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Identification of risk factors associated with the progression of knee-osteoarthritis: a prospective longitudinal study

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SUMMARY

Osteoarthritis (OA) is the most common chronic degenerative joint disease with the knee as the most affected joint. A report on the global burden of disease indicated knee OA as one of the leading causes of disability. The number of knee replacements is small compared to the number of subjects with knee OA. Therefore, it appears that preventing progression to severe joint damage may offer a more effective public health strategy than attempting to prevent disease incidence. Developing strategies to prevent (progression of) knee OA requires a thorough understanding of the factors associated with disease incidence and progression. Despite the high prevalence of knee OA, the information on the underlying causes is limited. Better understanding of the factors contributing to the onset and progression of the disease is imperative for better prevention and improvement in the treatment for OA.

The objective of this doctoral thesis was to contribute to the knowledge on the objective functional differences and their relation to the clinical and structural characteristics, as well as changes over time, in women with early medial knee OA compared to established medial knee OA and healthy controls. Also, to gain insight into the identification of risk factors associated with progression of knee OA. In **chapter 1**, the background and rationale behind this thesis are described. So far, our knowledge of knee OA is mostly based on data from heterogeneous patient populations with knee OA, but in order to better understand the knee OA trajectory it is important to study knee OA in the early stages of the disease. Therefore, additional studies are needed to further refine the structural, clinical and functional profile of the subjects with early knee OA and to assess how this profile evolves over time.

In **study I**, as described in chapter 2, we aimed to investigate whether weighting of proprioceptive input is altered in patients with early and established knee OA compared to asymptomatic controls. In this study the upright posture of participants with early OA, established OA, and asymptomatic controls was perturbed by vibrating ankle muscles and knee muscles. Center of pressure displacements of the participants were recorded using a force plate. Our findings showed that both patients with early and established OA were more sensitive to triceps surae vibration compared to their healthy peers. No such difference was found for the vibration of tibialis anterior or vastus medialis muscles between patients with knee OA and healthy controls. These results suggested that

the early stages of knee OA may already lead to reweighting of proprioceptive information, suggesting more reliance on ankle proprioceptive input for postural control.

In **study II** (chapter 3), we evaluated the presence and magnitude of varus thrust and its relation with the Knee Adduction Moment in women with early medial knee OA, and compared it to that in a group of controls and in a group of subjects with established medial knee OA. Varus thrust was estimated as an increase of the knee varus angle during the weight-bearing phase of gait at self-selected speed, assessed by 3D motion analysis. We found that varus thrust was significantly higher in both early and established OA groups compared to the control group, but not different between OA groups. While the knee adduction moments were higher than controls only in the established OA group, the magnitude of varus thrust was significantly correlated with the second peak knee adduction moment. Our findings suggested that problems with dynamic stabilization of the knee are present early in the development of knee OA. This highlights the necessity of considering dynamic alignment in rehabilitation already in the early stages of the disease.

Previously, our group reported reduced time-averaged knee local stability, in the unaffected, but not the affected leg of elderly with established knee osteoarthritis OA compared to controls. Since stability may show phase-related changes , in **study III** (chapter 4), we reanalyzed the dataset reported previously using time-dependent local stability, $\lambda(t)$, and also calculated time-averaged local stability, λs, for comparison. We studied treadmill walking at increasing speeds, focusing on sagittal plane knee movements, in three groups of established OA, healthy elderly, and young controls. We found stance phase maximum value of time-dependent local stability of both legs to be significantly higher in the OA than the young control group. Values for healthy elderly fell between those of the other groups, were significantly higher than in young adults, but there was only a trend towards a significant difference with the stance phase maximum value of time-dependent local stability of the OA group's affected side. Results from this study indicated that time-dependent local dynamic stability might provide a more detailed insight into the problems of gait stability in OA than conventional averaged local dynamic stability measures and support the notion that the paradoxical decline in unaffected side time-averaged local stability may be caused by a trade-off between affected and unaffected side stability.

In **study IV**, described in chapter 5, we assessed structural, clinical, and functional changes over time in patients with early medial knee osteoarthritis (OA), and compared the changes to the ones in a group of patients with established medial knee OA, as well as to a group of healthy controls. Structural features as detected on MRI, clinical, functional, as well as knee muscle strength were

measured at baseline and after 2 years for all participants. After 2 years, the only significant structural change was observed in the early OA group, and that was an increase in the presence of meniscal extrusion in this group compared to the baseline. No other significant structural changes were found in any of the other groups compared to baseline. Regarding muscle strength, a decline in quadriceps strength was found to be present after two years in all three groups, compared to baseline. No significant clinical or functional changes were found for any of the three groups after two years compared to baseline. Our findings suggested that, although the early and established OA groups showed a different structural, clinical, and functional profile at baseline, in a 2 year time frame, this profile seemed to be stable.

In **study V**, we evaluated gait changes in a prospective longitudinal study, in order to determine whether the early osteoarthritis (OA) group would evolve towards gait characteristics observed in the established OA group. Gait analysis was performed on women with early and established medial knee OA, as well as a group of controls. Kinematic and kinetic data were measured and calculated at baseline and after 2 years follow-up. Results indicated that the early OA group, similar to established OA group, showed significantly higher maximum knee adduction angles compared to the healthy controls during the early stance phase of gait. None of the kinematic or kinetic measures of gait, changed over two years in the early OA group compared to baseline. The established OA group showed more significant differences in gait kinematics and kinetics compared to the healthy controls. We found that increased maximum knee adduction angle during stance phase was the only alteration in the gait pattern of subjects with early knee OA compared to the controls, a finding similar to the established OA group. Our results suggested that, unlike in the later stages of the disease, gait is rather stable over two years in the early OA patients.

In **study VI**, we investigated the association of static and dynamic alignment with structural, clinical, and functional progression associated with knee OA in a longitudinal study. Static and dynamic alignment as well as MRI detected structural features, clinical, and functional characteristics of women with early and established medial knee OA were assessed at baseline and at 2 years follow-up. Associations between baseline static and dynamic alignment with structural, functional, and clinical characteristics at the time of entry, as well as the changes over 2 years were evaluated. Both static and dynamic varus alignment at baseline were significantly associated with OA related tibio-femoral joint structural abnormalities detected on MRI, at the time of entry. Only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. None of the static or dynamic measures of knee joint alignment were associated with clinical characteristics associated with medial knee OA. The key finding of this study was that both

frontal plane dynamic and static alignment, are associated with structural abnormalities in patients with medial knee OA. Therefore, results from the current study highlighted the role of frontal plane static and dynamic alignment in the disease process and hence, suggested that attempts for therapy are probably more successful when efforts are made to correct alignment, as well.

In **study VII**, we tried to identify prognostic factors for progression of knee OA, by evaluation of structural, clinical, and biomechanical characteristics of women with medial knee OA at the time of study entry. In this longitudinal study, we included subjects with both early and established medial knee OA and studied their structural, clinical, and functional changes over two years. Progression criteria were defined, and for each progression criterion (structural, clinical, and functional), two groups of subjects, namely, fast and slow progressors, were defined. The baseline characteristics between the fast and slow progressors were compared. Our results demonstrated that there are different progressors as assessed by structural, clinical, and functional criteria, and each may be associated with specific structural, clinical, and biomechanical variables at the time of entry.

In conclusion, and as discussed in **chapter 9**, this thesis further complete the picture of what the specific functional characteristics of the early OA population are. We found that, subjects with early OA do have an altered proprioceptive weighting, and demonstrated a stronger ankle-steered proprioceptive postural strategy, during standing. This was in contrast with proprioceptive accuracy that was still on the level of the control subjects and only deteriorated in the established phase. Additionally, we found that varus thrust is more common and that the magnitude of varus thrust is greater in women with early medial knee OA than in healthy controls. Based on the longitudinal studies included in this project, we found that after 2 years, only in the early OA group, the presence of meniscal extrusion increased compared to the baseline. Pain, symptoms, and function showed a stable course over two years. Moreover, finding suggest that longitudinal changes in gait pattern are only in the established phase of OA, and are not likely adaptive but may indeed reflect reduced strength, which seems likely to be a result rather than a cause of disease progression. We also concluded that the disease progression is very variable amongst this study population with knee OA, which further highlights the heterogeneity of the knee OA population. And that patients vary based on the different criteria for assessment of progression.

GENERAL INTRODUCTION

In this general introduction we will provide the framework of this doctoral thesis and identify some **gaps in the literature**, that lead to the **research questions** addressed in the different studies of this PhD. Next, the general objectives of the thesis, as well as the specific objectives of the different studies are defined. Finally, the general methodology is described.

Knee Osteoarthritis

"A 60-year-old woman, overweight, walks into the clinic, apparently avoiding weight-bearing on her left leg. She reports having had knee pain for several months, while she can't think of a specific cause like a trauma for the onset of the pain. The pain gradually increased and she has started taking stronger medications to overcome the pain and to be able to do her usual activities. She reports morning stiffness in the knee that lasts for a short while after getting out of bed, and occasions of a feeling of giving away of the knee during daily activities such as stair walking. She has no pain in other joints and her daily activities are limited due to the complaints."

This is a clinical picture of a typical patient presenting with knee osteoarthritis (OA). Osteoarthritis is the most common chronic degenerative joint disease with the knee as the most affected joint [1]. Estimates from the global burden of disease, reported knee OA as the 11th highest contributor to global disability [2]. Knee OA is prevalent in 10% of the population above 50 years of age, exceeding 50 % of the population over the age of 65 years [3]. According to data produced by the Dutch Institute for Public Health, the prevalence of knee OA in those aged 55 and above was 15.6% in men and 30.5% in women [4]. Radiographic knee OA is evident in 33% of the population above 65 years [5]. Symptomatic knee OA, defined as the presence of radiographic knee OA in combination with characteristic knee symptoms attributable to knee OA, such as pain or stiffness in the knee joint, is present in 10 – 15% of the population above 60 years of age [5]. The burden of knee OA on society is rising due to the aging of the population and the increasing prevalence of obesity. Over half of the adults in the U.S. diagnosed with knee osteoarthritis will undergo a total knee replacement [6]. Considering the aging of the population and the rise in the prevalence of obesity, it is expected that knee OA will become the fourth leading cause of disability by a 40% increase in prevalence [7]. Knee

OA is a major cause of pain and disability, leading to functional deterioration, and its management causes serious challenges for Health Systems [8, 9].

The osteoarthritic knee joint

Several researchers have tried to establish the natural course of the disease, to improve the understanding of the underlying disease process. In a normal knee joint, intact articular cartilage and subchondral bone composing the joint surface act as a smooth, gliding structure and as a cushion between the long bones (Figure 1). They perceive acute or chronic stress, strain and load, and react sufficiently [10], thus preventing biomechanical damage caused by loading [10, 11]. In patients with knee OA, the balance between breakdown, and repair processes is disturbed and cannot compensate sufficiently for destructive mechanisms, resulting in structural impairments [11, 12]. Increasing evidence suggests that OA should be considered a disease of the whole joint [10]. Not only cartilage, synovium, bone and bone marrow, but also menisci, ligaments, muscles and neural tissues all seem to be involved in the complex initiation and progression of the disease [10, 13] (Figure 1).

Biomechanical factors such as increased localized loads on the areas with damaged cartilage, as well as, spatial shifts in normal load on the areas that are not used to loading, might be responsible for such structural changes [11]. Whether cartilage destruction precedes bony changes, is still a matter of debate. The early changes have not been studied in detail, as clinical manifestations occur only later in the disease process. But, evidence from longitudinal animal studies of OA indicates occurrence of cartilage destruction before bone pathology [14]. Despite the non-inflammatory nature of knee OA, still some degree of episodic, non-erosive synovial inflammation is common in the areas close to the cartilage, even during early stages of the disease (Figure 1) [15, 16].
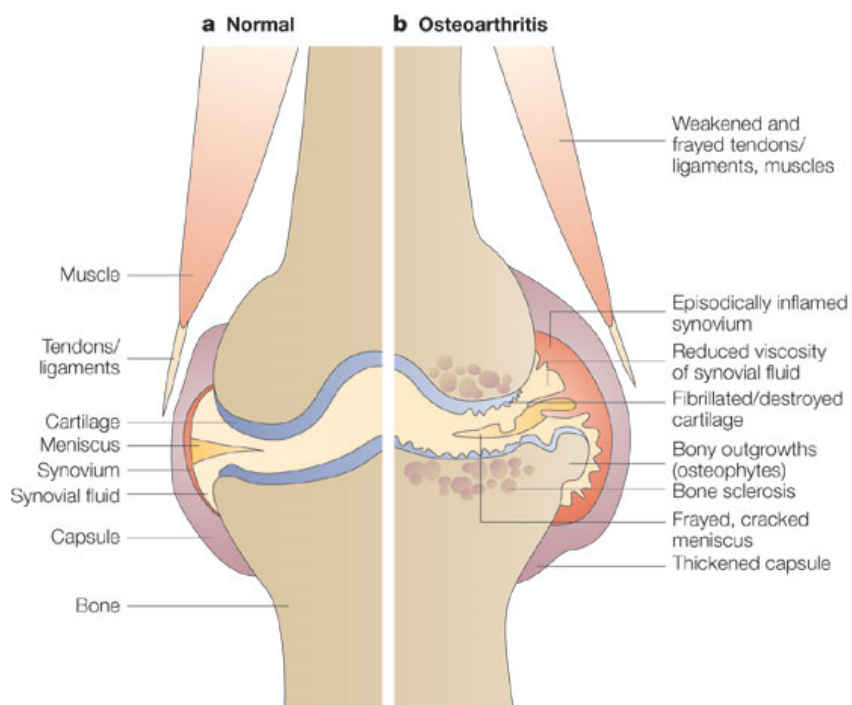
Figure 1. Articular structures that are affected in osteoarthritis. **a)** Healthy tissue is shown: normal cartilage without any fissures, no signs of synovial inflammation. **b)** Early focal degenerate lesion and 'fibrillated' cartilage, as well as remodeling of bone, is observed in osteoarthritis. This can lead to bony outgrowth and subchondral sclerosis. (Reprinted with permission from Wieland et al [11])

Diagnosis and classification of knee OA

Despite its high prevalence, knee OA is still an enigmatic condition. There have been several definitions proposed in the literature regarding diagnosis of knee OA. Perhaps the most accepted one is the definition based on the American College of Rheumatology (ACR) criteria for knee OA published by Altman et al. [17]. These diagnostic criteria, identify subjects as having knee OA if they present with: knee pain, age above 50, stiffness less than 30 minutes and crepitus, combined with structural changes, i.e., osteophytes and joint space narrowing (Kellgren II on standardized radiographs).

Classification of knee OA is primarily based on plain radiography [18]. Joint space narrowing (JSN) has been considered as the hallmark of presence and progression of knee OA. The Kellgren and Lawrence grading system has been developed and is widely used as a grading system for diagnosis

and progression of knee OA [19, 20]. Although plain radiography has been used frequently in the literature for diagnosis and monitoring of the progression of knee OA, the weak associations between structural changes detected on plain radiography and clinical symptoms and signs, make radiography less suitable for monitoring the effect of treatment on the progression of the disease [21, 22]. Also, change in JSN over time is generally slow and does not keep up with the clinical changes [23-25]. Therefore, the need for more sensitive and specific outcomes, has been recognized recently.

Over the last few years, new imaging techniques, in particular Magnetic Resonance Imaging (MRI), have enhanced our ability to identify a spectrum of joint tissue changes, especially at the very early stages of the disease [26]. These techniques allow detection of joint surface fibrillation, single or multiple cartilage defects, more diffuse cartilage loss, meniscal damage with tears, degeneration and extrusion of the meniscus, bone marrow lesions (BMLs), subchondral sclerosis and cysts, synovitis and presence of joint fluid, to mention the most important ones. Thus, early structural changes that are not seen on plain radiography yet, can be detected with these tools, which may help to identify subjects in the early stages of the disease or at higher risk of developing knee OA. Clinically it is important to identify these patients in order to initiate early interventions and therapeutic approaches that could prevent progression and severe structural changes in the joint associated with later stages of OA. Also, longitudinal studies on different severities of subjects with knee OA will help to better understand the development of disease process and further identification of modifiable prognostic factors to focus on more specific management strategies in order to slow down further progression.

Novel classification of early knee OA: The diagnosis and classification of early knee OA has not been defined very well in the literature and therefore studies related to investigation of this subpopulation of knee OA subjects are hard to compare with each other. Most studies use only structural changes for classification of patients at the early stages of knee OA, but this subpopulation of OA patients display a combination of clinical signs and symptoms, as well as a number of structural changes that are detectable on MRI [26]. Luyten at al. proposed a classification of subjects with early knee OA, combining clinical and structural characteristics on both x-ray and MRI (Table 1).

Table 1. Classification criteria for early knee osteoarthritis [26]

1	Knee pain	At least two episodes of **pain** for > 10 days in the last year
2	Standard radiographs	Kellgren and Lawrence **grade 0 or 1 or 2**- (osteophytes only)
3	At least **one** of:	
	Arthroscopy	ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling
	MRI	At least **two**: ■ ≥ BLOKS grade 2 for size cartilage loss ■ ≥ BLOKS grade 2 for percentage full-thickness cartilage loss ■ Signs of meniscal degeneration ■ ≥ BLOKS grade 2 for size of bone marrow lesions

ICRS = International Cartilage Repair Society; BLOKS = Boston-Leeds Osteoarthritis Knee Score

Using the classification of early knee OA proposed by Luyten et al., in the current project we tried to further investigate the structural, clinical, functional, and biomechanical characteristics of patients in the early stages of knee OA, and how these characteristics change over time in this group compared to subjects with established OA.

Structural, clinical and functional profile of subjects with early OA

Is early OA a distinct group?

Compared to moderate or severe knee OA, identification of early knee osteoarthritis seems more complicated due to the limited and periodic signs and symptoms, which only become apparent during/after certain circumstances such as high/long-term loading. A number of tissue level phenomena are related to early knee OA, and it is thought that they might lead to a breakdown in the homeostasis of the knee and, consequently, to further progression towards the established knee OA [26]. The complaints of the individuals of recurrent pain and discomfort of the knee, short periods of stiffness, with in between long periods of very little clinical manifestations, usually shape up a clinical picture for the health professional to perform further investigations through radiographs, ultrasound, MRI or arthroscopy [26]. Often, in such cases, the history, coupled with additional clinical

examination, as well as no systemic manifestations, points to a more local joint problem with mechanical nature [26].

In the early phases of the disease, pain is related to activity and becomes more constant over time [27]. Baert et al. reported more knee pain and symptoms in women with early medial knee compared to the healthy controls, and comparable to women with established medial knee AO [28]. Reduced functional ability is also reported to be already present in this stage of the disease [29]. Several **structural** changes have been associated with early knee OA. In this sub-population of knee OA, the articular cartilage surface increasingly becomes discontinuous, displaying fibrillation and vertical fissures [30]. Also, a gradual increase in subchondral plate and subarticular spongiosa thickness have been reported as early changes in the subchondral bone [30]. Articular cartilage and the subchondral bone are not the only affected structures of the joint. Other structural changes such as the menisci, the synovial membrane, the joint capsule, ligaments, and the infrapatellar fat pad have also been reported during the early stages of the disease [30].

Studies on **biomechanical characteristics** of subjects with early knee OA are limited and due to the non-consistent classification of knee OA in these studies, results are barely comparable. Baert et al. investigated gait characteristics in women with early medial knee OA, compared to a group of subjects with established medial knee OA (K&L $\geq$ 2$^+$) as well as a group of healthy controls [28]. They reported no altered gait pattern or increase in knee joint loading during walking in patients with early medial knee OA, compared to the healthy controls [28]. The authors concluded that, perhaps, gait changes, which reflect mechanical overload, are most likely the consequence of structural degeneration associated with knee OA [28]. **Quadriceps weakness** had also been reported in patients with early knee OA [28, 31], which is in line with evidence on quadriceps weakness preceding the onset of knee OA [32, 33]. Investigation of postural balance and **proprioceptive accuracy** in patients with early knee OA showed no significant differences in this group compared to healthy controls [31]. It was suggested that impaired proprioceptive deficits is most likely a consequence of structural degeneration, rather than a risk factor in the pathogenesis of knee OA [31].

So far, our knowledge of knee OA is mostly based on data from heterogeneous patient populations with knee OA, but in order to better understand the knee OA trajectory it is important to study knee OA in the early stages of the disease. Therefore, additional studies are needed to further refine the **structural, clinical and functional** profile of the subjects with early knee OA and to assess how this profile evolves over time.

What are the risk factors associated with the incidence and progression of knee OA?

Despite the high prevalence of knee OA, the information on the underlying causes is limited [34]. Better understanding of the factors contributing to the onset and progression of the disease is imperative for better prevention and improvement in the treatment for OA.

Non-modifiable risk factors

One of the most well-known risk factors for the incidence of knee OA is **Age** [8, 35]. The increased incidence of knee OA with aging can be considered in the context of biological, morphological, and neuromuscular changes to the musculoskeletal system that occur with aging. In particular ligament stiffness [36, 37], muscle strength [38] and muscle activation [39] decline with aging. Therefore, abnormal knee kinematics observed with aging, may be related to a gradual decline in passive (ligamentous) and active (muscular) joint stability. Conflicting evidence is found in the relationship between progression of knee OA and age [40]. Schouten et al and Miyazaki et al found significant association between age and progression of knee OA [41, 42]. On the other hand, Dieppe et al and Felson et al reported no significant association between age and progression of knee OA [43, 44].

Symptomatic knee OA is more prevalent in women than in men, and hence **Female sex** is considered as a risk factor for the incidence of knee OA [45, 46]. One possible explanation might be a thinner cartilage layer (corrected for height, weight, and bone size differences), as well as lower limb anatomical differences in women compared to men [47]. Conflicting evidence exists on the effect of female sex on the progression of knee OA, with some high-quality studies showing no association and others finding positive associations [40, 48].

Post-menopausal **Hormonal changes** produce changes [49-51] similar to those described for aging and might serve as an explanation for the higher prevalence of knee OA reported in women over the age of 50 [52]. Moreover, hormonal changes, coupled with aging, reduce the cartilage's ability to adapt and repair itself to the changes happening in the load bearing areas of the cartilage [50, 53, 54]. The presence of **OA in multiple joints** is reported as a risk factor for progression of knee OA [40, 48].

Only a few genes have been identified as risk factors for the incidence and progression of knee OA, nevertheless **Genetic predisposition** of OA is well established [55-57]. Between 39% and 65% of

osteoarthritis in the general population can be attributed to genetic factors [58]. Genetic predisposition might be a key difference between a patient who sustained a traumatic knee injury and fully recovers and a patient who develops early OA as a result of similar injury [30]. Some genes, such as GDF5, are now known to be consistently associated with the risk of knee OA, highlighting potential pathways for therapeutic intervention [56].

Modifiable risk factors

Obesity is a well-known and modifiable risk factor for knee OA. The risk of developing knee OA is three times higher in obese individuals compared to their peers with normal weight [59]. The possible effect of obesity on progression of knee OA has been supported by some studies [40, 48, 60]. An increased risk of structural knee OA progression, by 26%, was reported in obese individuals with 60-64 years of age compared to their non-obese peers during a 10-year period [61].

The role of **Occupational exposures** on the incidence of knee OA are rather controversial, most probably due to methodological weaknesses of studies in this area [62]. Specific activities such as excessive as well as repetitive kneeling, squatting, climbing steps, prolonged standing (>2h per day) and lifting have been suggested to be associated with development of knee OA [59].

The role of **Physical activity and Exercise** as a risk factor for development of knee OA is controversial. There are longitudinal studies that found no association between physical activity and incidence of knee OA [63-65], as well as studies which indicate physical activity is related with deterioration of knee OA [66]. On one hand, beneficial effects of physical activity are likely. First, maintaining the integrity of the cartilage is dependent on knee joint loading [67]. Second, the knee joint can benefit from physical activity as it may decrease joint pain, improve muscle strength and proprioception, and improve function in patients with knee OA [68-71]. On the other hand, excessive and repetitive physical activity could be damaging for the joint, especially if the joint is already at high risk of developing abnormal and excessive joint loading, for example due to malalignment . There is a lack of evidence for a positive effect of mild or moderate exercise and sports on normal knee joint without traumatic injury [72], but reports are present for increased risk of knee OA in athletes who engage in a greater volume and intensity of training [72]. It should be noted that studies on the associations between sports participation and the incidence of knee OA may be confounded by knee injuries that may occur in sports. A four-fold increase in the risk of development of knee OA has been reported after **Knee injury** [59]. Reports exist on the higher incidence of knee OA in subjects with meniscal or Anterior Cruciate Ligament (ACL) tears [73-75].

Knee joint alignment is among the modifiable risk factors associated with the *incidence* of knee OA [76]. Malalignment of the knee either in varus or valgus direction influences the load distribution over the medial and lateral compartments of the knee joint [77]. A neutrally aligned knee bears approximately 60-80% of the compressive load on the medial compartment [78] and a 5 degrees increase in varus alignment results in a 20% increase of total load on the medial compartment [77]. Such an increase in medial compartment loading will put extra stress on articular cartilage and the subchondral bone and might subsequently lead to degenerative changes. Several authors have reported an association of increased static varus alignment with increased OA severity [76, 79]. Dynamic knee malalignment is assessed by varus thrust which has been defined as an abrupt increase of the knee varus angle when the leg is bearing weight, with a decrease during the non-weight-bearing phase of ambulation (swing phase) [80, 81] (Figure 2). Only a few previous studies investigated varus thrust in OA [80-83] and in some of these only the presence of varus thrust was studied by visual observation and not by quantitative motion analysis [80, 82, 83]. However, neither the presence nor the magnitude of varus thrust have been investigated in the early OA population [26]. *In the present PhD project we will therefor assess dynamic alignment in this early OA population.*

Static and dynamic knee joint alignment have also been associated with *progression* of knee OA [48, 79]. Sharma et al. reported that in primary knee OA varus alignment increases risk of medial OA progression [84, 85]. In a longitudinal study on the effect of dynamic alignment at baseline on structural progression of medial knee OA, Chang et al reported a 4-fold increased likelihood of progression of medial knee OA over 18 months [80]. Quantification of varus thrust in the early stages of the disease and identification of its relationship with KAM, as a risk factor associated with the progression of medial knee OA, may lead us to develop a tool for screening subjects at higher risk of disease progression. There is only one single longitudinal study on the association of baseline dynamic alignment, assessed as presence of varus thrust by visual observation, and radiographic progression of knee OA [80]. Assessing the association of objectively measured magnitude of varus thrust during gait with clinical and structural changes associated with OA progression over time might lead to identification of subsets of individuals who are at higher risk for OA related disability and progression. In the present PhD project we will *investigate this further.*

Figure 2. Visual representation of the observed varus thrust from two sequential video frames (initial contact on the **left**, early stance on the **right**) Note the lateral displacement of the right knee during early stance as evidenced by increased tibial varus and inter knee displacement. (Reprinted with permission from Hunt et al. [86])

Impaired **Muscle function** has been observed in patients with knee OA [87, 88]. Some evidence even exists suggesting that quadriceps weakness precedes disease onset [89]. Also, quadriceps muscle weakness has been associated with an increase in the risk of symptomatic knee OA, particularly in women [33, 90, 91]. The role of muscle strength in progression of knee OA is controversial [92]. A 9% lower quadriceps muscle strength was reported in women with progressive OA (based on worsening of the K&L score) compared to the more radiographically stable patients with knee OA [90], although the results were not statistically confirmed. Using MRI to investigate cartilage loss over 30 months, failed to confirm a relationship between isokinetic quadriceps muscle strength and structural disease progression [93]. In contrast, a study on the effect of quadriceps strength on the risk of joint space narrowing over 30 months demonstrated that women in the lowest tertile of relative isokinetic strength had an increased risk of tibiofemoral joint space narrowing compared to women in the highest strength tertile [91]. A previous study on muscle strength in women with early

medial knee OA, reported that quadriceps weakness is already present at the early stages of the disease [31]. <u>Little is known however about the evolution of muscle strength over time with respect to OA severity</u> ***which motivated one of the research questions in this doctoral thesis.***

Knee proprioception has been assumed to play a role in disease initiation through its effect on dynamic joint stability [94]. Disturbed proprioception of the knee joint could result in abnormal stresses on the tissue through altered control of movement [95]. Proprioceptive deficits have been reported in patients with established knee OA [31, 96, 97]. In two recent longitudinal studies, no association was shown between impaired proprioception and radiographic knee OA incidence [98, 99]. In this respect, despite the evidence on proprioceptive deficits in moderate to severe patients with knee OA, a study on patients with early knee OA, showed that proprioceptive accuracy was comparable to healthy controls in this subpopulation of knee OA patients [31]. The absence of deficits in proprioceptive accuracy in the early stages of the disease makes it unlikely that proprioceptive accuracy is a risk factor for the incidence of knee OA, but rather a consequence of the disease. <u>But whether other measures of proprioception such as weighting of proprioceptive input are already altered in the early stages of the disease, as found in severe knee OA (K&L 3or 4) [100], is still unknown.</u> ***In this project we will elaborate further on this issue***.

External knee adduction moment has been related to disease severity and progression [42, 101-103]. The external knee adduction moment, a proposed non-invasive indirect index of the load on the medial compartment of the knee joint [104], is present throughout the stance phase of gait [104], and is a result of ground reaction force passing medial to the knee joint center [105] (Figure 3). There are reports on the absence of an increased KAM early in the disease process [28]. <u>While external knee adduction moment has been described extensively in cross-sectional studies on OA, little is known about its evolution over time with respect to OA severity.</u> ***In this respect, in the present project the changes in external knee adduction moment as well as other gait characteristics were studied over 2-years follow-up in women with early medial knee OA.***
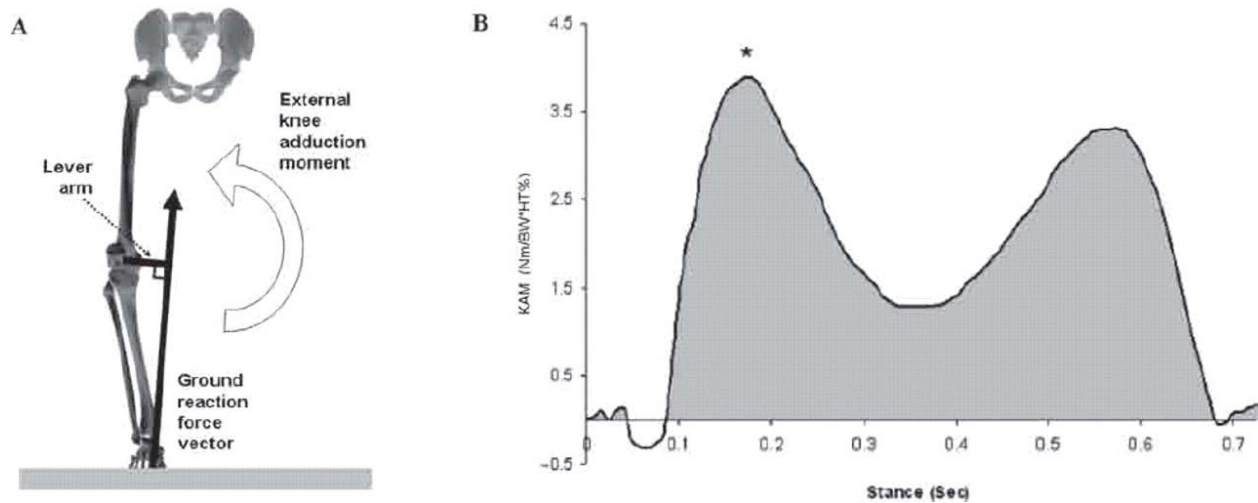
Figure 3. (A) Diagram of the knee adduction moment (KAM), which forces the knee into varus, loading the medial compartment. The KAM is primarily the product of the ground reaction force and the length of the lever arm, defined as the perpendicular distance from the center of the knee joint to the line of action of the ground reaction force. (B) Tracing of a typical KAM over the stance phase of walking showing the peak KAM (*) and the KAM impulse representing the positive area under the curve (shaded region). (Reprinted with permission from Bennell et al. [106])

Definition of progression in knee OA

Studies to date tried to identify patients with disease progression mostly based on the assessment of structural progression detected on radiography (joint space narrowing) or the amount of cartilage loss detected on MRI [80, 107]. Considering weak associations between structural abnormalities detected on radiograph [21, 22] or MRI [108] with clinical characteristics associated with knee OA, <u>there is a need for a more comprehensive evaluation of progression and prognostic factors associated with progression in knee OA.</u> *In this doctoral thesis, we tried to elaborate more on this, by studying progression based on different clinical and functional outcomes.*

The study during the mobility period in Amsterdam

As part of this doctoral thesis we performed a methodological study on an available dataset [109]. One of the most pervasive threats to mobility in elderly is knee OA. Self-reported instability of the knee is one of the symptoms in knee OA, especially in the advanced stages of the disease [110] and has negative functional implications [111-113]. While the importance of self-reported instability is

well accepted by researchers and clinicians, there is still no consensus about objective, accurate and reliable ways to measure "true" dynamic stability of the knee. One of the most accepted ones is the local divergence exponent (λs). The local divergence exponent measures the rate of divergence after small perturbations, and thus assesses the stability of a movement pattern [114, 115]. Reduced time-averaged knee local stability, in the unaffected, but not the affected leg of elderly with knee osteoarthritis OA compared to controls, was reported previously [109]. Since stability may show phase-related changes, we reanalyzed **as part of this doctoral thesis** the dataset reported previously, using time-dependent local stability ($\lambda(t)$), and also calculated time-averaged local stability, λs, for comparison.

Objectives:

General objective

This doctoral project is part of a prospective longitudinal observational cohort study that aims to identify the structural, clinical, and functional markers that are related with the progression of medial knee OA. This doctoral thesis is arranged in three parts, describing a number of studies aimed at investigating structural, clinical, and functional characteristics of subjects with early medial knee OA at baseline and after two years. It is further sub-divided in nine chapters, elaborating the specific objectives of this doctoral project, which are extensively studied and discussed.

Specific objectives

Part 1. Cross-sectional studies to further refine the profile of the (early) OA population.

Objective part I

- To investigate functional (neuromuscular, biomechanical) differences of subjects with early and established medial knee OA compared to the healthy controls.

Chapter 2. Changes in proprioceptive weighting in women with knee osteoarthritis during quiet standing compared to healthy controls.

This study aimed to 1) to investigate weighting of proprioceptive input during stance in a group of patients with early knee OA, patients with established knee OA and to compare them with healthy peers; 2) to explore whether the sensitivity of the knee muscles to vibration decreases with increasing severity of knee OA; 3) to explore if there is a relationship between proprioceptive weighting and proprioceptive accuracy in subjects with knee OA.

Chapter 3. A quantitative assessment of varus thrust during walking in women with medial knee osteoarthritis.

This study aimed to investigate static knee alignment and varus thrust in subjects with early medial knee OA, compared to subjects with established knee OA and asymptomatic controls. Furthermore, to study the relationship between static alignment and varus thrust on one hand and KAM on the other hand.

Chapter 4. Phase-dependent changes in local dynamic stability during walking in elderly with and without knee osteoarthritis.

This study aimed to investigate whether knee stability would be different for different phases during the stride cycle in subjects with established knee OA, and that if these differences explain why previously we found instability only in the unaffected leg in knee OA.

Part 2. Longitudinal studies to further the knowledge on the natural disease trajectory from a structural, clinical and functional / biomechanical perspective.

Objective part II

- To explore the changes in structural, functional and clinical characteristics over a 2 year-time frame time in subjects with early and established medial knee OA compared to the healthy control subjects.

Chapter 5. Changes on MRI features, symptoms, function and muscle strength in women with early medial knee osteoarthritis over 2 years.

This study aimed to determine the natural history of structural abnormalities, visualized on MRI, and clinical features including knee pain and clinical symptoms, as well as physical performance and muscle strength compared to a group of healthy controls, along with a group of women with established medial knee OA.

