee OA has been considered mainly cartilage driven, recent evidence suggests additional role of bone and synovial tissue. Synovial inflammation is thought to be secondary to cartilage debris. Synovial macrophages produce catabolic and pro-inflammatory mediators and inflammation starts negatively affecting the balance of cartilage matrix degradation and repair. In result, the articular and periarticular tissue enters a vicious cycle in which breakdown dominates over synthesis leading to progressive joint failure.

The development of knee OA is often conceptualized as a combination of local joint-specific factors acting in the context of systemic risk factors. Systemic risk factors may include age, gender, obesity, diet, race/ethnicity, genetics and congenital/developmental conditions. Joint-level factors may involve knee malalignment, joint injury and/or surgery and muscle weakness.

Clinical symptoms

The predominant clinical symptom of knee OA is pain, which is described as worsening by activity and relieved by rest. More persistent rest and night pain can occur in advanced knee OA. Joint stiffening occurs especially in the morning or after other long periods of immobilization. Eventually, range of motion decreases in advanced stages as a consequence of adaptive changes in the joint shape and surrounding bone. Other symptoms include joint inflammation, crepitus and muscle atrophy. Knee instability has also been recently recognized as an important clinical feature in persons with knee OA. These symptoms frequently lead to limitations in performing daily activities.

Activity limitations

Activity limitations are defined as difficulties a person might have in performing daily activities such as walking, rising up, sitting down and stair climbing. Activity limitations are frequent among persons with knee OA, and therefore, are considered one of the most important outcome measures for OA. Activity limitations are often referred to by health care professionals and researchers as a person's physical functioning, thus, the term physical function is also used in this context. Activity limitations are measured with self-report questionnaires and performance-based tests. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a recommended questionnaire to measure activity limitations in the setting of knee OA. Performance-based tests to assess activity limitations, require a person to perform one or more tasks (e.g. walking, rising up from a chair) that are evaluated in a standardized manner using predefined criteria. Activity limitations can affect one's aerobic capacity and consequently risk of disability and quality of life. For those reasons, activity limitations, along with other clinical symptoms, should be a target for treatment in persons with knee OA.

Knee joint instability

Knee instability is defined as an inability of the knee joint to maintain a position or to control movements under different external loads, and has been related to activity limitations in persons with knee OA. In the setting of OA, knee instability has been suggested to involve a spectrum of signs, including a feeling of low overall...
valgus bracing may result in little or no effect on pain and physical function, and adherence to this treatment in persons with knee OA is low. Soft knee braces - elastic, non-adhesive orthoses - might be used as an alternative to valgus braces in persons with knee OA because of ease of use and access, lack of complications and low cost as well as different working mechanisms (Figure 1).

Figure 1. Knee soft brace

Soft knee bracing in knee OA
Soft brace efficacy and effectiveness in persons with knee OA has been assessed in laboratory and ambulatory settings. A laboratory setting allows the assessment of the immediate efficacy of an intervention under controlled conditions, while an ambulatory setting allows the assessment of the effectiveness in real life, where uncontrollable factors may be present. Bryk et al. observed a 0.6 mm reduction in the Visual Analog Scale (VAS) for pain during Stair Climb Power Test (SCPT), while Schween et al. and Hassan et al. reported a similar decrease in VAS for pain during level walking. To our knowledge, only Bryk et al. used performance-based physical tests to evaluate the immediate effect of a soft brace on activity limitations in persons with knee OA. Thus, the evidence for the immediate efficacy of soft knee bracing on pain and activity limitations in knee OA is limited. Anecdotally, persons with knee OA state that using a soft brace improves their perceived knee stability. Nevertheless, there is only one study that has shown improvement in self-reported knee stability while wearing a soft brace. Although the effect on self-reported knee instability is important, it has its limitations, e.g. being susceptible to bias from the placebo effect. An evaluation of objectively assessed dynamic knee instability could strengthen

Management of knee OA
Knee OA management consists of conservative (non-pharmacological and pharmacological) and surgical treatment options. Non-pharmacological options consist of education, weight loss, exercise, braces and physical therapy. Pharmacological options include pain medication, anti-inflammatory medication, and potentially disease modifying agents. Surgery is recommended for end-stage knee OA and/or when conservative treatment is unsuccessful. Although knee joint replacement has good clinical benefit, this treatment strategy should be postponed as long as possible to prevent costly revision surgery at a later phase with less good outcome than initial joint replacement. For this reason, the first step in the management of persons with knee OA should be conservative treatment.

Exercise therapy can be considered a cornerstone therapy in knee OA. Nevertheless, the effect of exercise therapy on pain and physical functioning in persons with knee OA has been found to be small to moderate. In addition, adherence to exercise therapy declines significantly over time among persons with knee OA.