Chapter 6. A longitudinal study on changes in gait characteristics of women with medial knee OA: results from a 2-years follow-up study.

This study assesses the kinematic and kinetic characteristics of gait in a women with early knee OA, women with established knee OA and in healthy controls over a two-year follow-up period, in order to better understand the natural disease trajectory from a functional and biomechanical perspective.

Part 3. Prognostic factors of progression in structural, clinical, and functional profile of OA.

Objective part III

- To identify the factors related with progression of OA in a population of women with medial knee OA.

Chapter 7. Dynamic and static knee alignment at baseline predicts structural changes on MRI associated with progression of medial compartment knee osteoarthritis.

This study aimed to assess the relationship of frontal plane static and dynamic alignment in a group of individuals with early and established symptomatic medial knee OA at baseline, with MRI based structural and clinical changes over 2 years follow-up.

Chapter 8. Identification of progressors in medial knee osteoarthritis based on structural, clinical, and functional changes over two-year follow-up

This longitudinal study, aimed to identify critical structural, clinical, neuromuscular, and biomechanical characteristics of women related with progression in either structural, clinical or functional OA profile after 2 years.

The thesis ends with a ***general discussion (Chapter 9)***, in which the main findings of the doctoral thesis are summarized, interpreted, and clinical implications as well as recommendations for future research are proposed. As chapters 2-8 were originally written separately in a form of articles for publication in international peer reviewed scientific journals, some overlap between chapters is inevitable. We tried to make a link between the studies, through the general introduction and the general discussion. At the end of the general discussion the overall conclusion of the whole study project is presented.

General Methodology

In this section we will present the general methodology that accounts for most studies included in this PhD and elaborate on the study population of the larger project

Study group

For the longitudinal study on identification of risk factors associated with progression of knee medial OA, 120 women with and without medial knee OA were recruited between 2008 and 2011 and followed up over a period of 4 years. **Participants with knee OA** were recruited during their regular visit to a rheumatologist or orthopedic surgeon at the University Hospitals Leuven. Participants in the healthy **control group** were recruited through social organizations. All participants were informed about the study procedure and signed informed consent forms. The study was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium prior to testing and was conducted in agreement with the principles of Declaration of Helsinki. Each participant was referred for a physical exam and bilateral standard anterior-posterior weight-bearing radiographs.

The inclusion criteria for the control group were as follows, K&L grade 0 or 1 on the radiography of either knee, asymptomatic, no history of knee OA or other pathology involving any lower extremity joints. Participants with knee OA were further sub-classified, into *early* and *established* medial knee OA groups [26]. The inclusion criteria for the early OA group were: presence of knee pain, a K&L grade 0, 1 or 2- for the medial compartment, and presence of two of four MRI criteria: (1) ≥ BLOKS grade 2 for size cartilage loss, (2) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment [26].

The classification of participants in the established knee OA group was based on the slightly adjusted American College of Rheumatology (ACR) classification criteria [116], which includes knee pain, age above 50, stiffness less than 30 minutes and crepitus, combined with structural changes defined as presence of minimum K&L grade 2+, indicating a moderate to severe disease severity.

All studies presented in the PhD project belong to this larger project. The number of subjects is not the same in all studies due to:

- Wrong side MRI measurement at follow-up;
- 3D movement data corruption;
- Presence of pain in hip or ankle joints during testing according to lab notes;
- Subject exclusion due to higher grade of K&L in the lateral compartment of the knee.

Also, some dropouts occurred after 2 years which resulted in a decrease in the number of subjects for the longitudinal studies. Dropouts were due to:

- Death (n = 2);
- Development of other knee joint diseases such as Chondrocalcinosis (n = 3);
- Development of hip joint arthrosis (n = 2);
- Progression of lateral compartment knee OA (n = 6).

Table 2 gives an overview of the number of subjects per group that we could finally include in different studies.

Figure 2. Overview of the number of subjects per group for each study.

	Total No. subjects	Early OA	Established OA	Control
Study I	79	27	26	27
Study II	72	27	21	24
Study III	43	NA	16	elderly: 12 young: 15
Study IV	77	29	20	28
Study V	66	25	18	23
Study VI	47	27	20	NA
Study VII	49	28	21	NA

OA = osteoarthritis; NA = not applicable

Knee radiographic assessment

A standard bilateral anterior-posterior (AP) weight-bearing radiograph of the knee joint in was taken in a fixed flexed position for each subject (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). In order to evaluate the presence and severity of structural knee OA, the K&L grading system with recent adjustments, was used [116], and each radiograph was scored by a single experienced observer (FPL).

Assessment of static knee joint alignment

A full-leg AP weight-bearing plain radiographs of the lower extremities was used by an experienced musculoskeletal radiologist to assess static knee joint alignment [85]. Knee alignment between -2° and +2° was classified as neutral. Malalignments of less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively. [76, 117].

Knee MRI protocol and analysis

For all participants, MRI was performed at the time of entry, at 2 years follow-up, and after 4 years follow-up. For the patients' group, the (most) affected knee and for the control group a randomly selected knee was selected for MRI. All images were taken in a non-weight bearing supine position, on a 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) by using an eight-channel phased array knee coil. The knee imaging protocol consisted of sagittal and transversal proton density turbo spin echo (TSE) sequence images (36 slices, 2.5 mm slice thickness with 0.3-mm intersection gap, field of view (FoV) 150 × 150 mm, matrix of 428 × 331 and TR/TE = 3,000/30 ms), sagittal and coronal high-resolution T2 TSE sequence images with fat saturation (26 slices, 2.8 mm slice thickness with 0.3-mm intersection gap, FoV 160 × 160 mm, matrix of 472 × 384 and TR/TE = 2,726/66 ms), a sagittal 3D gradient echo with different echo times (180 slices, 0.5 mm slice thickness, FoV 150 × 150 mm, matrix of 260 × 242 and TR = 26 ms and TE = 9.2, 15.3 and 21.4 ms) and a sagittal 3D gradient echo with water-selective excitation (60 slices, 1.5 mm slice thickness, FoV 140 × 140 mm, matrix of 284 × 283 and TR/TE = 20/5.2 ms).

The Boston-Leeds Osteoarthritis Knee Score (BLOKS) was used to analyze and score all images [118]. BLOKS semi-quantitatively evaluates nine intra-articular knee joint regions and assesses structural abnormalities that are often involved in the OA process [119]. The BLOKS has proved to have high reliability and validity [118, 120]. Two readers (NN and GVDS), who were blind to radiographic results and patient symptoms, scored images separately. Full agreement between both readers was achieved for 91 % of all scored items, and disagreements were resolved by consensus. In order to provide a feasible overview in this study, 12 relevant MRI parameters (4 categories) were extracted from the BLOKS.

Pain, symptoms and disability assessment

In order to assess pain, symptoms, and disability, the Dutch version of the 'Knee Injury and Osteoarthritis Outcome Score' (KOOS) was used in this study. KOOS contains 5 separate subscales assessing pain, symptoms (as swelling, stiffness, crepitation, clicking), ADL, sports and recreational function and knee-related quality of life. Each question was scored on a 5-point Likert scale (from 0-4) and for each subscale a transformed score from 0 to 100 was calculated. A score of 100 was the best possible result, the lower the score the more functional problems and disability was presented [121]. In this doctoral thesis, we assessed and reported the subjects' pain, other symptoms and subjective disability (ADL and QOL). Due to the missing data for some of the questions on the subscale

'function in sports and recreation', results of this section were excluded from further analysis in this thesis.

Performance-based measures

To assess performance-based physical function, two tests of Timed Up–and-Go (TUG) and Stair Climbing Test (SCT) were used. To perform the timed up–and-go test (TUG), the participant was seated in a standardized chair and needed to get up, walk 3 m, cross the line with one foot and return seated on the chair as quickly as possible. The total time to perform the task was measured in seconds, using a stop watch. During the Stair Climbing Test (SCT), participants were asked to ascent and descent 5 stairs as quickly as possible, and using stopwatch, the total time in seconds was measured. A longer time on the TUG and/or SCT represented greater functional limitation. Each test was performed 3 times and a mean value was calculated. The test has been shown previously to have good reliability and validity [122, 123]. For both tests, the subjects were allowed to wear their own comfortable shoes.

Muscle strength

Maximal voluntary muscle strength of the knee muscles were measured, using isokinetic dynamometry (Biodex System 3 Pro, Biodex Medical Systems, NY, USA). All measurements were performed according to standard procedures, and the Biodex was calibrated before every test session [124]. The maximum *isometric strength of knee extension and flexion* was assessed. Flexion and extension movements were performed at angles of 60° and 90°. Each test was performed three times with maximal contraction for 5s. Between each trial, 10s of rest was given. Between the tests at different angles the patient had 30s rest. *Isokinetic (dynamic) knee extension* was also measured with three trials for knee extension at 60°/s (low speed) and three trails at 240°/s (high speed). The same instructions and verbal encouragement were used for all subjects, in order to achieve a maximal effort. For each test, the peak torque normalized for body weight (Nm/kg) was used for further analysis.

Proprioceptive weighting and postural control assessment

To assess postural control a force plate (Bertec, Corporation, Ohio, USA) was used to record the center of pressure coordinates, while participants were asked to comfortably stand barefoot on it. For all trials, vision was occluded by using a blindfold, and each participant underwent three

experimental conditions during which they were instructed to stand still and relaxed. By using two muscle vibrators (VB100, Dynatronic, Valence, France), illusory joint movements were induced [125]. The three conditions were: 1) bilateral vibration of the Triceps Surae (TS) tendons; 2) bilateral vibration of the Tibialis Anterior (TA) muscle bellies; and 3) bilateral vibration of the Vastus Medialis (VM) muscle bellies. Each trial lasted 45 seconds, during which muscle-tendon vibration was applied for 15 s, initiated 15 s after the start of the trial. Data collection continued for 15 s after the vibration was stopped. The position of the center of pressure (CoP) was calculated and averaged over the first 15 s of the trial (pre-vibration) and during the 15 s of vibration. The **response** to muscle vibration was defined and quantified as the difference in mean CoP position before and during vibration.

Proprioceptive accuracy

An active repositioning test was used to examine proprioceptive accuracy [126]. The participant was seated on a chair with knees flexed over the edge of the chair and with the eyes closed. The knee was extended passively from the resting position. This knee angle (criterion angle) was maintained by the participant for 3 seconds. The knee was then flexed back to the resting position and relaxed for 3 seconds. Then, the participant was asked to replicate the test position and hold it for 3 seconds. After familiarization with the test, each participant performed the tests twice in each of the knee angles in a standardized order. The motion was tracked using an active three dimensional (3D) motion capture system at 100 samples/s (Krypton, Metris), using a previously described protocol [31]. Repositioning error (RE) was defined as the absolute difference between the criterion angles and reproduced angles.

Gait data acquisition and analysis

A 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group) was used to record the spatial position of markers on relevant body (Figure 4).
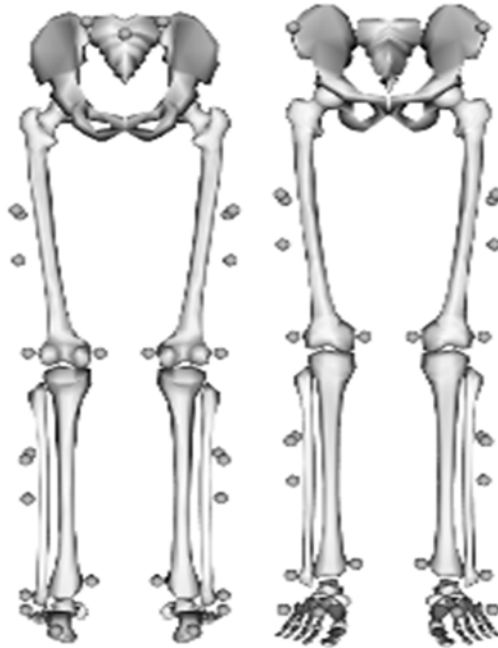
Figure 4. Marker set used for motion capture

Ground reaction forces were recorded through two force plates (Bertec Corporation, Ohio, USA and AMTI, Watertown, MA, USA) placed in a 12m walkway. All the analyses were done using Custom-made MATLAB 7.14.0 (The MathWorks, Natick, MA) programs. Participants walked along the walkway at a comfortable habitual speed, while they were asked to 'walk naturally'. Three complete force plate strikes for each foot were registered. All participants were asked to walk bare-footed, since footwear can affect the distribution of loads on the joints in the lower quadrant [127]. 3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay [128]. Knee moments were calculated through a bottom-up dynamic linked segment model, using kinematics of the body segments and the ground reaction forces [129]. Extracted joint moments were normalized to the product of body mass and height [130].

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Part 1: Cross-sectional studies to further refine the profile of the early and established OA population

Chapter 2

Changes in proprioceptive weighting during quiet standing in women with early and established knee osteoarthritis compared to healthy controls

Abstract

Knee osteoarthritis (OA) is highly prevalent in people above the age of 60, and is typically associated with pain, stiffness, muscle weakness and proprioceptive deficits. Muscle-tendon vibration has been used to assess the spatial reweighting of proprioceptive input during standing. The current study aimed to investigate whether weighting of proprioceptive input is altered in patients with early and established knee OA compared to asymptomatic controls. The upright posture of 27 participants with early OA, 26 with established OA, and 27 asymptomatic controls was perturbed by vibrating (frequency: 70 Hz and amplitude: approximately 0.5 mm) ankle muscles (i.e. tibialis anterior and triceps surae) and knee muscles (vastus medialis). Center of pressure displacements of the participants were recorded using a force plate. Both patients with early and established OA were more sensitive to triceps surae vibration compared to their healthy peers ($P < 0.01$ for both). No such difference was found for the vibration of tibialis anterior or vastus medialis muscles between patients with knee OA and healthy controls. These results suggest that the early stages of knee OA may already lead to reweighting of proprioceptive information, suggesting more reliance on ankle proprioceptive input for postural control.

1. Introduction

Maintaining upright posture requires the central nervous system (CNS) to accurately observe the instantaneous state of the body relative to the environment. The body state is observable through a range of sensory inputs arising from vestibular, visual, and somatosensory systems [1]. The proprioceptive input from the lower limb muscles is crucial in preserving postural stability [2], which implies that impoverished afferent signals from these muscles might compromise postural stability. As an example, subjects with dorsal root ganglionopathy show severe balance impairments, due to absence of lower limb proprioception [3]. Certain conditions such as injury, disease, or aging may negatively affect the quality of input from affected body parts [4]. In such cases, the CNS needs to substitute for the impaired source by using more information from other available sources such as vision or proprioceptive information from other body parts, to maintain a stable posture [5].

Knee osteoarthritis (OA) is highly prevalent in people above the age of 60 and has been associated with proprioceptive deficits [6-8] and postural control deficits [9, 10]. However, reports of impaired proprioception in knee OA populations have thus far mostly been based on testing conscious perception of posture or movement [6-8], while a better understanding of the role of a specific sensory system in postural control might be achieved through bypassing the role of conscious perception in testing [11]. Muscle-tendon vibration has been used to assess the weight allocated to proprioceptive inputs from different body parts [4]. Muscle vibration stimulates the primary afferents of muscle spindles [12] and results in an illusory perception of muscle lengthening [13]. The vibrated muscle is perceived to lengthen, and as a result of this distorted sensory information, a corrective movement is made. The direction of this corrective postural response differs depending on the origin of the distorted information, and the magnitude depends on the weight that the CNS allocates to input from this body part compared to the other sources of information [4]. For instance, in a study on postural weighting of patients with low back pain by Brumagne et al., persons with low back pain showed larger CoP shifts towards posterior direction compared to the healthy individuals when vibration was applied bilaterally on the triceps surae, suggesting more reliance on ankle input [4]. Only one recent study by Shanahan et al. used muscle vibration to assess the proprioceptive weighting (PW) in a group of subjects with severe knee OA (Kellgren and Lawrence grade 3 or 4) [11]. Participants with knee OA were initially perturbed more by triceps surae (TS) than vastus medialis (VM) vibration compared to control subjects [11], from which it was concluded that these participants were unable to compensate the induced and non-veridical sensory signals from the TS by using the information from the VM [11]. To the best of our knowledge, proprioceptive weighting

has not yet been studied in the early stage of knee OA. Such understanding might be helpful for development of more purposive preventive or therapeutic strategies.

Proprioceptive deficits associated with knee OA have been considered as a potential cause for observed changes in proprioceptive weighting in this population [11], however, there are no studies on the relationship between PW and proprioceptive accuracy in the population of subjects with knee OA. In the current study we also investigated this relationship by including the proprioceptive accuracy of subjects with early and established knee OA [8].

Consequently, to better understand the progression of proprioceptive impairments with the progression of knee OA, the aim of this study was: (1) to investigate proprioceptive weighting in a group of patients with early knee OA, patients with established knee OA and to compare them with healthy peers; (2) to explore whether the sensitivity of the knee muscle to vibration decreases with increasing severity of knee OA; (3) to explore if there is a relationship between proprioceptive weighting and proprioceptive accuracy in subjects with knee OA.

2. Materials and methods

Fifty-two women with medial knee OA and 27 asymptomatic women participated in this study. Participants with knee OA were recruited during their regular visit to a rheumatologist or orthopedic surgeon at the University Hospitals Leuven. Participants in the healthy control group were recruited through social organizations. All participants were informed about the study procedure and signed informed consent forms. The study was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium prior to testing and was conducted in agreement with the principles of Declaration of Helsinki.

Each participant was referred for a physical exam and bilateral standard anterior–posterior weight-bearing radiographs in fixed flexed position were obtained (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). Diagnosis and categorization of knee OA were based on the K&L grading system [14] and a single experienced observer (FPL) graded each radiograph. A magnetic resonance image (MRI) was taken from the (most) affected side of the OA patients, based on radiography, and a random side in the control group, as described by Baert et al. [15].

The standardized Boston–Leeds Osteoarthritis Knee Score (BLOKS) scoring system was used by two separate readers (NN, GVDS) to score structural features in the tibiofemoral joint [16]. On 91% of all scored items, the two readers had full agreement and disagreements were resolved by consensus.

Participants with knee OA were further sub-classified, into early ($n = 27$) and established ($n = 26$) medial knee OA groups [17]. The inclusion criteria for the early OA group were: presence of knee pain, a K&L grade 0, 1 or 2− for the medial compartment, and presence of two of four MRI criteria: (1) ≥BLOKS grade 2 for size cartilage loss, (2) ≥BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment.

The classification of participants in the established knee OA group was based on the slightly adjusted American College of Rheumatology (ACR) classification criteria [18], which includes knee pain, age above 50, stiffness less than 30 min and crepitus, combined with structural changes defined as presence of minimum K&L grade 2+, indicating a moderate to severe disease severity.

The inclusion criteria for the control group were as follows, K&L grade 0 or 1 on the radiography of either knee, asymptomatic, no history of knee OA or other pathology involving any lower extremity joints.

2.1. Clinical assessment

To assess knee symptoms and function, the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Dutch version) was filled in by all participants. Validity and reliability of the KOOS has been verified for evaluation of short- and long-term symptoms and function in knee OA patients [19, 20].

2.2. Proprioceptive weighting and postural control assessment

Postural control was assessed using a six-channel force plate (Bertec, Corporation, Ohio, USA). Force plate data were sampled at 1000 samples/s. Participants were asked to comfortably stand barefoot on the force platform with arms crossed in front of the chest and the feet slightly separated. In all trials, vision was occluded by means of a blindfold. Each participant underwent three experimental conditions during which they were instructed to stand still and relaxed. The three conditions were:

(1) bilateral vibration of the Triceps Surae (TS) tendons; (2) bilateral vibration of the Tibialis Anterior (TA) muscle bellies; and (3) bilateral vibration of the Vastus Medialis (VM) muscle bellies. Two muscle vibrators (VB100, Dynatronic, Valence, France) were attached over the most proximal part of the tendon of the triceps surae muscles, and vastus medialis muscle belly using straps. The tightness of these straps was subjectively checked with the subject. The activation (frequency of 70 Hz, amplitude of approximately 0.5 mm) and deactivation of the vibrators was controlled manually. These characteristics of vibration were chosen to induce the maximal illusory joint movement [21]. Each trial lasted 45 s, during which muscle-tendon vibration was applied for 15 s, initiated 15 s after the start of the trial. Data collection continued for 15 s after the vibration was stopped.

All participants were asked to stop the test whenever they felt discomfort or pain during the test procedure. In case a participant lost her balance and tended to fall, the trial was excluded and repeated. As all subjects participated in the current study fulfilled every test trial without difficulty, we do assume that they did not experience pain related to the test procedures.

The center of pressure (CoP) position was calculated and averaged over the first 15 s of the trial (pre-vibration) and during the 15 s of vibration. The response to muscle vibration was defined and quantified as the difference in mean CoP position before and during vibration (Fig. 1).
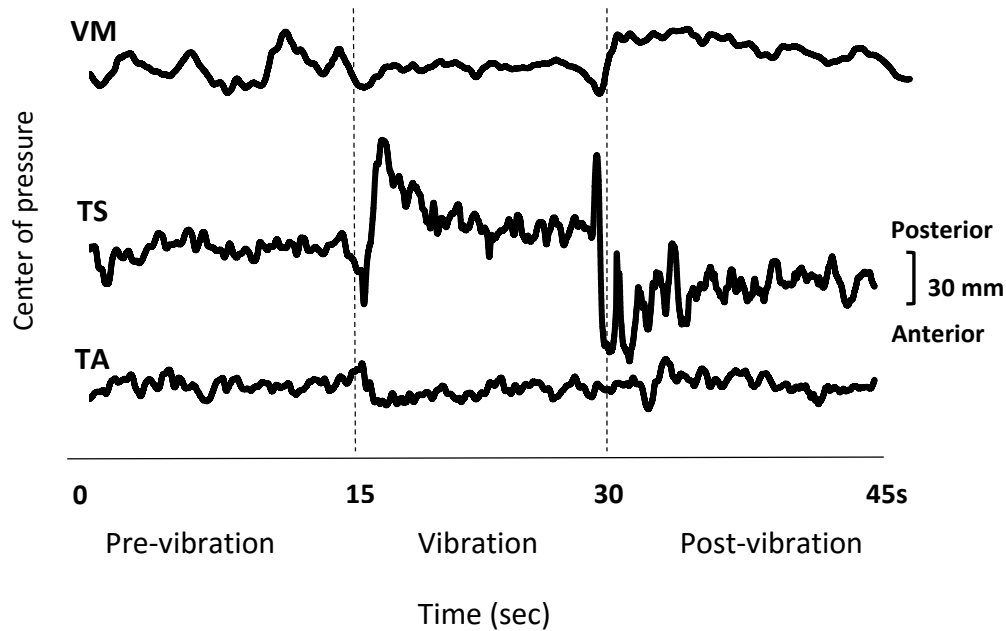
Figure 1. CoP (anteroposterior) position of a representative participant. Vibration was applied to tibialis anterior (TA), triceps surae (TS), and vastus medialis (VM).

Proprioceptive weighting between ankle and knee muscles was calculated as:

$PW_{TA\text{-}VM} = |TA_{response}| / (|TA_{response}| + |VM_{response}|)$, and

$PW_{TS\text{-}VM} = |TS_{response}| / (|TS_{response}| + |VM_{response}|)$,

where PW stands for proprioceptive weighting.

2.3. Proprioceptive accuracy

Proprioceptive accuracy was examined using an active repositioning test [22]. The participant was seated on a chair with knees flexed (90° flexion, hanging relaxed and unsupported) over the edge of the chair and with the eyes closed. The knee was extended passively from the resting position to one of the three test positions: 70°, 45°, and 20° flexion. This knee angle (criterion angle) was maintained by the participant for 3 s. The knee was then flexed back to the resting position (90° flexion) and relaxed for 3 s. Subsequently, the participant was asked to replicate the test position and hold it for 3 s. After familiarization with the test, each participant performed the tests twice in each of the knee

angles in a standardized order. The motion was tracked using an active three dimensional (3D) motion capture system at 100 samples/s (Krypton, Metris), using a previously described protocol [8].

Repositioning error (RE) was defined as the absolute difference between the criterion angles and reproduced angles. Four variables were calculated: mean RE of all six tests together and mean RE for the three different test positions separately.

3. Statistics

Descriptive statistics were used to summarize the characteristics of the study population. One-way analyses of variance (ANOVA) (if data were normally distributed and had equal variances) or Kruskal–Wallis tests (if data were not normally distributed or variances were not equal) were used to test for group differences in demographic and clinical characteristics. If indicated, Bonferroni corrected paired *t*-tests or Wilicoxon tests were used post-hoc in conjunction with the ANOVA's and Kruskal–Wallis tests, respectively.

Differences between groups for: response, recovery, proprioceptive weighting, and repositioning error were tested with general estimating equations (GEEs), with group as factor. For post hoc analysis, pairwise comparisons were used.

To assess associations between proprioceptive weighting and proprioceptive accuracy, Pearson product moment correlation coefficients were used within the total OA group, the early OA and established OA group. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, USA), with level of significance set at $P < 0.05$.

4. Results

Participants' characteristics are reported in Table 1. No significant differences were detected between groups in age, height, weight, and BMI. As expected, participants with OA had higher KOOS scores on all subscales but there was no significant difference between the two OA groups regarding any of the KOOS sub-scores.

Table 1. Participant characteristics and results for tests of differences between groups.

Characteristics	Control (n = 27)	Early (n = 27)	Established (n = 26)	P	P Established vs. control	P Early vs. control	P Early vs. established
Age (years)[a, d]	64.63 (7.6)	66.85 (6.5)	66.13 (7)	0.471			
Weight (kg)[a, d]	65.08 (11.1)	69.72 (11.4)	71.46 (11.8)	0.076			
Height (m)[a, c]	1.60 (0.1)	1.63 (0.1)	1.60 (0.1)	0.264			
BMI (kg/m^2)[a, d]	25.23 (4)	26.35 (4.3)	27.82 (4.6)	0.058			
KOOS pain score[b, d]	100 (2.8)	86.1 (27.8)	80.5 (33.3)	**<0.001***	**<0.001***	**<0.001***	0.241
KOOS symptoms score[b, d]	100 (8.3)	83.33 (33.3)	75 (33.3)	**<0.001***	**<0.001***	**<0.001***	0.156
KOOS ADL score[b, d]	100 (1.5)	88.2 (28)	85.2 (39.7)	**<0.001***	**<0.001***	**<0.001***	0.256

OA= osteoarthritis; BMI=Body mass index; KOOS = Knee injury and Osteoarthritis Outcome Score.
Data are presented as mean (SD)[a] or Median (IQR)[b]. The *P* value corresponds to an ANOVA[c], Kruskal-Wallis test (with post hoc tests) [d] comparing the three groups.
*Significant difference between groups (P < 0.05)

4.1. Proprioceptive weighting and postural control assessment

As can be seen in Fig. 1, vibration of all three muscles resulted in a shift of the CoP, but the direction, in which the CoP shifted, was different between muscles. Vibration of the TS led to a posterior shift of the CoP, while vibration of TA and VM resulted in an anterior shift of the CoP. For all three muscles, a shift of the CoP back towards baseline occurred after termination of the vibration.

In response to TS vibration, the early and established OA groups showed a larger posterior shift of the CoP compared to the controls, but did not differ from each other (Table 2). Vibration of the VM resulted in an anterior shift of the CoP in all three groups, but this response did not differ between groups (P = 0.521). Regarding the effect of TA vibration, there was no significant difference between the three groups (Table 2).

Table 2. Mean values (SD) of CoP displacements during and after muscle vibration, and GEE results with Group (Established OA vs. Early OA vs. controls) as factor.

	Control (n = 27)	Early OA (n = 27)	Established OA (n = 26)	P	P Established vs. control	P Early vs. control	P Early vs. established
CoP displacement							
Response TA (mm)	15.35 (2.2)	15.11 (2.2)	14.6 (2.3)	0.99			
Response TS (mm)	-20.44 (3.7)	-38.86 (3.7)	-36.62 (3.7)	**0.001***	**0.005***	**<0.001***	0.484
Response VM (mm)	1.45 (1.6)	3.69 (1.6)	4.24 (1.8)	0.521			
Proprioceptive weighting							
PW$_{TA-VM}$	0.71 (0.04)	0.70 (0.05)	0.70 (0.05)	0.963			
PW$_{TS-VM}$	0.81 (0.02)	0.87 (0.02)	088 (0.02)	**0.036***	**0.017***	**0.049***	0.647

OA=osteoarthritis; TA=Tibialis anterior; TS=Triceps surae; VM=Vastus medialis; PW= Proprioceptive weighting**.**
The negative sign indicates sway towards posterior direction.
Data are presented as mean (SD).
*Significant difference between groups (P < 0.05)

Proprioceptive weighting between TS and VM ($PW_{TS\text{-}VM}$) was significantly different between the three groups, showing higher PW ratio's for both groups with early and established knee OA compared to healthy participants (Table 2), but no differences between these groups. On the other hand, proprioceptive weighting between TA and VM ($PW_{TA\text{-}VM}$) was not significantly different between the three groups ($P = 0.963$).

4.2. Proprioceptive accuracy

The mean repositioning error values for all three groups are presented in Figure 2. Proprioceptive accuracy was not significantly different between early OA and control groups (Fig. 2). The established OA group showed significantly higher RE values compared to the control group ($P = 0.003$) when combining all tests and compared to both the early OA group and the control group ($P = 0.026$ and $P = 0.006$, respectively) for tests in 45° flexion.
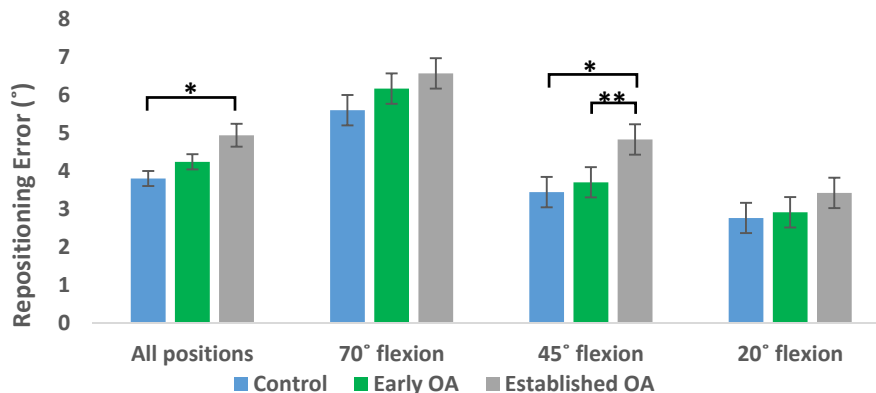

Figure 2. Comparison of the mean absolute repositioning error and standard deviation of the early OA group, established OA group and control group.

*Significant difference between established OA group and control group based on paired comparisons (P < 0.05)

**Significant difference between established OA group and early OA group based on paired comparisons (P < 0.05)

4.3. Relationship between proprioceptive accuracy and proprioceptive weighting

Considering patients with early and established knee OA, no significant correlations were found between TS response and RE in any of the testing positions ($r_{70} = 0.008$, $P_{70} = 0.946$; $r_{45} = -0.105$, $P_{45} = 0.355$; and $r_{20} = 0.108$, $P_{20} = 0.341$).

5. Discussion

The current study investigated the association of proprioceptive impairments with the progression of knee OA by comparing proprioceptive weighting in women with early and established medial knee OA and control participants. Results showed that women with knee OA are more sensitive to vibration of the triceps surae muscle, than vibration of the vastus medialis muscle, compared to healthy controls. Both OA groups included in this study showed an enhanced response to TS muscle vibration, manifested as an increased posterior shift of the CoP compared to the healthy controls. Shanahan et al. also reported increased sensitivity to TS muscle vibration in a group of participants with severe knee OA (with KL grade of 3 or 4) [11]. The present study extended the previous findings by showing that these changes already exist at time of early joint degeneration.

The aforementioned changes in sensitivity to vibration of the TS with knee OA could result from changes in the central processing of this afferent information. It has been established that participants with knee OA suffer from knee joint proprioception deficits [6-8], therefore, the proprioceptive information from the knee might be inadequate or distorted in a way that the CNS cannot use it for postural control and as a result CNS has to compensate for this loss by relying more on other sources of sensory information, in this case on proprioceptive input from ankle muscles (TS) [5, 23]. Similar results have been reported in patients with low back pain [4, 24]. Reliance on ankle muscles for postural control, known as inverted pendulum model of postural control [25], might be efficient during quiet standing but for more complex tasks, this kind of strategy might result in loss of postural control and even falling.

In the current study, similar to Shanahan et al. [11], no significant differences in response to vibration of VM muscle were found for any of the three groups. A possible explanation of this finding might be that the sensory contribution of quadriceps muscle to postural control is limited in the presence of intact sensory information from the TS muscle [26] both in the control and OA participants. But

participants with knee OA show a larger response to TS vibration and thus seem to upweight the input from TS for balance control.

Although there was a trend of larger CoP shifts under TS vibration in participants with established OA compared to participants with early OA, we did not find statistically significant differences in vibration responses and in proprioceptive weighting between the two OA groups. Therefore, this might suggest that upweighting of TS information was already present in early stages of knee OA rather than a contributing factor for progression of the disease.

In the present study, an upweighting of TS information was also observed in participants with early knee OA, despite the fact that in this group as opposed to the established OA group, no significant changes in proprioceptive accuracy were measured by the active repositioning test. There were no significant correlations between proprioceptive weighting and repositioning error. Knee joint mechanoreceptors and knee muscle spindles both have major roles in joint position and movement perception [27, 28]. Knee joint mechanoreceptors are at the primary site of pathology in knee OA and muscle spindles are also known to be altered by knee OA [29, 30]. Differences in proprioceptive accuracy as tested with repositioning tests may be explained by differences in the damage to the joint and consequently to the joint mechanoreceptors, which is more severe in established OA compared to the early group. However, the proprioceptive weighting changes observed in the current study already in the early stage of OA, might be more related with movement detection thresholds. This is in agreement with previous findings of increased movement detection thresholds in OA patients irrespective of the stage of the disease and even present in the unaffected knee [7]. A limitation of this study is that all of the participants in the current study were females, and as such the results of this study cannot be generalized to the whole population of patients with knee OA. In addition, postural control in this study was assessed in a static position, so the results cannot be generalized to more dynamic situations. The present study was cross-sectional in nature, considering the progressive nature of the knee OA, it would be useful to investigate the proprioceptive impairments in a longitudinal study.

The results from this study suggest that the early knee OA as well as the established knee OA were associated with up-weighting of the proprioceptive information from TS muscle in control of upright stance, which implies an increased reliance on ankle proprioceptive input in both early and established OA groups compared to the asymptomatic controls.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

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Chapter 3

Varus thrust in women with early medial knee osteoarthritis and its relation with the external knee adduction moment

Abstract

Varus thrust, defined as an abrupt increase of the knee varus angle during weight-bearing in gait, has been shown to be present in patients with moderate to severe knee osteoarthritis (OA) and is considered to be one of the risk factors for progression of symptomatic medial knee OA. We evaluated the presence and magnitude of varus thrust and its relation with the Knee Adduction Moment in women with early medial knee OA, and compared it to that in a group of controls and in a group of subjects with established medial knee OA. Twenty-seven women with early medial knee OA, 21 women with established medial knee OA and 24 asymptomatic controls were evaluated. Varus thrust was estimated as an increase of the knee varus angle during the weight-bearing phase of gait at self-selected speed, assessed by 3D motion analysis. Varus thrust was significantly higher in both early and established OA groups compared to the control group ($p < 0.001$), but not different between OA groups. While the knee adduction moments were higher than controls only in the established OA group, the magnitude of varus thrust was significantly correlated with the second peak knee adduction moment. Higher varus thrust was found both in early and established stages of knee OA, suggesting that problems with dynamic stabilization of the knee are present early in the development of knee OA. This highlights the necessity of considering dynamic alignment in rehabilitation already in the early stages of the disease.

1. Introduction

Knee osteoarthritis (OA) is one of the major causes of disability in the elderly population, whereby the medial knee compartment is affected most [1]. Knee joint alignment has been put forward as one of the risk factors for knee OA [2, 3] and several authors have reported an association of increased static varus alignment with increased OA severity [4, 5]. Malalignment of the knee either in varus or valgus direction influences the load distribution over medial and lateral compartments of the knee joint [6]. A neutrally aligned knee bears approximately 60-80% of the compressive load on the medial compartment [7] and a 5 degrees increase in varus alignment results in a 20% increase of load on the medial compartment [6]. Such an increase in medial compartment loading will put extra stress on articular cartilage and the subchondreal bone and might subsequently lead to degenerative changes.

Assessment of static knee alignment using standing radiographs comes with some limitations such as availability and costs [8]. Moreover, the alignment is affected during the radiography by foot position [9] and weight-bearing status [10]. Moreover, since pain and functional limitations during dynamic activities are the major complaints among subjects with knee OA, assessment of the change in alignment during functional activities such as gait could provide essential information.

Varus thrust is a dynamic malalignment of the knee that has been defined as an abrupt increase of the knee varus angle when the leg is bearing weight, with a decrease during the non-weight-bearing phase of ambulation (swing phase) [11, 12]. In a prospective study, the presence of varus thrust was shown to be related to disease progression [11]. Also, pain and discomfort felt by the patient in relation to this thrust can cause difficulties in Activities of Daily Living (ADL) and consequently to functional impairment [13]. Varus thrust can be quantified as the difference between the knee adduction angle at heel contact and the maximum knee adduction angle during the early stance phase of gait [11, 12]. Only a few previous studies investigated varus thrust in OA [11-14] and in some of these only the presence of varus thrust was studied by visual observation and not by quantitative motion analysis [11, 13, 14]. However, neither the presence nor the magnitude of varus thrust have been investigated in the early OA population [15].

Varus thrust has been associated with a higher external knee adduction moment (KAM), a proposed non-invasive indirect index of the load on the medial compartment of the knee joint [5]. Barrios et al. found that the peak knee adduction angle during gait was more strongly related to the KAM than static radiographic alignment [16]. There are reports on the absence of higher KAM early in the disease process, which might imply that the KAM may not be increased in the early stages of knee OA [17], which would suggest that it is a consequence rather than a cause of OA

progression. Therefore, it is important to assess varus thrust and KAM in patients with early knee OA. Quantification of varus thrust in the early stages of the disease and identification of its relationship with KAM, as a risk factor associated with the progression of medial knee OA, may lead us to develop a tool for screening subjects at higher risk of disease progression.

In the present study, we investigated static knee alignment and varus thrust in subjects with early medial knee OA, classified based on the presence of pain and a combination of early structural changes detected on radiography and Magnetic Resonance Imaging (MRI) [15], and this was compared to subjects with established knee OA and asymptomatic controls. Furthermore, we studied the relationship between static alignment and varus thrust on one hand and KAM on the other hand. We defined varus thrust as the increase in varus angle between heel contact and its peak value during stance and also investigated the presence of varus thrust by dichotomizing the varus thrust as either present (above the median) or not present (below the median).

We hypothesized that, 1) varus thrust would be more common and the magnitude of varus thrust would be higher in subjects with medial knee OA compared to the asymptomatic controls, 2) the differences expected based on hypotheses 1 would also exist between established and early OA patients, 3) there would be a positive correlation between the magnitude of varus thrust and KAM.

2. Materials and Methods

Forty-seven women with medial knee OA (27 with early and 20 with established OA) 24 healthy controls participated in this study. All participants were informed about the study procedure and signed informed consent forms. The study was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium prior to testing and was conducted in agreement with the principles of the Declaration of Helsinki.

Participants with knee OA were recruited during their visit to a rheumatologist or orthopedic surgeon in the University Hospitals Leuven, and they were further sub-classified, into early (n = 27) and established (n = 21) medial knee OA groups, based on the classification system introduced by Luyten et al. [15]. The inclusion criteria for the early OA group were: presence of knee pain, a Kellgren & Lawrence (K&L) grade 0, 1 or 2- (osteophytes only) for the medial compartment on radiography and presence of two of four MRI criteria: (1) ≥ BLOKS grade 2 for size cartilage loss, (2) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one

compartment. Participants in the healthy control group (n = 24) were recruited through social organizations. The inclusion criteria for the control group were as follows, K&L grade 0 or 1 on the radiography of either knee, asymptomatic, no history of knee OA or other pathology involving any lower extremity joints.

Each participant was referred for a physical exam and bilateral standard anterior-posterior weight-bearing radiographs in fixed flexed position were obtained (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). Diagnosis and categorization of knee OA were based on the K&L grading system [18] and a single experienced observer (FPL) graded each radiograph. A magnetic resonance image (MRI) was taken from the (most) affected side of the OA patients, based on radiography, and a random side in the control group. A 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) with an eight-channel phased array knee coil was used, and subjects were scanned in a non-weight bearing supine position, as described by Baert et al. [19].

The standardized Boston-Leeds Osteoarthritis Knee Score (BLOKS) scoring system was used by two separate readers (NN, GVDS) to score structural features of the tibiofemoral joint [20]. On 91% of all scored items, the two readers had full agreement and disagreements were resolved by consensus.

The classification of participants in the established knee OA group was based on the slightly adjusted American College of Rheumatology (ACR) classification criteria [21], which includes knee pain, age above 50, stiffness less than 30 minutes and crepitus, combined with structural changes defined as presence of minimum grade 2+ (osteophytes and joint space narrowing), on K&L scale for the medial compartment on radiography, indicating a moderate to severe disease severity. Patients with higher K&L grade on the lateral than on the medial compartment of the same knee were excluded.

2.1. Assessment of knee symptoms and function

All participants completed the Dutch version of Knee Injury and Osteoarthritis Outcome Score (KOOS). This version has been shown to be valid and reliable for patients with knee OA [22]. The KOOS has five distinct sections. To evaluate the knee OA signs and symptoms, the subscales 'pain' and 'symptoms' were used. The 'ADL' section was used to estimate participants' subjective physical performance. A converted score from 0 to 100 was computed for each subscale, with 100 indicating the best possible result.

Figure 1. Varus thrust magnitude calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait.

2.2. Assessment of static knee joint alignment

The static alignment of the knee joint was assessed by an experienced musculoskeletal radiologist on full-leg AP weight-bearing plain radiographs of the lower extremities [23]. Malalignments of less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively. Knee alignment between -2° and +2° was classified as neutral [2, 24].

2.3. Gait data acquisition and analysis

A 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group) was used to record the spatial position of markers on relevant body segments at 100 samples/s. Ground reaction forces were recorded through force plates (Bertec Corporation, Ohio, USA and AMTI, Watertown, MA, USA) placed in a 12m walkway at a sample rate of 1000 samples/s. Participants walked along the walkway at a comfortable habitual speed during gait analysis. To avoid force plates being targeted while performing the trials, no guidance on walking, except the instruction to 'walk naturally' was provided. Three complete force plate strikes for each foot were registered. Since footwear can affect the distribution of loads on the joints in the lower quadrant [25], all participants were asked to walk bare-footed. The "heel-strike" event was detected as the first sample of vertical ground reaction force that was above 10 N. The "toe-off" event was chosen as the first sample at which the vertical ground reaction force was below 10N [26]. 3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay [27]. External knee adduction moment (KAM) was calculated through a bottom-up dynamic linked

segment model, using kinematics of the body segments and the ground reaction forces [28]. To obtain the knee adduction moment from the 3D components of the net moments, the knee moments were projected onto the calf coordinate system. Extracted joint moments were normalized to the product of body weight and height (BW*Ht) [29].

2.4. Assessment of dynamic knee joint alignment
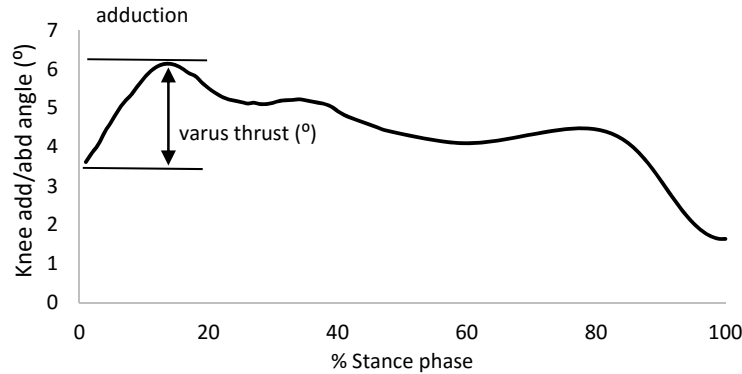
Varus thrust magnitude was calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait (Figure 1) [11, 12]. Varus thrust was subsequently dichotomized into groups of subjects with and without varus thrust, based on the median value of varus thrust (2.02˚) in the whole group of subjects [30].

2.5. Statistical analysis

Statistical analyses were performed using SPSS software (version 20, 2006, Chicago: SPSS Inc) and for all tests, p values less than 0.05 were considered statistically significant. Means and standard deviations were calculated and one-way analyses of variance (ANOVA) were used to test for group differences in height, weight, age, BMI. A Kruskal-Wallis test was used to test for differences between the three groups for KOOS sub-scores. Gait related, as well as static alignment, group differences were tested using Generalized Estimating Equations (GEE) with *Group* as factor and age, height, and weight as co-variates. Static alignment was also included as covariate when testing group differences for varus thrust. Relations between static alignment, varus thrust, and presence of varus thrust on one hand, and the first and second peak in the KAM on the other hand were assessed using univariate and multivariate linear regression analyses over the total group.

3. Results

As presented in Table 1, the three groups were comparable in age, height, weight, and BMI. Both OA groups had significantly more knee pain (P <0.001, for both) and more symptoms ($P_{established}$ <0.001 and P_{early} = 0.002) compared to asymptomatic controls, but without significant differences between the two OA groups (table 1). OA patients also demonstrated worse self-reported physical performance (P <0.001, for both) and Quality of Life (QoL) (P <0.001, for both), than controls. Preferred walking speed and stance time were not significantly different between the three groups (P = 0.32 and P = 0.44, respectively).

3.1. Static knee joint alignment

Static alignment was significantly different between the three groups, with the established OA group showing significantly higher varus malalignment compared to the early OA group and the healthy controls (p = 0.002 and p < 0.001 , respectively). There was no significant difference between the early OA and control groups (p = 0.202). In the control group, 79% and in the early OA group, 74% of the subjects had a neutral alignment; in the established OA group, 48% of the subjects showed varus malalignment and 48% showed a neutral alignment (Table 1).

3.2. Dynamic knee joint alignment

Knee adduction angles increased after initial stance phase in all three groups (figure 1). The amount of varus thrust was 1.41˚ (±0.3), 2.58˚ (±0.4), 3.26˚ (±0.5), for the control, early OA, and the established OA groups, respectively (figure 2).

Varus thrust magnitude was significantly different between the three groups; subjects with early and established knee OA showed significantly higher values of varus thrust compared to the asymptomatic control group (p = 0.019 and p = 0.001, respectively) (Figures 2.A & 3). There was no significant difference in varus thrust magnitude (p = 0.197) between the two OA groups. After adjustment for age, height, weight, and static alignment, the differences between the early and the established OA groups on one hand and the control group on the other hand were still significant (p = 0.028 and p = 0.009, respectively). The amount of varus thrust was significantly higher in subjects with static varus malalignment compared to the subjects with neutral static alignment (p = 0.003) also after adjustments for age, height, and weight (p = 0.002).

The presence of varus thrust was significantly more common in the early OA group and the established OA group, compared to the controls (p = 0.033 and p = 0.008, respectively). No such difference for the presence of varus thrust was found between the two OA groups (p = 0.454).

Varus thrust was significantly higher in subjects with static varus malalignment compared to the subjects with neutral static alignment (p = 0.003). Results stayed the same after adjustments for age, height, and weight (p = 0.002).

3.3. External knee adduction moment

There were no differences between groups in the magnitude of the first peak of the KAM. The second peak of the KAM was different between groups; subjects with established knee OA

demonstrated a significantly higher second peak compared to subjects with early medial knee OA and to the healthy controls (p = 0.011 and p = 0.004, respectively) (Figure 4). There was no such difference between the early OA group and the asymptomatic controls (P = 0.684) (Figure 4).

3.4. Correlations between knee alignment and external knee adduction moment

There was a significant correlation between the static alignment and the first peak KAM over the patients group (p = 0.018, r = 0.345). The static alignment showed also significant correlations with the second peak KAM (p = 0.021, r = 0.336).

There was a trend towards a significant correlation between the magnitude of varus thrust and the first peak KAM over the patients group (p = 0.057, r = 0.28). The magnitude of varus thrust also showed significant correlations with the second peak KAM (p = 0.037, r = 0.306).

Analysis of dichotomized varus thrust showed that the groups with a larger than median varus thrust had significantly higher first and second peaks of the KAM (p = 0.01 and p = 0.033, respectively).

Table 1. Subject's clinical characteristics

		Control (n = 24)	Early OA (n = 27)	Established OA (n = 21)	P-value	P Established vs. control	P Early vs. control	P Early vs. established
Weight (kg)[a]		65.71 (9.6)	72.52 (11.9)	69.94 (10.9)	0.089			
BMI (kg/m^2)[a]		24.81 (0.8)	27.45 (0.7)	27.16 (0.8)	0.073			
Height (m)[a]		1.63 (0.06)	1.63 (0.05)	1.6 (0.07)	0.291			
Age (years)[a]		63.95 (1.8)	67.38 (1.1)	66.05 (1.6)	0.068			
K&L score (MC)[c]		Grade 0: n=18 Grade 1: n= 6	Grade 0: n= 10 Grade 1: n= 18 Grade 2[-]: n= 1	Grade 2[+]: n= 15 Grade 3: n= 6				
KOOS Pain[b]		100 (4.9)	80.5 (33.4)	81.9 (28.5)	**<0.001**	**<0.001**	**<0.001**	0.471
KOOS Symptoms[b]		92.8 (10.8)	82.1 (25)	83.9 (29.4)	**<0.001**	**<0.001**	**0.002**	0.216
KOOS ADL[b]		100 (2.6)	89.7 (29.4)	86.7 (33.1)	**<0.001**	**<0.001**	**<0.001**	0.64
KOOS QoL[b]		100 (4.7)	75 (43.8)	59.4 (60.9)	**<0.001**	**<0.001**	**<0.001**	0.407
Static alignment[c]	Neutral Valgus Varus	n= 19 n= 4 n= 1	n= 20 n= 3 n= 4	n= 10 n= 1 n= 10				
Self-selected walking speed (m/s)[a]		1.24 (0.2)	1.21 (0.2)	1.15 (0.2)	0.32			
Stance time[a]		63.81 (5.8)	64.82 (5.7)	66.04 (6.4)	0.44			

OA=osteoarthritis; BMI= Body Mass Index; K&L= Kellgren & Lawrence (range 0-4), KOOS = Knee injury and Osteoarthritis Outcome Score.
Data are presented as [a]Mean (SD), [b]Median (IQR) or [c]frequencies. The P value corresponds to [a]ANOVA test or [b]Kruskal-Wallis test (with post hoc tests) comparing the three groups.
[†] Significant difference between groups (P < 0.05).

A

B
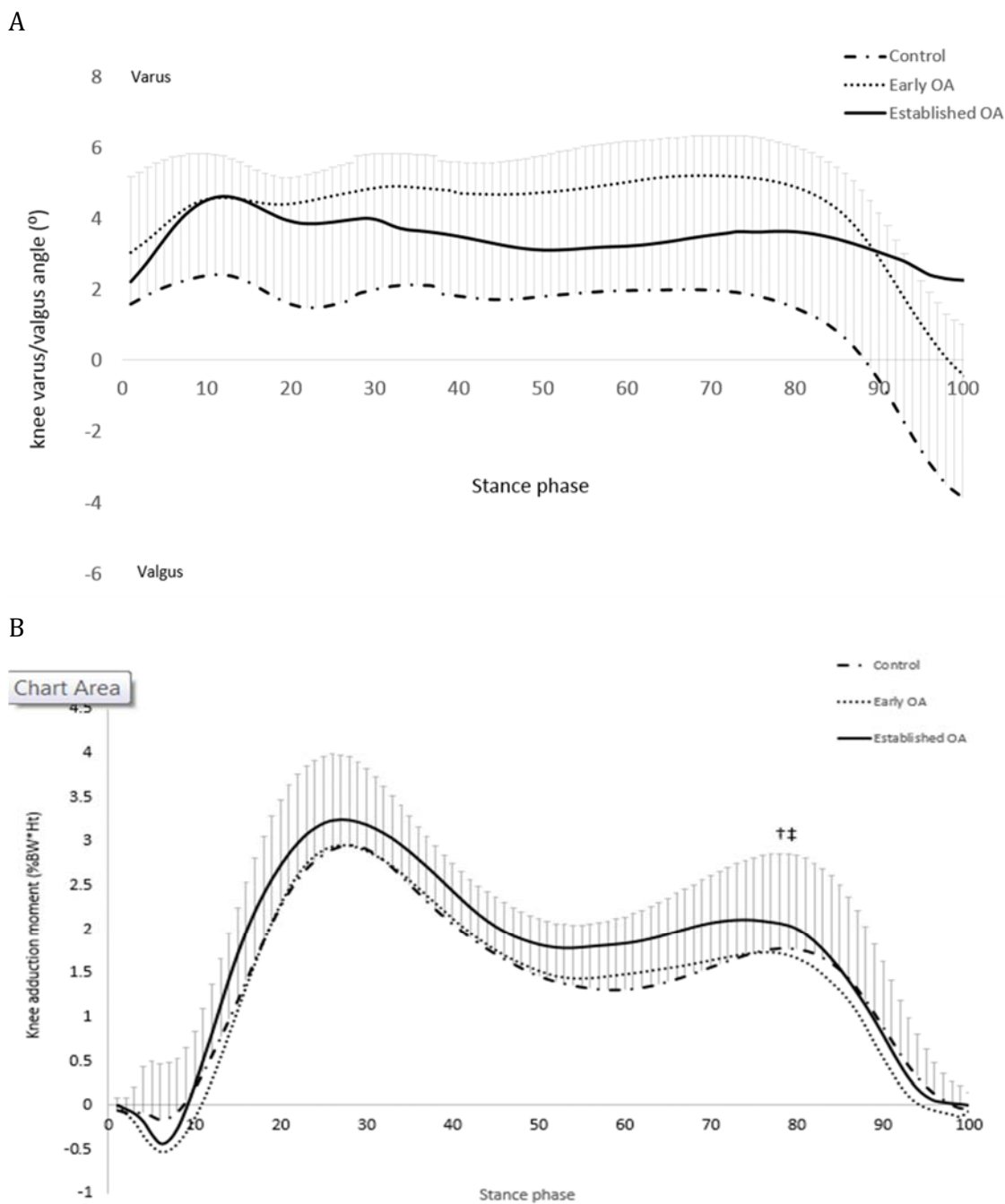
Figure 2. Mean waveform of the knee abduction-adduction angle for the early OA (**...**), established OA (_), and control group (__ .) with standard deviation of the control group (thin vertical lines) are compared for knee abduction-adduction angle (varus is in the positive direction) (A), external knee adduction moment (B).
† significant difference between established OA group and control group based on GEE with post hoc test ($P<0.05$)
‡ significant difference between early OA group and control group based on GEE with post hoc test ($P<0.05$)
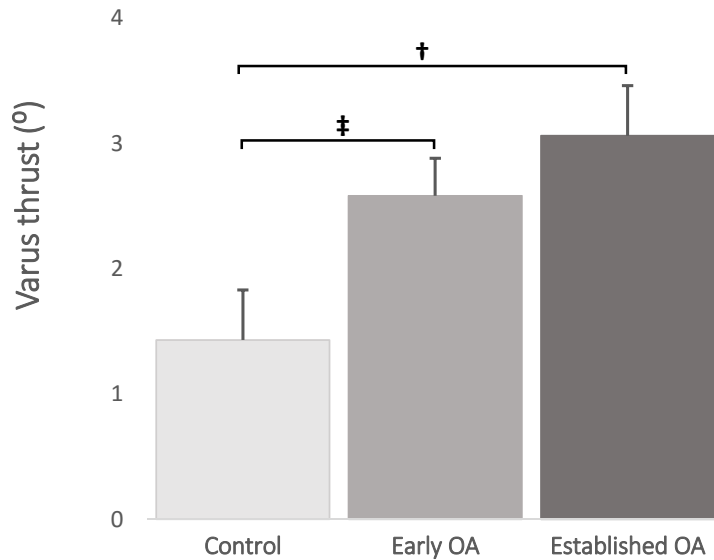
Figure 3. Mean and standard deviation for the varus thrust during stance phase of gait, of the early OA group, established OA group, and control group were compared.
† significant difference between established OA group and control group based on GEE with post hoc test (P<0.05)
‡ significant difference between early OA group and control group based on GEE with post hoc test (*P*<0.05)
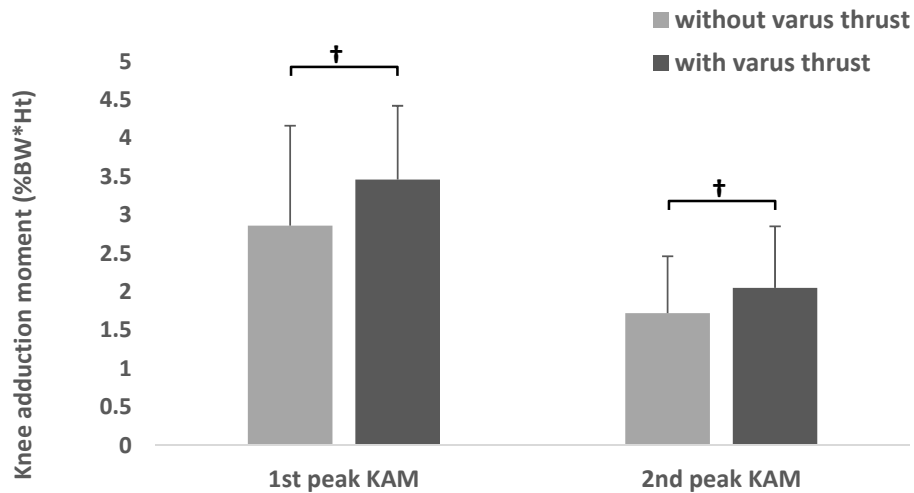
Figure 4. Mean and standard deviation for the first and second external knee adduction moment during stance phase of gait, of the two groups with and without varus thrust were compared.
† significant difference between subjects with and without varus thrust based on GEE (P<0.05)

4. Discussion

To the best of our knowledge, this is the first study that assessed the magnitude of varus thrust in a sub-population of subjects with early medial knee OA. Results showed that varus thrust is more common and that the magnitude of varus thrust is greater in women with early medial knee OA than in healthy controls, as it is in women with established medial knee OA. While a relation between peak KAM and varus thrust was found, peak KAM were higher compared to control in established OA only.

The magnitude of varus thrust reported in the current study corresponds to previously reported values [12]. Consistent with our finding, previous results also reported that varus thrust is more common and has a larger magnitude in subjects with established medial knee OA than in healthy controls [11-13]. Increased varus thrust observed in the two OA groups in the current study might partly be due to greater static varus alignment in this group. However, the difference was still significant when corrected for static alignment. Increased varus thrust, suggests a decreased control over knee joint motion in the frontal plane in subjects with knee OA, which has been associated with decreased proprioceptive acuity and reduced muscular strength [14, 31]. Further studies are needed to determine the causes of the increased varus thrust in OA patients.

In line with the present results, previous studies had already shown that the magnitude of varus thrust is significantly correlated with the external KAM [11, 12]. This might imply that varus thrust attributes to higher KAM, which in turn causes loading on the medial compartment of the knee joint that could contribute to disease progression [11, 12, 32]. This is further highlighted by the greater adduction moment in knees with varus thrust compared to the ones without a thrust. It should be noted that the present results suggest that increased varus thrust precedes changes in the KAM or that varus thrust is more sensitive to knee OA than KAM.

The presence of significantly elevated first and second peak KAM in subjects with varus thrust, based on dichotomized varus thrust data, suggest that visual observation of thrust during gait could offer a simple clinical tool to detect subjects at higher risk of developing excessive medial joint load. This would not require quantitative gait analysis or radiographic assessment of knee mechanical alignment. However, the validity and reliability of visual observation would need to be verified.

Current results suggests that the effort to stabilize the knee in the frontal plane both in early and established OA groups is not adequate to prevent the varus thrust and consequently counteracting greater KAM. Therefore, development and validation of specific exercise regime that targets

frontal plane dynamic instability, especially at the early stages of the disease process, seems necessary in order to slow down the knee OA progression by reducing the chance of developing greater medial loads. Patients with higher/presence of varus thrust can also benefit from stabilizing orthoses or probably lateral wedged insole, as it has been shown to be effective in reducing the greater force associated with varus thrust [33].

There are some limitations to our study and hence the conclusions that may be drawn from our data. First, although the classification criteria for early OA have been proposed as a result of several rounds of discussion (Delphi approach) between rheumatologists and orthopedic surgeons, it is still in its early days and further prospective validation of this classification is needed. Second, in the current study barefoot walking has been chosen in order to obtain a better tracking of the markers, however this limits generalization of the results. Therefore, our results may not apply to all real–life walking conditions, where shoes are worn. Finally, as only women were included in this study, generalization of the current results to men should be treated with care. Finally, thurst as observed, may be different from thrust as measured as it is hard to distinguish actual thrust from a combined flexion rotation movement. To the best of our knowledge no study to date specifically addressed this issue in knee OA population, despite disagreements between biomechanists and clinicians. At the same time, this phenomenon seems to happen and it could still be clinically relevant.

5. Conclusions

We evaluated the presence and magnitude of the varus thrust in women with early medial knee OA and compared it to a group of asymptomatic controls as well as to a group of subjects with established medial knee OA. Results showed that the varus thurst is more common and that magnitude of varus thrust is significantly larger in subjects with early knee OA, even after adjustment for static alignment, compared to healthy controls, as was also found for women with established OA. This study, along with the previous reports of varus thrust, further highlights the value of measuring thrust as a clinical index for medial knee OA. Whether presence and higher magnitude of varus thrust in knee OA subjects early in the disease process, predict OA progression merits further investigation.

Acknowledgements

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Chapter 4

Phase-dependent changes in local dynamic stability during walking in elderly with and without knee osteoarthritis

Abstract

Previously, we reported reduced time-averaged knee local stability, in the unaffected, but not the affected leg of elderly with knee osteoarthritis OA compared to controls. Since stability may show phase-related changes, we reanalyzed the dataset reported previously using time-dependent local stability, $\lambda(t)$, and also calculated time-averaged local stability, λ_s, for comparison. We studied treadmill walking at increasing speeds, focusing on sagittal plane knee movements. 16 patients, 12 healthy peers and 15 young subjects were measured. We found a clear maximum in $\lambda(t)$ (i.e. minimum in stability) at around 60% of the stride cycle (StanceMax $\lambda(t)$), a second clear maximum (SwingMax $\lambda(t)$) at around 95% followed by a minimum between 70% and 100% (SwingMin $\lambda(t)$). StanceMax $\lambda(t)$ of both legs was significantly higher in the OA than the young control group. Values for healthy elderly fell between those of the other groups, were significantly higher than in young adults, but there was only a trend towards a significant difference with the StanceMax $\lambda(t)$ of the OA group's affected side. Time-averaged and time-dependent stability measures within one leg were uncorrelated, while time-dependent stability measures at the affected side were inversely correlated with λ_s at the unaffected side. The results indicate that time-dependent local dynamic stability might provide a more detailed insight into the problems of gait stability in OA than conventional averaged local dynamic stability measures and support the notion that the paradoxical decline in unaffected side time-averaged local stability may be caused by a trade-off between affected and unaffected side stability.

1. Introduction

One of the most pervasive threats to mobility in elderly is knee osteoarthritis (OA). With the aging of the population and the increasing incidence of obesity [1, 2], the prevalence of knee OA, and consequently burden on the society is rising. Among adults in western populations, knee OA is one of the most frequent causes of pain, loss of function and disability [3, 4].

Self-reported instability of the knee is one of the symptoms in knee OA, especially in the advanced stages of the disease [5] and has negative functional implications [6-8]. Buckling, giving way [6], and varus thrust are common signs that bother patients with knee OA [9]. While the importance of self-reported instability is well accepted by researchers and clinicians, there is still no consensus about objective, accurate and reliable ways to measure "true" dynamic stability of the knee. One approach is to evaluate knee function by means of dynamic tests (hop tests, jump tasks, side-cutting maneuvers, etc.) [10, 11]. Such dynamic tests however have the problem that they reflect "knee stability" indirectly, and are influenced by other factors such as muscle strength, jump capacity, and familiarity with the task. Moreover, it is difficult and often impossible to perform these tests in older people or in subjects just after surgery (e.g., ACL reconstruction).

Another approach is through passive knee joint laxity measures [12]. In spite of ample clinical application, it has been reported that self-reported knee instability is not directly associated with medial laxity [13]. However, the direct effects of static laxity on functional abilities and perception of stability during activities of daily life appear to be relatively limited [14-17]. Similar results were reported in populations other than knee OA. For instance studies on individuals with anterior cruciate ligament (ACL) deficiency revealed that in some patients, no symptoms of self-reported knee instability were reported, in spite of increased anterior knee laxity [18-21].

Given the limitations of the above methods to capture knee stability, researchers continue to look for variables that capture dynamic stability during tasks such as walking. One of the most accepted ones is the local divergence exponent (λ_s). The local divergence exponent measures the rate of divergence after small perturbations, and thus assesses the stability of a movement pattern [22, 23]. Positive values of λ_s indicate instability, with higher values indicating higher instability. Usually, λ_s is estimated as an average across the gait cycle, which limits the assessment of possible variations in the instantaneous state space divergence [24]. However, according to recent studies, local stability changes within a stride cycle, especially during the transitions between single and double support phases [25-27].

In a previous study of our group, a significantly higher λs of knee kinematics (i.e. decreased stability) was reported in a group of knee OA patients at their unaffected side compared to their healthy peers, while no difference was present at the affected side [28]. Fallah Yakhdani et al. explained their findings as a compensatory strategy that patients used in order to reduce the kinetic demands on the affected leg, which consequently led to a higher unaffected λs. This hypothesis may be tested by looking into changes of λs over the gait cycle. More to the point, the new method of time-dependent local dynamic stability $\lambda(t)$, which is sensitive to state space divergence changes within a stride cycle, may be a better tool to look into the phase-related variation than the conventional λs [24].

Thus the current study aimed to reanalyze the dataset reported previously by [28] using phase-dependent stability measures. We hypothesized that knee stability would be different for different phases during the stride cycle, and that these differences might explain why previously we found instability only in the unaffected leg in knee OA. Since we previously calculated time averaged λ_s based on a state-space built from time delayed copies, which cannot be used when calculating time-dependent $\lambda(t)$, we also recalculated time averaged λ_s.

2. Patients and methods

The data set reported by [28] was reanalyzed for the current study. 16 subjects with unilateral knee osteoarthritis (age, 62.3±10.7 years) waitlisted for unilateral total knee arthroplasty were recruited from 2 university hospitals. In addition, 12 healthy (62.0±12.6 years), age and BMI matched elderly and 15 healthy young subjects (22.9±3.9 years) were recruited. Each subject signed an informed consent and the protocol was approved by the medical ethical committee of the VUmc.

All three groups were asked to walk on a treadmill (Bonte Technology, Culemborg, The Netherlands) at 6 different walking speeds, from 1.4 to 5.4 km/h (increments of 0.8 km/h). At each speed, subjects walked for 4-minutes, of which the last 2 minutes were recorded. Gait kinematics were measured using an opto-electric system, OptoTrak™ [22] (Northern Digital, Waterloo, Ontario, Canada), with two 3-camera arrays. Clusters of 3 markers (Infrared Light Emitting Diodes), fixed on light metal plates, were attached to the thighs, shanks, and heels with neoprene bands. A range of walking speeds was applied as it has been reported that stability is speed dependent [29, 30].

The subjects were informed about their right to stop the measurement whenever they wanted, in such a case the treadmill belt was stopped and the last speed was recorded as the highest speed for that subject.

To assess knee symptoms and function, subjects filled in the Western Ontario and McMaster Universities osteoarthritis index (WOMAC). A Dutch version of WOMAC was used, which is a reliable and valid instrument for evaluation of pain and physical functioning in OA patients [31]. By way of clinical characterization of the subjects, we included "pain", "stiffness", and "physical function" subscales of the WOMAC.

2.1. Data analysis

2.1.1. Pre-processing

Gait events (i.e. foot-strike and foot off) were calculated from the foot cluster marker trajectories. Heel strikes were inferred from the minimum vertical position of the heel markers; stride time was calculated as the average time difference between consecutive ipsilateral foot-strikes. Shank and thigh segment orientations were calculated and the sagittal plane angles of these segments were expressed as rotations around the transverse axis. Subsequently, angular velocities were calculated by taking the derivatives of the obtained angles. Next, to calculate phase dependent stability, the first 40 strides of each time series were selected, and normalized to $40 \times 100 = 4000$ data points, while maintaining temporal variability between strides [29]. Four-dimensional state spaces of knee motion were then made using the sagittal plane angle and angular velocity time series of the thigh and shank segments (Note that in using phase dependent stability, one can not use delay-embedding, as this would cause "mixing" of the phases) [24]. Next, for each data point that was at heelstrike, the nearest neighbor was found (i.e. the point with minimal Euclidean distance to that point), and the distance between these points was calculated and tracked for 100 samples (i.e. one stride) over time. Next, the mean of the logarithm of these curves was taken, to create a curve of divergence over a stride. These curves were then filtered, with a 2nd order 5 Hz low pass dual pass butterworth filter, after which the derivative with respect to time was calculated, resulting in a time series of local divergence exponents. Positive values imply divergence, that is, instability, with higher positive values revealing more instability. After inspection of these curves, we found a clear maximum between 40% and 70% (StanceMax $\lambda(t)$), and a second clear maximum (SwingMax $\lambda(t)$) followed by a minimum between 70% and 100% (SwingMin $\lambda(t)$). These maximum and minimum values were extracted from the third

stride in the divergence curve, since in the first stride(s), and used for statistical analysis (Figure 1). We also calculated time-averaged λs from the same state-spaces using Rosensteins algorithm [22, 32, 33].

A

B
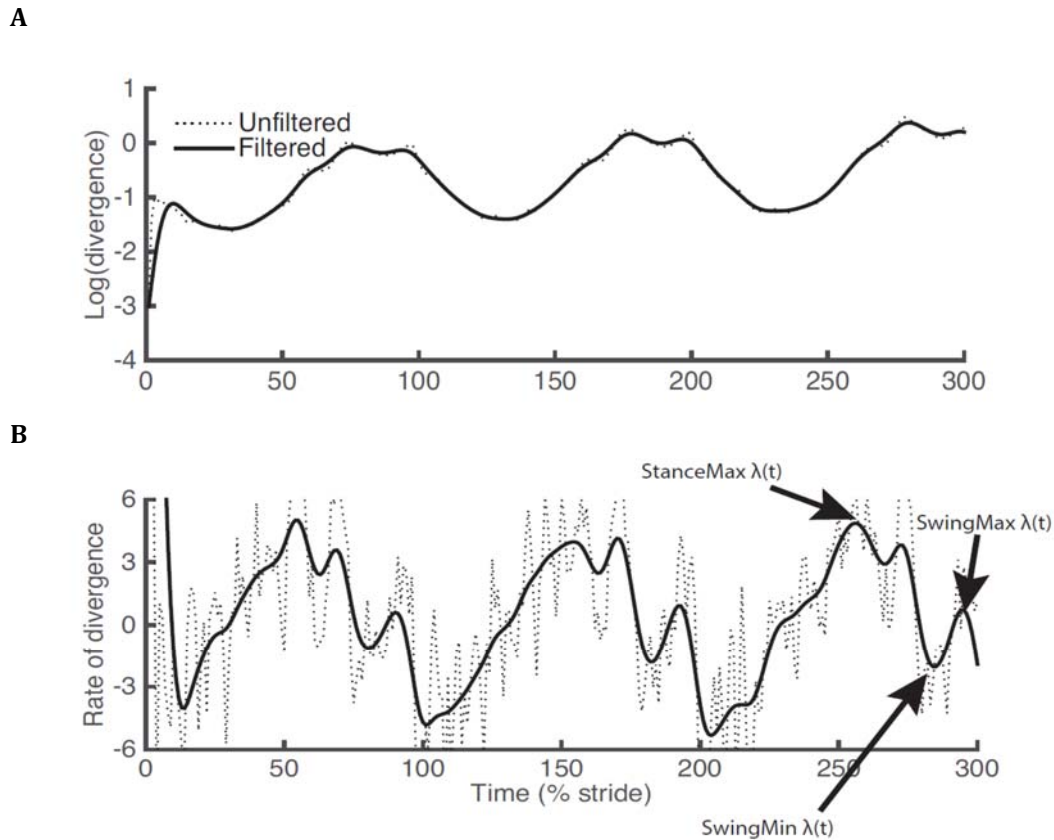
Figure 5. (A) Example of a divergence curve with divergence starting from heel strike. Dotted lines represent unfiltered data, solid filtered data. (B) λ(t) calculated from the unfiltered (dotted) and filtered (solid) data presented in (A). Areas where values for statistical analysis where extracted are indicated by arrows.