The Osteoarthritis Research Society International (OARSI) recommends knee bracing. Valgus knee braces designed to decrease loads on the knee medial compartment for patients with varus alignment are most common, given the increased load typically borne by that compartment during walking OA. It has been shown however, that confidence in the knees, perception of or actual buckling defined as the sudden loss of postural support across the weight-bearing knee and objectively measured excessive frontal plane motion during weight-bearing activities. Knee instability may influence one’s perception what he or she can do and, in turn, increase activity limitations. Thus, interventions aiming to reduce knee instability should be part of the treatment strategies for persons with knee OA.

The knee is actively stabilized by the neuromuscular system provided by proprioceptive input and muscle activity, and passively stabilized by passive restraints, provided by capsule and ligaments. Afferent and efferent neural deficits as a result of pain and damage to joint structures could impair the ability of the neuromuscular system to execute appropriate commands in response to external challenges to joint stability. Therefore, knee instability might be more pronounced in the presence of external perturbations during daily life of persons with knee OA. For this reason, efficacy of a treatment aiming to reduce knee instability should also be demonstrated in situations that might contribute to increased risk of knee instability e.g. external perturbations such like slip, sideward push etc.
the evidence for the use of a soft knee brace to reduce knee instability. However, to our knowledge, no evidence exists to show that a soft knee brace improves dynamic knee instability. Therefore, there are reasons to strengthen the evidence for the immediate efficacy of using a soft brace to target pain and activity limitations as well as to evaluate the efficacy of soft knee bracing on knee instability in persons with knee OA.

Mechanisms underlying the effect of soft knee bracing
The effects of a soft brace on clinical symptoms in knee OA have been attributed to the stimulation of cutaneous sensory fibers from skin mechanoreceptors. The skin mechanoreceptors are sensitive to tactile stimuli, and slight movement of a soft brace over the skin may stimulate the mechanoreceptors. Cutaneous contribution to the sensory input might enhance proprioception, one’s ability to detect joint position and motion. Tactile stimuli on the knee skin, can cause neural inhibition, facilitating the entry of impulses through the large afferent fibers. Consequently, it may lead to reduction in transmission of pain signals. A cutaneous contribution to proprioceptive acuity and a reduction of pain is expected to reduce knee joint instability, and thereby reduce activity limitations. A study model has been developed to determine whether wearing a soft brace reduces activity limitations; and whether this effect, if present, is driven via changes in proprioception, pain and knee stability (Figure 2).

To our knowledge, there is no study that explored the mechanisms responsible for the effects of soft braces in knee OA. Understanding the mechanisms that underpin the beneficial effects of soft braces will assist with developing and refining knee bracing strategies aimed at reducing activity limitations in persons with knee OA.

In addition, the mode of action of a soft brace might depend on how tight a soft knee brace fits the knee. It has been previously reported that a non-tight brace elicited significant effects on pain and postural sway but not a tight brace. The authors suggested that a non-tight brace provides more recurrent stimuli to cutaneous mechanoreceptors, whereas a tight brace provides constant pressure, to which skin mechanoreceptors adapt. There is a clear need to replicate this study to determine whether tightness of a soft brace is of influence on clinical outcomes in knee OA.

Study aims and outline of the thesis
The aims of the thesis were: i. to evaluate the effects of soft braces in persons with knee OA; ii. to compare the effects between a non-tight and a tight soft brace; and to identify mechanisms underlying beneficial effects of a soft brace in persons with knee OA.

In Chapter 2, the scientific evidence is summarized in a systematic review and meta-analysis on the effects of soft knee braces on pain and physical functioning in persons with knee OA. In Chapter 3, the mediation effect of proprioception on the association between systemic inflammation and muscle strength is presented. In Chapter 4, the results for the immediate effect of wearing a soft brace on activity limitations, pain, self-reported knee instability and self-reported knee confidence are demonstrated. Chapter 5 answers the question whether wearing a brace reduces objective dynamic knee instability in persons with knee OA. In Chapter 6, the mechanisms underpinning beneficial effects of wearing a soft brace in the studied group are identified. An overall discussion of the findings in this thesis is provided in Chapter 7. Finally, the thesis is summarized in English and Dutch languages.

It should be noted that one study in the thesis (Chapter 3) has been conducted with data from the Amsterdam Osteoarthritis (AMS-OA) cohort of Reade. This is ongoing cohort, which explains differences in sample sizes between studies.

![Figure 2](image-url). Study model showing the hypothesized mediating effect of proprioception, pain and dynamic knee instability on the effect of wearing a soft brace on activity limitations.)
Chapter 1 – General introduction

18 World Health Organization: International classification of functioning, disability and health:ICF.


16 Buckwalter JA, Martin J, Mankin HJ: Synovial joint degeneration and the syndrome of osteoarthritis.

1514


Reference List
Chapter 2

Effect of soft braces on pain and physical function in patients with knee osteoarthritis: systematic review with meta-analyses