All analysis was done using Custom-made MATLAB 7.14.0 (The MathWorks, Natick, MA) programs. As not all patients could walk at all speeds, we used General Estimating Equations (GEE) [34], which is a technique capable of dealing with missing values. GEEs for time-averaged λs, StanceMax λ(t), SwingMax λ(t), and SwingMin λ(t) were calculated with Speed as covariate and Group as factor. When there was a significant effect, or interaction with, Group, the Least Significant Difference (LSD) post-hoc test was used to perform a pairwise comparison of the three groups. Non-significant interactions were left out. For the patient group, the analysis was done for their affected and unaffected leg

separately (and later separate GEE's for the difference between the legs were performed), while for the controls, the average of the two sides was used.

Relations between time-averaged λs and time dependent measures of stability (StanceMax λ(t), SwingMax λ(t), SwingMin λ(t)), were assessed with partial correlation coefficients corrected for speed for the affected and unaffected legs of the patient group. A significance level of P <0.05 was used for all tests.

3. Results

The two elderly groups were comparable in age, height, weight, and BMI (Table 1). The number of subjects included for analysis, in each group for each speed, is shown in Table 2. Subjects' data were excluded if there were not enough strides for that speed, or if the data quality was low.

Table 1. Subjects' characteristics

Groups	Patients (n=16)	Healthy Elderly (n=12)	Young controls N=(15)	*P* value		Post hoc *P* value	
					Patients vs. elderly	Patients vs. Young controls	Elderly vs. Young controls
Basic characteristics							
Age (years)[a]	62.3 (10.7)	62.0 (12.6)	22.9 (3.9)	0.95			
Height (cm)[a]	169.7 (11.6)	171.7 (10.2)	173.5 (8.3)	0.64			
Weight (kg)[a]	85.9 (16.4)	86.9 (17.2)	66.7 (9.4)	0.88			
BMI (kg/m²)[a]	29.7 (4.1)	29.4 (4.9)	22.1 (1.5)	0.85			
Gender (M/F)	5/11	4/8	5/10				
Clinical characteristics							
WOMAC Pain Score[b]	2.35 (0.21)	0.09 (0.07)	0.01 (0.01)	**<0.001**	**<0.001**	**<0.001**	0.35
WOMAC Joint Stiffness Score[b]	2.56 (0.27)	0.23 (0.18)	0.03 (0.03)	**<0.001**	**<0.001**	**<0.001**	0.35
WOMAC Physical Activity Score[b]	2.3 (0.19)	0.07 (0.05)	0.00	**<0.001**	**<0.001**	**<0.001**	0.09

OA=osteoarthritis; BMI=Body mass index
[a]Data are presented as mean (SD). The *P* value corresponds to an ANOVA comparing the two elderly groups.
[b]Data are presented as mean (SD). The *P* value corresponds to Kruskal-Wallis test (with post hoc tests) comparing the three groups.

Table 2. Number of subjects included in the analysis for each group per speed

Groups	Patients n = 16			Healthy Elderly n = 12			Young controls n = 15		
	Included	Excluded		Included	Excluded		Included	Excluded	
		(not enough strides)	(low quality data)		(not enough strides)	(low quality data)		(not enough strides)	(low quality data)
Speed 1	7	1	8	9	2	1	2	10	3
Speed 2	11	7		12			15		
Speed 3	7	8	1	10	2		15		
Speed 4	7	8	1	10	2		15		
Speed 5	6	10		10	2		15		
Speed 6	4	12		10	2		15		

Six different walking speeds, from 0.61 to 1.5 m/s (increments of 0.22 m/s)

3.1. Time-averaged stability

While results on λs (see Fig. 2, compared to Figure 2 in [28]), were qualitatively similar as reported previously, there were some quantitative differences, most likely due to the different state spaces used. In the current study, there was a significant Speed ×Group interaction for analyses with affected and unaffected sides (Table 3), indicating that healthy elderly showed a steeper decrease in time-averaged λs with increasing speed, compared to young controls (Table 3). Time-averaged λs showed no significant difference between the three groups neither for the affected, nor for the unaffected side (Table 3). Comparing the two sides of the patients group, there was a trend towards significantly higher value of time-averaged λs at the unaffected side compared to the affected side (*p*=0.066).

Figure 2. Mean values of λs for the affected and unaffected leg of patients, healthy controls and young controls, at all speed levels. Error bars represent standard deviations.

Table 3. Regression coefficients (B) from GEEs on λ(t) with Speed as covariate (from 0.39 through 1.50 m/s), and Group as factor (young controls, knee OA patients, and healthy elderly), separately for the patients' affected and unaffected leg.

	Group	**post-hoc**			**Speed**	**Speed* Group**	*P*
	P	*OA vs. HE*	*OA vs. Y*	*Y vs. HE*	*P*	*P*	
Affected leg							
Time-averaged λ_s	0.741				**<0.001**	**0.002**	**OA vs. Y**: 0.514 **OA vs. HE**: 0.079 **HE vs. Y**: **0.001**
StanceMax λ(t)[a]	**<0.001**	**0.072**	**<0.001**	**<0.001**	**<0.001**		
SwingMax λ(t)[b]	0.597				**<0.001**		
SwingMin λ(t)[c]	**0.002**	0.676	0.208	**0.039**	**<0.001**	**0.045**	**OA vs. Y**: 0.884 **OA vs. HE:** 0.174 **HE vs. Y**: **0.013**
Unaffected leg							
Time-averaged λ_s	0.583				**<0.001**	**0.003**	**OA vs. Y**: 0.273 **OA vs. HE**: 0.238 **HE vs. Y**: **0.001**
StanceMax λ(t)	**<0.001**	0.245	**<0.001**	**<0.001**	**<0.001**		
SwingMax λ(t)	0.838				**<0.001**		
SwingMin λ(t)	**<0.001**	0.241	0.399	**0.038**	**<0.001**	**0.029**	**OA vs. Y :** 0.129 **OA vs. HE :** 0.626 **HE vs. Y :** **0.014**

OA = Osteoarthritic patients; HE = Healthy elderly; Y = young controls.
[a] Maximum value of λ(t)during the late stance.
[b] Maximum value of λ(t)during the swing phase.
[c] Minimum value of λ(t) during the swing phase.
The bold p-values are significant according to the Least significant difference.

4. Time dependent stability

On the affected side, patients, had a higher (indicating lower stability) StanceMax λ(t) compared to young controls (Table 3) and a trend towards being significantly higher compared to their healthy peers (Table 3 and Figure 3). StanceMax λ(t) was also significantly higher for the unaffected side of the OA patients, when compared to the young controls (p<0.001), but not when compared to healthy elderly. Healthy elderly had a significantly higher StanceMax λ(t) than young controls (p<0.001).

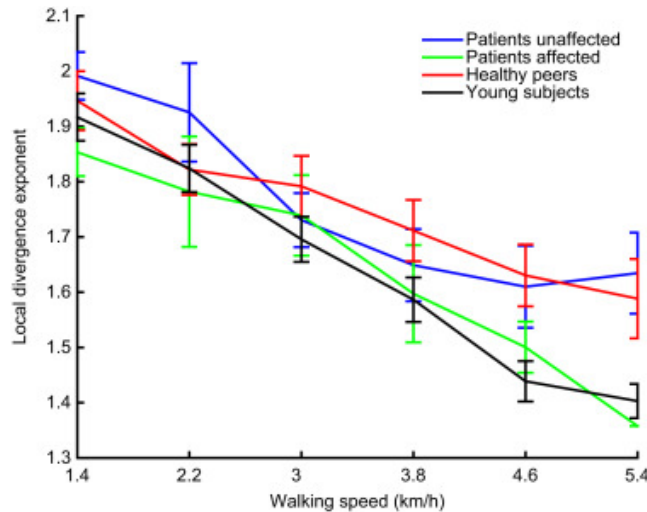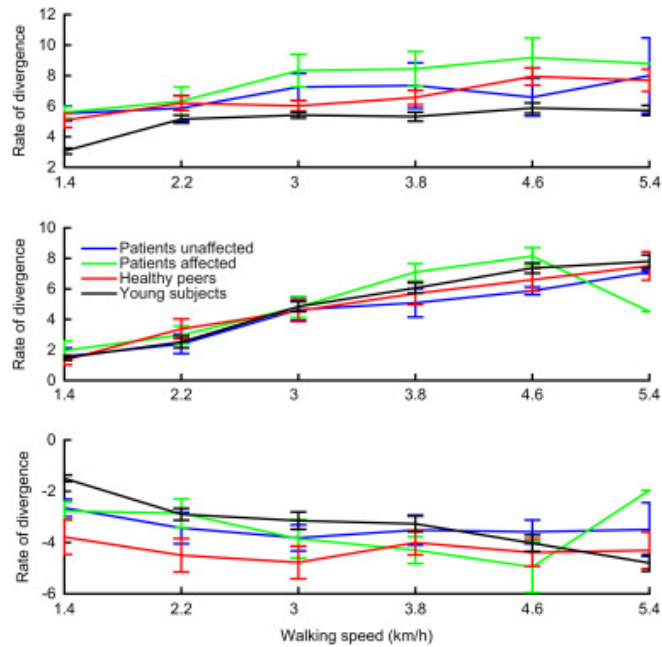**Figure 3.** Mean values of (A) StanceMax λ(t), (B) SwingMax λ(t), and (C) SwingMin λ(t) for the affected and uaffected leg of the patients, healthy controls and young controls, at all speed levels. Error bars represent standard deviations.

SwingMax λ(t) at both affected and unaffected sides showed no significant difference between the three groups (no main effect of Group or Group × Speed interaction).

Regarding SwingMin λ(t), there was a significant Speed × Group interaction (Table 3), indicating that healthy elderly showed a steeper decrease in the SwingMin λ(t) with increasing speed, compared to young controls. There was also a significant effect of Group at both affected and unaffected sides for SwingMin λ(t) and post-hoc analysis identified that SwingMin λ(t) was significantly lower for the healthy elderly group compared to the young controls.

Separate GEE comparing the affected and unaffected sides in the OA group showed no significant differences between the two sides regarding the four variables, but only revealed a significant interaction of Side × Speed for SwingMax λ(t) (p=0.019), revealing that the SwingMax λ(t) increased more on the Subjects' affected side with increasing speed, compared to the unaffected side.

5. Partial correlations

For the ipsilateral legs, the time-averaged λs values were not correlated to the time-dependent stability measures StanceMax λ(t), SwingMax λ(t), and SwingMin λ(t) (Table 4). However, time-averaged λ_s of the unaffected leg was negatively correlated to StanceMax λ(t) and SwingMax λ(t) and positively correlated with SwingMin λ(t).

Table 4. Partial correlations, corrected for speed, between time-averaged λ_s and time dependent measures (StanceMax λ(*t*), SwingMax λ(*t*), and SwingMin λ(*t*)). Of the unaffected and affected legs of the patients.

	Unaffected				Affected		
	StanceMax λ(t)	SwingMax λ(t)	SwingMin λ(t)	λ_s	StanceMax λ(t)	SwingMax λ(t)	SwingMin λ(t)
Unaffected							
StanceMax λ(t)							
SwingMax λ(t)	0.197						
SwingMin λ(t)	**−0.631**	−0.266					
λs	−0.217	−0.202	0.232				
Affected							
StanceMax λ(t)	**0.485**	0.071	**−0.385**	**−0.344**			
SwingMax λ(t)	0.050	**0.580**	0.038	**−0.438**	0.117		
SwingMin λ(t)	**−0.332**	−0.055	0.202	**0.459**	**−0.378**	**−0.429**	
λs	−0.144	−0.004	0.296	0.379	−0.153	−0.229	**0.372**

Values printed in bold are significant at 0.05 level.

StanceMax λ(t) and SwingMax λ(t) were significantly or tended to be negatively correlated to SwingMin λ(t) within the same leg and finally StanceMax λ(t) and SwingMaxλ(t) were positively correlated between legs (Table 4).

6. Discussion

The main aim of the present study was to assess whether differences in knee stability across the gait cycle could explain our earlier seemingly contradictory findings that subjects with knee OA had lower knee stability on their unaffected side. Our hypothesis was partially confirmed, that is, OA patients showed lower knee stability compared to the young control group on both sides and a tendency towards a lower knee stability compared to healthy elderly on the affected side, between 40% and 70% of the stride cycle (StanceMax λ(t)).

The results on λs that we reported here are quantitatively different from those of [28]. Nonetheless, qualitatively, results appear similar, and correlations between the previous estimates of λs and our current estimates are high. Most importantly, as previously, λs tended to be higher for the unaffected leg than for the affected leg in OA patients, a finding that is rather surprising, and that we sought to better understand in this study. Fallah-Yakhdani et al. argued that the findings for the unaffected side, might be the result of an adaptation that these patients make in order to ease the kinetic demands on the affected side [35]. The negative correlations between time-averaged λs and StanceMax λ(t) found here suggest that the patients may be compromising the unaffected side's stability for the stability of the affected side. Interestingly, time dependent measures were not correlated to time averaged values within the same leg, suggesting that these measures really contain different information. In addition, the time dependent stability measures showed patterns that were more logical from a clinical point of view (i.e. higher instability in the affected leg, albeit non-significant). These findings suggest that time dependent measures of stability may provide more sensitive information about stability.

We found negative correlations between SwingMin and StanceMax within the same leg (amplitude of the time-dependent lambda increases), which suggests that fast divergence in stance phase is compensated by fast convergence in swing phase.

The Maximum value of λ(t) was observed around 60% of the stride cycle, which is known to be the transition from the stance phase to the swing phase of the same side (also known as the weight transfer phase). Similar intra-cyclical changes during weight transfer were reported by [24, 26] Ihlen et al., 2012a and Ihlen et al., 2012b [24, 26] with a higher maximum for healthy older adults compared to youngs controls. Hubley-Kozey et al. [36] reported a reduced push-off burst of gastrocnemius activity during gait in severe OA patients. Considering that the OA patients who participated in the current study were suffering from severe knee OA, the absence of proper gastrocnemius activity prior to toe-off might be an explanation for the observed higher instability during weight transfer in this study. Interestingly, a recent paper [37] showed that by manipulating push off, stability could be either increased or decreased, thereby suggesting an important role for push-off in maintaining a stable gait. In addition, a recent modeling study [38] showed that an otherwise unstable limit cycle model could be stabilized by including intermittent control in the form of a push-off burst. Altogether, these findings highlight the importance of transition from the stance phase to the swing phase in gait stability. However, why this would show up as an unstable phase remains somewhat unclear.

The current study was able to objectively quantify and more specifically pinpoint the local dynamic instability within a stride during walking. These findings lead us to conclude that a decreased stability of knee movement in the sagittal plane was found in OA, but the fact that the instability was also increased at the unaffected side, puts into question whether this is a specific impairment of gait in the knee OA group or a more generic effect also present to some extent in the healthy elderly [28, 39].

7. Limitations

This study has several limitations. First, it has been reported that the statistical precision of estimates of λ_s depends on the number of strides projected into the state space [29] and this is likely true also for $\lambda(t)$. But in the current study, to avoid excessive effort for patients, we used only 40 strides per speed level. Including six speed levels however, increases statistical precision, if effects are consistent across speeds.

Second, our methods differed in several aspects from the studies of Ihlen et al. First, we time normalized data before calculating divergence curves, to be able to calculate the mean rate of divergence as it is normally calculated. An analysis in which the divergence curves were normalized to the gait cycle did not yield different results. Second, our choice of state space is different from Ihlen's, as we choose to specifically investigate knee kinematics, and to remain as close to the Fallah Yakhdani paper as possible. This may have led to somewhat different results, but checks on the location of the initial nearest neighbors indicated that our 4 Dimensions were sufficient.

Finally, although the group size is comparable to other biomechanical OA papers, it is still relatively small, and final conclusions should be made with caution. However, findings are inspiring for further research in this area.

8. Conclusion

In conclusion, the present study used a new method to identify the changes of local dynamic stability within a stride in a group of patients with knee OA and compared the results to healthy peers and a group of healthy young adults. The results indicate that time-dependent local dynamic stability might provide a more detailed insight into the problems of gait stability in OA than conventional averaged

local dynamic stability measures. Its potential clinical relevance needs to be established in studies with larger samples.

Conflict of interest statement

None of the authors of this paper have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) the presented work.

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Part 2: Structural, clinical, and functional changes associated with severity and progression of knee OA over 2 years follow-up

Chapter 5

Changes in MRI features, symptoms, function and muscle strength in women with early medial knee osteoarthritis over 2 years

In preparation

Abstract

To assess structural, clinical, and functional changes over time in patients with early medial knee osteoarthritis (OA), and compare the changes to the ones in a group of patients with established medial knee OA, as well as to a group of healthy controls. We included 49 women with medial knee OA, as well as a group of 28 women as controls. Structural features as detected on MRI, clinical and functional characteristics, as well as knee muscle strength were measured at baseline and after 2 years for all participants. Knee OA patients were further subdivided in to early and established knee OA. After 2 years, the only significant structural change was observed in the early OA group, and that was an increase in the presence of meniscal extrusion in this group compared to the baseline. No other significant structural changes were found in any of the other groups compared to baseline. Regarding muscle strength, a decline in quadriceps strength was found to be present after two years in all three groups, compared to baseline. No significant clinical or functional changes were found for any of the three groups after two years compared to baseline. Our findings suggest that, although the early and established OA groups showed a different structural, clinical, and functional profile at baseline, in a 2 year time frame, this profile seemed to be stable. Over two years only the presence of meniscal extrusions increased in the early OA group, which might confirm the significant advantage of MRI in detection of early structural changes associated with knee OA.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disorder that leads to functional limitations, reduced quality of life, and has a negative impact on the Social Health Care System [1, 2]. Osteoarthritis most frequently affects weight-bearing joints, especially the knee [3, 4]. By aging of the population and the increasing proportion of obese people, it is expected that the incidence and/or progression of knee OA will increase [5, 6]. Therefore, it seems pivotal to understand the natural course of knee OA in order to target preventative therapies and reduce risk factors for both the incidence and progression of knee OA [7].

Knee OA is characterized by joint pain, stiffness, and structural abnormalities which include focal damage and loss of articular cartilage, abnormal attrition of subarticular bone, osteophytes (bone growth at the joint margins), and muscle weakness [8-10]. Plain radiography and the Kellgren and Lawrence grading system has been the primary method to assess the presence, severity, and progression of the disease based on structural abnormalities [11]. However, reports on the association between radiographic features of knee OA and clinical features of the disease are inconsistent [12, 13]. Subtle structural changes commonly remain undetected on radiography, while Magnetic Resonance Imaging (MRI) allows direct visualization of multiple structures in OA joint pathology that cannot be seen with radiography [14-17]. Therefore MRI is known to be more sensitive in detecting the variable natural course of knee OA especially at the early stages of the disease process [18].

There is an increasing interest in identifying a subpopulation of patients that have a greater risk of developing knee OA, and more importantly that have a higher chance to progress fast. Paying more attention to an OA population in the very early stage will help us to understand the pathway of OA development and progression. The combination of the natural course of osteoarthritis and information about the factors associated with or leading to progression will make it possible to identify the patient at risk, and eventually allowing more intense management and earlier, targeted intervention. Luyten et al. published a classification criteria for subjects with early OA of the knee with the particular aim to allow shorter clinical studies with patients at risk and responders to treatment [18]. Efforts are ongoing to validate these criteria.

Although reports on structural, clinical, and functional changes in patients at the early stages of knee OA exist, but the classification of subjects in the aforementioned studies are mainly based on plain radiography [19, 20]. In addition, the natural course of knee OA has so far mainly been described for subjects with structural OA already detectable on radiography [21, 22]. In this

respect declines in structural, clinical, functional, and strength have been described by longitudinal studies, in patients with established knee OA. For instance, in a 2 year follow-up study on the natural history of cartilage defects in patients with established knee OA, reported a progression in cartilage defects [23]. On evolution of Bone Marrow Lesions (BMLs), Hunter et al reported that BMLs are unlikely to resolve and frequently increase in size over time [9].

With respect to clinical and functional characteristics of knee OA patients, a recent report on the evolution of pain and physical functioning, from two different cohorts of early phase of osteoarthritis, reported that over 4 years, pain and physical functioning remained fairly stable [19]. On the other hand, in a study by Sharma et al on patients with established knee OA, the sit-to-stand test performance significantly worsened after a follow-up period of three years [24]. Roos et al. investigated the change in self-reported outcomes and physical function over 7 years in subjects with OA (K&L grade 2 or worse) [25]. They found a greater decline in knee-related pain and function over time in subjects with knee OA compared to controls [25]. Since the functional deterioration associated with knee OA, can have a great influence on quality of life, it needs to be better understood. To prevent further functional decline in patients with knee OA, more longitudinal studies are needed to decipher the cause(s) of functional status and the relationship between structural joint deterioration and functional changes over time. A number of studies have assessed and reported functional changes in patients with knee OA, but no study to date, evaluated the effect of OA severity and time on functional changes in OA patients.

The role of muscle strength in initiation, progression, and management of knee OA have been reported extensively in the literature [26]. Our group previously reported decreased quadriceps strength in both groups of women with early and established medial knee OA [27]. A recent study on the evolution of muscle strength in patients with established knee OA showed that, over two years follow-up, an overall 16% increase in the mean knee muscle strength, 19% increase in knee extensor muscle strength, and a 17% increase in knee flexor muscle strength, was reported [28]. While quadriceps weakness has been described extensively in cross-sectional studies in OA, little is known about its evolution over time with respect to OA severity.

In this study, we focused therefor on the progression of structural and clinical parameters in women with early medial knee osteoarthritis during a two-year follow-up, and we compared the results to progression in asymptomatic control subjects as well as a group of patients with established medial knee OA. Our interest in this study population was based on the hypothesis that structural defects might still be reversible in early stages of the disease, and this population might be a target for treatment options aiming at stabilization of the disease process, even potentially reversal.

Therefore, we performed a 2-year cohort study of individuals with early medial knee OA to determine the natural history of structural abnormalities, visualized on MRI, and clinical features including knee pain and symptoms, as well as physical performance and muscle strength compared to a group of healthy controls, and a group of women with established medial knee OA.

2. Materials and methods

2.1. Study design and population

Seventy-seven women (29 early OA, 20 established OA, and 28 asymptomatic) were enrolled in this 24-month prospective longitudinal study of knee OA. Forty-nine participants were recruited during a weekly consultation by a rheumatologist or orthopedic surgeon at the University Hospitals Leuven. Current research was conducted in compliance with the Helsinki Declaration and was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium. Written informed consent was obtained from each participant prior to testing.

Subjects with knee OA were further sub-classified to two groups of subjects with early and established medial knee OA. Inclusion criteria for the *early OA* group were: presence of knee pain, Kellgren and Lawrence grades of 0, 1 or 2- (only osteophytes) on standard radiographs, and at least one of the two following findings: arthroscopic findings of cartilage lesions or MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or sub-chondreal BMLs [18].

For the *established OA* group, diagnosis of was made based on the slightly adapted American College of Rheumatology (ACR) Classification criteria [29]. These inclusion criteria were knee pain on most days of the last month and one of the following findings: age above 50, crepitation during active movements, morning stiffness less than 30 minutes, together with structural changes defined as minimum a grade 2+ on the K&L scale.

Twenty-eight asymptomatic controls were recruited from cultural and social organizations. These women were included because they had no knee pain or symptoms, no history of knee OA or other pathology involving any joints of the lower extremity. General exclusion criteria was: musculoskeletal disorders other than knee OA in both lower limbs in the last six months, previous surgery of lower extremities or low back, chronic intake of corticoids or specific contra-indications for MRI and neurological disorders.

2.2. Knee radiographic assessment

A standard anterior-posterior (AP) weight-bearing radiographs of the knee joint in a fixed flexed position was taken bilaterally for each subject (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). A single experienced observer (FPL) scored each radiograph in order to evaluate the presence and severity of structural knee OA based on the K&L grading system with recent adjustments [29].

An experienced musculoskeletal radiologist assessed the static alignment of the knee joint on full-leg AP weight-bearing plain radiographs of the lower extremities [30]. Malalignments of less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively. Knee alignment between -2° and +2° was classified as neutral [31, 32].

2.3. Knee MRI protocol and analysis

For each participant, an MRI of the selected knee was performed on a 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) by using an eight-channel phased array knee coil in a non-weight bearing supine position as described by Baert et al. [33]. Furthermore, semi-quantitative scoring of specific structural features in the tibiofemoral joint was performed separately by two readers (NN, GVDS) using the standardized Boston-Leeds Osteorathritis Knee Score scoring system [34]. For 91% of all scored items full agreement between both readers was achieved, while disagreements were resolved through consensus.

2.4. Pain, symptoms and disability assessment

The Dutch version of the 'Knee Injury and Osteoarthritis Outcome Score' (KOOS) was used in this study [35]. It is an extension of the WOMAC questionnaire and contains 5 separate subscales assessing pain, symptoms (as swelling, stiffness, crepitation, clicking), ADL, sports and recreational function and knee-related quality of life. Each question was scored on a 5-point Likert scale (from 0-4) and for each subscale a transformed score from 0 to 100 was calculated. A score of 100 was the best possible result, the lower the score the more functional problems and disability was presented [36]. For this study we assessed the subjects' pain, other symptoms and subjective disability (ADL and QOL). The subscale 'function in sports and recreation' was not included since several subjects answered less accurately to these questions.

2.5. Performance-based measures

For performing the timed up–and-go test (TUG), the participant was seated in a standardized chair. A line marked a distance of 3m from the chair. On the comment 'go' the patient needed to get up, walk 3 m, cross the line with one foot and return seated on the chair as quickly as possible but without running. Using a stopwatch, the total time in seconds was measured to get up, walk 3 m and sit down on the chair again. The patients wore their own comfortable shoes while performing the test. A longer time on the TUG represented greater functional limitation. The test was performed 3 times and a mean value was calculated. The test has been shown previously to have good reliability and validity [37, 38].

During the Stair Climbing Test (SCT), participants were asked to ascent and descent 5 stairs as quickly as possible. On the comment 'go' the patients started climbing. Both feet needed to tread upon the 5th step before returning. The participants were allowed to use the handrail if they wanted to. Using a stopwatch, the total time in seconds was measured from the comment 'go' till the patient was with both feet back on the ground level. The patients wore their own comfortable shoes during the test. The test was performed 3 times and an average was calculated. A longer time on the SCT represented greater functional limitations.

2.6. Muscle strength

Using isokinetic dynamometry (Biodex System 3 Pro, Biodex Medical Systems, NY, USA), the evaluation of maximal voluntary muscle strength of the knee muscles were measured. Before every test session, the Biodex was calibrated and measurements were performed according to standard procedures (Biodex Medical. Manual, 1993). Subjects were tested in a seated position. Support for their back was provided and straps at the level of the chest, pelvis and thighs were placed to ensure that the recorded moment is generated by the examined joint muscles only, without any contribution from other actions. The maximum isometric strength of knee extension and flexion was assessed. The tibia was strapped to the lever arm and its axis of rotation was aligned with the anatomic axis of the knee joint. Flexion and extension movements were performed at angles of 60° and 90°. Each test was performed three times with maximal contraction for 5s. Between each trial, 10s of rest was given. Between the tests at different angles the patient had 30s rest.

Isokinetic (dynamic) knee extension was also measured with three trials for knee extension at 60°/s (low speed) and three trials at 240°/s (high speed). All subjects received the same instructions and verbal encouragement to achieve a maximal effort. For each test, the peak torque

normalized for body weight (Nm/kg) was used for analysis. The highest peak torque from three trials was recorded. All data were corrected for gravity and weight.

3. Statistical analysis

In order to compare subjects' characteristics, One-way Analysis of Variance (ANOVA) (when the distribution was normal) or The Kruskal Wallis Signed rank test (when the distribution was not normal) were used. Wilcoxon signed rank test was used for comparisons over time for KOOS subscores. To investigate Group differences and the effect of Time (as well as interaction of Time × Group effects) on measures of muscle strength and performance-based functional tests, Generalized Estimating Equations (GEEs) were used. When a main effect or an interaction was significant, a post hoc analysis was conducted to test the pairwise differences. In order to determine the associations between baseline structural features on MRI (independent variables) and the KOOS subscore of physical activity (KOOS ADL) after two years follow-up as well as its change, univariate linear regression analysis was used. Statistical analysis was performed using SPSS software (version 10.0). The significance level was set at $P < 0.05$.

4. Results

Seventy-seven women were enrolled in this study. Twenty-eight women (36%) were categorized as the control group, twenty-nine women (38%) were classified as having early medial knee OA and 20 women (26%) as having established medial knee OA. Baseline demographic characteristics for each group of subjects are presented in table 1.

Table 1. Subject's clinical characteristics at the time of entry

	Control (n = 28)	Early OA (n = 29)	Established OA (n = 20)	P-value
Weight (kg)[a]	65.76 (10.7)	71.98 (11.5)	69.29 (10.3)	0.086
BMI (kg/m^2)[a]	25.12 (3.8)	27.16 (4.3)	26.9 (3.9)	0.112
Height (m)[a]	1.62 (0.06)	1.63 (0.06)	1.61 (0.07)	0.426
Age (years)[a]	63.7 (7.5)	66.69 (6.3)	67.22 (5.4)	0.143
K&L score (MC)[b]	Grade 0: n=19 Grade 1: n= 9	Grade 0: n= 12 Grade 1: n= 15 Grade 2$^-$: n= 2	Grade 2$^+$: n= 15 Grade 3: n= 5	

OA=osteoarthritis; BMI= Body Mass Index; K&L= Kellgren & Lawrence (range 0-4), MC = Medial Compartment.
Data are presented as [a]Mean (SD) or [b]frequencies. The P value corresponds to ANOVA test comparing the three groups.
[†] Significant difference between groups (P < 0.05).

4.1. Changes in clinical features and physical performance

Both subjects with early and established medial knee OA reported significantly more knee pain and worse symptoms on KOOS subscales compared to healthy controls (Table 2). Similarly, both groups of patients showed significantly worse score for activity daily living and quality of life on KOOS compared to the healthy control group (Table 2). None of the self-reported pain, symptoms, ADL, or QoL scores changed over time in any of the three groups (Table 2).

The three groups showed no differences regarding objective functional measures of TUG and SCT (Table 2). Also, neither TUG, nor SCT changed over 2 years in any of the groups (Table 2).

Table 2. Group differences and changes over two-year time in clinical characteristics in three groups (asymptomatic controls, early OA, and established OA)

	Control		Early OA		Established OA		P	P	P	P	P
	Baseline	2YFU	Baseline	2YFU	Baseline	2YFU	Group	Early vs. Control	Established vs. Control	Early vs. Established	Time
KOOS pain	100 (3.5)	100 (4.2)	84.7 (22.2)	83.3 (29.2)	83.3 (27.8)	80.5 (36.15)	<0.001*	<0.001*	<0.001*	0.555	0.402
KOOS symptoms	95.5 (10.8)	94.6 (10.8)	82.1 (21.4)	83.9 (17.8)	85.7 (23.2)	82.1 (28.6)	<0.001*	<0.001*	<0.001*	0.46	0.573
KOOS ADL	100 (1.9)	100 (3.0)	88.9 (25.4)	87.5 (28.2)	88.2 (31.6)	85.2 (30.9)	<0.001*	<0.001*	<0.001*	0.956	0.435
KOOS QoL	100 (1.6)	100 (14.1)	75 (42.2)	71.8 (43.7)	62.5 (59.4)	68.7 (56.2)	<0.001*	<0.001*	<0.001*	0.376	0.986
TUG	5.35 (0.2)	5.55 (0.2)	5.94 (0.2)	6.06 (0.3)	5.79 (0.2)	5.82 (0.2)	0.19				0.195
SCT	5.39 (0.2)	5.58 (0.2)	5.94 (0.2)	6.12 (0.3)	5.82 (0.2)	5.83 (0.2)	0.196				0.191

OA=osteoarthritis; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; TUG = Timed Up and Go; SCT = Stair Climbing Test.
† Significant difference between groups (P < 0.05).

4.2. Changes in muscle strength

As seen in table 3, both subjects with early and established knee OA had significantly weaker isometric strength of quadriceps and hamstring than controls (Table 3). The established OA group additionally had significantly weaker isokinetic strength of the quadriceps than controls (Table 3). Also, the established OA group showed significantly weaker hamstring than early OA group in isometric measurements (Table 3).

Both isometric quadriceps muscle strength decreased significantly over two years in all three groups (Table 3). No significant effect of *Group × Time* was found for any of the isometric or isokinetic measurements.

Table 3. Group differences and changes over two-year time in maximal knee muscle strength in three groups (asymptomatic controls, early OA, and established OA)

	Control		Early OA		Established OA		P	P	P	P	P	P
												Group × Time
	Baseline	2YFU	Baseline	2YFU	Baseline	2YFU	Group	Early vs. Control	Established vs. Control	Early vs. Established	Time	
Knee extension 60 (Nm/kg)	1.64 (0.08)	1.65 (0.07)	1.38 (0.08)	1.39 (0.08)	1.46 (0.07)	1.39 (0.07)	**0.012***	**0.006***	**0.017***	0.559	0.323	
Knee flexion 60 (Nm/kg)	0.84 (0.04)	0.83 (0.04)	0.69 (0.04)	0.71 (0.05)	0.68 (0.04)	0.59 (0.04)	**<0.001***	**0.008***	**<0.001***	0.346	0.165	
Knee extension 90 (Nm/kg)	1.79 (0.07)	1.68 (0.06)	1.43 (0.09)	1.39 (0.09)	1.53 (0.09)	1.46 (0.08)	**0.003***	**0.002***	**0.018***	0.417	**0.003***	0.572
Knee flexion 90 (Nm/kg)	0.68 (0.03)	0.67 (0.03)	0.58 (0.03)	0.6 (0.03)	0.56 (0.03)	0.53 (0.02)	**0.002***	**0.03***	**0.001***	0.304	0.141	
Knee extension 60º/sec (Nm/kg)	1.33 (0.05)	1.29 (0.04)	1.11 (0.06)	1.15 (0.07)	1.06 (0.08)	1.03 (0.07)	**<0.001***	**0.011***	**<0.001***	0.33	0.488	
Knee extension 240º/sec (Nm/kg)	0.73 (0.03)	0.68 (0.03)	0.6 (0.03)	0.59 (0.04)	0.62 (0.03)	0.61 (0.06)	**0.009***	**0.005***	**0.038***	0.646	0.309	

OA=osteoarthritis; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; TUG = Timed Up and Go; SCT = Stair Climbing Test.
† Significant difference between groups (P < 0.05).

4.3. Changes in MRI features

As seen in table 4, both early and established knee OA groups showed a significant larger amount and cumulative score for size of BMLs, the amount and cumulative score for size and percentage of full thickness cartilage loss in the tibiofemoral (TF) region, meniscal lesions, and cumulative size and presence of synovitis and/or effusion (Table 4). There were no significant differences between the early OA and the control group for meniscal maceration and the score for size of effusion (Table 4). Patients with early knee OA had a significantly lower amount and cumulative size of BMLs, amount and cumulative score for percentage of full-thickness cartilage loss, meniscal lesions, and size of effusion compared to the established OA group (Table 4).

Changes were seen in several MRI features over time but only the increase in the presence of meniscal extrusions over 2 years in the early OA group was significant compared to baseline (Table 4). In the early OA group 27% of subjects (n = 7) showed meniscal extrusions over two years, whereas, in the established OA group, 5% (1 subjects) developed meniscal extrusion over 2 years (Table 5), Even though no significant changes were present in the total group in any other parameter (p>0.05), this should not be interpreted as no change at all. As shown in table 5, some parameters of some subjects stayed stable, some improved and others worsened. Cartilage degeneration was present in about 14-20% in both early and established OA groups after 2 years (Table 5). However, in none of the groups a significant reduction in the amount of cartilage lesions or a reduction in size of cartilage loss in the tibiofemoral region was detected (Table 4). Table 5 presents a descriptive picture of how different structural features, detected on MRI, changed over 2 years in each group.

Table 4. Group differences and changes in MRI features over two years in three groups (asymptomatic controls, early OA, and established OA)

	Control Baseline	Control 2YFU	Early OA Baseline	Early OA 2YFU	Established OA Baseline	Established OA 2YFU	P Group	P Early vs. Control	P Established vs. Control	P Early vs. Established	P Time	P Group × Time
Bone Marrow Lesions and cysts												
Amount of BMLs TF	0 (0)	0 (1)	0 (1)	0 (1)	3 (1)	2 (1)	<0.001*	0.036*	<0.001*	<0.001*	0.648	
Cum score for size of BMLs TF	0 (0)	0 (1)	0 (2)	0 (2)	5 (3)	4.5 (3)	<0.001*	0.007*	<0.001*	<0.001*	0.627	
Cartilage lesions												
Amount of cartilage lesions TF	2 (2)	2 (2)	3 (2)	3 (2)	4 (1)	4 (1)	<0.001*	<0.001*	<0.001*	0.041*	0.98	
Cum score for size of cartilage loss TF	3.5 (4)	3.5 (4)	6 (4)	6 (4)	7 (3)	7 (3)	<0.001*	<0.001*	<0.001*	0.058	0.881	
Cum score for % full-thickness cartilage loss TF	0 (1)	0 (1)	1 (2)	1 (2)	3 (4)	3 (4)	<0.001*	<0.001*	<0.001*	<0.001*	0.295	
Meniscal lesions												
Presence of extrusion	9 (30%)	9 (30%)	15 (50%)	22 (67%)	18 (78%)	19 (83%)	<0.001*	0.007*	<0.001*	0.001*	0.039	0.019* Early: 0.021*
Presence of increased signal	5 (17%)	7 (23%)	19 (59%)	18 (56%)	17 (74%)	18 (78%)	<0.001*	<0.001*	<0.001*	0.03*	0.339	
Presence of tear	4 (13%)	5 (17%)	16 (50%)	16 (50%)	15 (65%)	15 (65%)	<0.001*	<0.001*	<0.001*	0.132	0.552	
Presence of maceration	0	0	1 (3%)	1 (3%)	10 (43%)	11 (48%)	<0.001*	0.309	<0.001*	<0.001*	0.305	
Synovitis and Effusion												
Score for size of effusion (score 0-3)	0 (0)	0 (0)	0 (1)	0 (1)	0 (2)	0.5 (2)	0.002*	0.137	0.001*	0.013*	0.2	
Cum score for presence of synovitis + size effusion (0-6)	0 (0)	0 (0)	0 (2)	0 (1)	2 (3)	1 (2)	0.005*	0.048*	0.003*	0.092	0.1	
Score for presence of synovitis and/or effusion (0-2)	0 (0)	0 (0)	0 (2)	0 (1)	1 (2)	1 (1)	0.013*	0.029*	0.008*	0.461	0.052	

OA=osteoarthritis; BML=Bone Marrow Lesion; Cum = Cumulative; 2YFU = 2 years follow-up.
† Significant difference between groups (P < 0.05).

Table 5. Changes in MRI features of the three groups over 2 years

	Control			Early OA			Established OA		
	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened
Bone Marrow Lesions and cysts									
Amount of BMLs TF	23 (80%)	2 (8%)	3 (12%)	24 (83%)	1 (3%)	4 (14%)	13 (65%)	4 (20%)	3 (15%)
Cum score for size of BMLs TF	23 (80%)	2 (8%)	3 (12%)	22 (76%)	2 (7%)	5 (17%)	11 (55%)	5 (25%)	4 (20%)
Cartilage lesions									
Amount of cartilage lesions TF	27 (96%)		1 (4%)	28 (97%)	1 (3%)		20 (100%)		
Cum score for size of cartilage loss TF	27 (96%)		1 (4%)	28 (97%)	1 (3%)		19 (95%)		1 (5%)
Cum score for % full-thickness cartilage loss TF	27 (96%)		1 (4%)	26 (90%)	1 (3%)	2 (7%)	16 (80%)		4 (20%)
Meniscal lesions									
Presence of extrusion	24 (82%)	2 (8%)	2 (8%)	22 (76%)		7 (24%)	19 (95%)		1 (5%)
Presence of increased signal	26 (92%)		2 (8%)	28 (28%)		1 (3%)	20 (100%)		
Presence of tear	27 (96%)		1 (4%)	27 (94%)	1 (3%)	1 (3%)	20 (100%)		
Present of maceration	28 (100%)			29 (100%)			19 (95%)		1 (5%)
Synovitis and Effusion									
Score for size of effusion (score 0-3)	26 (92%)	1 (4%)	1 (4%)	25 (86%)	1 (3%)	3 (11%)	20 (100%)		
Cum score for presence of synovitis + size effusion (0-6)	25 (89%)	2 (8%)	1 (4%)	21 (72%)	5 (17%)	3 (11%)	15 (75%)	3 (15%)	2 (10%)
Score for presence of synovitis and/or effusion (0-2)	25 (89%)	2 (8%)	1 (4%)	17 (59%)	7 (24%)	5 (17%)	14 (70%)	4 (20%)	2 (10%)

OA=osteoarthritis; BML=Bone Marrow Lesion; Cum = Cumulative; 2YFU = 2 years follow-up.

5. Discussion

The aim of the present study was to study the natural course of structural and clinical features associated with medial knee OA over two years in a group of subjects with early knee OA compared to a group of established knee OA and a group of asymptomatic controls. The main findings of our study for this part were that early OA patients differed from controls in several structural and clinical characteristics and that only in the early OA group, the presence of meniscal extrusion increased after 2 years compared to the baseline. Also, quadriceps strength decreased in all three groups over two years.

Pain and symptoms: Joint pain and symptoms among subjects with knee OA have been reported to have an intermittent and variable pattern over the course of the disease, and pain experience is modified due to adaptation and avoidance strategies [39, 40]. In the current study the control group but also patients with early and established knee OA did not significantly change in pain and symptoms over 2 years. In the Framingham study, approximately in one third of patients with symptomatic knee OA, symptoms improved over time [2]. In the current study 17% (n = 5) of patients in the early OA group and 15% (n= 3) of patients in the established OA group, showed less pain after 2 years. Patients in the early stages of knee OA often present themselves with severe knee pain and disability while those in advanced stages may present themselves with only minor intermittent symptoms [41], which shows the variable course of pain. Because many factors can play a role in a person's response to pain (e.g. genetic predisposition, previous experience, current mood, coping strategies and sociocultural environment) [42], comparison between subjects is complex.

Muscle strength: Patients with early knee OA in the present study had weaker quadriceps and hamstring isometric strength compared to the healthy controls. Similarly, the established OA group had weaker quadriceps and hamstring muscles compared to the healthy controls as well as the early OA group. Muscle weakness in a well-known deficiency in knee OA [43]. Previous studies show that patients with knee OA are 20% to 40% weaker in relative quadriceps strength than healthy controls [44-46]. Baert et al reported quadriceps weakness in subjects with early medial knee OA compared to healthy controls [10]. Hortobagyi et al reported weaker quadriceps in a group of subjects with established knee OA (K&L ≥ 2) compared to a control group [47]. The negative effect of aging on muscle strength has been established previously [48]. The negative effect of aging on muscle strength has been established previously [1]. Although, not significant, patients in both early and established OA groups, in the present study, had higher-although not significantly- mean age compared to the healthy control group.Hence, the observed lower muscle

strength in the OA patients in this study compared to the healthy elderly could be partly attributable to the higher age of this population. However, including age as covariate in the analysis, yielded similar results of significantly lower extension/flexion muscle strength in both early and established OA groups compared to the healthy control group (all P < 0.02). Therefore, it seems unlikely that the lower muscle strength observed in OA patients in this study, is just an effect of age.

The causes underlying decreased muscle strength associated with knee OA is likely to be multifactorial. Pain, joint effusion and abnormal joint mechanics may contribute to lower strength. Both groups of subjects with early and established knee OA in the current study had more knee pain and effusion compared to the healthy controls, but the decreased isometric quadriceps strength that was observed over 2 years in this study, is unlikely to be an effect of knee osteoarthritis, but rather an aging effect, as it was present in all three groups. One possible explanation for this finding might be that, as quadriceps muscle strength is already declined at the very early stages of the disease, it seems that further decrease in strength over time is then similar as the age-related one [49, 50]. Several studies reported decreased muscle strength in elderly population and its relations with functional limitations [48, 49].

In addition, in the current study, 18% of the patients (early and established knee OA) demonstrated an increase in isometric knee extension and flexion muscle strength, after 2 years. But we did not have an average increase in strength on group level, just a few people in our study showed an increase in strength (20%). These results are in contrast with findings of a recent study on the evolution of muscle strength in patients with established knee OA, that reported an average increase in strength, over 2 years [28].

Structural abnormalities: The early OA group in this study differed from the control group, in ten out of twelve MRI criteria and the established OA group showed significant differences compared to the asymptomatic controls in all structural features detected on MRI. This is in accordance to the finding of Link et al, which demonstrated significant associations between abnormalities detected on MR imaging, including cartilage defects, bone marrow changes, and meniscal lesions with increasing K&L grades, and thus disease severity [51]. Our results showed that patients in early stages of OA differed from controls based on structural features that would not have been detected on plain radiography, from which we can infer that MRI can have an additional value in the diagnosis of patients with beginning joint degeneration or early knee OA.

Over two years, the presence of meniscal extrusion significantly increased by 17% in the early OA group compared to baseline, which was not the case for the established OA or the control group. Meniscal damage has been reported to be associated with baseline to 2-year quantitatively

measured cartilage loss [52]. Reports from the Boston osteoarthritis of the Knee study demonstrated that meniscal extrusion was a predictor of deterioration in the cartilage morphology score [53]. Although in the current study significant changes in cartilage loss over two years were not detected, but the increase in the presence of meniscal extrusion over two years could be an underlying factor for future cartilage loss and progression towards more severe knee OA. Further follow up of those subjects might reveal that those are the Early OA subjects with more risk for progression.

Cartilage lesions and defects are common findings in both healthy subjects and subjects with knee OA [51, 54-56]. In an experimental model of femoral condylar defects, Lefkoe et al showed that cartilage defects could lead to the development of osteoarthritis [57]. Cartilage defects seem to be especially important in the process of early OA, as they could result in increased cartilage breakdown, which again could lead to decreased cartilage volume and joint space narrowing [57, 58]. The natural history of cartilage defects seems to be variable. In the study of Ding et al, in women with a mean age of 45 years, thirty-three percent had worsening and thirty-seven percent had improvement in cartilage defect score over 2.3 years [59]. Worsening has been shown to be more prominent in the early stages of osteoarthritis when cartilage defects are mild, but in those with the highest defect severity, regression to a lower grade cartilage defect was likely to occur, which again suggests that a process of cartilage repair could occur [54, 60]. In the present study, we found cartilage lesions to be present in all groups with significantly more and larger defects in the early and established OA groups compared to the asymptomatic controls. But in contrast to the above mentioned studies, no distinct worsening or improving over time could be found except for the worsening of the full thickness cartilage lesion in 20% of the subjects with established knee OA versus 7% in the early OA subjects. This discrepancy could be due to different scoring measures being used as well as to the small sample size in our study. The reported cartilage losses have indeed been suggested to vary dependent on study population [61], the stage of the disease and the definition of progression used [62]. However, evidence showed that cartilage could not only become thinner, but also become thicker [63-66]. Le Graverand et al showed that cartilage volume increased in early OA patients: volumes were found to be thicker in early OA patients in comparison to volumes measured in healthy subjects [67]. This thickening has been shown in animal models to be a result of cartilage hypertrophy (metabolic stimulation of cells by mechanical irritation that causes an increase in matrix production) [68, 69], while other authors contribute this thickening to cartilage swelling (higher water content, possibly produced during collagen cleavage) [70, 71]. Cartilage thickening/improvement in our subjects was rather rare, only 1 subject in the early OA group had cartilage thickening over time, and therefore we cannot confirm that cartilage thickening/improvement is a characteristic of early knee OA.

The natural history of BMLs has been a recent subject of interest because of its role in the pathogenesis of knee osteoarthritis [9]. Studies have found changes in the subchondral bone in very early OA, before radiographic evidence of increase in subchondral bone thickness [72-74]. BMLs have thus been suggested to be a hallmark of knee OA [75]: they have been demonstrated to be a predictor of the progression of cartilage defects [8], cartilage loss [9] and total knee replacement surgery [76]. The natural course of BMLs remains unclear, but appears to be variable. In a recent MOST study, 244 OA knees or knees at risk of developing OA with BMLs at baseline were examined after a 30 month follow-up period. In 23.8% of the knees, only stable BMLs were present, in 38.9% only BML regression and in 10.2% only BML progression was found [75]. Interestingly, Garnero et al found that changes in BMLS could occur over a limited time period as short as 3 months in subjects with symptomatic knee OA [77]. Most BMLs remained stable in both amount and size in the controls (75% and 77.5% respectively), in the early OA group (63.3% and 67.9% respectively) and in the established OA group (70.5% and 67.6% respectively). However a proportion of each group improved in the amount of BMLs (controls 5%, early OA 9%, established OA 29,4%) and in size of BMLs (10%, 18% and 41.1% respectively), and another proportion worsened in the amount of BMLS (20%, 18% and 0% respectively) and in size of BMLs (12.5%, 18.1%and 11.7% respectively). Differences in ratings could be explained in part based on the scoring system used (e.g. BLOKS vs WORMS), the study population included or the imaging modality being used.

Effusion is thought to be an indirect sign of synovitis, due to synovial activation [78]. Synovitis is present in both early and late OA [79]. In some studies measurements of inflammation were significantly greater in very early OA [79, 80] while others reported more synovitis with increasing K/L grades [81]. In our study population no effusion was present in the early stage, but some subjects in the established OA groups did show effusion. Moreover, the established group had significantly more effusion than the control and the early OA group. Synovial effusion associated with knee OA is suggested to be associated with pain and stiffness in patients with knee OA [82]. In the current study no significant changes, regarding the score of effusion or synovitis, were detected for the patients after 2 years follow-up. This might partly explain the findings on no significant changes over two years, in pain and symptoms is OA patients of this study.

6. Limitations
Our study has some limitations which need to be taken into account when interpreting the results. First, in an attempt to have a reasonable homogenous patient group, we only included women with medial compartment disease in our study. The prevalence of medial knee OA in women is

much higher than in men [82] and there are differences in body size characteristics, occupational demands and structural and clinical manifestations in women [82, 83]. Consequently generalization of results to men is not possible. Also, the recruitment of asymptomatic controls was through social and cultural organizations. This way of recruitment of healthy controls, although common, might have resulted in a more active or more educated elderly in the control group, compared to the patients' group, as their voluntary participation in the study might reflect them being more active in society. Second, it should be noted that the strength data reported in our study is limited to concentric contraction. This is important in stabilizing the knee during ambulation, whether eccentric contraction is responsible for providing shock absorption in the knee during gait and would be relevant, for example, in descending stairs. A few studies investigated the peak torque for eccentric and concentric quadriceps contraction, and Hortobagyi et al found greater weakness only for the eccentric contractions compared to concentric contractions in OA patients [47]. Furthermore, to assess the structural changes, we used the BLOKS system. Previous studies assessed these changes using WORMS. Because substantial differences in scoring methods exist, comparison between studies is not trivial. Finally, our study may be underpowered despite the fact that we attempted to come up with a reasonably homogenous group of patients. However, since longitudinal data for the parameters we studied, in particular in an early OA patient population, are not really available, it remains a challenge to calculate power at the start of such cohort studies.

7. Conclusions

Results from this study showed that during a two-year time frame, from a clinical and functional perspective, no significant changes were found neither in the early OA, nor in the established OA group, except for an age-related decline in quadriceps strength as observed in all three groups after 2 years. Structurally, only the early OA group showed a significant increase in the presence of meniscal extrusions over 2 years, compared to baseline. For a better characterization of patients at risk for progression of OA, identification of specific clinical and functional features in early or established knee OA and their evolution over time is of relevance to clinical practice. Indeed, a better understanding of the course of the disease development and progression, may lead to more efficient use of resources in our health care system, and potentially the identification of modifiable factors at the early stage of the disease.

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Chapter 6

Changes in gait characteristics of women with early and established medial knee OA: results from a 2-years longitudinal study

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Abstract

To evaluate gait changes in a prospective longitudinal study, in order to determine whether the early osteoarthritis (OA) group would evolve towards gait characteristics observed in the established OA group. Gait analysis was performed on 25 women with early (based on combined MRI, radiographic and clinical findings) and 18 with established medial knee OA, as well as a group of 23 healthy controls. Subjects were asked to walk barefoot, at their comfortable speed, along a 12-meter walkway. Kinematic and kinetic data were measured and calculated at baseline and after 2 years follow-up. Results indicated that the early OA group, similar to established OA group, showed significantly higher maximum knee adduction angles compared to the healthy controls during the early stance phase of gait. None of the kinematic or kinetic measures of gait, changed over two years in the early OA group compared to baseline. Increased first and second peak knee adduction moment, as well as higher knee adduction moment impulse were observed at the time of entry, in established OA compared to the healthy controls and the early OA group. Knee adduction moment impulse, further increased over two years only in the group of subjects with established knee OA. For all three groups, the peak knee flexion angle during the stance phase significantly decreased over time. We found that increased maximum knee adduction angle during stance phase was the only alteration in the gait pattern of subjects with early knee OA compared to the controls, a finding similar to the established OA group. Our results suggest that, unlike in the later stages of the disease, gait is rather stable over two years in the early OA patients.

Introduction

Knee osteoarthritis (OA) has been reported as one of the major causes of disability in the elderly population, mainly in women [1]. As the knee joint is stressed in many activities of daily living, such as walking, pain and discomfort in this joint will result in drastic negative influence on locomotion, and consequently on the quality of life [2, 3].

The role of biomechanical factors in the initiation and progression of knee OA has been supported by a vast number of studies [4, 5]. Altered gait patterns, compared to controls, have been reported frequently in subjects suffering from knee OA [6-9]. They walk with lower walking speed [8, 10], increased knee flexion at heel strike [11, 12], and reduced knee flexion excursion during the stance phase of gait [6, 10]. Several studies have shown that the external knee adduction moment (KAM), an indirect measure of medial knee joint loading, is greater in people with knee OA compared to healthy controls [8, 13].

The observed gait deviations in subjects suffering from knee OA may be compensatory strategies that are aimed at reducing stresses on, and the range of motion of the affected joint [6-9]. However, with progression of the disease and associated morphological changes, the effectiveness of the aforementioned strategies may decrease. Moreover, previous reports suggest that neuromuscular and proprioceptive deficits exist in subjects with knee OA, which may actually lead to altered gait strategies that increase joint loading [14-17].

Gait alterations associated with knee OA, are found to vary with OA severity [18-20]. Thorp et al. reported an increase in both the peak knee adduction moment and the knee adduction impulse, with an increase in radiographic severity of knee OA [21]. A study on gait alteration in patients with early knee OA, reported no gait alterations in this group compared to the healthy controls [13]. Hurwitz et al, found decreased stance phase knee flexion angles, as well as decreased early stance phase knee flexion moments in patients with severe knee OA compared to controls but not in subjects with moderate knee OA [10].

Despite the huge number of cross-sectional studies on gait of subjects with knee OA [8, 21-24] there are hardly any longitudinal studies on gait changes in knee OA. However, to obtain more insight in the role of disease severity and time on gait alterations, longitudinal studies on gait following subjects from the early onset of the disease are necessary. Therefore, in order to investigate the evolution of gait characteristics associated with knee OA, over time with respect to disease severity, we performed a longitudinal study on the kinematic and kinetic characteristics

of gait in women with early knee OA, women with established knee OA and in healthy controls over a two-year follow-up period.

Methods

Study population

Sixty-six women (43 with knee OA and 23 healthy controls) participated in this study. All subjects were informed of the procedures of the study and signed informed consent forms approved by the local ethical committee of Biomedical Science, KU Leuven, Belgium prior to testing. The study was conducted in agreement with the principles of the Declaration of Helsinki.

Forty-three individuals with knee OA were clinically diagnosed by a rheumatologist or orthopedic surgeon while visiting the University Hospitals Leuven for weekly consultations. Recruitment of the control subjects (n=25) was done through social organizations. The inclusion criteria for the control group were, K&L grade 0 or 1 on the radiography of both knees, asymptomatic, no history of knee OA and other pathology involving any lower extremity joints. The Standard anterior-posterior weight-bearing radiographs in fixed flexed position were obtained from each subject bilaterally (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). A single experienced observer (FPL) graded each radiograph, using K&L grading scale to establish and categorize the presence of structural knee OA. An MRI was taken only from the (most) affected side of the OA patients and one side in the control group. A 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) using an eight-channel phased array knee coil in a non-weight bearing supine position as described by Baert et al was used [25].

The standardized Boston-Leeds Osteoarthritis Knee Score (BLOKS) scoring system was used by two separate readers (NN, GVDS) to score structural features in the tibiofemoral joint [26]. The two readers had full agreement on 91% of all scored items. Disagreements were resolved by consensus.

OA group was sub-classified into groups of "Early OA" and "Established OA" based on the classification by Luyten et al [27]. Subjects were categorized as early OA (n=25) if they had knee pain, KL grade of 0 to 2- (just joint space narrowing) for the medial compartment on radiography, and two out of four MRI criteria: (1) ≥ BLOKS grade 2 for size cartilage loss, (2) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment.

Subjects in the established OA (n=18) group were classified based on the mildly adjusted American College of Rheumatology (ACR) classification criteria [14], which includes knee pain,

age above 50, stiffness less than 30 minutes and crepitus, combined with structural changes defined as presence of minimum grade 2+ (osteophytes and joint space narrowing), on K&L scale for the medial compartment on radiography, indicating a moderate to severe disease severity. The patients that showed higher K&L grade on the lateral than on the medial compartment of the same knee were excluded.

The general exclusion criteria for all groups of subjects were musculoskeletal disorders other than knee OA in both lower limbs in the last six months, previous surgery of lower extremities and/or low back, neurological disorders, chronic intake of corticosteroids or contra-indications for MRI.

Knee symptoms and function

The Knee Injury and Osteoarthritis Outcome Score (KOOS) (Dutch version) was filled in by all subjects to assess knee symptoms and function. The reliability and validity of KOOS to evaluate short and long-term symptoms and function for knee OA patients has been studied and reported previously [28, 29]. The KOOS subscales of 'pain' and 'symptoms' were used to evaluate subjects' self-reported signs/symptoms associated with knee OA. Subjects' self-reported physical performance was assessed via the subscale 'activities of daily living (ADL)'. Scores were converted to a scale of 0 to 100 for each subscale, with extreme knee problems presenting as 0 and 100 expressing no knee problems.

Gait data acquisition and analysis

A 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group) was used to record the spatial position of markers on relevant body segments at 100 samples/s (Figure 1). Markers and clusters were firmly fixed by means of two-sided adhesive tape.
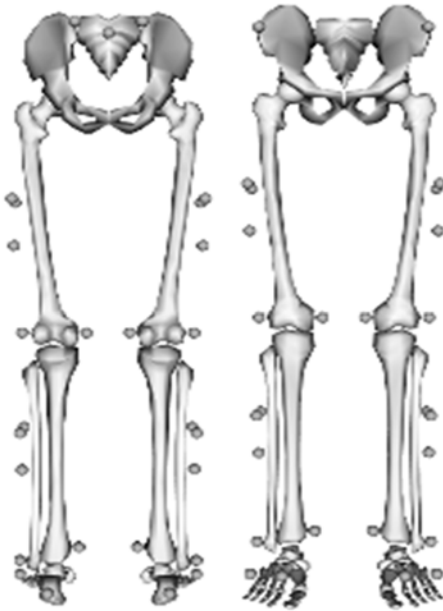
Figure 1. Marker set used for motion capture.

- Ground reaction forces were recorded through two force plates (Bertec Corporation, Ohio, USA and AMTI, Watertown, MA, USA) placed in a 12m walkway at a sample rate of 1000 samples/s. The recorded data were low-pass filtered with a fourth-order filter with a cutoff frequency at 25 Hz. The force time series were down-sampled to match the kinematic data. All the analyses were done using Custom-made MATLAB 7.14.0 (The MathWorks, Natick, MA) programs. Marker data from Krypton motion analysis system were labeled and smoothed using a spline routine [30].

- Participants walked along the walkway at a comfortable habitual speed during gait analysis. To avoid force plates being targeted while performing the trials, no guidance on walking, except the instruction to 'walk naturally' was provided. Three complete force plate strikes for each foot were registered. Since footwear can affect the distribution of loads on the joints in the lower quadrant [31], all participants were asked to walk bare-footed.

- Before the start of the experimental trials, one recording was made in an upright reference posture, in which all the marker clusters and bony landmark markers were visible. Based on the pelvis bony landmark markers, the position of the hip joint centers was estimated using regression equations reported by Bell et al [32]. Subsequently, the hip joint centers were used together with the medial and lateral femoral epicondyle marker data to calculate the thigh Anatomical coordinate systems (ACSs) according to the ISB recommendations [33].

- The longitudinal axis was defined as the vector between the ankle joint center (midpoint between medial and lateral malleolus) and the knee joint center (midpoint between medial and lateral femoral epicondyle).
- The anterior-posterior axis was defined as the vector perpendicular to the plane containing the ankle joint center and the medial and lateral femoral epicondyle.
- The sideward axis was defined as vector perpendicular to the frontal and longitudinal axis (sagittal plane).

Finally, for each segment the rotation matrix between the ACSs and the corresponding marker cluster coordinate systems was calculated. This rotation matrix was used to calculate the ACSs in the experimental walking trials based on the measured marker cluster data.

Calculation of Spatiotemporal variables

To determine stance time, the vertical ground reaction force was used. The "heel-strike" event was detected as the first sample of vertical ground reaction force that was above 10N. The "toe-off" event was chosen as the first sample at which the vertical ground reaction force was below 10N [34]. Stance time was defined as the time from one heel strike to the toe off on the same side. Walking speed was calculated by taking the time derivative of the pelvic displacement. For each subject, this information was used to calculate their average comfortable walking speed for each trial.

Calculation of knee joint kinematics and kinetics

3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay [35]:

- First rotation: flexion-extension (sideward axis of the proximal thigh segment)
- Second rotation: abduction-adduction (floating axis)
- Third rotation: internal-external rotation (longitudinal axis of the distal shank segment).

Note that because the frontal plane of the shank was based on the femur epicondyles, the knee internal-external rotation was assumed to be zero in the reference posture.

Knee moments were calculated through a bottom-up dynamic linked segment model, using kinematics of the body segments and the ground reaction forces [36]. To obtain the knee (adduction and flexion) moment from the 3D components of the net moments, the knee moments were projected onto the calf coordinate system. Extracted joint moments were normalized to the

product of body weight and height (BW*Ht) [37]. Knee adduction moment impulse, was calculated as the integral of all the frontal plane joint moments during the stance phase of gait [21].

Dependent variables

The variables of interest were *walking speed*, *stance time*, *knee flexion angle at initial contact*, *peak knee flexion angle*, *knee flexion excursion*, *knee adduction angle at the initial contact*, *peak knee adduction angle, first and second peak knee flexion moment, first and second peak knee adduction moment*, and *knee adduction moment impulse*. All kinematic and kinetic variables were calculated from the stance phase of gait.

Statistics

Descriptive statistics were used to report subjects' demographic characteristics in each group at baseline (Table 1). In order to compare subjects' characteristics, One-way Analysis of Variance (ANOVA) (when the distribution was normal) or The Kruskal Wallis Signed rank test (when the distribution was not normal) were used. Wilcoxon signed rank test was used for comparisons over time for KOOS subscores. To investigate Group differences and the effect of Time (as well as interaction of Time × Group effects) on gait related parameters, Generalized Estimating Equations (GEEs) were used. When a main effect or an interaction was significant, a post hoc analysis was conducted to test the pairwise differences. In order to count for the possible effect of static (mal)alignment on fontal plane kinematics during stance phase of gait, static alignment was included as covariate when testing group differences for *knee adduction angle at the initial contact* as well as for the *peak knee adduction angle during stance phase of gait*. P-values < 0.05 were used to indicate significance in all cases.

Results

Subjects' demographic characteristics at the time of entry are presented in **Table 1**. There was no significant difference between groups regarding the age, weight, height, and BMI. After 2 years, in the early OA group, 3 patients progressed by 1 unit on K&L score. In addition, 5 patients in the established OA group progressed based on K&L score.

Table 1. Subject characteristics at the time of entry and results for tests of differences between groups.

		Control	Early OA	Established OA	P
		(n = 23)	(n = 25)	(n = 18)	
Age (years)[b]		63.5 (8.2)	67.57 (4.9)	67.0 (4.7)	0.144
Height (m)[a]		1.62 (0.1)	1.62 (0.1)	1.61 (0.1)	0.685
Weight (kg)[a]		66.33 (10.3)	72.57 (12.1)	69.14 (9.5)	0.161
BMI (kg/m^2)[b]		25.23 (3.9)	27.57 (4.2)	27.01 (3.6)	0.085
K&L score[c]		Grade 0: n=18 Grade 1: n= 5	Grade 0: n= 8 Grade 1: n= 16 Grade 2[-]: n= 1	Grade 2[+]: n= 14 Grade 3: n= 4	
Static alignment[c]	Neutral Valgus Varus	n= 19 n= 3 n= 1	n= 18 n= 2 n= 5	n= 9 n= 9	

OA=osteoarthritis; BMI=Body mass index.
Data are presented as mean (SD). The P value corresponds to an ANOVA[a], Kruskal-Wallis test[b] (with post hoc tests) comparing the three groups.

The early and established OA groups reported significantly more knee pain along with worse symptoms and lower self-reported functional ability compared to the healthy controls at baseline (table 2). There was no significant difference between the two OA groups regarding pain, symptoms, or self-reported functional ability (table2). Comparing the baseline measures with the follow-up data, no changes were detected for any of the study groups (table 2).

No significant group differences were found for the TUG or SCT between the three groups (table 2). Similarly, none of the measures of TUG or SCT changed over time in any of the three groups (table 2).

Table 2. Subject's clinical characteristics and results for tests of differences between groups and over time (2 years follow-up)

	Control		Early OA		Established OA		P-value[a]	P-value[b]	P	P	P
	Baseline	2YFU	Baseline	2YFU	Baseline	2YFU	Time	Group	Established vs. control	Early vs. control	Early vs. established
KOOS pain score[a]	100 (5.6)	100 (22.3)	86.1 (52.8)	88.8 (22.3)	80.5 (83.4)	80.5 (52.8)	0.359	**<0.001†**	**<0.001†**	**<0.001†**	0.371
KOOS symptoms score[a]	96.4 (21.5)	96.4 (25)	82.1 (50)	85.7 (46.5)	83.9 (96.5)	82.1 (57.2)	0.417	**<0.001†**	**<0.001†**	**0.002†**	0.307
KOOS ADL score[a]	100 (14.8)	100 (22.1)	93.35 (63.3)	92.6 (73.6)	85.95 (73.6)	85.2 (51.5)	0.539	**<0.001†**	**<0.001†**	**<0.001†**	0.834
TUG (sec)[b]	5.32 (0.2)	6.64 (0.2)	5.79 (0.3)	5.66 (0.2)	5.85 (0.3)	5.84 (0.3)	0.508	0.321			
SCT (sec)[b]	5.34 (0.2)	5.65 (0.2)	5.78 (0.3)	5.65 (0.2)	5.88 (0.3)	5.83 (0.3)	0.232	0.357			
Walking speed (m/s)	1.19 (0.04)	1.17 (0.03)	1.18 (0.04)	1.08 (0.06)	1.21 (0.05)	1.12 (0.06)	**0.028†**	0.656			
Stance time (sec)	64.49 (1.2)	65.08 (1)	65.44 (1.1)	66.28 (1.1)	65.85 (2)	64.61 (0.9)	0.939	0.747			

OA=osteoarthritis; KOOS = Knee injury and Osteoarthritis Outcome Score; FU = 2-years follow-up
Data are presented as [a]Median (IQR or [b]Mean (SD)). The *P* value corresponds to Kruskal-Wallis test[b] or an ANOVA test (with post hoc tests) comparing the three groups, or to a two-factor ANOVA or a Wilcoxon signed rank test[a] comparing each group at baseline and after 2 years follow-up.
†Significant differences are shown in bold (P < 0.05).

Spatiotemporal variables

No statically significant differences were found between the three groups in the *walking speed* and *stance time* (Table 2). The main effect of *Time* was significant for *walking speed*, but no significant differences were found between baseline and follow-up measures of *walking speed* for any of the three groups (Table 2). Similarly, no significant changes were found for *stance time* over two years of follow-up in any of the three groups (Table 2).

Kinematic variables

There was a trend towards a significant difference between groups regarding *knee flexion angle at the initial contact* with the established OA group showing the highest value (P = 0.099) (Figure 2). *Knee flexion angle at the initial contact* decreased after two years compared to the baseline measures in all three groups (P = 0.001) (Figure 3). There were no significant differences among the groups regarding *peak knee flexion angle* during the stance phase (Figure 2), but the *peak knee flexion* angle during the stance phase significantly decreased over time in all three group (P = 0.009) (Figure 3). The three groups were significantly different with respect to *flexion excursion* during the early stance phase of gait (P = 0.004), with the established OA groups showing significantly less knee *flexion excursion* compared to the early OA, as well as the controls (P = 0.007 and P = 0.004, respectively). There was no significant difference between the baseline and follow-up measures of knee *flexion excursion* during early stance phase for any of the three groups (P = 0.486).

Regarding frontal plane knee kinematics, no significant differences were found between the three groups for *knee adduction angle at the initial contact* of the stance phase (P = 0.105). Over the 2 years follow-up, none of the groups showed changes in *knee adduction angle at the initial contact* (P = 0.556). For the *peak knee adduction angle* during the stance phase, the main effect of the group was significant (P = 0.031) and post hoc analysis revealed that both the early OA group and the established OA group had significantly higher maximum knee adduction angle right after initial contact compared to the healthy controls (P = 0.036 and P = 0.02 respectively). After adjustment for static alignment, the differences between the early and the established OA groups compared to the control group stayed significant (p = 0.023 and p = 0.021, respectively). There were no significant differences between the two OA groups regarding the *peak knee adduction angle* (P = 0.919). No significant effect of time was found for any of the groups regarding the *peak knee adduction angle* during the stance phase (P = 0.098).

Kinetic variables

No significant differences were found between the three groups regarding the *first or second peak external knee flexion moment* (P = 0.457 and P = 0.754, respectively) (Figure 2). There was a significant *Time × Group* interaction for the *second peak external knee flexion moment* during the stance phase (P = 0.047) (Figure 3). Post hoc analysis revealed that the *second peak knee flexion moment* significantly decreased in the established OA group after 2 years follow-up compared to baseline, while this was not the case for the other groups. No significant changes were found for any of the other sagittal plane kinetic characteristics of the stance phase of gait, after 2 years follow-up.

For the frontal plane kinetics, there was a significant effect of group for the *first peak knee adduction moment* (P = 0.007). Post hoc analysis revealed that the *first peak knee adduction moment* was significantly higher in the established OA group compared to the early OA as well as the healthy control group (P = 0.004 and P = 0.005, respectively) (Figure 2). There was a significant effect of group for the *second peak knee adduction moment* (P = 0.002) as well (Figure 2). Post hoc analysis revealed that the *second peak knee adduction moment* was significantly higher in the established OA group compared to the early OA as well as the healthy control group (P = 0.001 and P = 0.004, respectively). No significant differences were found for the *first and second knee adduction moment* between the early OA and the control groups (P = 0.823 and P = 0.587, respectively). There was no significant effect of time for any of the groups regarding *first and second peak knee adduction moment* (Figure 4). The *knee adduction moment impulse* was significantly higher in the established OA group compared to the early OA and the healthy control group (P < 0.001, both). No significant differences were found between the *knee adduction moment impulse* in the early OA group and the healthy control group (P = 0.815). There was a significant *Time × Group* interaction for the *knee adduction moment impulse* (P = 0.028). Post hoc analyses revealed that in the established OA group the *knee adduction moment impulse* during the stance phase of gait increased over two years (P = 0.012). No such differences were found between the baseline and follow-up measures of *knee adduction moment impulse* after 2 years for the early OA or the control group.

A

B

C

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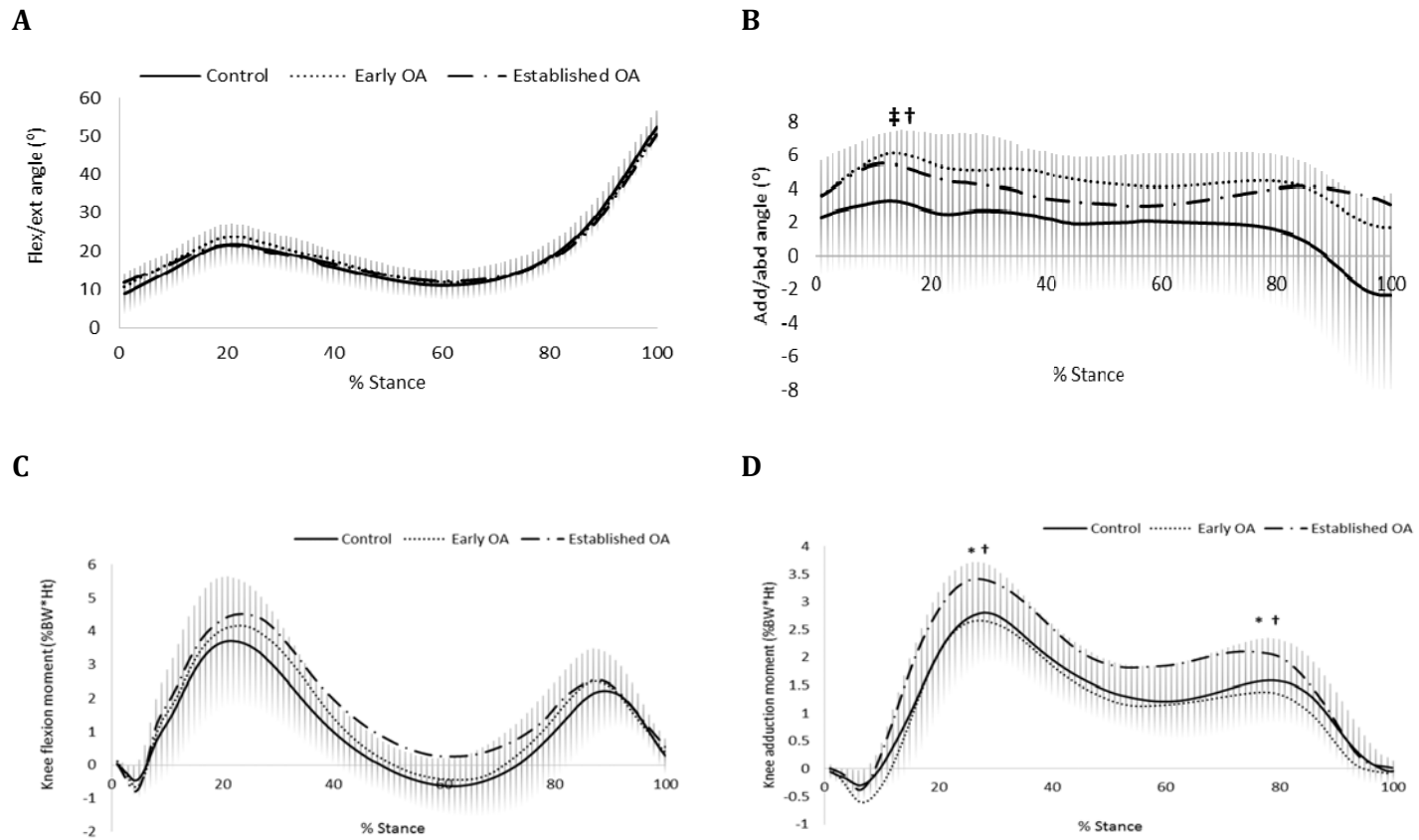
Figure 2. Mean waveforms of the early OA group, established OA group, and control group at baseline with standard deviation of the control group, for: A) knee flexion-extension angle, B) knee adduction-abduction angle, C) external knee flexion moment, and D) external knee adduction moment during stance phase of gait.

†significant difference between established OA group and control group (P < 0.05).

‡significant difference between early OA group and control group (P < 0.05).

*significant difference between early OA group and established OA group (P < 0.05).

Figure 3. Mean waveforms of the early OA group, established OA group, and control group at baseline and after 2 years follow-up with standard deviation of the baseline, for: knee flexion-extension angle, knee abduction-adduction angle during stance phase of gait.
† significant difference between baseline and follow-up measures (P < 0.05).

Control **Early OA** **Established OA**

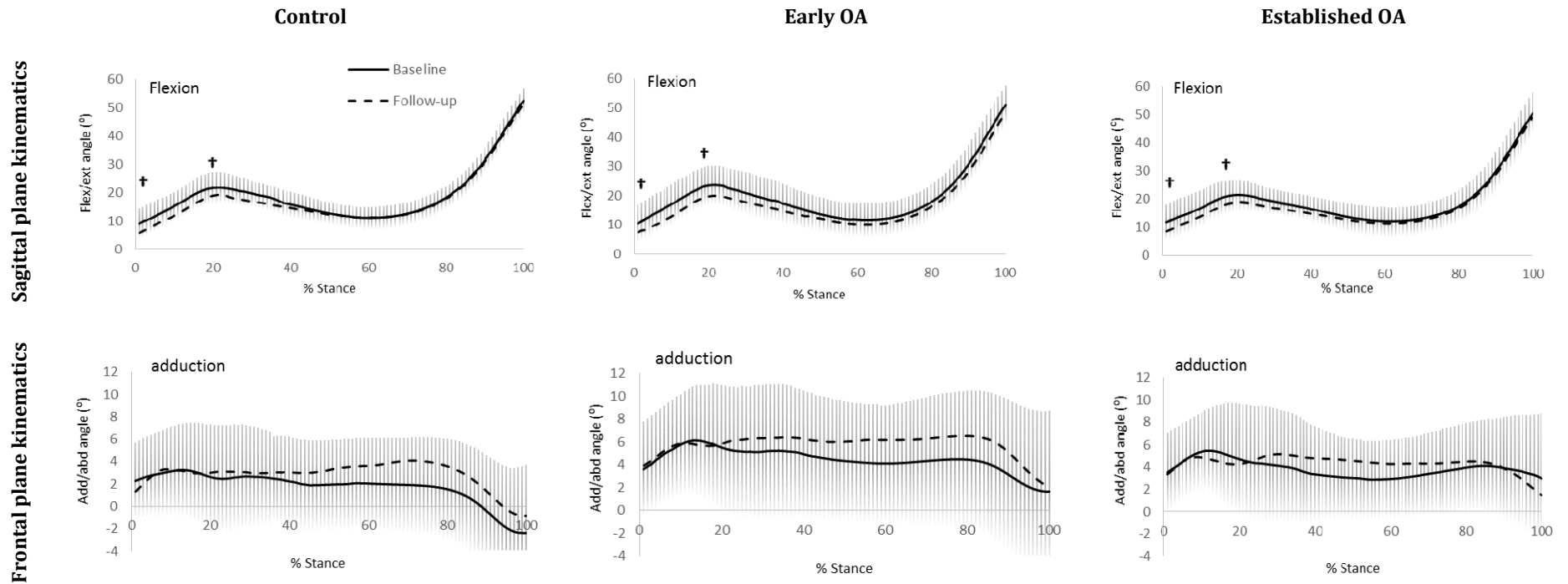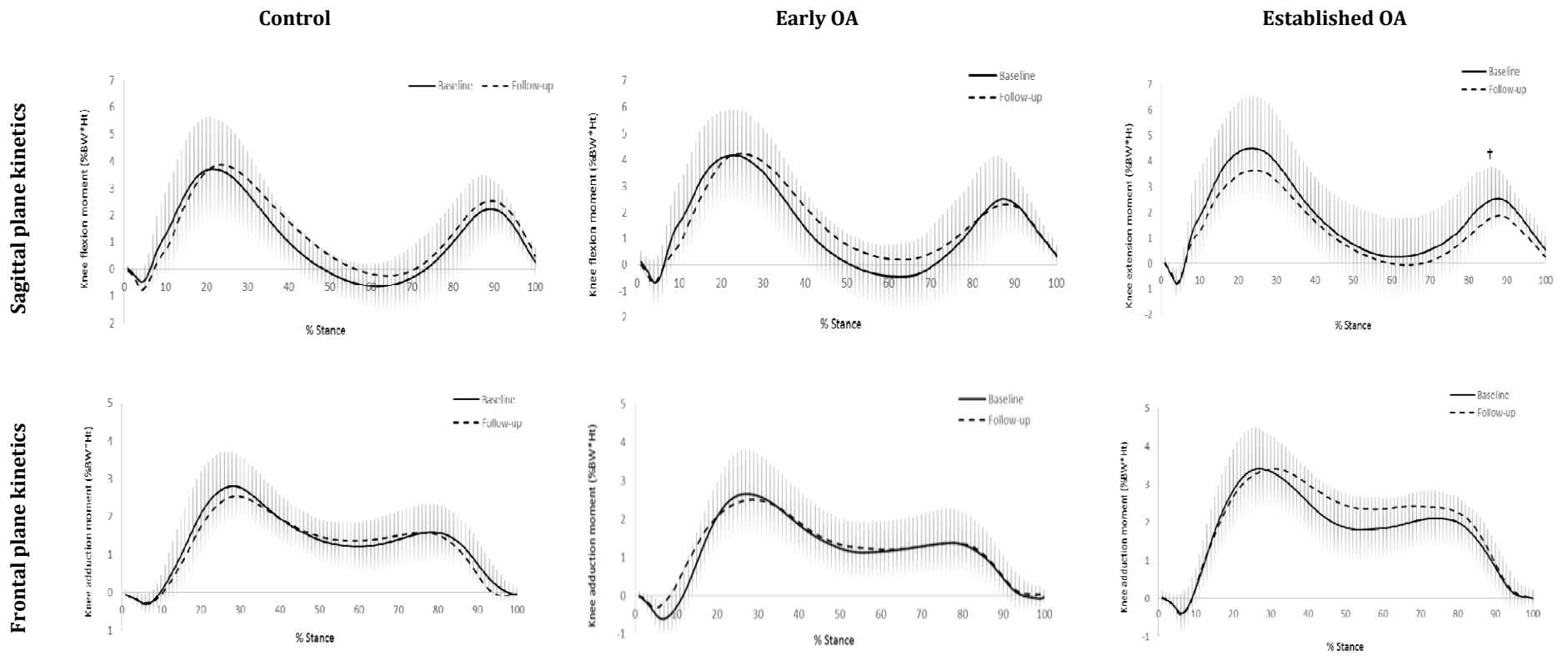**Figure 4.** Mean waveforms of the early OA group, established OA group, and control group at baseline and after 2 years follow-up with standard deviation of the baseline, for: external knee flexion moment and external knee adduction moment during the stance phase of gait.
† significant difference between baseline and follow-up measures (P < 0.05).

Discussion

To the best of our knowledge this was the first study that evaluated the effect of OA severity and time on gait characteristics through a two-year follow-up study. Results from a current study indicated that the early OA group, similar to established OA group, showed significantly higher maximum knee adduction angles compared to the healthy controls during the early stance phase of gait. While this was the only alteration in gait pattern of subjects with early knee OA observed in this study, the established OA group showed other significant differences in gait kinematics and kinetics compared to the healthy controls. Increased first and second peak knee adduction moment, as well as higher knee adduction moment impulse were observed at the time of entry, in established OA compared to the healthy controls and the early OA group. Knee adduction moment impulse, further increased over two years only in the group of subjects with established knee OA.

Our results underscore previous literature that the increased maximum knee adduction angle is already present at the early stages of the disease, regardless of static (mal)alignment, prior to the presence of elevated medial joint loading. Early OA subjects in the present study showed no significant increase in KAM magnitude and impulse, which implies no alterations in medial knee joint loading during stance phase of gait in the early stages of the disease. Barrios et al [38], previously reported an increased maximum knee adduction angle in a group of subjects with moderate to severe medial knee OA (minimum K&L grade 2), and they reported the maximum knee adduction angle is a strong predictor of KAM magnitude and impulse. Results from current study might be able to confirm these findings, as the established OA group in this study showed increased peak adduction angle coupled with elevated KAM magnitude and impulse.

All three groups in this study showed decreased knee flexion angle at the initial contact, as well as a decrease in peak knee flexion angle during the stance phase of gait, after two years compared to the baseline. Changes in sagittal plane knee kinematics, observed in this study suggest an age-related alteration on gait, over two years. Therefore, the only longitudinal gait changes observed over 2 years in the early OA group, was age-related, which can be explained by decreased knee joint range of motion and knee muscle strength, observed with aging [39-41].

Also, the knee joint loading did not change over 2 years follow-up in patients with early medial knee OA. For the established OA group, on the other hand, increased first and second peak KAM as well as knee adduction moment impulse compared to the healthy controls and the early OA at the time of entry were observed, which was in line with previous findings [6, 8, 13]. It is believed that knee OA progresses more rapidly with an increase in load of the affected knee [42]. Load bearing studies have revealed that the effect of the time integral of load on the articular surface is

as important as that the effect of the load magnitude itself [43]. This increased impulse that further increases over time once OA is established might be due to more severe impairments, such as severe structural abnormalities, decreased muscular strength, proprioceptive deficiency, or increased varus malalignment at the more severe stages of the disease [13, 44].

Gait speed is an important factor when measuring gait kinematics and kinetics [45, 46]. An increase in the acceleration of the center of mass, might coincide with a higher GRF and higher joint moments. In patients with knee OA, increased joint loading has been shown to play an essential role in disease progression [47]. Therefore, decreased walking speed, as observed in patients with knee OA, has been suggested as a potential mechanism to reduce knee joint loading [48]. In the current study, we found no significant differences in gait speed between groups. Also, after 2 years, regardless of some changes in gait speed, none of the changes were significant for any of the groups.

Findings of the current study is the first reference to a longitudinal gait changes associated with OA severity in a population of women with medial knee OA. Current results implies that in the early stages of knee OA, gait is relatively normal and gait characteristics associated with knee OA is quite stable over 2 years. The only longitudinal changes related to knee OA, were decreased second peak external knee flexion moment and increased KAM impulse in the established OA group, which are not likely to serve as compensatory strategies, but rather to be cause of disease progression.

There are some limitations of this study that should be taken into account. First, although the classification criteria for early OA have been proposed as a result of several rounds of discussion (Delphi approach) between rheumatologists and orthopedic surgeons, it is still in its early phase and further confirmation of this classification is needed. Furthermore, in the current study barefoot walking has been chosen in order to a better motion tracking of the markers, however this limits generalization of the results. Therefore, our results may not apply to all real–life walking conditions, were shoes are worn. Lastly, in the current study due to specific aims of the study, only knee joint was tested, while previous reports demonstrated secondary gait changes associated with knee OA also in hip and ankle joints.

Conclusion

The current study was conducted to examine the effect of OA severity and time on kinetics and kinematics during the stance phase of gait. Our aim was to evaluate gait changes in a prospective longitudinal study, in order to determine whether the early OA group patterns would show gait

characteristics close to the established OA group. We found that increased maximum knee adduction angle during stance phase was the only alteration in the gait pattern of subjects with early knee OA compared to the controls, a finding similar to the established OA group. The only longitudinal changes in the gait pattern of patients with early OA, were age-related, as they were also present in the two other groups. Established OA group, on the other hand, showed decreased second peak external knee flexion moment and increased KAM impulse after 2 years, compared to baseline.

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Part 3: Prognostic factors for progression in structural, clinical, and functional profile of OA

Chapter 7

Dynamic and static knee alignment at baseline predict structural abnormalities on MRI associated with medial compartment knee osteoarthritis after 2 years

Abstract

Dynamic and static varus alignment, both, have been reported as risk factors associated with structural progression of knee osteoarthritis. However the association of none of the static and dynamic alignment with structural, clinical, and functional progression associated with knee OA has not been assessed yet in a longitudinal study. Forty-seven women with early and established medial knee OA were evaluated. Static and dynamic alignment as well as MRI detected structural features, clinical, and functional characteristics of patients were assessed at baseline and at 2 years follow-up. Associations between baseline static and dynamic alignment with structural, functional, and clinical characteristics at the time of entry, as well as the changes over 2 years were evaluated. Both static and dynamic varus alignment at baseline were significantly associated with OA related tibio-femoral joint structural abnormalities detected on MRI, at the time of entry. Only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. None of the static or dynamic measures of knee joint alignment were associated with clinical characteristics associated with medial knee OA. The key finding of this study is that both frontal plane dynamic and static alignment, are associated with structural abnormalities in patients with medial knee OA. Therefore, results from the current study highlight the role of frontal plane static and dynamic alignment in the disease process and hence, suggest that attempts for therapy are unlikely to be successful unless efforts are made to correct alignment.

1. Introduction

Osteoarthritis (OA) is a chronic joint disease that typically affects weight-bearing joints [1]. The disease causes serious irreversible joint damage over time, which in turn results in functional limitations and consequently a dramatic decrease of Quality of Life (QoL) [1, 2]. A report on the global burden of disease indicated knee OA as one of the leading causes of disability [3]. The number of knee replacements is small compared to the number of subjects with knee OA [4, 5]. Therefore, as suggested by Cooper et al, preventing progression to severe joint damage may offer a more effective public health strategy than attempting to prevent disease incidence [4]. Developing strategies to prevent (progression of) knee OA requires a thorough understanding of the factors associated with disease incidence and progression. The incidence and progression of radiographic knee OA may involve different processes [4]. Several risk factors have been reported to be associated with the incidence of knee OA [2, 4], but the number of studies in which risk factors and incidence of knee OA have been investigated longitudinally, is relatively small.

Knee OA is characterized by symptoms such as pain and functional decline along with structural changes detected on radiography or on Magnetic Resonance Imaging (MRI) such as Bone Marrow Lesions (BMLs), Cartilage Lesions (CL), and Meniscal Injuries (MI)) [5]. Lesions of bone marrow have been proposed as structural indices for progression of knee OA [6]. Especially in the early stages of the disease, these structural changes can be better identified on MRI [7].

The role of mechanical factors, such as knee joint static (mal)alignment, in progression of knee OA has been well-established [8-10]. In a study by Hunter et al, it was concluded that the location of BMLs and change in BMLs were mediated by static (mal)alignment [6]. This effect of (mal)alignment may be due to an increase in medial tibiofemoral joint loading with increased varus alignment, through the associated displacement of the knee joint away from the line of action of the ground reaction force, causing an increased external knee adduction moment [11]. On the other hand, evidence exists that *dynamic* knee alignment as measured based on the peak knee adduction angle during walking is a stronger predictor of the knee adduction moment (and thus indirectly loading) than *static* radiographic (mal)alignment, [12]. Frontal plane dynamic alignment, and more specifically varus thrust, is defined as an abrupt increase of the knee varus alignment during weight-bearing in gait, and it is one of the newly proposed clinical indices for knee OA [13-15]. However, the relation between dynamic knee alignment on one hand, and clinical and structural progression of knee OA on the other, is insufficiently understood.

There is only one single longitudinal study on the association of baseline dynamic alignment, assessed as presence of varus thrust by visual observation, and radiographic progression of knee OA [13]. In this study, *the presence of varus* thrust at baseline was associated with a 4-fold increased likelihood of progression of medial knee OA over the next 18 months, as measured with the Kellgren and Lawrence scale [13]. Assessing the association of objectively measured *magnitude of varus thrust* during gait with clinical and structural changes associated with OA progression over time might lead to identification of subsets of individuals based on degree of thrust who are at higher risk for OA related disability and progression. An association of varus thrust magnitude with clinical and structural abnormalities associated with knee OA and their changes over time would support the role of varus thrust, as a measure of dynamic (mal)alignment, in progression of medial knee OA.

In a recent cross-sectional study, Lo et al. compared two groups of subjects with knee osteoarthritis with and without varus thrust as detected by visual inspection, and reported the association of pain with varus thrust to be stronger compared to its relation with static varus alignment [16]. Varus thrust was shown to be associated with external knee adduction moments (KAM), an indirect measure of dynamic medial knee loading [13, 17], which itself is related with a higher prevalence of BMLs in the medial compartment [18]. Medial compartment BMLs in turn have been related to pain [19-22]. But the relationship between the presence and magnitude of varus thrust with BMLs as well as other structural abnormalities associated with medial knee OA has not yet been investigated. Increased varus thrust can be observed early in the disease process, before signs of an increase in KAM [17].

Therefore, the aim of the present study was to assess both cross-sectionally and longitudinally, the relationship between frontal plane static and dynamic alignment (by quantification of varus thrust magnitude during the stance phase of gait) with structural and clinical characteristics of OA in a group of individuals with early and established symptomatic medial knee OA. We hypothesized that higher values of baseline varus thrust magnitude during gait would be associated with structural and clinical abnormalities <u>at the time of entry, as well as with the changes over 2 years</u>.

2. Materials and Methods

Forty-seven patients with medial knee OA participated in this study. The study was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium prior to testing and was

conducted in agreement with the principles of the Declaration of Helsinki. All participants were informed about the study procedure and signed informed consent forms.

Participants were recruited during their visit to the University Hospital Leuven and assessed by a rheumatologist or orthopedic surgeon. The inclusion criteria for the early OA group were: presence of knee pain, a Kellgren & Lawrence (K&L) grade 0, 1 or 2- (osteophytes only, no joint space narrowing) for the medial compartment on radiography and presence of two of four MRI criteria: (1) ≥ BLOKS grade 2 for size cartilage loss, (2) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss, (3) signs of meniscal degeneration and (4) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment [7]. Patients with established OA were included in the study based on the slightly adjusted American College of Rheumatology (ACR) classification criteria [15], which includes knee pain, age above 50, stiffness less than 30 minutes and crepitus. Patients with higher K&L grade on the lateral than on the medial compartment of the same knee were excluded. Subjects were excluded if they had: musculoskeletal disorders other than knee OA in both lower limbs in the last six months, previous surgery of lower extremities and/or low back, neurological disorders, chronic intake of corticosteroids or contra-indications for MRI.

2.1. Assessment of structural OA features and static alignment on radiography

Standard anterior-posterior weight-bearing radiographs in fixed flexed position (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30) were taken for each participant. Each radiograph was graded by a single experienced observer (FPL) and the K&L grading system with recent adjustments was used for grading of each tibiofemoral compartment [16, 17].

In addition, an experienced skeletal radiologist assessed the static alignment of the knee joint on full-leg AP weight-bearing plain radiographs of the lower extremities (Oldelft, Triathlon, Agfa ADC M Compact Plus) [18]. Knee alignment between -2° and +2° was classified as neutral, while malalignments less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively [9, 23].

2.2. Assessment of structural OA features on MRI

All MRI studies were performed with a 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) with an eight-channel phased array knee coil. Subjects were scanned

in a non-weight bearing supine position, as described by Baert et al. [21]. The (most) affected side of the subjects, based on radiography, was selected for MRI. Two separate readers (NN, GVDS), using the standardized Boston-Leeds Osteoarthritis Knee Score (BLOKS) scoring system, graded structural features of the tibiofemoral joint [22]. On 91% of all scored items, the two readers had full agreement and disagreements were resolved by consensus. The number and amount of BMLs for the tibiofemoral (TF) joint were calculated. For cartilage lesions, cumulative scores for size and % full thickness cartilage loss were calculated for the TF joint. The presence of meniscal extrusion, tear, maceration, or increased signal was also detected.

2.3. Assessment of knee symptoms and function

To evaluate self-reported knee symptoms and function, the Dutch version of Knee Injury and Osteoarthritis Outcome Score (KOOS), was completed by each subject. The validity and reliability of this version for patients with knee OA have been demonstrated in the past [24]. The KOOS contains five distinct sections. Using the subscales 'pain' and 'symptoms', the knee OA pain and symptoms were evaluated. Subjective physical performance was assessed via the 'Activities of Daily Living' (ADL) section. A converted score from 0 to 100 was computed for each subscale, with 100 indicating the best possible result.

In addition, with the use of two functional tests: The 'Stair Climbing Test' (SCT) and the 'Timed Up & Go test' (TUG), objective physical performance was assessed. The SCT is quantified by measuring the time needed to go up five steps, turning around and to go down the same five steps. The TUG test is quantified by measuring the required time to stand up from a chair, walking three meters, turning around, going back to the chair and sit down. An average of three trials for each test was calculated, to determine the final value. The reliability and validity of these two tests have been shown before [25, 26].

2.4. Assessment of varus thrust

The spatial position of markers on relevant body segments, was recorded using a 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group), at 100 samples/s (Figure 1).
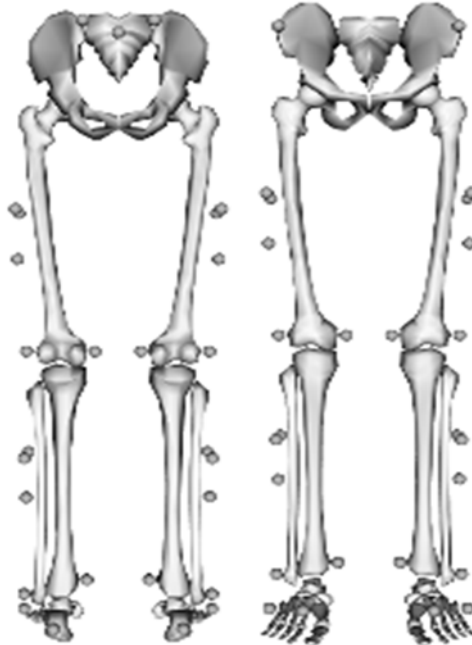
Figure 1. Marker set used for motion capture.

By use of embedded force plates (Bertec Corporation, Ohio, USA and AMTI, Watertown, MA, USA) in a 12m walkway, ground reaction forces were recorded at a sample rate of 1000 samples/s. Participants were asked to walk naturally at their comfortable speed, until three complete force plate strikes for each foot were recorded. All participants were asked to walk bare-footed, in order to avoid the effect of different footwear on the load distributions on the joints in the lower quadrant [27]. The "heel-strike" event was identified as the first sample of vertical ground reaction force that was above 10 N. The "toe-off" event was detected as the first sample at which the vertical ground reaction force was below 10N [28].

The recorded data were low-pass filtered with a fourth-order filter with a cutoff frequency at 25 Hz. The force time series were down-sampled to match the kinematic data. All the analyses were done using Custom-made MATLAB 7.14.0 (The MathWorks, Natick, MA) programs. Marker data from Krypton motion analysis system were labeled and smoothed using a spline routine [29]. 3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay [30]. The gait analysis protocol is described in more details in a previous study of our group [31].

Varus thrust was calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait [13, 32] (Figure 2).
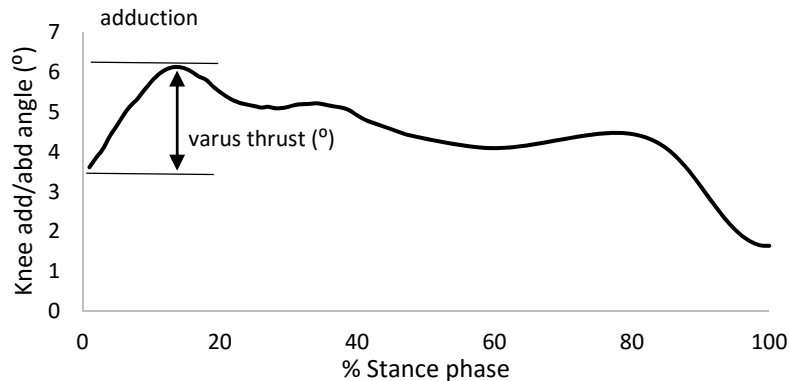
Figure 2. Varus thrust magnitude calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait.

2.5. Statistical analysis

The knee selected for MRI was used for further analysis. Statistical calculations were carried out using SPSS software (version 20, 2006, Chicago: SPSS Inc) and for all tests, *p* values less than 0.05 were considered statistically significant. To examine the association of static and dynamic measures of knee alignment (independent variables), with structural features measured <u>at baseline and their changes over 2 years</u> (dependent variables), univariate regression analyses were used for continuous values. For the dichotomous variables (e.g. Presence of meniscal tear), logistic regression analysis was used. Similarly, the association of static and dynamic measures of knee alignment (independent variable) with the clinical features associated with knee OA (pain/symptoms and physical performance) measured <u>at baseline and their changes over 2 years</u> (dependent variables) were determined using univariate regression analyses. As the regression analyses revealed that both static and dynamic alignment were associated with the size of BMLs, at baseline, a final model with standard multiple regression analysis was used to assess the association between the size of BMLs and knee alignment, after checking for multicollinearity.

3. Results

Forty-seven women with a mean BMI of 27.17 (SD = 0.7) kg/m^2 and mean age of 68 (SD = 0.9) years were included in the analysis. Subjects' characteristics are presented in Table 1.

Table 1. Characteristics of the study population (n = 47)

	Mean (SD)[a] or Median (IQR)[b] or n (%)[c]	Range	95% CI of the mean
Weight (kg)	70.64 (1.8)[a]	51.2 – 98.1	66.92 – 74.36
BMI (kg/m^2)	27.17 (0.7)[b]	20.52 – 35.6	25.74 – 28.59
Height (m)	1.61 (0.01)[a]	1.47 – 1.77	1.59 – 1.63
Age (years)	68.00 (0.9)[a]	57 - 83	66.23 – 6
K&L score (MC)			
K&L 0	10 (22%)[c]		
K&L 1	16 (36%)[c]		
K&L 2-	1 (2%)[c]		
K&L 2+	12 (27%)[c]		
K&L 3	6 (13%)[c]		
Static alignment			
Neutral	27 (60%)[c]		
Valgus	5 (11%)[c]		
Varus	13 (29%)[c]		

SD = Standard Deviation; IQR = Inter Quartile Range; CI = Confidence Interval; BMI = Body Mass Index; MC = Medial Compartment; K&L = Kellgren & Lawrence (range 0-4); K&L 2- = Definite osteophytes without joint space narrowing; K&L 2+ = Definite osteophytes with joint space narrowing.

3.1. Cross-sectional association between knee frontal plane alignment and structural features of OA

Details of the regression analyses between measures of static and dynamic (varus thrust magnitude) frontal plane alignment, with MRI features at the time of entry are presented in Table 2. The magnitude of varus thrust was significantly associated with the **cumulative score for size of BMLs in the tibiofemoral joint** (Table 2). Considering static alignment, the **amount and cumulative**

score for size of BMLs in the tibiofemoral joint, as well as the **cumulative score for percentage of full-thickness cartilage loss** and **presence of a meniscal maceration** were significantly associated with static varus alignment (Table 2).

A standard multiple regression model, including both varus thrust and static alignment as potential predictors of the cumulative score for size of BMLs in the tibiofemoral joint was made. The Variance Inflation Factor (VIF) to assess multicollinearity of the two independent variables was 1.024 and thus well below the cut-off of 10. Both static alignment and varus thrust remained significantly associated with the **cumulative score for size of BMLs in the tibiofemoral joint** (p = 0.039 and p = 0.049, respectively) and these alignment variables together explained, 20% of its variance.

3.2. Association between knee frontal plane alignment at baseline and <u>changes</u> in structural features over a period of 2 years

The magnitude of varus thrust at baseline was significantly associated with an increase in the score for **presence of meniscal macerations** over two years (Table 2). No other associations were found between baseline varus thrust magnitude and changes in structural features over 2 years (Table 2). Considering frontal plane static alignment no associations were detected between baseline measures and changes in any of the structural feature over 2 years (Table 2).

Table 2. Associations between knee joint frontal plane (static and dynamic) alignment and structural features on MRI

	Independent variables							
	with structural features at <u>baseline</u>				*with <u>changes</u> in structural features over 2 years*			
	Varus thrust		**Static alignment**		**Varus thrust**		**Static alignment**	
Dependent variables **Structural MRI features**	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Bone Marrow Lesions and cysts								
Amount of BMLs	0.194	0.206	**0.368**	**0.012†**	0.2	0.216	0.141	0.373
Cum score for size of BMLs	**0.34**	**0.024†**	**0.352**	**0.016†**	0.004	0.983	0.014	0.93
Cartilage lesions								
Amount of cartilage lesions	0.061	0.693	0.182	0.226	0.049	0.762	0.03	0.85
Cum score for size of cartilage loss	0.087	0.575	0.212	0.157	0.011	0.946	-0.047	0.769
Cum score for % full-thickness cartilage loss	-0.002	0.992	**0.302**	**0.042†**	-0.004	0.979	0.068	0.671
Meniscal lesions								
Presence of extrusion	0.035	0.823	0.156	0.301	0.005	0.976	-0.208	0.187
Presence of increased signal	0.042	0.801	-0.191	0.231	-0.09	0.58	0.032	0.842
Presence of tear	0.192	0.213	0.138	0.359	-0.196	0.228	-0.119	0.453
Presence of maceration	0.117	0.448	**0.443**	**0.002†**	**0.504**	**0.001†**	0.236	0.132
Synovitis and effusion								
Score for size of effusion (score 0-3)	0.062	0.691	0.105	0.489	0.277	0.083	0.008	0.962
Cum score for presence of synovitis + size effusion (0-6)	-0.012	0.943	0.242	0.123	0.17	0.295	-0.035	0.824
Score for presence of synovitis and/or effusion (0-2)	0.038	0.807	0.162	0.281	0.11	0.5	-0.047	0.766

BML=Bone Marrow Lesion; Cum = Cumulative.
†Significant association based on regression analysis (*P* < 0.05)

3.3. Association between knee frontal plane alignment at baseline and clinical characteristics at baseline

No significant associations were found between any of the static or dynamic (varus thrust magnitude) measures of frontal plane knee alignment, and self-reported pain, symptoms and physical function as measured with KOOS subscale ADL (Table 3). Similarly, neither static, nor dynamic alignment showed significant associations with performance-based physical function as measured by the TUG and SCT, (Table 3).

3.4. Association between knee frontal plane alignment at baseline and changes in clinical characteristics over a period of 2 years

Neither the magnitude of varus thrust nor frontal plane static alignment at baseline showed any significant associations with the changes in any of the self-reported pain, symptom, and physical function, as measured with the KOOS subscales over 2 years follow-up (Table 3). Identical results were found for the baseline static alignment and varus thrust at baseline, with 2-years changes in measures of physical function, as measured with TUG and SCT (Table 3).

Table 3. Associations between knee joint frontal plane (static and dynamic) alignment and clinical and functional characteristics

	Independent variables							
	with structural features at <u>baseline</u>				*with <u>changes</u> in structural features over 2 years*			
	Varus thrust		Static alignment		Varus thrust		Static alignment	
Dependent variables	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Pain and other symptoms								
KOOS pain	0.017	0.91	0.046	0.763	-0.014	0.927	-0.111	0.469
KOOS symptoms	-0.001	0.997	0.132	0.381	0.015	0.923	-0.049	0.748
Physical performance								
KOOS ADL	0.069	0.657	0.072	0.636	-0.08	0.62	-0.141	0.366
TUG	-0.031	0.844	-0.093	0.539	-0.077	0.622	0.102	0.506
SCT	-0.03	0.846	-0.087	0.567	-0.09	0.569	0.072	0.642

OA=osteoarthritis; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; TUG = Timed Up and Go; SCT = Stair Climbing Test.
†Significant association based on regression analysis ($P < 0.05$)

4. Discussion

To the best of our knowledge, this is the first study to assess the associations between the magnitude of varus thrust and static alignment, both, with structural features associated with medial knee OA detected on MRI both cross-sectionally and longitudinally. The main findings of the present study were that both static and dynamic (as measured by varus thrust) alignment in the frontal plane were significantly associated with OA related tibiofemoral joint structural abnormalities detected on MRI, at the time of entry. Another finding of the current study was that only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years. In contrast, none of the static and dynamic measures of knee joint alignment were associated with any clinical or functional characteristics of the subjects.

4.1. Association between knee frontal plane alignment at baseline and structural features associated with knee OA

The role of static varus alignment in the incident and progression of knee OA have been reported before [9, 33]. In a study on the effect of baseline static alignment on progression of knee OA, in a group of patients with established medial knee OA, varus alignment at baseline was reported to be associated with a 4-fold increase in the odds of medial progression [8]. Also, regarding dynamic alignment, a previous report suggests an association between presence of thrust during walking, with structural progression of knee OA detected on plain radiographs [13]. During walking, even in a neutrally aligned knee, the transmission of load is in favor of the medial compartment, due to the ground reaction force passing medial to the knee joint [34, 35]. An increase in (static/dynamic) varus alignment of the knee, further increases the total load passing medial to the joint, during walking [36]. Varus thrust, as the sudden worsening of the varus angle during the stance phase of gait, results in a shift of the GRF towards the medial compartment of the knee, with each step. As a result a shift in loading occurs, and an extra load will be exerted on (medial) regions in the cartilage that have not been adapted to the high loads that occur at heel strike [14]. Previous reports showed positive associations between magnitude of varus thrust and external knee adduction moment in a group of subjects with and without symptomatic knee OA [32], as well as in a group of subjects with early and established medial knee OA [17]. It has been demonstrated that those with elevated KAM showed higher prevalence of bone marrow lesions in the medial compartment, a feature that has also been associated with knee pain [18-22]. Previous reports illustrated that BMLs increased the risk of joint

space loss [37]. This suggests that BMLs could be a strong indicator of the structural deterioration related to knee OA, and that their relationship to disease progression could be explained, to some extent, by their association with limb static and dynamic (mal)alignment [37]. The relationship between varus thrust and BMLs shows its possible indirect effect on development of joint space narrowing after 2 years, considering the strong association between BMLs and joint space loss on radiographs [37]. In a diseased knee this may result in meniscal macerations. The main finding of the current study that higher values of baseline varus thrust and varus static alignment were significantly associated with larger size of bone marrow lesions in the tibiofemoral joint, confirms the role of dynamic and static (mal)malalignment in the structural abnormalities associated with knee OA.

4.2. Association between knee fontal plane alignment at baseline and clinical characteristics associated with knee OA

Previous reports showed higher values of knee pain in subjects with varus thrust as detected by visual observation, but the present study could not confirm these results [16]. Lo et al, reported significantly higher knee pain, especially during weight-bearing and standing, in a group of subjects "with definite varus thrust" compared to a group of "without definite varus thrust" [16]. A possible explanation for this controversy might be related to differences in methodology. In the current study, participants were restricted to women with medial tibiofemoral knee OA only, but this was not the case in the study of Lo et al [16]. In the study by Lo et al, both male and female subjects were tested, which might affect the results as they reported higher number of males in the group of subjects with definite varus thrust [16].

In the present study, we did not find significant associations between the magnitude of varus thrust at baseline with physical function, as measured by KOOS, TUG, and the SCT at baseline and their changes over 2 years follow-up. Similarly, in a study by Chang et al, the presence of varus thrust at baseline, as detected by observation, did not significantly predict poor physical function, as assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale for physical function and the chair-stand performance [13]. The current study, adds to the existing literature by showing that varus thrust, apart from its effect on KAM, is directly associated with increased bone marrow lesions.

There are some limitations of this study that should be taken into account. First, in the current study barefoot walking has been chosen in order to obtain a better tracking of the markers of the motion analysis system, however this limits generalization of the results. Therefore, our results may not

apply to all real–life walking conditions, where shoes are worn. Second, as only women were included in this study, generalization of the current results to men should be treated with care. Finally, thurst as observed, may be different from thrust as measured as it is hard to distinguish actual thrust from a combined flexion rotation movement. To the best of our knowledge no study to date specifically addressed this issue in knee OA population, despite disagreements between biomechanists and clinicians. At the same time, this phenomenon seems to happen and it could still be clinically relevant.

5. Conclusion

The key finding of this study is that <u>both frontal plane dynamic and static alignment</u>, are associated with structural abnormalities in patients with medial knee OA. Therefore, results from the current study highlight the role of frontal plane static and dynamic alignment in the disease process and hence, suggested that attempts for therapy are probably more successful when efforts are made to correct alignment, as well.

Acknowledgements

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Chapter 8

Identification of Progressors in medial knee osteoarthritis based on structural, clinical, and functional changes over two-years follow-up

Abstract

To identify prognostic factors for progression of knee OA, by evaluation of structural, clinical, and biomechanical characteristics of women with medial knee OA at the time of study entry. In this longitudinal study, we included subjects with both early and established medial knee OA and studied their structural, clinical, and functional changes over two years. Progression criteria were defined, and for each progression criterion (structural, clinical, and functional), two groups of subjects, namely, fast and slow progressors, were defined. The baseline characteristics between the fast and slow progressors were compared. Results showed that, compared to slow-progressors, fast progressors identified: 1) based on structural deterioration, had more and larger BMLs and meniscal lesions; 2) based on clinical criteria (pain) as well as self-reported function showed weaker quadriceps and hamstrings, as well as higher second peak knee adduction moment at baseline compared to slow progressors; 3) based on performance-based physical function, showed higher percentage of subjects with meniscal tears in this group, compared to the slow progression group. Based on our findings, we were able to identify fast-progressors based on different progression criteria, and each group was linked with different baseline risk factors. Also, our results further highlights the role of clinical characteristics of patients with knee OA, such as pain and self-reported physical function, in evaluation of disease progression.

1. Introduction

Knee osteoarthritis (OA) is one of the most common causes of disability in the elderly [1]. Prevention of the development of knee osteoarthritis and of progression of the disease is therefore a key objective. Hence, knowledge of factors associated with progression of knee osteoarthritis is of paramount importance as only a limited number of the patients progress rapidly [2, 3]. Leyland et al. for example described subjects in whom the disease progressed slowly to unilateral or bilateral (radiographic) OA over a time period of 15 years, while in others the disease progressed to bilateral (radiographic) OA in only 5 years [4]. The most valid clinical endpoint of knee OA is total knee replacement [5], a costly surgery, that imposes huge burden on the society and medical system [6, 7]. But not all patients with knee OA end up having their knee replaced.

The need to identify subjects at higher risk of progression or in other words fast progressors is of great importance, as they could be targeted for more specific management strategies, to improve their prognosis and possibly delay or avoid knee replacement surgery. Studies to date have assessed progression mainly in terms of structural changes detected on radiography, resulting in an increase in K&L grade[8, 9]. Structural joint damage is typically monitored by joint space narrowing (JSN) from plain radiographs. Since JSN has limited sensitivity to change [10-12], large study populations are required. As an alternative to JSN for monitoring progression of knee OA, clinical and functional markers may provide a useful substitute.

Several factors such as body mass index (BMI), bone marrow lesions (BMLs), meniscal lesions, lower limb muscle strength, dynamic and static alignment, and external knee adduction moment (KAM) (an indirect measure of medial joint loading) have been associated with the progression of knee OA [13-20]. The aforementioned risk factors have been associated with structural progression but, so far, there has been no research on the effect of these factors on clinical and functional progression of knee OA.

Therefore, in this longitudinal study, we included patients with both early and established medial knee OA and we studied structural, clinical, and functional changes over two years. We classified subjects into two groups of fast and slow progressors, first, based on their structural changes over 2 years as detected on plain radiography (K&L grading); second, based on their clinical changes (pain) over 2 years follow-up; third, based on their changes in self-reported physical function over 2 years; and lastly, based on their changes over two years in performance-based physical function. Next, we

compared the baseline characteristics between fast and slow progressors, for each category, separately. Our objective was to identify structural, clinical, and biomechanical factors associated with structural, clinical, and functional progression of knee OA over 2 years in women with early and established medial knee OA.

2. Materials and Methods

Forty-nine women with symptomatic medial knee OA, participated in this study. The radiographs, MRI scans, outcome measures, and functional tests for this study were acquired at baseline (BL) and at follow-up after 2 years (2YFU). Subjects were recruited by a rheumatologist or orthopedic surgeon at the University Hospitals Leuven during their routine ambulatory consultations. Current research was conducted in compliance with the Helsinki Declaration and was approved by the ethical committee for Biomedical Sciences of the KU Leuven in Belgium. Written informed consent was obtained from each participant prior to testing.

The inclusion criteria for the *early OA* group were: presence of knee pain, Kellgren and Lawrence grades of 0, 1 or 2⁻ (only osteophytes) on standard radiographs, and at least one of the two following findings: arthroscopic findings of cartilage lesions or MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or sub-chondreal bone marrow lesions (BMLs) [21]. Subjects were included in the *established OA* group, based on the slightly adapted American College of Rheumatology (ACR) Classification criteria [22]. These criteria were knee pain on most days of the last month and one of the following findings: age above 50, crepitation during active movements, morning stiffness less than 30 minutes, together with structural changes defined as minimum a grade 2⁺ on the K&L scale. In general, subjects were excluded if they had: musculoskeletal disorders other than knee OA in both lower limbs in the last six months, previous surgery of lower extremities or low back, chronic intake of corticoids or specific contra-indications for MRI and neurological disorders.

2.1. Knee radiographic assessment

For each subject, a standard anterior-posterior weight-bearing radiograph of was taken of each knee joint in a fixed flexed position (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30). The presence

and severity of structural knee OA was confirmed by a single experienced observer (FPL), based on the Kellgren & Lawrence grading system with recent adjustments [23]. The high intra- and inter-rater reliability of the K&L scale have been assessed and reported previously ($r<0.85$) [24]. The most affected side of the OA patients, and the side with K&L grade 0 for the control subjects, was selected for further analysis.

2.2. Knee MRI protocol and analysis

An MRI of the most affected knee was performed, for each subject, on a 3.0 Tesla scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) by using an eight-channel phased array knee coil in a non-weight bearing supine position as described by Baert et al [25]. Furthermore, semi-quantitative scoring of specific structural features in the tibiofemoral joint was performed separately by two readers (NN, GVDS) using the standardized Boston-Leeds Osteorathritis Knee Score scoring system [26]. For 91% of all scored items full agreement between both readers was achieved, while disagreements were resolved through consensus.

2.4. Pain, symptoms and physical function assessment

All participants completed the Dutch version of the Knee Injury and Osteoarthritis Outcome Score (KOOS). This version has been shown to be valid and reliable for patients with knee OA [31]. The KOOS has five distinct sections. To evaluate symptoms, the subscales 'pain' and 'symptoms' were used. The 'Activities of Daily Living' (ADL) section was used to estimate participants' subjective physical function. A converted score from 0 to 100 was computed for each subscale, with 100 indicating the best possible result.

Performance-based physical function was assessed by means of two functional tests: The 'Stair Climbing Test' (SCT) assessed the time needed to go up five steps, turning around and go down the same five steps. The 'Timed Up & Go test' (TUG) quantified the required time to stand up from a chair, walk three meters, turn around, walk back to the chair and sit down. To determine the final value, an average of three trials for each test was calculated. These tests have good reliability and validity [32, 33].

2.5. Muscle strength

Maximal voluntary muscle strength was assessed using the Biodex System 3 Pro (Biodex Medical Systems, Shirley, NY, USA). All measurements were performed according to standard procedures and the Biodex system was calibrated before every test session [27]. Muscle strength was measured for knee extension and flexion isometrically at two different knee angles (60º and 90º knee flexion). Each test was performed three times with a maximal contraction for 5s. Between trials, 10s of rest was given. Between the tests at different angles the patient had 30s rest. Additionally, isokinetic knee extension was measured at two different slow (60º/sec) and fast (240º/sec) speeds. All subjects received the same instructions and verbal encouragement to achieve a maximal effort. For each test, the peak torque normalized to body mass (Nm/kg) was used for analysis. The highest peak torque over three trails was recorded. All data were corrected for gravity and weight.

Assessment of frontal plane static alignment

The static alignment of the knee joint was assessed by an experienced musculoskeletal radiologist on full-leg AP weight-bearing plain radiographs of the lower extremities [19]. Malalignments of less than -2 ° or more than +2 ° were categorized as valgus or varus alignment respectively. Knee alignment between -2° and +2° was classified as neutral [28, 29].

2.6. Assessment of dynamic alignment and loading during the stance phase of gait

A 3D motion analysis system (Krypton, Metris and Vicon Nexus, Oxford Metrics Group) was used to record the spatial position of markers on relevant body segments at 100 samples/s.

Ground reaction forces were recorded through force plates (Bertec Corporation, Ohio, USA and AMTI, Watertown, MA, USA) placed in a 12m walkway at a sample rate of 1000 samples/s. Participants walked along the walkway at a comfortable habitual speed during gait analysis. To avoid force plates being targeted while performing the trials, no guidance on walking, except the instruction to 'walk naturally' was provided. Three complete force plate strikes for each foot were registered. Since footwear can affect the distribution of loads on the joints in the lower quadrant [30], all participants were asked to walk bare-footed. The "heel-strike" event was detected as the first sample of the vertical ground reaction force that was above 10 N. The "toe-off" event was chosen as the first sample at which the vertical ground reaction force was below 10N [31]. 3D Cardan angles of the knee were calculated using the decomposition order according to Grood & Suntay [32]. The external knee

adduction moment (KAM) was calculated through a bottom-up dynamic linked segment model, using kinematics of the body segments and the ground reaction forces [33]. To obtain the knee adduction moment from the 3D components of the net moments, the knee moments were projected onto the calf coordinate system. The external knee adduction moment was normalized to body mass. The gait analysis protocol was described in more details in a previous study of our group [34]. The first and second peak KAM during the stance phase of gait were detected and used for further comparison between groups of fast and slow progressors (Figure 1).

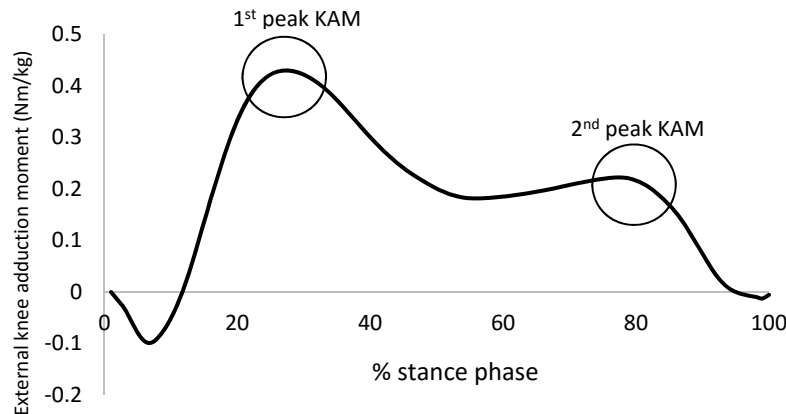**Figure 1.** First and second peak knee adduction moment for a representative patient during the stance phase of gait.

Dynamic alignment was measured via Varus thrust, and was calculated as the difference between the knee adduction angle at heel strike and the first maximum knee adduction angle during the stance phase of gait [20, 35] (Figure 2).
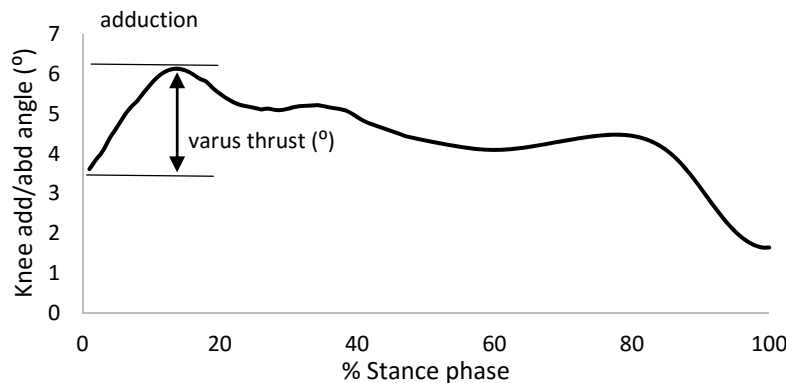
Figure 2. Varus thrust magnitude during the stance phase of gait.

2.3. Assessment of OA progression

Medial tibiofemoral OA progression was defined based on structural, clinical, and functional changes over two years separately. For the structural progressors, the K&L grading system was used and progression was defined as any worsening in the grade for radiographic medial joint space between baseline and 2 years [36]. Regarding clinical progressors, self-reported pain (pain subscale of KOOS) was used and subjects who declined by ten points on their KOOS pain subscale, were categorized as fast progressors [37]. To categorize patients based on functional progression, first, a self-reported measure of physical function (KOOS subscore of ADL) was used for the identification of fast progressors, and patients with 10 points drop over two years (worse physical function over two years) were categorized as fast progressors [37]. Second, patients were categorized based on decline in physical function, which was assessed by the TUG and SCT. Here, subjects with a 20% decline (more time spent to perform the task after 2 years) in the TUG or/and SCT, were categorized as fast-progressors.

2.6. Statistical analysis

Statistical analysis was performed using SPSS software (version 20, 2006, Chicago: SPSS Inc). Descriptive statistics were used to report clinical characteristics of subjects at the time of entry. For each progression criterion (structural, clinical, and functional), two groups of subjects, namely, fast and slow progressors, were defined. Differences in MRI features between the fast and slow progressors were tested with Fisher exact test or Mann-Whitney *U* test. To test for group differences between fast and slow progressors for baseline measures of static alignment as well as for the KOOS subscores, the Mann-Whitney *U* test was used. For BMI, dynamic alignment, muscle strength, and dynamic loading an independent sample's t-test was used. The level of significance was set at $P<0.05$.

3. Results

3.1. Patients characteristics

Forty-nine women with a mean BMI of 27.17 (SD = 0.7) kg/m² and mean age of 68 (SD = 0.9) years were included in the analysis. Subjects' characteristics are presented in detail in Table 1. Comparing fast-progressors based on different classification criteria, showed that one of the subjects were

common between structural, clinical (pain), and functional (self-reported) fast-progressors. Eight subjects were categorized both as clinical (pain) and functional (self-reported) fast-progressors. Also, one subject was common between the two groups of structural and functional (performance-based) fast-progressors. No subjects were identified as functional fast-progressor, based on both self-reported and performance-based measures of physical function.

Table 1. Characteristics of the study population (n = 49)

	Mean (SD)[a] or Median (IQR)[b] or n (%)[c]	Range	95% CI of the mean
Weight (kg)	70.87 (1.8)[a]	51.2 – 98.1	67.29 – 74.44
BMI (kg/m²)	27.26 (0.7)[b]	20.57 – 36.98	25.89 – 28.62
Height (m)	1.61 (0.01)[a]	1.48 – 1.77	1.59 – 1.63
Age (years)	66.91 (0.8)[a]	55 - 81	65.21 – 68.61
K&L score (MC)			
K&L 0	15 (27%)[c]		
K&L 1	16 (29%)[c]		
K&L 2⁻	3 (6%)[c]		
K&L 2⁺	15 (27%)[c]		
K&L 3	6 (11%)[c]		
Static alignment			
Neutral	27 (60%)[c]		
Valgus	5 (11%)[c]		
Varus	13 (29%)[c]		

SD = Standard Deviation; IQR = Inter Quartile Range; CI = Confidence Interval; BMI = Body Mass Index; MC = Medial Compartment; K&L = Kellgren & Lawrence (range 0-4); K&L 1 = Doubtful narrowing of joint space and possible osteophytic lipping, K&L 2⁻ = Definite osteophytes without joint space narrowing; K&L 2⁺ = Definite osteophytes with joint space narrowing, K&L 3 = Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour.

3.2. Baseline characteristics of fast versus slow progressors based on the K&L grading system

Ten subjects (18%) with either early or established medial knee OA worsened in the K&L score after two years compared to baseline, and were categorized as fast progressors. The baseline characteristics of the fast and slow progressors are shown in Table 2. The fast progressor group showed at baseline significantly more and larger tibiofemoral joint BMLs, more subjects with meniscal extrusion and meniscal maceration, and finally worse self-reported QoL, as measured with the KOOS QoL subscale (table 2).

Table 2. Structural, clinical, and functional characteristics at baseline in patients with slow and fast structural progression of knee OA over 2 years

	slow progressors	fast Progressors	P Group
Demographics	(n = 39)	(n = 10)	
Weight (kg)	70.77 (11.8)	71.29 (8.2)	0.895
BMI (kg/m²)	26.94 (4.3)	27.91 (3.5)	0.513
Height (m)	1.62 (0.1)	1.6 (0.1)	0.359
Age (years)	67.09 (5.5)	67.7 (5.3)	0.755
Bone Marrow Lesions and cysts[a]			
Number of BMLs TF	0 (2)	2.5 (3)	**0.026***
Cum score for size of BMLs TF	0 (4)	5 (6)	**0.019***
Cartilage lesions[a]			
Number of cartilage lesions TF	3 (2)	3 (2)	0.515
Cum score for size of cartilage loss TF	6 (4)	5.5 (2)	0.511
Cum score for % full-thickness cartilage loss TF	2 (3)	2.5 (5)	0.105
Meniscal lesions[b]			
Presence of extrusion	27 (60%)	10 (100%)	**0.021***
Presence of increased signal	9 (20%)	1 (10%)	0.426
Presence of tear	26 (58%)	9 (90%)	0.076
Presence of maceration	8 (18%)	5 (50%)	**0.038***
Synovitis and effusion[a]			
Score for size of effusion (score 0-3)	0 (1)	0 (2)	0.736
Cum score for presence of synovitis + size effusion (0-6)	1 (2)	0 (2)	0.977
Score for presence of synovitis and/or effusion (0-2)	1 (1)	0 (1)	0.584
Muscle strength[c]			
Knee extension 60	1.41 (0.4)	1.39 (0.3)	0.879
Knee flexion 60	0.68 (0.2)	0.66 (0.1)	0.782
Knee extension 90	1.5 (0.5)	1.35 (0.3)	0.350
Knee flexion 90	0.58 (0.2)	0.60 (0.1)	0.719
Knee extension 60°/sec	1.13 (0.3)	0.92 (0.3)	0.098
Knee extension 240°/sec	0.61 (0.2)	0.58 (0.1)	0.697
Clinical characteristics			
BMI[c]	26.95 (4.3)	27.91 (3.5)	0.513
KOOS pain[a]	86.1 (22.9)	80.55 (27.8)	0.508
KOOS symptoms[a]	85.7 (21.4)	73.2 (18.7)	0.283
Physical function			
KOOS ADL[a]	89.7 (23.9)	87.45 (27.3)	0.284
KOOS QoL[a]	78.1 (56.3)	53.1 (23.4)	**0.049***
SCT[c]	5.91 (1.3)	5.97 (1.2)	0.910
TUG[c]	5.89 (1.3)	5.98 (1.3)	0.853
Frontal plane alignment			
Varus thrust[c]	2.76 (2)	3.02 (1.4)	0.719
Static alignment[b] varus:	11 (24%)	4 (40%)	0.412
Frontal plane dynamic loading[c]			
1st peak KAM[c]	0.50 (0.1)	0.55 (0.2)	0.368
2nd peak KAM[c]	0.30 (0.1)	0.36 (0.1)	0.153

Cum = Cumulative; BML=Bone Marrow Lesion; TF = TibioFemoral; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; SCT = Stair Climbing Test; TUG = Timed Up and Go; KAM = external Knee Adduction Moment.
Data are presented as [a]Median (IQR), [b]frequencies or [c]Mean (SD).
*Significant association based on regression analysis ($P < 0.05$)

3.3. Baseline characteristics of fast versus slow progressors based on pain score

Eleven patients (20%) showed increased self-reported pain levels as measured by KOOS pain subscale. As shown in table 3, fast progressors (based on pain) had lower isometric and isokinetic quadriceps strength than slow progressors. Also, they had lower isometric hamstring strength. In addition, the second peak knee adduction moment was significantly higher in the fast progressors compared to the slow progressors (Table 3). No other significant differences were found for baseline structural, clinical, or functional characteristics (Table 3).

Table 3. Structural, clinical, and functional characteristics at baseline in patients with slow and fast clinical progression of knee OA (based on pain exacerbation over 2 years)

	slow progressors	fast Progressors	*P Group*
	(n = 38)	(n = 11)	
Demographics			
Weight (kg)	69.97 (11.5)	74.72 (9.5)	0.216
BMI (kg/m^2)	26.85 (4.1)	28.45 (4.2)	0.262
Height (m)	1.61 (0.1)	1.62 (0.1)	0.650
Age (years)	67.17 (5.1)	66.91 (6.9)	0.890
Bone Marrow Lesions and cysts[a]			
Amount of BMLs TF	1 (3)	1 (2)	0.991
Cum score for size of BMLs TF	1 (5)	1 (4)	0.833
Cartilage lesions[a]			
Amount of cartilage lesions TF	3.5 (2)	3 (1)	0.446
Cum score for size of cartilage loss TF	6 (4)	6 (2)	0.337
Cum score for % full-thickness cartilage loss TF	2 (3)	2 (2)	0.444
Meniscal lesions[b]			
Presence of extrusion	28 (64%)	9 (82%)	0.379
Presence of increased signal	7 (16%)	2 (18%)	0.794
Presence of tear	26 (57%)	9 (82%)	0.197
Presence of maceration	11 (25%)	2 (18%)	0.556
Synovitis and effusion[a]			
Score for size of effusion (score 0-3)	0 (1)	0 (0)	0.269
Cum score for presence of synovitis + size effusion (0-6)	1 (2)	0 (2)	0.536
Score for presence of synovitis and/or effusion (0-2)	1 (1)	0 (1)	0.481
Muscle strength[c]			
Knee extension 60	1.46 (0.4)	1.23 (0.4)	0.082
Knee flexion 60	0.72 (0.2)	0.52 (0.2)	**0.007***
Knee extension 90	1.56 (0.5)	1.96 (0.4)	**0.02***
Knee flexion 90	0.61 (0.2)	0.48 (0.1)	**0.025***
Knee extension 60º/sec	1.13 (0.4)	0.95 (0.3)	0.134
Knee extension 240º/sec	0.64 (0.2)	0.49 (0.2)	**0.012***
Clinical characteristics			
BMI[c]	26.85 (4.1)	28.45 (4.2)	0.262
Physical function			
KOOS ADL[a]	88.2 (28.4)	89.7 (11.8)	0.955
KOOS QoL[a]	75 (45.4)	62.5 (62.5)	0.903
SCT[c]	5.78 (1.3)	6.40 (1.2)	0.156
TUG[c]	5.76 (1.3)	6.37 (1.2)	0.166
Frontal plane alignment			
Varus thrust[c]	2.96 (2.1)	2.31 (0.8)	0.388
Static alignment[b] varus:	11 (25%)	3 (27%)	0.823
Frontal plane dynamic loading			
1st peak KAM[c]	0.49 (0.1)	0.59 (0.1)	0.072
2nd peak KAM[c]	0.29 (0.1)	0.39 (0.1)	**0.024***

Cum = Cumulative; BML=Bone Marrow Lesion; TF = TibioFemoral; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; SCT = Stair Climbing Test; TUG = Timed Up and Go; KAM = external Knee Adduction Moment.
Data are presented as [a]Median (IQR), [b]frequencies or [c]Mean (SD).
*Significant association based on regression analysis ($P < 0.05$)

3.4. Baseline characteristics of fast versus slow progressors based on decline in self-reported physical function

Table 4 present baseline structural, clinical, and functional characteristics of patients with fast and slow progression over two years based on decline in self-reported physical function. Compared to slow progressors, the fast progressors showed significantly lower isometric and isokinetic quadriceps strength and lower isomentric hamstrings strength (Table 4). Moreover, fast progressors demonstrated a higher second peak external knee adduction moment compared to the slow progressors (Table 4).

Table 4. Structural, clinical, and functional characteristics at baseline in patients with slow and fast progression of knee OA (based on decline in self-reported physical function)

	slow progressors	fast Progressors	*P Group*
Demographics	(n = 38)	(n = 10)	
Weight (kg)	70.64 (11.8)	72.58 (9.5)	0.619
BMI (kg/m^2)	26.93 (4.3)	28.12 (4)	0.408
Height (m)	1.62 (0.1)	1.61 (0.1)	0.636
Age (years)	66.73 (4.8)	68.55 (7.8)	0.338
Bone Marrow Lesions and cysts[a]			
Amount of BMLs TF	1 (3)	1 (1)	0.81
Cum score for size of BMLs TF	1 (6)	1 (1)	0.756
Cartilage lesions[a]			
Amount of cartilage lesions TF	3 (2)	3 (2)	0.733
Cum score for size of cartilage loss TF	6 (4)	6 (4)	0.878
Cum score for % full-thickness cartilage loss TF	2 (3)	2 (2)	0.916
Meniscal lesions[b]			
Presence of extrusion	27 (61%)	9 (82%)	0.356
Presence of increased signal	7 (16%)	2 (18%)	0.823
Presence of tear	25 (57%)	8 (73%)	0.53
Presence of maceration	11 (25%)	2 (18%)	0.531
Synovitis and effusion[a]			
Score for size of effusion (score 0-3)	0 (1)		0.118
Cum score for presence of synovitis + size effusion (0-6)	1 (2)	0 (0)	0.229
Score for presence of synovitis and/or effusion (0-2)	1 (1)	0 (0)	0.157
Muscle strength[c]			
Knee extension 60[a]	1.47 (0.4)	1.18 (0.4)	**0.031***
Knee flexion 60[a]	0.71 (0.2)	0.54 (0.2)	**0.015***
Knee extension 90[a]	1.56 (0.5)	1.19 (0.4)	**0.023***
Knee flexion 90[a]	0.6 (0.2)	0.51 (0.1)	0.085
Knee extension 60°/sec[a]	1.12 (0.4)	0.96 (0.3)	0.186
Knee extension 240°/sec[a]	0.63 (0.2)	0.49 (0.2)	**0.025***
Clinical characteristics			
BMI[c]	26.93 (4.3)	28.13 (4)	0.408
KOOS pain[a]	86.1 (26.4)	86.1 (25)	0.954
KOOS symptoms[a]	82.1 (23.2)	85.7 (21.4)	0.448
Physical function			
SCT[c]	5.76 (1.2)	6.46 (1.3)	0.11
TUG[c]	5.74 (1.2)	6.44 (1.4)	0.115
Frontal plane alignment			
Varus thrust[c]	2.86 (2.1)	2.57 (0.9)	0.69
Static alignment[b]	10 (20%)	4 (36%))	0.516
Frontal plane dynamic loading			
1st peak KAM[c]	0.49 (0.1)	0.57 (0.2)	0.178
2nd peak KAM[c]	0.29 (0.1)	0.39 (0.1)	**0.025***

Cum = Cumulative; BML=Bone Marrow Lesion; TF = TibioFemoral; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; SCT = Stair Climbing Test; TUG = Timed Up and Go; KAM = external Knee Adduction Moment.
Data are presented as [a]Median (IQR), [b]frequencies or [c]Mean (SD).
*Significant association based on regression analysis ($P < 0.05$)

3.5. Baseline characteristics of fast versus slow progressors based on performance-based physical function

For both TUG and SCT seven patients (same patients) showed 20% decline in function (more time spent to accomplish each task) after 2 years and table 5 summarizes the baseline characteristics of the fast versus slow progressors. The percentage of subjects with meniscal tears was higher in the fast progression group compared to the slow progression group. No other structural, clinical, or functional characteristics were significantly different between groups at baseline (Table 5).

Table 5. Structural, clinical, and functional characteristics at baseline in patients with slow and fast progression of knee OA (based on 20% decline in performance-based physical function)

	slow progressors	fast Progressors	*P Group*
Demographics	(n = 42)	(n = 7)	
Weight (kg)	70.88 (11.1)	68.93 (5.1)	0.653
BMI (kg/m^2)	27.23 (4.1)	26.01 (2.9)	0.459
Height (m)	1.61 (0.1)	1.63 (0.1)	0.520
Age (years)	67.45 (5.4)	65 (6.2)	0.281
Bone Marrow Lesions and cysts[a]			
Amount of BMLs TF	0.5 (2)	2 (3)	0.408
Cum score for size of BMLs TF	0.5 (5)	4 (3)	0.665
Cartilage lesions[a]			
Amount of cartilage lesions TF	3 (2)	3 (3)	0.743
Cum score for size of cartilage loss TF	6 (4)	6 (6)	0.74
Cum score for % full-thickness cartilage loss TF	2 (2)	2 (4)	0.652
Meniscal lesions[b]			
Presence of extrusion	30 (63%)	6 (86%)	0.31
Presence of increased signal	8 (17%)	1 (14%)	0.768
Presence of tear	27 (56%)	7 (100%)	**0.039***
Presence of maceration	11 (23%)	2 (28%)	0.815
Synovitis and effusion[a]			
Score for size of effusion (score 0-3)	0 (1)	0 (1)	0.494
Cum score for presence of synovitis + size effusion (0-6)	1 (2)	0 (2)	0.632
Score for presence of synovitis and/or effusion (0-2)	1 (1)	0 (2)	0.875
Muscle strength[c]			
Knee extension 60	1.43 (0.4)	1.3 (0.4)	0.425
Knee flexion 60	0.69 (0.2)	0.55 (0.2)	0.109
Knee extension 90	1.51 (0.5)	1.24 (0.5)	0.16
Knee flexion 90	0.59 (0.2)	0.52 (0.1)	0.283
Knee extension 60^0/sec	1.12 (0.3)	0.96 (0.4)	0.264
Knee extension 240^0/sec	0.62 (0.2)	0.49 (0.2)	0.101
Clinical characteristics			
BMI[c]	27.41 (4.3)	26.01 (1)	0.405
KOOS pain[a]	86.1 (27.1)	75 (18)	0.27
KOOS symptoms[a]	85.7 (21.4)	78.5 (19.7)	0.657
Physical function			
KOOS ADL[a]	89.7 (27.3)	85.2 (19.2)	0.555
KOOS QoL[a]	75 (54.7)	56.2 (31.3)	0.318
Frontal plane alignment			
Varus thrust[c]	2.89 (1.9)	2.39 (1.6)	0.564
Static alignment[b] varus:	14 (29%)	1 (14%)	0.328
Frontal plane dynamic loading			
1st peak KAM[c]	0.52 (0.1)	0.38 (0.1)	0.08
2nd peak KAM[c]	0.31 (0.1)	0.22 (0.04)	0.126

Cum = Cumulative; BML=Bone Marrow Lesion; TF = TibioFemoral; KOOS = Knee injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; QoL = Quality of Life; SCT = Stair Climbing Test; TUG = Timed Up and Go; KAM = external Knee Adduction Moment.

Data are presented as [a]Median (IQR), [b]frequencies or [c]Mean (SD).

*Significant association based on regression analysis (*P* < 0.05)

4. Discussion

Very few studies have investigated prognostic factors for fast structural, clinical or functional progressors in patients with medial knee OA. In this longitudinal study, baseline structural, biomechanical, and clinical characteristics of a group of fast progressors (based on different structural, clinical, and functional criteria) were compared to a group of slow progressors, We found that based on the type of progression criterion used, various baseline differences were found. Fast progressors as categorized based on an increase in K&L grade, showed more and larger BMLs in the tibiofemoral joint, higher prevalence of meniscal extrusions and macerations, as well as worse self-reported Quality of Life, as measured with KOOS, at baseline. Fast progressors, as defined based on pain exacerbation over 2 years, showed weaker quadriceps and hamstrings, as well as higher second peak knee adduction moment at baseline compared to slow progressors. Identification of fast progressors based on performance-based physical function, showed higher percentage of subjects with meniscal tears in this group, compared to the slow progression group. Fast progressors, defined based on deterioration in self-reported physical function, demonstrated weaker quadriceps and hamstring muscle strength, as well as higher second peak knee adduction moment in the fast progressor group compared to the slow progressors, at the time of entry.

Despite the similar inclusion and exclusion criteria for all patients in the current study, still different subpopulations of progressors were identified within this group, based on different classification criteria. And, prognostic factors that defined progression of pain, differed from those which defined structural progressors. The presence of structural progression in this study was related to the presence of more and larger BMLs, presence of more meniscal abnormalities, as well as worse self-reported quality of life at the time of entry. Previous reports also showed an association of BMLs as well as meniscal lesions with progression of knee OA [14, 18]. BMLs predispose the knee joint to further joint space loss and potentially play a role in cartilage loss as detected on MRI [38, 39]. An increase in the size of BMLs appears to accelerate cartilage loss [14]. Joint space narrowing (as detected on radiograph) can, apart from cartilage loss, be caused by mescal lesions and extrusion [40], and the presence of higher number of meniscal extrusions and macerations in the group of structurally fast-progressors compared to the slow progressors in the current study, supports a role of meniscal lesions in the progression of structural knee OA.

The role of muscle strength in progression of knee OA is controversial [41]. Barandt et al reported a 9% lower quadriceps muscle strength in women with progressive OA (based on worsening of the

K&L score) compared to the more radiographically stable patients with knee OA [42], although the results were not statistically confirmed. Amin et al [43], using MRI to investigate cartilage loss over 30 months, failed to confirm a relationship between isokinetic quadriceps muscle strength and structural disease progression [43]. In contrast, a study on the effect of quadriceps strength on the risk of joint space narrowing over 30 months demonstrated that women in the lowest tertile of relative isokinetic strength had an increased risk of tibiofemoral joint space narrowing compared to women in the highest strength tertile [16]. A previous report on the association between knee muscle strength and activity limitations related to knee OA, demonstrated that increased knee muscle strength was associated with decreased activity limitations in patients with knee OA, over 2 years [44]. The abovementioned study, also reported that an increased average knee muscle strength was associated with better self-reported physical function [44]. Findings of the current study showed no significant difference in muscle strength between fast and slow progressors as categorized based on radiographic worsening. But, when the fast and slow progressors were classified based on clinical and functional deterioration over 2 years, lower quadriceps and hamstring muscle strength were found in the fast progressing patient group. This might further underline the possible role of muscle strength in the functional deterioration associated with knee osteoarthritis [15].

The external knee adduction moment is an indirect measure of medial knee joint loading [45]. The peak knee adduction moment has been associated with the rate of progression of medial knee OA [17, 46]. Henriksen et al, replicated gait changes associated with knee OA through inducing experimental knee pain [47]. They reported that, experimentally induced pain significantly lowered frontal and sagittal plane knee joint moments during walking, and it was suggested that pain could act as a protective mechanism in this context [47]. This is supported also by previous studies that showed an increase in the peak knee adduction moment with pain relief [48-50]. In our study population, patients with more pain and worse self-reported physical function after two years, or thus the fast clinical and functional progressors, showed a higher second peak external knee adduction moment at the time of entry compared to the slow progressors. This may suggest that the slow progressors had developed a mechanism to protect their knee (lower KAM), which prevented increase in pain over time.

An interesting finding of this study was that subjects who showed self-reported functional decline after two years, were different from the ones who showed functional deterioration based on performance-based measures of function. Research suggests that psychosocial variables, including pain catastrophizing, kinesiophobia and maladaptive pain coping styles have been associated with knee pain and physical performance in knee OA patients [51-54]. OA patients who catastrophize

about pain, who have pain-related fear or who use a maladaptive coping style report more pain and higher levels of physical disability [52, 54]. Although, we did not report results on psychosocial characteristics of fast and slow progressors in this study, the current findings suggest that these factors may be important in explaining variations in progression based on self-reported or performance-based physical function.

There were more subjects with meniscal tears in the latter group. Moreover, fast progressors in self-reported function showed weaker quadriceps and hamstring for isometric measurements at baseline compared to the slow progressors, as well as a higher knee adduction moment during the stance phase of gait. Eight (73%) of 11 subjects who showed functional deterioration, as measured via the KOOS ADL subscore, were also categorized as fast progressors based on the pain exacerbation over 2 years, suggesting a strong correlation between pain and self-reported physical function [55].

Possible predictors of progression found in this study, may help to identify sub-population of patients with knee OA, whose disease is likely to progress over time, as well as in whom the therapeutic intervention is more effective in order to prevent further damage or functional decline. Our findings might suggest that clinical characteristics of patients with knee OA, such as pain and self-reported physical function, and not just structural abnormalities, should be considered in evaluation of knee OA progression. As, these are the main complaints of patients with knee OA and perhaps what makes one to opt for surgery [56].

5. Limitations

There are some limitations of this study that should be taken into account. First, this study only included women with medial knee OA, as osteoarthritis of the knee is more common in women than men, and in the medial compartment than the lateral. Therefore, results from this study cannot be generalized to men and patients with lateral compartment OA. Second, only patients with medial knee OA were included in this study, therefore findings of the current study cannot be generalized to patients with lateral knee OA. The possibility of Type I error is a particular concern in the current study, due to multiple testing. Still, we did not correct the P-value as, we included several variables but not all of them had the same weight in our analysis and we were concerned of a possibility of occurrence of Type II errors due to very low corrected P-values, for some variables. Also, we avoided any P-hacking and reported all significant as well as non-significant results, so that the readers can make their own judgment based on the whole picture and not just some selected results. Another

limitation of this study that has to be considered is that in categorization of subjects into two groups of fast and slow progressors, patients with improvements over two years, based on either classification criterion, were also considered as slow progressors. In the current study, due to small sample size, it was not possible to consider slow progressors and patients improving as separate groups. Perhaps, future longitudinal research, should classify them as such.

6. Conclusion

In this longitudinal study, of 55 women with symptomatic medial knee OA, we identified fast progressors based on either structural worsening, pain exacerbation, or functional deterioration over two years. Our results demonstrated that fast progressors, based on structural criteria, had, more and larger BMLs and meniscal lesions. Fast progressors, based on clinical criteria (pain) as well as self-reported function showed weaker quadriceps and hamstrings, as well as higher second peak knee adduction moment at baseline compared to slow progressors. Fast progressors, based on performance-based physical function, showed higher percentage of subjects with meniscal tears in this group, compared to the slow progression group. Our data may contribute to ongoing efforts to identify a patient at risk to progress fast at the time of diagnosis with early or established OA. Enhanced attention for this patient population with regard to interventions and management may affect the long-term outcome. Based on the findings in our study, there are different progressors as assessed by structural, clinical, and functional criteria, and each may be associated with specific structural, clinical, and biomechanical variables at the time of entry.

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GENERAL DISCUSSION

Overview

Osteoarthritis of the knee is associated with several progressive structural, clinical, and functional abnormalities. While the progressive nature of these changes are well-known, depending on the stage of the disease, some of these abnormalities are irreversible. In contrast, there are changes, in particular at the early stages of the disease that may be arrested or even reversible by risk factor modification. Therefore, assessment of clinical and functional characteristics of early knee OA patients with pre-radiographic structural changes, and the identification of patients at higher risk of disease progression may provide an opportunity for a proactive modification of the course of the disease. This may present the potential for limiting direct but also indirect costs of the disease caused by loss of participation at work, sick leave, lost productivity, premature retirement and life-time burden.

The scope of this doctoral project was to contribute to the knowledge on the <u>objective functional differences</u> and their relation to the clinical and structural characteristics, as well as changes over time, in women with early medial knee OA compared to established medial knee OA and healthy controls. Also, to gain insight into the identification of risk factors associated with progression of knee OA.

This general discussion will give a summary of the main findings of the doctoral project and recommendations for clinical practice along with some critical reflections. At the end, recommendations for future research will be discussed.

Part 1. Cross-sectional studies to further refine the profile of the early and established OA population.

In this part we were interested to assess neuromuscular and clinical characteristics of subjects with early and established medial knee OA, to further characterize the profile of patients at the early stages of the disease.

Objective part I

- To investigate functional (neuromuscular, biomechanical) differences of subjects with early and established medial knee OA compared to the healthy controls.

In **study I**, we tried <u>to evaluate the role of proprioception in postural control of women with early and established medial knee OA compared to control participants</u> by using muscle vibration (1). Proprioceptive and postural control deficits have been reported in patients with knee osteoarthritis (2-6), but limited information was available for the early stage of knee OA. <u>Results showed that women with knee OA, both early and established, demonstrated a stronger ankle-steered proprioceptive postural strategy, during standing, which may lead to decreased postural robustness in this group</u>. The finding suggests a reduced multi-segmental strategy, which might be adequate in stable support conditions but leads to decreased postural robustness in unstable support conditions and more dynamic tasks.

The upweighting of triceps surae information, observed in patients with early knee OA, was in spite of any changes in proprioceptive accuracy in this group, as measured by the active repositioning test, compared to the established OA group. This, might imply that the proprioceptive weighting changes observed in the current study already exists in the early stages of OA, might be more related with movement detection thresholds. This is in agreement with previous findings of increased movement detection thresholds in OA patients irrespective of the stage of the disease and even present in the unaffected knee (3). <u>The absence of differences between two OA groups, regarding changes in proprioceptive weighting, might suggest that this phenomenon is already present in early stages of knee OA rather than a contributing factor for progression of the disease.</u>

In **study II**, we assessed the static knee alignment and varus thrust, as a measure of dynamic alignment, in women with early medial knee OA, and compared it to women with established knee OA and asymptomatic controls. Results revealed that the presence and magnitude of varus thrust is greater in women with early medial knee OA than in healthy controls, similar to the findings in women with established medial knee OA. Although a relation between peak KAM and varus thrust was found, peak KAM was higher compared to control in established OA only.

During walking, even in a neutrally aligned knee, the transmission of load is in favor of the medial compartment, due to the ground reaction force passing medial to the knee joint (7, 8). An increase in the varus alignment of the knee, further increases the total load passing medial to the knee joint, during walking (9). The abnormal motion causes load to be shifted to infrequently loaded areas of the cartilage that cannot accommodate the loads and initiates a cascade of degenerative changes. Thus, loading remains an important consideration in the breakdown of the cartilage, meniscus and changes of the underlying bone (10).

The highest loads at the knee occur at heel strike with the knee at nearly full extension (11). The thickest regions of femoral and tibial load bearing articular cartilage are aligned when the knee is in full extension, perhaps an adaptation to high loads at heel strike. Therefore, malaligned knees put parts of the cartilage under excessive loads that are not designed to bear this load. Healthy cartilage thickness increases on the medial condyle in subjects with a higher adduction moment (10). In contrast, for osteoarthritic cartilage, the medial to lateral condyle thickness ratio decreases with an increase in the adduction moment (10). In addition, overloading may cause subchondral bone stiffening, leading to compression of the cartilage on a much harder bone plate. Thus, degenerative changes to the cartilage can be caused by a kinematic change to the knee (10). This has also been supported by previous studies that showed an initiation of knee OA in a canine knee without concurrent cartilage damage, following isolated ACL transection (12). Our findings also suggested that increased varus thrust precedes changes in the KAM or that varus thrust is more sensitive to knee OA than KAM.

This study set the stage for **chapter 6** on the third part of this thesis, in which we tried to investigate the relationship between varus alignment and structural as well as clinical and functional characteristics of patients with knee OA.

Clinical and functional profile of the early OA subpopulation

Based on the cross-sectional studies included in this project and previous studies of our group, we are now able to further complete the picture of what the specific functional characteristics of the early OA population are. Previously we did report that subjects with early knee OA have a decrease in muscle strength, but that no alterations in gait pattern was found for this group of patients with knee OA. We found that, subjects with early OA do have an altered proprioceptive weighting, and demonstrated a stronger ankle-steered proprioceptive postural strategy, during standing. This was in contrast with proprioceptive accuracy that was still on the level of the control subjects and only deteriorated in the established phase. Additionally, we found that varus thrust is more common and that the magnitude of varus thrust is greater in women with early medial knee OA than in healthy controls. In Table 1, the so far known, characteristics of early OA subpopulation is summarized.

Table 1. A summary of what is known so far about early OA, as identified based on classification of Luyten et al (13)

Studied characteristics	Different between **early and control**	Different between **established and control**	Different between **early and established**
Structural features as detected on MRI	+	+	+
Clinical characteristics			
Pain	+	+	-
Symptoms	+	+	-
Physical function			
KOOS ADL	+	+	-
Performance-based physical Function	-	-	-
Static alignment	-	+	-
Kinematics and Kinetics			
Dynamic alignment	+	+	-
KAM and KAM Impulse	-	+	+
Neuromuscular characteristics			
Proprioceptive deficit	+	+	-
Muscle strength	+	+	-

ADL = Activity daily living as measured with KOOS subscore of ADL; KAM = external knee adduction moment impulse during stance phase of gait;
+ is indicative of existing difference
- is indicative of no difference

Highlights

- Early OA is associated with altered proprioceptive weighting.
- Dynamic varus malalignment is already present at the early stages of the disease.
- Increased varus thrust precedes changes in the KAM or that varus thrust is more sensitive to knee OA than KAM.

In **study III**, we investigated changes in gait stability over the gait cycle, in a group of patients with established knee OA, using the new method of time-dependent local dynamic stability λ(t) (14). While self-reported instability and its negative functional implications in knee OA have been reported by several researchers and clinicians (15-18), there is still no consensus about objective, accurate and reliable ways to measure "true" dynamic stability of the knee. Our results showed that patients with established knee OA present with decreased knee stability, in both sides, during walking compared to the young control group. Also, a tendency towards a decreased knee stability, between 40% and 70% (the weight transfer phase) of the stride cycle, was found for the affected side compared to the healthy elderly.

The presence of decreased Maximum time-dependent local dynamic stability, during the weight transfer phase of gait, might be due to reduced push-off burst of gastrocnemius activity during gait, as reported in severe OA patients (19). In line with that, a recent study suggested an increase or decrease in gait stability by manipulating push off (20). These results further reveal the problem of dynamic stability in subjects with established knee OA, and that the transition phase from stance to swing are a crucial phase for gait stability.

Highlights

- Decreased stability of knee movement in the sagittal plane exists in patients with established knee OA, during the weight transfer phase of gait.
- Time dependent measures of stability may provide more sensitive information about stability.

Part 2. Structural, clinical, and functional changes associated with severity and progression of knee OA over 2 years follow-up

Better understanding of the natural course of knee OA makes it possible to target preventative therapies and reduce risk factors for both the incidence and progression of knee OA (21). Therefore in **chapters 5 and 6**, we focused on the natural progression of OA, more specifically on the progression of structural, clinical, and functional parameters in patients with early medial knee osteoarthritis during two-year follow-up, and we compared the results to progression in asymptomatic control subjects as well as a group of patients with established medial knee OA. Our interest in the early OA population was based on the hypothesis that better understanding of the characteristics of this subpopulation might be helpful in targeting for treatment options aiming at arrest of the disease process or even reversing the process.

Objective part II

- To explore the changes in structural, functional and clinical characteristics over a 2 year-time frame in women with early and established medial knee OA compared to healthy control subjects.

In **study IV**, <u>structural, clinical, and functional changes over two years in a group of patients with early medial knee OA were assessed</u>, and compared to a group of patients with established medial knee OA, and a group of asymptomatic controls. The main findings of this study were that <u>over two years, only in the early OA group, the presence of meniscal extrusion increased after 2 years compared to the baseline.</u> In addition, <u>overall changes over a 2 year period were minor, and only a few subjects showed a deterioration in structural, clinical or functional characteristics.</u>

Association of meniscal damage at baseline with 2-year cartilage loss have been reported before (22). The increase in the presence of meniscal extrusion over two years in the early OA group could be an underlying factor for future cartilage loss and progression towards more severe knee OA. Higher meniscal damage was already present in the established OA group (compared to the healthy controls as well as the early OA), at the time of entry. Therefore, it was not surprising that meniscal damage did not show significant changes over two years in this group. The finding that meniscal damage was the only significant structural change observed over two years in the early OA group, further highlights the role of meniscus in maintaining the integrity of joint structure (23).

Patients with early medial knee OA reported more knee pain and symptoms compared to the asymptomatic subjects but did not significantly change over 2 years in any of the two patients' groups. Our findings are in line with recently reported findings by Wesseling et al., where a five year follow up of a mostly early OA population defined as knee pain in an age group 45-65 years and radiographically Kellgren 0 or I revealed fairly stable values in WOMAC scores for pain and physical functioning (24). This might be due to many factors including possible adaptations of patients. An intermittent and variable pattern have been reported for knee joint pain and symptoms, over the course of the disease, among patients with knee OA (25). Many factors can play a role in a person's response to pain (e.g. genetic predisposition, previous experience, current mood, coping strategies and sociocultural environment) (26), and the experience of pain can be modified due to adaptation and avoidance strategies (27, 28).

In the current study, quadriceps strength for both isometric and isokinetic measurements decreased over two years in both OA groups as well as in the asymptomatic controls. Therefore it seems that, as strength is already decreased form very early stages of the disease, further decrease in strength over time, more than what is observed by aging, is unlikely to occur.

In **study V**, we performed a <u>longitudinal study on the kinematic and kinetic characteristics of gait in women with early knee OA</u>, and compared results with longitudinal changes in women with established knee OA and in healthy controls over a two-year follow-up period. Findings of the current study is the first reference to the longitudinal gait changes associated with OA severity in a population of women with medial knee OA. Results indicated that <u>at baseline, the early OA group showed significantly higher maximum knee adduction angles compared to the healthy controls during the early stance phase of gait</u>. Knee loading was unaltered. This might imply that in the early stage of knee OA, gait is relatively normal. Also there were no changes in any of the gait parameters over time, and thus gait in OA is quite stable over 2 years.

Unlike early stages of knee OA, later stages of established disease are associated with several alterations in kinematic and kinetic characteristics of the gait. The established OA group, showed significantly less knee flexion excursion, higher peak knee adduction angle, increased first and second external knee adduction moment, as well as higher adduction moment impulse compared to the controls. Over two years, second peak external knee flexion moment during terminal stance phase of gait decreased compared to baseline measurements, in the established OA group. Also, knee adduction moment impulse increased significantly in patients with established knee OA after 2 years

compared to baseline. As reported in study II, static and dynamic varus malalignment is present (or higher) in patients with established medial knee OA, as well as quadriceps and hamstrings muscle weakness, as reported in study IV. Increased (static and dynamic) varus malalignment, coupled with muscle weakness in this population at baseline, might suggest decreased control over the knee joint and set the stage for further increase in medial knee joint loading.

Longitudinal changes of clinical and functional profile of the early OA subpopulation

Based on the longitudinal studies included in this project, we found that after 2 years, only in the early OA group, the presence of meniscal extrusion increased compared to the baseline. Pain, symptoms, and function showed a stable course over two years. Moreover, finding suggest that longitudinal changes in gait pattern are only in the established phase of OA, and is not likely adaptive but may indeed reflect reduced strength, which seems likely to be a result rather than a cause of disease progression.

Highlights

- In the early OA group, the presence of meniscal extrusion increased over 2 years compared to the baseline.
- Muscle strength is already decreased at the very early stages of knee OA, but further decrease in strength over time is similar as the age-related muscle weakness.
- In the early stages of knee OA, gait is relatively normal and gait characteristics associated with knee OA is quite stable over 2 years.

Part 3. Prognostic factors of progression in structural, clinical, and functional profile of OA

There is an increasing interest in identifying a subpopulation of patients with a greater risk of progression in knee OA. Knowledge of risk factors associated with progression of knee osteoarthritis is of paramount importance as only a few number of the patients progress rapidly (29, 30). The combination of the natural course of joint damage (**chapters 5 and 6**) and information about the prognostic factors (**chapters 7 and 8**) will make it possible to identify a knee potentially in danger to progress towards end-stage OA requiring total knee arthroplasty.

Objective part III

- To identify the factors related with progression of OA in a population of women with medial knee OA.

In **study VI**, we were interested to know <u>if varus malalignment at the time of entry would affect structural, clinical, and functional outcomes after two years, as well as its relationship with progression of knee OA</u>. <u>The main findings of this study were that both static and dynamic alignment in the frontal plane were significantly associated with OA related tibiofemoral joint structural abnormalities detected on MRI.</u> Also, that <u>only the magnitude of varus thrust at baseline was predictive of the changes in the presence of meniscal maceration over two years</u>.

Static and dynamic varus malalignment of the knee, both, have been related to radiographic progression of knee OA (31-34). Structural abnormalities such as BMLs have been associated with pain, further cartilage degeneration and joint space narrowing in patients with knee OA (35-40). KAM is related with chronic knee pain and a higher prevalence of BMLs in the medial compartment (41, 42). As, both KAM and BMLs were associated with static and dynamic alignment, we hypothesized that perhaps there is a relationship between alignment and clinical symptoms, such as pain, as well. But, surprisingly, none of the static or dynamic measures of knee joint alignment were associated with any clinical characteristics of the patients with knee OA.

In patients with early knee OA, higher levels of pain and more and larger BMLs are present. But dynamic medial knee joint loading is not altered in this group. Therefore it seems unlikely that the cause of pain and symptoms in this group, is increased medial joint loading.

From a biomechanical point of view, varus thrust, as the sudden worsening of the varus angle during the stance phase of gait, results in a shift of the GRF towards the medial compartment of the knee, with each step. As a result a shift in loading occurs, and an extra load will be exerted on (medial) regions in the cartilage that have not adapted to the high loads that occur at heel strike. Repetitive high loads may simply accelerate the meniscal degradation and eventually exceed the threshold for tearing (43, 44).

In **study VII**, fast progressors were identified based on structural worsening, pain exacerbation, and functional deterioration over two years, separately. Our findings showed that different progressors exist based on the type of outcome used for assessment of changes over time. Fast progressors as categorized based on a 1 point increase in K&L grade, showed more and larger BMLs in the tibiofemoral joint, higher prevalence of meniscal extrusions and macerations, as well as worse self-reported Quality of Life, as measured with KOOS, at baseline. Fast progressors, as defined based on pain exacerbation over 2 years, showed weaker quadriceps and hamstrings, as well as higher second peak knee adduction moment at baseline compared to slow progressors. Identification of fast progressors based on performance-based physical function, showed higher percentage of subjects with meniscal tears in this group, compared to the slow progression group. Fast progressors, defined based on deterioration in self-reported physical performance, demonstrated weaker quadriceps and hamstring muscle strength, as well as higher second peak knee adduction moment in the fast progressor group compared to the slow progressors, at the time of entry.

Based on the findings in our study, there are distinct risk factors for progression depending on the outcomes as assessed by structural, clinical, and functional criteria. Each may be associated with specific structural, clinical, and biomechanical variables at the time of entry. From a clinical point of view, perhaps the patient's clinical and functional deterioration matters the most. Interestingly, subjects that do progress in pain and in self-reported physical function over 2 years, <u>do show</u> lower quadriceps and hamstring muscle strength. <u>This might further underline the essential role of muscle strength in the clinical and functional deterioration associated with knee osteoarthritis</u> (45) and thus the need to focus on strength in the rehabilitation. Meniscal injuries also have to be followed up closely as they are related with further structural deterioration.

Disease progression is very variable amongst this study population with knee OA, with only 20% of subjects showing progression in structural features as detected on MRI, which further highlights the heterogeneity of the knee OA population. Another interesting finding of this study was that subjects

who showed self-reported functional deterioration after two years were different from the ones with performance-based functional deterioration.

Highlights

- Both static and dynamic alignment in the frontal plane were significantly associated with OA related tibiofemoral joint structural abnormalities detected on MRI.
- Different risk factors have been identified based on the defined outcome

General conclusions

This doctoral project revealed that in addition to structural and clinical abnormalities, altered proprioception, as well as increased dynamic varus malalignment already exist in patients with early medial knee OA. A follow-up on the structural, clinical, and functional characteristics of this group compared to the healthy controls and the established OA patients, revealed that over 2 years, structural, clinical, and functional characteristics of patients with early knee OA were rather stable except for the presence of meniscal extrusions which increased over two years in the early OA group. On the other hand, for the established OA group, several differences were found compared to the controls, which further confirms previous findings on this group in the literature.

The presence of quadriceps and hamstring weakness, coupled with altered proprioception and the presence of dynamic varus malalignment at the early stages of the disease, might imply that the control over the knee joint is already decreased at the early stages of the disease. In a diseased knee, this might set the stage for further progression of knee OA and development of further irreversible changes in the knee joint.

Also, results from the current doctoral project were the first to show that clinical, structural, and functional progression of knee OA are associated with different risk factors at baseline. Indeed, the identification of a patient at higher risk of progression may depend on the type of outcome measure used for the assessment of progression.

Implications for clinical practice

This doctoral project tried to elaborate more on understanding the disease characteristics at the early stages of knee OA with a focus on objective functional assessments. Future research in an independent patient population has to confirm our findings on the clinical and functional characteristics of subjects at the early stages of the disease. Our findings from current projects set the stage for development of a better definition of "early knee OA", and therefore to create homogeneous patient subsets for the purpose of management and clinical trials (46).

Not all subjects with medial knee OA should be treated the same. Results from this thesis showed that even though the inclusion criteria for each subpopulation of patients with knee OA were the same, still only few subjects in each group progressed over two years, while the others did not show significant worsening over 2 years. Therefore it is recommended that for each subject a specific treatment strategy is planned which is specific to the characteristics of that patient. For example,

knee joint static and dynamic alignment both should be considered in the therapy and alignment corrections should precede or be in parallel with routine knee OA treatments like muscle strengthening exercises. Development and validation of specific exercise regimes that target frontal plane dynamic instability, especially at the early stages of the disease process, seems necessary in order to slow down the knee OA progression by reducing the chance of developing greater medial loads. Patients with higher/presence of varus thrust can also benefit from stabilizing orthoses or probably lateral wedged insole, as it has been shown to be effective in reducing the greater force associated with varus thrust (47).

The presence of significantly elevated first and second peak KAM in subjects with varus thrust, based on dichotomized varus thrust data, suggest that visual observation of thrust during gait could offer a simple clinical tool to detect subjects at higher risk of developing excessive medial joint load, as well as more and larger BMLs. This would not require quantitative gait analysis or radiographic assessment of knee mechanical alignment. However, the validity and reliability of visual observation would need to be verified.

Longitudinal results from this doctoral thesis, suggests that patients, when identified at early stages of the disease, might keep a stable structural, clinical, and functional profile for quite some time. Specific management protocols could be planned for these patients during their stable period, in order to prevent the disease from further progression and beginning of irreversible changes.

Recently, proactive treatment of rheumatic diseases has resulted in preservation of structure and function and the discussion of a new classification of disease remission. For example, in osteoprosis, recent evolution in medical care, with the appropriate institution of antiresorptive therapy, caused a marked reduction in fracture rates with their associated morbidity. Unfortunately, current therapeutic approaches for knee OA are mainly palliative, as we do not have such a proactive intervention available in osteoarthritis. Therefore, focusing on earlier stages of the disease in which changes may be reversible might help. Findings of the current PhD project on early OA such as presence of dynamic malalignment, decreased lower limb muscle strength, and altered proprioceptive weighting, migh help to build the bigger picture of what can be done as a proactive treatment, already at in the very early stages of the disease, before destructive changes associated with the disease, become irreversible.

Limitations and implications for future research

The findings of this doctoral project have to be interpreted taking the methodological limitations into account.

A first limitation of this study is about the study group: All of the participants in the current study were **female**s, and several gender differences have been reported for clinical (such as muscle strength) (48, 49) and structural features (such as alignment and patellofemoral abnormalities) (50-52). As such, the results of this study cannot be generalized to the whole population of patients with knee OA. Also, in the current project only characteristics of patients with **osteoarthritis of the medial compartment** were investigated. As, there are reports on differences in structural, clinical and biomechanical characteristic of patients with medial and lateral knee OA. Therefore, the results of this study cannot be generalized to the patients who suffer from lateral compartment knee OA. The **study population** in this thesis is rather small compared to other prospective longitudinal studies. Therefore the small sample size in the current project may have resulted in loss of statistical power and caution is advised when extrapolating results obtained from project.

In the current project, focus was only on the frontal and sagittal plane kinetics of the knee joint, but it is likely that mechanical alterations at adjacent joints, like the pelvis, hip and ankle can affect knee joint loading. Furthermore, trunk movements were not considered. In the literature, it has been reported that some patients with medial compartment knee OA show an altered gait pattern that reduces the KAM and is driven by a change in the medio-lateral trunk sway (53). Trunk positioning and movement also are recognized to affect gait strategies and might reflect significant compensation mechanisms in patients with knee OA (54). Also, although in the current thesis we found some differences between women with early and established knee OA, there are still many other parameters that have to be studied to further discriminate these two populations, and further complete the profile of early OA group, such as psychosocial factors, the role of specific genes, EMG etc.

Previous research demonstrated that differences in marker placement can be a significant source of error in kinematic measurements of the knee (55), and a recent assessment of 12 gait analysis laboratories identified marker placement variation between examiners as the principle cause of variability between centers (56). Also, in longitudinal studies, the source and magnitude of measurement error and variability are of concern, especially due to different examiners. In the present doctoral thesis, data were collected by several examiners and therefore, some inconsistency

in marker placement was inevitable. Although, we tried to overcome this issue by using detailed guidelines specific for each test.

It is important to note that we evaluated knee joint loading indirectly by measuring knee joint moments. However, the contact forces to which the knee articular surfaces are subjected during daily activities cannot be based on moment data alone. Muscle contractions and tension in passive soft tissues in and around the knee joint also contribute to knee joint loading and should be taken into consideration. In this respect, modeling and simulation techniques (including data on external knee joint moments, active muscle contractions (EMG) and passive soft tissue tension) with computational prediction of contact forces during specific activities of daily living might provide relevant information. Currently, a parallel doctoral thesis is working on this part (57).

The current thesis, as well as previous literature, mainly focuses on frontal plane knee kinematics and kinetics during walking, while sagittal plane movement of the knee (or adjacent joints) also contributes to and affects load distribution in the tibiofemoral joint. For example, stiff knee gait pattern might be compensated by excessive motion in the frontal plane and therefore alter frontal plane kinematics and consequently load distribution. Therefore, future research should also further study knee joint kinematic and kinetic characteristics in the sagittal plane in patients with knee OA.

With the studies of this doctoral project, a first step was made to gain more insight into functional parameters that can be associated with early joint degeneration and these studies and measurements form the basis for longer and more comprehensive longitudinal studies. Indeed, to know whether such functional parameters can be considered as functional markers predictive of knee OA progression, more work is needed. Most importantly, the present study was a 2 years longitudinal study. Considering the nature of the knee OA, which progresses slow, it is required to investigate the impairments in a longer period study. As mentioned before, this doctoral thesis is part of a bigger longitudinal project that aims to identify prognostic factors associate with progression of knee OA. Therefore, as part of the bigger picture, we also measured all parameters reported in this doctoral thesis, at 4 years follow-up, but according to the time frame of this doctoral thesis 4-years follow-up of the subjects is outside the scope of this project.

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APPOSITIONS

Negative, unexpected, or controversial, results are not a failure of the research. Scientists should move away from positive bias, as negative results are as important.

Holding an opinion with extreme passion, indeed, is a sign of lack of rational conviction. Political and religious opinions are almost always held passionately.

Coming out of our comfort zone, and exposing ourselves to new people and cultures will broaden our mind and help to realize that this world is a small place, and that despite our differences, we are all similar and interconnected.

CURRICULUM VITAE

Armaghan Mahmoudian was born in 1984 in Tehran, Iran. She received her Bachelor's degree in Physiotherapy in 2006 at the Iran University of Medical Sciences. In 2009 she received her Master's degree in Physiotherapy at the University of Social Welfare and Rehabilitation Sciences. During and after her studies as a master student she also collaborated with Iran's Handball and Volleyball National Federations. During this time she worked as a sports physiotherapist with several women's National and club teams and participated in several international championships. In September 2010, she started her career as a full-time lecturer at the Faculty of Physiotherapy and Rehabilitation sciences, at the Catholic University of Daegu, South Korea. In September 2011, she moved to Belgium and started her joint doctoral project as part of the first generation of Move-Age, an Erasmus Mundus Joint Doctorate program. Since 2011, she has been working as a doctoral student affiliated with the Musculoskeletal Rehabilitation Research Group (Department of Rehabilitation Sciences) at KU Leuven, Belgium, under supervision of Prof. Sabine Verschueren and Prof. Dr. Frank Luyten. As part of her joint PhD project, she also worked for 6 months (Sep. 2013-March 2014) as a PhD student, at the MOVE Research Institute, VU University, Amsterdam. There, in the Musculoskeletal Biomechanics Research Group, she worked under supervision of Prof. Jaap van Dieen. During her PhD program she also coached several students at the master level in Kinesiology and Rehabilitation Sciences. Her work during her doctoral training at KU Leuven and VU University, is presented in this thesis.

LIST OF PUBLICATIONS

Publications in peer-reviewed journals

Mahmoudian A., Bruijn SM., Yakhdani HR., Meijer OG., Verschueren SM., van Dieen JH. "Phase-dependent changes in local dynamic stability during walking in elderly with and without knee osteoarthritis." *Journal of biomechanics* , 2016. 49(1): p. 80-86.

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Supervision undergraduate students

Belmans, E. & Lambrechts, P., **Mahmoudian, A.**, Verschueren, S. (2015) Longitudinal study of the kinetic and kinematic characteristics of step negotiation in patients with early and established medial knee osteoarthritis, non published master thesis, KU Leuven.

Lie, V. & Huludeţ, D., **Mahmoudian, A.**, Verschueren, S. (2015) Movement pattern and knee joint loading during a sit to stand task in women with early and established knee osteoarthritis: results from a 2-years follow up study, non published master thesis, KU Leuven.

Monzari Mofrad, M., & Roozdar, A., **Mahmoudian, A.**, Verschueren, S. (2014) The relationship between varus thrust and physical function in patients with knee osteoarthritis, non published master thesis, KU Leuven.

Hawinkel, S., & van den Broek, A., **Mahmoudian, A.**, Verschueren, S. (2014) Changes in static postural control associated with progression of knee osteoarthritis, non published master thesis, KU Leuven.

Goovaerts, J. & Dewit, J., **Mahmoudian, A.**, Verschueren, S. (2014) Quadriceps and hamstrings coordination during gait in knee ostheoarthritic subjects, is it related to disease severity? , non published master thesis, KU Leuven.

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Hendrix, E. & Maes, K., **Mahmoudian, A.**, Verschueren, S. (2013) Changes in structural and clinical parameters related to the progression of knee osteoarthritis: a two year follow up study, non published master thesis, KU Leuven.

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سپاس

Bedankt

Thank you

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